

THIRD EDITION

Principles and Practice of GERIATRIC PSYCHIATRY

Editors Mohammed T. Abou-Saleh, Cornelius L.E. Katona, Anand Kumar



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Third Edition

Edited by

Mohammed T. Abou-Saleh

St George's Hospital Medical School, London, UK

Cornelius Katona

University College London, London, UK

Anand Kumar

University of Illinois, Illinois, USA



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111 River Street, Hoboken, NJ 07030-5774, USA

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Dedication

Dedicated to our wives and families

Associate Editors

Dave Anderson

Mersey Care NHS Trust
Older People's Mental Health Services
Sir Douglas Crawford Unit, Mossley Hill Hospital
Park Avenue
Liverpool L18 8BU, UK

Chris Fox

Folkestone Health Centre
15-25 Dover Road
Folkestone
Kent CT20 1JY, UK

Mary Ganguli

Western Psychiatric Institute and Clinic
3811 O'Hara St.
Pittsburgh, PA 15213, USA

Constantine G. Lyketsos

The Johns Hopkins Bayview Medical Center
5300 Alpha Commons Drive
Alpha Commons Building, 4th Floor
Baltimore, MD 21224, USA

Zuzana Walker

Department of Mental Health Sciences
St Margaret's Hospital
Epping
Essex, CM16 6TN UK

Kenneth Wilson

St Catherine's Hospital
Church Road
Birkenhead
Wirral L42 OLQ, UK

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Contributors

Charlene S. Aaron University of Iowa College of Nursing, 101 Nursing Building, 50 Newton Road, Iowa City, IA 52242-1121, USA

Melanie Abas Institute of Psychiatry, Kings College London, Box P060, De Crespigny Park, London SE5 8AF, UK

Mohammed T. Abou-Saleh Division of Mental Health, St George's, University of London, Cranmer Terrace, London SW17 0RE, UK

Marc E. Agronin University of Miami Miller School of Medicine, and Medical Director for Mental Health and Clinical Research, Miami Jewish Health Systems, Miami, FL 33137, USA

Howard Aizenstein University of Pittsburgh School of Medicine, Pittsburgh, USA

Olusola Ajilore Department of Psychiatry, University of Illinois-Chicago, 5841 S. Maryland Ave, Chicago, IL 60637, USA

David N. Anderson Mersey Care NHS Trust, Older People's Mental Health Services, Sir Douglas Crawford Unit, Mossley Hill Hospital, Liverpool L18 8BU, UK

David N. Anderson Mersey Care NHS Trust, Older People's Mental Health Services, Sir Douglas Crawford Unit, Mossley Hill Hospital, Liverpool L18 8BU, UK

Toni C. Antonucci Institute for Social Research, University of Michigan, 426 Thompson Street, Ann Arbor, MI 48106-1248, USA

Carolina Aponte Urdaneta Duke University Medical Center, Room 3059 Yellow Zone, 200 Trent Dr, Durham, NC 27710 2, USA

Liana G. Apostolova Department of Neurology, UCLA David Geffen School of Medicine, Los Angeles, CA 90095, USA

Brian S. Appleby Division of Geriatric Psychiatry and Neuropsychiatry, The Johns Hopkins Hospital, Baltimore, MD 21287, USA

Tom Arie University of Nottingham, Ageing and Disability Research Unit, The Medical School, Queen's Medical Centre, Nottingham NG7 2UH, UK

Kunle Ashaye Hertfordshire Partnership NHS Trust, Mental Health Unit, Lister Hospital, Coreys Mill Lane, Stevenage, Hertfordshire SG1 4AB, UK

Stefanie Auer MAS Alzheimerhilfe, Bad Ischl, Austria

Olusegun Baiyewu Department of Psychiatry, College of Medicine, University of Ibadan, Nigeria

Robert Baldwin Manchester Mental Health & Social Care Trust, Edale House, Manchester Royal Infirmary, Manchester M13 9BX, UK

Clive Ballard Wolfson Centre for Age Related Diseases, King's College London, Guy's Campus, London SE1 1UL, UK

Sube Banerjee Institute of Psychiatry, King's College London, 16 De Crespigny Park, London, SE5 8AF, UK

Stephen J. Bartels Department of Psychiatry, Dartmouth Centers for Health and Aging Dartmouth Medical School, Hanover, NH 03755-1404, USA

Aartjan T. F. Beekman VU Medical Center and GGZ in Geest, A.J. Ernststraat 887, Amsterdam 1081 HL, and EMGO Institute for Health and Care Research, VU University and VU University Medical Center, Amsterdam, The Netherlands

Jean Beh King's College London, London SE1 1UL, UK

Lynn M. Bekris Departments of Medicine, Neurology and Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA 98195, USA

Susan Mary Benbow Centre for Ageing and Mental Health, Staffordshire University, Stafford ST18 0AD, UK

German E. Berrios Department of Psychiatry, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK

John L. Beyer Duke University Medical Center, Room 3059 Yellow Zone, 200 Trent Dr, Durham, NC 27710 2, USA

Ashok J. Bharucha University of Miami Miller School of Medicine, Miami, Florida, 33136 USA

David Bienenfeld Department of Psychiatry, Wright State University Boonshoft School of Medicine, Dayton, OH 3640, USA

Thomas D. Bird Geriatrics Research Service, Veterans Affairs Puget Sound Health Care System, Seattle, WA 98108, USA

Douglas Blackwood Division of Psychiatry, University of Edinburgh, The Royal Edinburgh Hospital, Edinburgh, EH10 5HF, UK

Dan G. Blazer Duke University School of Medicine, Duke University Medical Center, Durham, NC 27710, USA

Mats Bogren Department of Clinical Sciences, Psychiatry, The Lundby Study, Lund University Hospital, SE-221 85 Lund, Sweden

Susan Y. Bookheimer Center for Cognitive Neurosciences, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA

Walter Pierre Bouman Mental Health Services for Older People, University Hospital, Nottingham NG7 2UH, UK

Ann Bowling Department of Primary Care and Population Health, University College London, London WC1E 6BT, UK

Carol Brayne – Chapter 48 Department of Public Health & Primary Care, Institute of Public Health, Robinson Way, Cambridge CB2 2SR, UK

John C. S. Breitner GRECC, VA Puget Sound Health Care System, Division of Geriatric Psychiatry, University of Washington School of Medicine, Seattle, WA 98108, USA

Dawn Brooker University of Worcester Association for Dementia Studies, Institute of Health and Society, University of Worcester, Henwick Grove Campus, Worcester WR2 6AJ, UK.

Kathleen C. Buckwalter University of Iowa College of Nursing, 101 Nursing Building, 50 Newton Road, Iowa City, IA 52242-1121, USA

Rob Butler Suffolk Mental Health Partnership NHS Trust, St Clement's Hospital, Foxhall Road, Ipswich, Suffolk IP3 8LS, UK

Ashley Cain Department of Psychiatry, University of California – San Diego, MC 0680, 9500 Gilman Drive, La Jolla, CA 92093-0680, USA

Veronica Cardenas Department of Psychiatry, University of California – San Diego, MC 0680, 9500 Gilman Drive, La Jolla, CA 92093-0680, USA

Ruoling Chen Centre for Health and Social Care Improvement, School of Health and Wellbeing, University of Wolverhampton, Wulfruna Street, Wolverhampton, WV1 1LY, UK

Nicolas Cherbuin Centre for Mental Health Research, Australian National University, 63 Eggleston Road, Canberra, ACT 0200, Australia

Carolyn Chew-Graham Primary Care Research Group, School of Community Based Medicine, University of Manchester, 5th Floor Williamson Building, Oxford Road, Manchester M13 9PL, UK

Ramilgan Chitramohan Birmingham and Solihull Mental Health Foundation Trust, Heartlands Hospital, Birmingham B9 5SS, UK

Helen Chiu Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

Linda Clare School of Psychology, Bangor University, Bangor, Gwynedd LL57 2AS, UK

Brian Clarke Department of Clinical Gerontology, King's College Hospital, Denmark Hill, London, SE5 9RS, UK

Mary Coats Department of Neurology, Washington University in St Louis, 660 S. Euclid Avenue, CB 8111, St. Louis, MO 63110, USA

Jiska Cohen-Mansfield George Washington University Medical Center and School of Public Health, Washington DC 20037, USA
Tel Aviv University Herzeg Institute on Aging and Sackler Faculty of Medicine, Tel-Aviv, Israel

Peter Connelly Murray Royal Hospital, Perth PH2 7BH, UK

J. E. Cooper Department of Psychiatry and Behavioural Science, Medical Research Foundation Building, Level 3 Rear, 50 Murray Street, Perth, WA 6000, Australia

John R. M. Copeland University of Liverpool, Department of Psychiatry, Section of Old Age Psychiatry, St Catherine's Hospital, Birkenhead, Wirral, CH42 0LQ, UK

Monica Crugel Oxleas NHS Foundation Trust, Memorial Hospital, Shooters Hill, London, SE18 3RZ, UK

Pim Cuijpers VU University Amsterdam, Van der Boechorststraat 1, Amsterdam 1081 BT, and EMGO Institute for Health and Care Research, VU University and VU University Medical Center, Amsterdam, The Netherlands

Hugo de Waal East of England Postgraduate School of Psychiatry, Fulbourne, Cambridge CB21 5XB, UK

Colin Depp Department of Psychiatry, University of California – San Diego, MC 0680, 9500 Gilman Drive, La Jolla, CA 92093-0680, USA

Davangere P. Devanand College of Physicians and Surgeons, Columbia University, and Division of Geriatric Psychiatry, New York State Psychiatric Institute, New York, NY 10032, USA

Markus Donix Center for Cognitive Neurosciences, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA

Brian Draper School of Psychiatry, University of NSW, Sydney, NSW 2052, Australia

Stephen B. Dunnett School of Biosciences, Cardiff University, Museum Avenue Box 911, Cardiff, CF10 3US, UK

Linda Ercoli Department of Psychiatry and Biobehavioral Sciences, Geriatric Psychiatry Division, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, Suite 37-440, Los Angeles, CA 90024, USA

Mavis Evans Elderly Mental Health Directorate, Wirral and West Cheshire Community NHS Trust, Clatter bridge Hospital, Bebington, Wirral L63 4JY, UK

Lisa T. Eyler University of California, San Diego, 9500 Gilman Drive, # 9151-B, La Jolla, CA 92093, USA

Waleed Fawzi Oxleas NHS Foundation Trust, Memorial Hospital, Shooters Hill, London, SE18 3RZ, UK

Steven Ferris Aging and Dementia Clinical Research Center, New York University Langone Medical Center, Center of Excellence on Aging, New York, NY 10016, USA

Cynthia D. Fields Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD 21287, USA

- Jonathan Folstein** Vanderbilt University, Nashville, Tennessee, USA
- Marshal Folstein** University of Miami Miller School of Medicine, Nashville, USA
- Susan Folstein** University of Miami Miller School of Medicine, Nashville, USA
- Brent Forester** Harvard Medical School, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA
- Hans Förstl** Klinik und Poliklinik für Psychiatrie und Psychotherapie, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, 81675 München, Germany
- Chris Fox** Folkestone Health Centre, 15-25 Dover Road, Folkestone, Kent CT20 1JY, UK
- Paul T. Francis** King's College London, Wolfson Centre for Age-Related Diseases, Guy's Campus, London SE1 1UL, UK
- Emile Franssen** Aging and Dementia Clinical Research Center, New York University Langone Medical Center, Center of Excellence on Aging, New York, NY 10016, USA
- D. Gallagher-Thompson** Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305-5717, USA
- Mary Ganguli** Western Psychiatric Institute and Clinic, 3811 O'Hara St. Pittsburgh, PA 15213, USA
- V. Gardner** Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 3950, USA
- Serge Gauthier** McGill Center for Studies in Aging, Douglas Hospital, Montreal, Quebec H4H 1R2, Canada
- J P Gibbons** Department of Psychiatry and Behavioral Sciences, Center for the Study of Aging and Human Development, Duke University Medical Center, Room 3521 Blue Zone Duke Clinics, Box 3003, Durham, NC 27710, USA
- Ben Green** Department of Psychiatry, University of Liverpool 147, UK
- Faith M. Gunning** Institute of Geriatric Psychiatry, Department of Psychiatry, Weill Cornell Medical College, 21 Bloomingdale Road, White Plains, NY 10605, USA
- Jeffrey T. Guptill** Duke University School of Medicine, Duke University Medical Center, Durham, NC 27710, USA
- David Gwyn Seymour** Medicine for the Elderly, University of Aberdeen, Aberdeen, AB24 3EN, UK
- Scott M. Hayes** Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Department of Psychiatry, Duke University, Durham, NC 27705, USA
- C. Michael Hendricks** Department of Psychiatry, Wright State University, Boonshoft School of Medicine, OH 3640, USA
- Adriana P. Hermida** Fuquay Center for Late Life Depression, Emory University School of Medicine, Atlanta, GA 30329-5120, USA
- N. Herrmann** Sunnybrook Health Sciences Centre, Toronto, Ontario, M4N 3M5, Canada
- Claire Hilton** Mental Health Service for Older Adults, Central and North West London NHS Foundation Trust, Bentley House, Harrow HA3 5QX, UK
- John V. Hindle** School of Medical Sciences, University of Bangor, Llandudno Hospital, Llandudno, Conwy, LL30 1LB, UK
- Juanita Hoe** Department of Mental Health Sciences, University College London, London W1W 7EJ, UK
- Allan House** School of Healthcare, University of Leeds, Leeds LS2 9JT, UK
- Julian C. Hughes** Northumbria Healthcare NHS Foundation Trust and Institute for Ageing and Health, Newcastle University, Newcastle Upon Tyne, NE1 7RU UK
- Celia F. Hybels** Department of Psychiatry and Behavioral Sciences, Center for the Study of Aging and Human Development, Duke University Medical Center, Room 1505 Blue Zone Duke Clinics, Box 3003, Durham, NC 27710, USA
- Thomas Idiculla** Mental Health Services Evaluation Dept, McLean Hospital, 115 Mill St, Belmont, MA 02478, USA
- James S. Jackson** Institute for Social Research, University of Michigan, Ann Arbor 48502, USA
- S. H. D. Jackson** Department of Clinical Gerontology, King's College Hospital, Denmark Hill, London, SE5 9RS, UK
- A. Jablensky** Department of Psychiatry and Behavioural Science, Medical Research Foundation Building, Level 3 Rear, 50 Murray Street, Perth, WA 6000, Australia
- Imran A. Jamil** Aging and Dementia Clinical Research Center, New York University Langone Medical Center, Center of Excellence on Aging, New York, NY 10016, USA
- Dilip V. Jeste** University of California, San Diego, 9500 Gilman Drive, # 0664, La Jolla, CA 92093, USA
- David Jolley** Personal Social Services Research Unit, Manchester University, Manchester M13 9PL, UK
- Rob Jones** Mental Health Services for Older People Directorate and Nottingham University Section of Old Age Psychiatry, Queen's Medical Centre, Nottingham NG7 2UH, UK
- Anthony Francis Jorm** ORYGEN Research Centre, Department of Psychiatry, University of Melbourne, Parkville, Victoria 3052, Australia
- Eileen M. Joyce** UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK
- Andrea June** University of Colorado at Colorado Springs, Colorado Springs, CO 80918, USA
- Barbara Kamholz** Department of Psychiatry, Duke University, Durham, NC 27708, USA
- Jason Karlawish** University of Pennsylvania Institute on Aging, Philadelphia, PA 19104, USA

- Robert J. Kastenbaum** Arizona State University at Tempe, Tempe, AZ 85287, USA
- Cornelius Katona** Department of Mental Health Sciences, University College London, Charles Bell House, 7-73 Riding House Street, London W1W 7EJ, UK
- Sharjeel Khan** Aging and Dementia Clinical Research Center, New York University Langone Medical Center, Center of Excellence on Aging, New York, NY 10016, USA
- Zunera Khan** King's College London, London SE1 1UL, UK
- Jeanne Kim** Memory and Aging Research Center, Geriatric Psychiatry Division, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, Suite 88-201, Los Angeles, CA 90024, USA
- Susan Kim** Geriatric Psychiatry Research Program, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA
- Paul D. Kirwin** Associate Professor of Psychiatry, Geriatric Psychiatry Fellowship Director, Yale University School of Medicine, VA CT Healthcare System
- Eran Klein** The Johns Hopkins Berman Institute of Bioethics, Baltimore, MD 21201, USA
- Alan Kluger** Aging and Dementia Clinical Research Center, New York University Langone Medical Center, Center of Excellence on Aging, New York, NY 10016, USA
- Anthony Klugman** Old Age Psychiatry, South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Monks Orchard Road, Beckenham, Kent, BR3 3BX, UK
- Robert Kohn** The Warren Alpert Medical School of Brown University, Miriam Hospital, 164 Summit Ave, Fain Building Suite 2B, Providence, RI 02906, USA
- Maritha J. Kotze** Department of Pathology, Faculty of Health Sciences, Stellenbosch University, Tygerberg, 7505, Cape Town, South Africa
- Peter Knapp** School of Healthcare, University of Leeds, Leeds LS2 9JT, UK
- Anand Kumar** Department of Psychiatry, University of Illinois-Chicago, 912 South Wood Street, Chicago, IL 60637, USA
- Yookyung Kwon** Stanford Geriatric Education Center, 1215 Welch Road, Stanford, CA 94304-5403, USA
- Helen H. Kyomen** McLean Hospital, 115 Mill Street, Belmont, MA, 02478, USA
- Iain Lang** Peninsula Medical School, University of Exeter, Plymouth, PL6 8BU, UK
- Nicole M. Lanouette** University of California, San Diego, 9500 Gilman Drive, # 0664, La Jolla, CA 92093, USA
- Maria I. Lapid** Mayo Clinic College of Medicine, Mayo Clinic Rochester, Rochester, MN 55905, USA
- Helen Lavretsky** Departments of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA
- Vanessa Lawrence** Institute of Psychiatry, King's College London, 16 De Crespigny Park, London, SE5 8AF, UK
- Orly Lazarov** Department of Anatomy and Cell Biology, College of Medicine, The University of Illinois at Chicago, Chicago, IL 60612, USA
- Barry D. Lebowitz** University of California, San Diego School of Medicine, 9500 Gilman Drive, La Jolla, CA 92093, USA
- Susan W. Lehmann** Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Meyer 279, Baltimore, MD 21287-7279, USA
- Alex D. Leow** Department of Psychiatry, University of Illinois at Chicago, Chicago, IL 60637, USA
- James Lindesay** Department of Health Sciences, University of Leicester, Leicester LE5 4PW, UK
- Benjamin Liptzin** Department of Psychiatry, Baystate Medical Center, 759 Chestnut Street, Springfield, MA, 01199, USA
- Gill Livingston** Department of Mental Health Sciences, University College London, London W1W 7EJ, UK
- Constantine G. Lyketsos** The Johns Hopkins Bayview Medical Center 5300 Alpha Commons Drive Alpha Commons Building, 4th Floor, Baltimore, MD 21224, USA
- David Aaron Maroof** Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Meyer 218, Baltimore, MD 21287-7218, USA
- Renee Marquett** Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305-5717, USA
- Meghan A. Marty** University of Colorado at Colorado Springs, Colorado Springs, CO 80918, USA
- E. Wayne Massey** Duke University School of Medicine, Duke University Medical Center, Durham, NC 27710, USA
- Fiona E. Matthews** MRC Biostatistics Unit, Institute of Public Health, Cambridge, CB2 2SR, UK
- Cecilia Mattisson** Department of Clinical Sciences, Psychiatry, The Lundby Study, Lund University Hospital, SE-221 85 Lund, Sweden
- Donna D. McAlpine** School of Public Health, University of Minnesota, Minneapolis, MN 55455, USA
- William M. McDonald** Fuquay Center for Late Life Depression, Emory University School of Medicine, Atlanta, GA 30329-5120, USA
- Bernadette McGuinness** Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, The Queen's University of Belfast, Belfast BT9 7BL, UK

- I. G. McKeith** Department of Old Age Psychiatry, Institute for Health of the Elderly, Wolfson Research Centre, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, UK
- David Mechanic** Institute for Health, Health Care Policy and Aging Research, Rutgers, the State University of New Jersey, New Brunswick, NJ 08901, USA
- David Melzer** Peninsula College of Medicine & Dentistry, Universities of Exeter and Plymouth, John Bull Building, Plymouth, PL6 8BU, UK
- Mario F. Mendez** Departments of Neurology and Psychiatry, VA Greater Los Angeles Healthcare System and David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA
- David A. Merrill** Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA and VA Greater Los Angeles Healthcare System
- Sujatha Merve** Chasefarm Hospital, Enfield EN2 8JL, UK
- Catherine Messinger** University of Iowa College of Nursing, 101 Nursing Building, 50 Newton Road, Iowa City, IA 52242-1121, USA
- Karen Miller** Aging and Memory Research Center, Geriatric Psychiatry Division, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, Suite 88-201, Los Angeles, CA 90024, USA
- Alisoun Milne** School of Social Policy, Sociology and Social Research, University of Kent, Canterbury, Kent CT2 7LZ, UK
- Gary S. Moak** University of Massachusetts Medical School, Worcester, MA and Medical Director, Moak Center for Healthy Aging, 18 Lyman Street, Suite 285 Westborough, MA 01581, USA
- Victor Molinari** University of South Florida, Tampa, FL 33620, USA
- Isabel Monteiro** Aging and Dementia Clinical Research Center, New York University Langone Medical Center, Center of Excellence on Aging, New York, NY 10016, USA
- John C. Morris** Department of Neurology, Washington University School of Medicine, 660 S. Euclid Avenue, St. Louis, MO 63110, USA
- Pat Mottram** Evidence Based Practice Centre, Department of Psychiatry, University of Liverpool 147, UK
- Cynthia A. Munro** Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Meyer 218, Baltimore, MD 21287-7218, USA
- Declan G. M. Murphy** Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry at the Maudsley, King's College London WC2R 2LS, UK
- Joanna Murray** Institute of Psychiatry, King's College London, 16 De Crespigny Park, London, SE5 8AF, UK
- Asim Naeem** Division of Mental Health (Psychiatry of Disability), Level 6 – Hunter Wing, St George's University of London, Cranmer Terrace, London, SW17 0RE, UK
- Per Nettelbladt** Department of Clinical Sciences, Psychiatry, The Lundby Study, Lund University Hospital, SE-221 85 Lund, Sweden
- Ruth O'Hara** Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford University, Stanford, CA 94305, USA
- VA Sierra-Pacific Mental Illness Research Education and Clinical Center, Palo Alto, USA*
- John O'Hare** Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, The Queen's University of Belfast, Belfast BT9 7BL, UK
- Esther Oh** Johns Hopkins School of Medicine and Johns Hopkins Bayview, Baltimore, MD 21224, USA
- Martin Orrell** Department of Mental Health Sciences, 48 Riding House Street, University College London, London W1W 7EY, UK
- Dana Scherr Parchi** The Child and Family Institute at St. Luke's and Roosevelt Hospitals, New York, NY 10025, USA
- Laura Parisi** Clinica Neurologica University Campus Bio-Medico, Rome, Italy
- A. Peter Passmore** Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, The Queen's University of Belfast, Belfast BT9 7BL, UK
- Vikram Patel** London School of Hygiene and Tropical Medicine (UK) and Sangath (India); Sangath Centre, 841/1 Alto Porvorim, Goa 403521, India
- Thomas L. Patterson** Department of Psychiatry, University of California – San Diego, MC 0680, 9500 Gilman Drive, La Jolla, CA 92093-0680, USA
- Ian Peate** School of Nursing and Midwifery, Thames Valley University, London W5 5RF, UK
- Renee Pepin** University of Colorado at Colorado Springs, Colorado Springs, CO 80918, USA
- Robert Perneczky** Klinik und Poliklinik für Psychiatrie und Psychotherapie, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, 81675 München, Germany
- Richard Perry** Department of Neurosciences, Imperial College and Imperial College Healthcare NHS Trust, Charing Cross Hospital, Fulham Place Road, London, W6 8RF, UK
- Adolf Pfefferbaum** Neuroscience Program, SRI International, 333 Ravenswood Ave., Menlo Park, CA 94025, USA
- Michael Philpot** Mental Health of Older Adults, South London and Maudsley NHS Foundation Trust, Maudsley Hospital, London SE5 8AZ, UK
- Ben Pickard** Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS), University of Strathclyde, The John Arbuthnott Building, 27 Taylor Street, Glasgow, G4 0NR, UK

Felix C.V. Potocnik Department of Psychiatry, Faculty of Health Sciences, Stellenbosch University, Tygerberg, 7505, Cape Town, South Africa

Bevin Powers VA Sierra-Pacific Mental Illness Research Education and Clinical Center, Veterans Administration Health Care System, Palo Alto, CA 94304, USA

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, USA

Aparna Prasanna Wolverhampton Primary Care Trust, Penn Hospital, Wolverhampton WV4 5HN, UK

Neil Prentice Murray Royal Hospital, Perth PH2 7BH, UK

Martin Prince Centre for Global Mental Health, Department of Health Service and Population Research, Institute of Psychiatry, King's College London, 16 De Crespigny Park, London, SE5 8AF, UK

Patrick Rabbitt Age and Cognitive Performance Research Centre, University of Manchester, Oxford Road, Manchester M13 9PL, UK

Peter V. Rabins Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD 21287, USA

Oyepeju Raji Division of Mental Health (Psychiatry of Disability), Level 6 – Hunter Wing, St George's University of London, Cranmer Terrace, London, SW17 0RE, UK

Barry Reisberg New York University Langone Medical Center, Center of Excellence on Aging, New York, NY 10016, USA

Kenneth Rockwood Division of Geriatric Medicine, Dalhousie University, 1421–5955 Veterans' Memorial Lane, Halifax, NS, B3H 2E1, Canada

Joanne Rodda Department of Mental Health Sciences, University College London, WC1E 6BT, UK

Heather R. Romero Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Department of Psychiatry, Duke University, Durham, NC 27705, USA

Steven P. Roose College of Physicians and Surgeons, Columbia University, and Division of Geriatric Psychiatry, New York State Psychiatric Institute, New York, NY 10032, USA

Paolo Maria Rossini Clinica Neurologica University Campus Bio-Medico, Rome, Italy

Teresa A. Rummans Mayo Clinic College of Medicine, Mayo Clinic Rochester, Rochester, MN 55905, USA

Marwan Sabbagh Cleo Ruberts Center, Banner-Sun Health Research Institute, Sun City, AZ 85351, USA

Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Sunita Sahu Oxleas NHS Foundation Trust, Memorial Hospital, Shooters Hill, London, SE18 3RZ, UK

M. Sajatovic Case Western Reserve University School of Medicine and University Hospitals Case Medical Center, Cleveland, OH, 44106, USA

Oludamilola Salami Johns Hopkins School of Medicine and Johns Hopkins Bayview, Baltimore, MD 21224, USA

George M. Savva Department of Public Health and Primary Care, University of Cambridge, Institute of Public Health, Cambridge CB2 0SR, UK

Stephen M. Scheinthal New Jersey Institute for Successful Aging, University of Medicine and Dentistry of New Jersey – School of Osteopathic Medicine, Stratford, NJ 08084, USA

Martin M. Schmidt Division of Mental Health, St George's University of London, London SW17 0RE, UK

Jerome J. Schulte Department of Psychiatry, Wright State University, Boonshoft School of Medicine, OH 3640, USA

Daniel L. Segal University of Colorado at Colorado Springs, Colorado Springs, CO 80918, USA

Sati Sembhi Suffolk Mental Health Partnership NHS Trust, St Clement's Hospital, Foxhall Road, Ipswich, Suffolk IP3 8LS, UK

Andrew Moore Severn Department of Anaesthesia, Royal Lancaster Infirmary, Lancaster LA1 4RP, UK

K.S. Shaji Department of Psychiatry, Government Medical College, Thrissur, Kerala 680596, India

Bart Sheehan Health Sciences Research Institute, Medical School Building, Warwick Medical School, Coventry CV4 7AL, UK

Melanie B. Shulman Aging and Dementia Clinical Research Center, New York University Langone Medical Center, Center of Excellence on Aging, New York, NY 10016, USA

K.I. Shulman Sunnybrook Health Sciences Centre, Toronto, Ontario, M4N 3M5, Canada

Marcus Simmgen Thomas Addison Unit, St George's Hospital NHS Trust, Blackshaw Road, Tooting, London SW17 0QT, UK

Ingmar Skoog Institute of Neuroscience and Physiology, Unit of Neuropsychiatric Epidemiology, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Gary W. Small Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA

Gary W. Small Parlow-Solomon

Filip Smit Professor of Public Mental Health Trimbos Institute (Netherlands Institute of Mental Health and Addiction) and EMGO Institute of Health and Health Care Research, VU University Medical Centre. PO Box 725, Utrecht 3500 AS, The Netherlands

B. Joy Snider 660 S. Euclid Avenue, CB 8111, Department of Neurology, Washington University in St Louis, St. Louis, MO 63110, USA

Christian Sorg Klinik und Poliklinik für Psychiatrie und Psychotherapie, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, 81675 München, Germany

Reisa A. Sperling Memory Disorders Unit, Brigham and Women's Hospital, Alzheimer's Disease Research Center and Gerontology Research Unit, Massachusetts General Hospital, Department of Neurology and Psychiatry, Harvard Medical School, Boston, MA 02215, USA

D. C. Steffens Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 3702, USA

Dan J. Stein Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

Elliott M. Stein Jewish Home of San Francisco, 302 Silver Avenue San Francisco, CA 94112, USA and Department of Psychiatry, University of Miami School of Medicine, Miami, FL 33136, USA

Max L. Stek Department of Psychiatry, VUmc Medical Centre and GGZinGeest, AJ Ernst street 887, 1081HL Amsterdam, The Netherlands

Martin Steinberg Johns Hopkins Bayview Medical Center, 5300 Alpha Commons Drive, Baltimore, MD 21224, USA

Robert Stewart King's College London (Institute of Psychiatry), De Crespigny Park, London SE5 8AF, UK

Mary Ellen Stolder University of Iowa College of Nursing, 101 Nursing Building, 50 Newton Road, Iowa City, IA 52242-1121, USA

David L. Sultzer Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA and VA Greater Los Angeles Healthcare System 11301 Wilshire Blvd. Los Angeles, CA 90073, USA

Edith V. Sullivan Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Rd., Stanford, CA 94305, USA

Cindy Tam Department of Psychiatry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

Giles MY Tan Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry at the Maudsley, King's College London WC2R 2LS, UK

Rawan Tarawneh Department of Neurology, Washington University in St Louis, 660 S. Euclid Avenue, CB 8111, St. Louis, MO 63110, USA

John-Paul Taylor Department of Old Age Psychiatry, Institute for Health of the Elderly, Wolfson Research Centre, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, UK

Alexander M. Thomson Department of Elderly Care, Salford Royal Hospitals NHS Foundation Trust, Stott La, Salford M68HD, UK

Dolores Gallagher-Thompson Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305-5717, USA

Paul M. Thompson Department of Neurology, UCLA David Geffen School of Medicine, Los Angeles, CA 90095, USA

Stephen Todd Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, The Queen's University of Belfast, Belfast BT9 7BL, UK

Carol Torossian Aging and Dementia Clinical Research Center, New York University Langone Medical Center, Center of Excellence on Aging, New York, NY 10016, USA

Adrian Treloar Oxleas NHS Foundation Trust, Memorial Hospital, Shooters Hill, London, SE18 3RZ, UK

JoAnn T. Tschanz Department of Psychology and Center for Epidemiologic Studies, Utah State University, Logan, UT 84322, USA

Joshua Tsoh Associate Consultant in Psychiatry, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

Debby Tsuang Geriatric Research, Education, and Clinical Center and Mental Illness Research, Education, and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA 98108, USA

H. W. J. van Marwijk Department of General Practice, VUmc Medical Centre and GGZinGeest, AJ Ernst street 887, 1081HL Amsterdam, The Netherlands

Susan J. van Rensburg Division of Chemical Pathology, National Health Laboratory Service, Sandringham, Cape Town, South Africa

Vijay Venkatraman University of Pittsburgh School of Medicine, Pittsburgh, USA

Martin J. Vernon Department of Elderly Medicine, Burton House, Withington Hospital, Nell Lane, West Didsbury, Manchester M20 8LR, UK

Ottavio V. Vitolo Memory Disorders Unit, Brigham and Women's Hospital, Massachusetts General Hospital, Department of Psychiatry, Harvard Medical School, Boston, MA 02215, USA

Zuzana Walker Department of Mental Health Sciences, St Margaret's Hospital, Epping, Essex, CM16 6TN UK

John P. Wattis Professor of Old Age Psychiatry, Centre for Health and Social Care Research, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK

Jerzy Wegiel New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York 10306, USA

Kathleen A. Welsh-Bohmer Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Department of Psychiatry, Duke University, Durham, NC 27705, USA

Eric Wexler Division of Geriatric Psychiatry and Center for Neurobehavioral Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA

Kirsten M. Wilkins Assistant Professor of Psychiatry, University of Oklahoma College of Medicine-Tulsa, Tulsa, OK

David G. Wilkinson Moorgreen Hospital, Botley Road, West End, Southampton SO30 3JB, UK

Philip Wilkinson Department of Psychiatry, University of Oxford, Warneford Hospital, Old Road, Headington, Oxford OX3 7JX, UK

Kenneth C. M. Wilson St Catherine's Hospital, Church Road, Birkenhead, Wirral L42 OLQ, UK

Anders Wimo KI Alzheimer's Disease Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska institutet, Stockholm, Sweden

Philip Wong Johns Hopkins School of Medicine and Johns Hopkins Bayview, Baltimore, MD 21224, USA

Matthew R. Woodward Geriatric Psychiatry Research Program, McLean Hospital, Belmont, MA 02478, USA

Graeme A. Yorston St Andrew's Hospital, Northampton NN1 5DG, UK

Chang-En-Yu Geriatric Research, Education, and Clinical Center and Mental Illness Research, Education, and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA 98108, USA

Natalie M. Zahr Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Rd., Stanford, CA 94305, USA

L. McKenzie Zeiss University of California, Irvine, CA 92697-2800, USA

Richard A. Zweig Ferkauf Graduate School of Yeshiva University, Bronx, NY 10461, USA

Preface

It has been eight years since the second edition of *Principles and Practice of Geriatric Psychiatry* was published. During this time there has been substantial progress in the science and practice of geriatric psychiatry. This third edition attempts to capture these advances and provide an up-to-date summary for trainees and practitioners.

Two of the Editors of the previous editions, John R M Copeland and Dan G Blazer, decided to withdraw and two new Editors (one from the UK and one from the US) have been recruited. We wish first of all to express our grateful thanks to John and Dan for their remarkable stewardship over the production of the two previous editions. We would also like to acknowledge the invaluable contribution of the six Associate Editors in bringing this third edition to completion.

The previous edition received good reviews as well as some helpful criticisms. We therefore decided to maintain the textbook's overall scope, structure, headings, list of contents and international authorship. The majority of the textbook's chapters have been updated by the original authors. We have, however, recruited several new

authors who are internationally recognized experts in their fields and commissioned substantial completely new material.

We believe that the value and the strengths of this textbook rest in its comprehensive coverage of the basic and clinical sciences of normal and abnormal ageing, of the full range of psychiatric disorders in the elderly, and of the organization of psychogeriatric services in the UK and the US as well as chapters on prevention, training and education.

We hope that this third edition is well received by its readers and that it proves to be a useful and readable way for them to update their knowledge of the science and practice of geriatric psychiatry.

Mohammed T Abou-Saleh
Cornelius L E Katona
Anand Kumar

Preface to Second Edition

The editors were very gratified that the first edition of this textbook was generally well received and that a second edition has been called for. It is now seven years since the original book appeared, and there have been many more advances in the subject. In spite of new sections and some wholesale rewriting, it has been possible once again, to contain the information in one volume. Very sadly some of our original contributors have died. New authors have replaced them while others have been added in an endeavour to keep the text authoritative and up-to-date. The helpful criticisms of the first edition have been carefully considered in the preparation of this one. Having so many distinguished authors with such a breadth of interest, while

greatly enhancing the book, has led to a long gestation period, but we believe that it has been worthwhile. Much of the original format has been retained in order to continue to stimulate lively debate and exchange of views. If the book contributes to the growing strength of Geriatric Psychiatry internationally, it will have done its work.

John R. M. Copeland
Mohammed T. Abou-Saleh
Dan G. Blazer

Preface to First Edition

The discipline of the psychiatry of old age has moved rapidly in recent years and the number of practitioners has expanded worldwide. An authoritative text is required which draws on the knowledge of these experts and which reflects both new scientific advances and innovations in service development.

In a comparatively new subject many of the issues are still contentious and on some of these we have tried to provide the opportunity for the expression of different points of view. Readers are asked to judge the issues for themselves from the evidence set out.

Here and there short, special articles have been commissioned which present research findings in more detail and describe new aspects of care.

They are intended to enliven the text and their choice has been dependent on timing and opportunity.

We have also tried to give a "feel" for what is happening in developing countries and the scope of the problems experienced by local practitioners.

Even a book of this size can never be complete and no doubt gaps in the coverage of subjects will be identified. We would be glad to have them pointed out. The more comprehensive a book aims to be the longer it takes to come to publication and in a fast-moving area of knowledge this can be a problem. Many of our authors have been kind enough to update their contributions at a late stage, which we hope has overcome this difficulty to some extent.

In the early stages of the development of a subject there is insufficient corpus of knowledge to assemble in book form. This situation has changed dramatically for geriatric psychiatry in recent years. We hope that the knowledge gathered here from our distinguished international panel of authors bears this out.

***John R. M. Copeland
Mohammed T. Abou-Saleh
Dan G. Blazer***

Historical Background

A Conceptual History in the Nineteenth Century

German E. Berrios

Department of Psychiatry, Addenbrooke's Hospital, Cambridge, UK

The history of geriatric psychiatry can be written from two viewpoints. The 'externalist' approach focuses on the social and political variables that have controlled attitudes towards abnormal behaviour in old age, and on the professionalization of those charged with the care of the mentally infirm elderly. The 'internalist' approach – to be followed in this chapter – concentrates on the origin of the scientific language of psychogeriatrics. An adequate historical account should include information on theories of ageing, both physical and mental, brain sclerosis and the formation of a viable concept of mental illness. On the first rubric much research has been done^{1–9}; far less work exists on the other two. On psychogeriatric care before the nineteenth century^{10,11} there is very little: this may simply reflect a historical reality.

VIEWS ON AGEING BEFORE THE NINETEENTH CENTURY

Like most other aspects of human life, ageing has also been portrayed in terms of metaphors. Classical views, following the nature–nurture controversy, conceived of ageing as resulting from either internal instructions or from the buffeting of foreign factors^{4,8}.

The 'wear and tear' view happened to be popular during the early nineteenth century, the period on which this chapter will concentrate. It was based, as it had always been, on the ageless observation that all natural objects, whether animate or not, are subject to the ravages of time. Surprisingly enough, the 'wear and tear' view has not always generated an understanding attitude. In fact, across times and cultures great ambiguity has existed in regard to the treatment of old folk. Fortunately, a realistic acceptance seems to have predominated although there is plenty of evidence of hostility. The Hebrew tradition, and indeed its Christian offshoot, encouraged much reverence towards the wisdom and value of old age. But even in societies that have made great play of this view, veneration has been reserved for those in positions of power or influence¹². Little is known about attitudes towards elderly women or old men in humbler stations¹¹.

So, it can be concluded that, all in all, a view seems to have predominated that ageing was undesirable and that the identification of wear factors was important to devising ways of prolonging life^{5,13}.

A second ambiguity can be detected in these earlier writings. It concerns the extent to which the ageing process necessarily involves the human mind. While it was a palpable fact that all human frames decayed, not everyone accepted that this had necessarily to affect the soul or mind. Extant descriptions of the psychological changes

brought about by old age suggest that people were aware that the mind also underwent a decline. However, theory and religion encouraged the view that the spirit could or did escape wear and tear, and that human beings grew ever more wise and useful, thanks to the accumulation of experience and knowledge. This belief must have been available in all those societies that felt the need to create adequate spaces for all manner of intellectual and/or sociopolitical gerontocracies². Some seem even to have separated chronological age and functional age in order to justify such concessions. From the point of view of the history of psychogeriatrics, it would be useful to know to what extent this belief was undermined by the occasional case of dementia among those elderly in positions of power¹. Historical evidence seems to show that these situations were neither more nor less perturbing than mental illness occurring at other periods of life. Indeed, fail-safe devices seem to have been available in these societies to cope with the upheavals created by such occurrences.

Men like Buffon, Darwin and Goethe reshaped ideas on ageing during the eighteenth century. Buffon¹⁴ wrote: 'All changes and dies in Nature. As soon as it reaches its point of perfection it begins to decay. At first this is subtle and it takes years for one to realise that major changes have in fact taken place' (p. 106). Buffon put this down to an 'ossification' process similar to that affecting trees: 'this cause of death is common to animals and vegetables. Oaks die as their core becomes so hard that they can no longer feed. They trap humidity, and this eventually makes them rot away' (p. 111).

Erasmus Darwin's views resulted from the application of yet another metaphor, namely that ageing results from a breakdown of 'communication' between man and his environment¹⁵. Darwin suggested that such breakdown followed a loss of irritability (a property of nerve fibres) and a decreased response to sensation:

It seems our bodies by long habit cease to obey the stimulus of the aliment, which support us . . . three causes may conspire to render our nerves less excitable: 1. If a stimulus be greater than natural, it produces too great an exertion of the stimulated organ, and in consequence exhausts the spirit of animation; and the moving organ ceases to act, even though the stimulus is continued. 2. If excitations weaker than natural be applied, so as not to excite the organ into action, they may be gradually increased, without exciting the organ into action, which will thus acquire a habit of disobedience to the stimulus. 3. When irritative motions continue to be produced in consequence of stimulus, but are not succeeded by sensation. (p. 365)

VIEWS ON AGEING DURING THE NINETEENTH CENTURY

In 1807 Sir John Sinclair¹⁶ published a major compendium on ageing and longevity, which included references to most pre-nineteenth century sources. It was, in a way, the last grand glance to the past. Soon afterwards work started by those who, like Léon Rostan (1791–1866), based their claims on empirical findings. Rostan, one of the most original members of the Paris school, published in 1819 his *Recherches sur le Ramollissement du Cerveau*¹⁷, where the view commenced that vascular disorders might be as important as parenchymal ones in brain ageing. Even more important was his uncompromising anti-vitalistic position enshrined in the claim that all diseases were related to pathological changes in specific organs^{18,19}.

During the 1850s Reveill -Parise³ saw his task as writing on ‘the history of ageing, that is, mapping the imprint of time on the human body, whether on its organs or on its spiritual essence’ (p. v). In regard to ageing itself he wrote: ‘the cause of ageing is a gradual increase in the work of decomposition . . . but how does it happen? What are the laws that control the degradation that affects the organization and mind of man?’ (p. 13). Reveill -Parise dismissed the toxic view defended by the Italian writer Michel L vy²⁰ according to which there was a gradual accumulation of calcium phosphates that led to petrification, to an ‘anticipation of the grave’. This view, he stated, had no empirical foundation and was based on a generalization from localized findings. Reveill -Parise supported the view that ageing results from a negative balance between composition and elimination, which equally affected the cardiovascular, respiratory and reproductive organs.

Finally, the views should be mentioned of J.M. Charcot, who in 1868 offered a series of 24 lectures on the diseases affecting the elderly²¹. Charcot dedicated Lecture 1 to the ‘general characters of senile pathology’; he started by saying that all books on geriatrics up to his time had ‘a particularly literary or philosophical turn [and had been] more or less ingenious paraphrases of the famous treatise De Senectute’ (p. 25). He praised Rostan for his views on asthma and brain softening in the elderly, and predictably also mentioned Cruveilhier, Hourman and Dechambre, Durand-Fardel and Prus. He criticized Canstatt and other German physicians because in their work, ‘imagination holds an immense place at the expense of impartial and positive observation’ (p. 26). Charcot’s own contribution was based on the general principle that ‘changes of texture impressed on the organism by old age sometimes become so marked, that the physiological and pathological states seem to merge into one another by insensible transitions, and cannot be clearly distinguished’ (p. 27).

THE DEVELOPMENT OF THE NOTION OF BRAIN SCLEROSIS

When in 1833 Lobstein²² described the basic pathology of arteriosclerosis, he did not imagine that it would, during the second half of the century, become the mechanism of ‘senility’ par excellence^{14,23,24}. Motor and sensory deficits, vertigo, delusions, hallucinations and volitional, cognitive and affective disorder were all attributed to the effect of arteriosclerosis^{25,26}. They related to the brain via a two-stage speculative pathophysiology: parenchymal and/or vascular disorders could affect the brain, and the distribution of the lesions could be diffused or focal. Vascular changes included acute ischaemia (on which clinical observation was adequate)^{27,28}

and chronic ischaemia, invented as a separate syndrome by extrapolating from the symptoms and signs observed during the acute states²⁴. The role of arteriosclerosis as a causal and prognostic factor in relation to the involutional psychoses was challenged early in the twentieth century²⁹ but this paper remained unnoticed. Hence, some of the old notions, such as that of ‘arteriosclerotic dementia’, remained active well into the 1960s³⁰.

Alienists during the same period, however, were already able to distinguish between states where a putative chronic and diffuse reduction in blood supply had taken place from focalized damage, i.e. what they called ‘multifocal arteriosclerotic dementia’ and was equivalent to what is currently called multi-infarct dementia^{24,31,32}.

NINETEENTH CENTURY VIEWS ON MENTAL DECAY IN THE ELDERLY

It is against this background that the history of the language and concepts dedicated to understanding mental disorders in the elderly must be understood. In addition to these neurobiological frameworks, a psychological theory that explained the manner of the decline was required. Such a psychopathology was provided by the heuristic combination of associationism, faculty psychology³³, and statistics³⁴ that characterized the early and middle parts of the nineteenth century.

Yet another perspective, originating in clinical observation, was added during the 1830s. It led to the realization that, in addition to the well-known forms of mental disorder, the elderly might exhibit specific forms of deterioration, and that these could be related to recognizable brain changes. There is only space in this chapter to deal with two examples: one typifying a ‘specific’ disorder of old age, namely the history of chronic cognitive failure or dementia; the other illustrating the effect of a general mental disorder (melancholia) on the elderly.

THE FORMATION OF THE CONCEPT OF SENILE DEMENTIA

The history of the word and concept of dementia before the nineteenth century has been touched upon elsewhere³⁵. Suffice it to say here that, at the beginning of the nineteenth century, ‘dementia’ had a ‘legal’ and a ‘medical’ meaning and referred to most acquired states of intellectual dysfunction that resulted in serious psychosocial incompetence. Neither age of acquisition nor reversibility was part of its definition. These two dimensions were only incorporated during the nineteenth century and completely changed the semantic territory of the dementia concept.

Anecdotal observation of cases of senile dementia abound both in the fictional literature and in historical documents³⁶, but the concept of ‘senile dementia’, as it is currently understood, only took shape during the latter part of the nineteenth century. Indeed, it could not have been otherwise, as the neurobiological and clinical language that made it possible only became available during this period^{37,38}. But even after the nosological status of senile dementia had become clearer, there were many who, like Rauzier³⁹, felt able to state: ‘it may appear either as a primary state or follow most of the mental disorders affecting the elderly’ (p. 615). Following Rogues de Fursac⁴⁰, Adrien Pic – the author of one of the most influential geriatric manuals during this period⁴¹ – defined senile dementia as: ‘a state of intellectual decline, whether or not accompanied by delusions, that results from brain lesions associated with ageing’ (pp. 364–365). It was against this background that the concept of Alzheimer’s disease,

which became the prototype for all senile dementias, was created during the first decade of the twentieth century³⁷. Recent work has shown that its 'discovery' was controlled by ideological forces well beyond what could be described as 'scientific'^{37,42}. These forces also introduced unwarranted clinical strictures, such as the exclusion of non-cognitive symptoms^{43,44} and false age boundaries, which took many years to disappear.

THE FORMATION OF THE CONCEPT OF INVOLUTIONAL MELANCHOLIA

The concept of 'senile or involutional psychoses', which featured so prominently in Kraepelin's early classification, included presenile delusional insanity, senile dementia, late catatonia and involutional melancholia^{45,46}. The reasons that led Kraepelin to separate this group were mostly theoretical, to wit, that they appeared during a period of life when 'sclerotic' changes were beginning to occur; the same factor accounted for their bad prognosis⁴⁶.

The general history of melancholia and depression has been analysed elsewhere^{47–49}. Suffice it to say here that by the 1860s depression was considered to be an independent syndrome resulting from a primary disorder of affect. This meant that hallucinations, delusions and cognitive impairment were secondary to the pathological feelings. This conviction was particularly strong towards the end of the century, when emotional mechanisms became popular in the explanation of most forms of mental disorder⁵⁰. By the end of the century the metaphor of depression as a form of 'reduction' or 'loss' had become firmly established. No better example can be found than the fact that up to 1893 (fourth edition) Kraepelin felt obliged to classify all forms of agitated depression as mania!⁵¹

KRAEPELIN AND INVOLUTIONAL MELANCHOLIA

Much of the current confusion on the meaning of involutional melancholia can be explained if attention is given to the circumstances of its historical development (for a full analysis of this process and list of references, see Berrios⁵²). The conventional story^{53–56} is that up to the seventh edition of his textbook Kraepelin considered involutional melancholia as a separate disease, and that when confronted by the evidence collected by Dreyfus⁵⁷, he decided to include it, in the eighth edition, under the general heading of manic depressive insanity. Indeed, this account was first offered by Kraepelin himself (see Dreyfus, p. 169).

The story is, however, more complex and it is unlikely that the findings of Dreyfus alone caused Kraepelin's change of heart. For example, Thalbitzer⁵⁸ claimed that his own work had also been influential (p. 41). In the eighth edition Kraepelin abandoned not only involutional melancholia but the entire group of 'senile psychoses'. A recent statistical analysis of Dreyfus's old series has also shown that his conclusion that the natural history of involutional melancholia was no different from that of depression affecting younger subjects was wrong⁵¹.

CONCLUSIONS

This short chapter, providing a historical vignette on the origin of the language of old age psychiatry, suggests that it was born during the nineteenth century from three conceptual sources: theories of ageing, neurobiological hypotheses concerning brain sclerosis, and

the realization that specific forms of mental disorder might affect the elderly. Two clinical illustrations were provided, one pertaining to the origins of the concept of senile dementia, and the other to the notion of involutional melancholia.

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The Development of Old Age Psychiatry in the UK

Claire Hilton¹ and Tom Arie²

¹Central and North West London NHS Foundation Trust, Harrow, UK

²University of Nottingham, Ageing and Disability Research Unit, Nottingham, UK

Old age psychiatry in Britain was born in the 1960s and 1970s, and came of age at its recognition by the government as a distinct specialty in 1989.¹ Yet the need for it had been recognized as far back as the 1940s. Why was the gestation so long, and how has it developed in the last twenty years since its recognition? What can we learn from this history?

THE EARLIEST DAYS

The likelihood that older people would become major users of psychiatric services was identified during the Second World War. Increasing longevity meant there were more, and even older, old people. Falling birth rates increased the proportion of old people and since more women were in employment it was harder for them to take on traditional caring roles. Some of the more frail older people were cared for in 'chronic sick' and mental hospitals, which might be needed for war casualties.

Until the 1940s mental and physical ill health in old age had been considered largely irremediable. In the 1940s Marjory Warren, the pioneering geriatrician, demonstrated the scope for rehabilitating old people¹, psychiatrist Felix Post wrote on psychiatric differential diagnosis and multidisciplinary approaches to treatment², and Willi Mayer-Gross described how severely depressed old people could improve with electroconvulsive therapy (ECT)³ⁱⁱ. Despite the evidence of successful treatment, older people were not given priority in health policy. In 1942 the Beveridge Report laid the foundations of the 'welfare state' and a National Health Service (NHS). However, it stated, 'It is dangerous to be in any way lavish to old age, until adequate provision has been assured for all other vital needs'⁴.

After the war, at the instigation of Professor Aubrey Lewis, a psychiatric 'geriatric unit' was opened at the Bethlem Hospital in South London, part of the Bethlem-Maudsley postgraduate psychiatric teaching hospital (see Chapter 03). This unit was for functionally ill patients regarded as treatable. Patients with dementia, especially those requiring long stay care, were excluded, in part because of

opposition from academic psychiatrists who did not see their care as being worthy of study and investigation.

We shall touch on matters relating to these early influences, since all run throughout the development of the specialty. In addition, each generation rediscovers the demography of ageing as if it were a new phenomenon. Yet unlike, say, trends in fertility, or in transportation, which cannot be predicted with certainty, we always know the size of prospective populations of older people and the epidemiology of the crucial illnesses⁵. Repeatedly, the government has laid plans and failed adequately to implement or fund them, and then has 'discovered' afresh the scale of need. In 1950 we hear, 'It is recognised that the present conditions of financial stringency limit opportunities for action at this time'⁶. In 2001, a national service 'framework' for older people had no allocated new funding for mental health⁷, whereas a parallel framework for mental health for younger people was substantially funded⁸.

Another initiative in 2007 to improve access to psychological therapies has followed an economic model and has been targeted towards getting unemployed younger people into work, although this may well be changing to become more inclusive across all ages⁹. A contrast exists even within Britain: since 2002, Scotland provides both free personal and nursing care, if deemed appropriate after assessment, while England and Wales do not.

WORKING WITH GERIATRICIANS

Working with geriatricians is crucial in view of the multiple and interlinked disorders of old people, yet at times this has been erratic. Although active treatment, both physical and mental, was being advocated by the 1940s, geriatrics developed much earlier than psychogeriatrics. This was in part because many early geriatricians saw themselves as holistic practitioners for older people, therefore requesting little psychiatric assistance. The advocacy of Lord Amulree, a civil servant and geriatrician, and the other founders of geriatrics drew the successes of rehabilitation, including emptying hospital beds, to the attention of the government¹⁰. Such a phenomenon did not occur in old age psychiatry until around 1970 when new local services, such as that established at Goodmayes Hospital in 1969¹¹, were drawn to the attention of the Department of Health and Social Security¹²: only then it was recognized that a modern approach could reduce bed occupancy, improve outcomes and save money. Until the 1970s old age psychiatry in the UK was

¹Originally called 'psychogeriatrics', 'old age psychiatry' is now more commonly used. However, the former is retained in some contexts, e.g. journal titles such as *International Psychogeriatrics*. The Royal College of Psychiatrists has a Faculty of the Psychiatry of Old Age, while many clinical departments refer to themselves as 'Mental Health Services' for older people or older adults.

ⁱⁱBefore antidepressants, ECT was the only effective physical treatment.

characterized by research in clinical treatment, nosology, pathology and epidemiology, with only small pockets of local service innovation.

In 1970 there were 200 geriatric medicine consultants¹³ but only a handful of psychogeriatricians^{14,15}. By 2006 there were 700 psychogeriatricians¹⁶. Where enthusiastic geriatricians and psychiatrists existed in a particular locality they collaborated. In addition, collaboration between the Royal College of Psychiatrists and the British Geriatrics Society¹⁷ since the 1970s has led to the development of guidelines for good practice and working collaboratively¹⁸. Moving services away from isolated mental and 'chronic sick' hospitals and their coming together in district general hospitals has given better access to each other's services. Sometimes this facilitated joint working, but formal joint services were rare. In 1977, a department of Health Care of the Elderly, comprising both medicine and psychiatry working together, along with other relevant disciplines and professions was set up in Nottingham. There was an orthopaedic-geriatric unit, a stroke unit and a continence service, and joint research, along with extensive teaching of medical students and postgraduate trainees of relevant disciplines, and of overseas workers^{19–21}.

'Memory clinics' are another development, now widespread, with their roots in both psychogeriatric and geriatric practice in the mid-1980s²². More recent developments include psychiatric liaison services for patients with acute physical illness in district general hospitals²³. Jointly run 'intermediate care' or 'convalescent' rehabilitation units for confused older people, especially those recovering from both delirium and physical illness, are also new. Geriatricians and psychiatrists still have much to learn from each other, and 'seamless' services remain the ideal. 'Guidelines for collaboration' have recently been updated²⁴.

WORKING WITH PSYCHIATRISTS CARING FOR YOUNGER PEOPLE

Before the establishment of the specialty, mentally ill old people requiring secondary care were the responsibility of general psychiatrists, but they rarely showed interest in actually working with them, especially those with dementia. However, some of the pioneering psychogeriatric services, such as Sam Robinson's in Dumfries (1958)²⁵, or Brice Pitt's at Claybury, Essex (1966)²⁶, emerged in part due to the far sightedness and encouragement of general psychiatrists who were medical superintendents of mental hospitals. Despite such early developments, it took until 1989 for the Royal College of Psychiatrists and the government to agree officially to the creation of the new specialty of old age psychiatry. Until then, lack of recognition meant that it had often been impossible to extract from official statistics adequate data on older people's use of services, and hence to establish the scale of need for services and for training.

Competition for resources is inevitable, so long as resources are limited. The low status of the aged, the perceived needs of people of working age, and the common misperception that young severely mentally ill people are frequently dangerous have generally resulted in funding for services for younger people disproportionately exceeding that for older people.

A CENTRAL BODY FOR COORDINATING DEVELOPMENT

A powerful national focus for securing improved recognition and better resources has been the flourishing Faculty of the Psychiatry

of Old Age at the Royal College of Psychiatrists (since 1988), and its predecessor bodies (from 1973). It has, among other things, encouraged research, innovation, multidisciplinary working, and links with voluntary and statutory organizations and with the government, and has taken an interest in architecture and design for elderly confused people²⁷. A first series of newsletters in the 1980s served as a constructive means of communication among clinicians. A second series since 1996, available online since 2000 (www.rcpsych.ac.uk/college/faculties/oldage/newsletter.aspx), often expresses thoughtful comment related to current clinical and policy dilemmas. Faculty meetings have remained a source of debate, education, inspiration and problem solving. The Faculty's website is a mine of information (www.rcpsych.ac.uk/college/faculties/oldage.aspx).

RESEARCH AND ACADEMIC DEVELOPMENT

Research on older people's mental health has flourished and has helped the development of evidence-based practice. Sir Martin Roth in the 1950s defined the major diagnostic categories in older people²⁸, rather as Emil Kraepelin had done 50 years earlier for younger people. Felix Post undertook follow-up studies of treatment of depression and psychotic disorders. Nick Corsellis²⁹ followed by Bernard Tomlinson, Martin Roth³⁰ and Elaine and Robert Perry unpicked the neurochemical and neuropathological features of Alzheimer's disease³¹. Early research by Raymond Levy into lecithin and later tacrine was a forerunner of today's evidence-based antidementia drugs³².

Difficulty in obtaining funding for research has been characteristic¹⁵. But the growth of the neurosciences, along with the influence of bodies such as the Alzheimer's Society, has enhanced the scale of funding for research into the dementias, and has attracted able workers.

Research has also grown through the development of academic departments of old age psychiatry. The first old age psychiatrist to be appointed professor became head of the joint department of Health Care of the Elderly in Nottingham in 1977. The first professor of old age psychiatry, at Guy's Hospital, London, was appointed in 1983. The *International Journal of Geriatric Psychiatry* was started in 1986. In 1989 there were half a dozen professorial departments³³; now most medical schools have an academic presence for old age psychiatry, and many NHS consultants are involved in teaching medical students and postgraduates. Many other departments in universities are now conducting relevant research, and there are further thriving journals.

TEACHING AND TRAINING

Biographical information reveals that many colleagues did not envisage becoming old age psychiatrists, but were *inspired* by others to do so; they saw and experienced what could be done to help old people. Such effective teaching is crucial¹⁵.

Sharing our knowledge with other specialties and disciplines can change the way colleagues respond to elderly mentally ill people – in primary care, in management, in palliative care, social services, learning disability services, voluntary organizations, Citizens Advice Bureaux, and within the multidisciplinary teams within which we work. Other groups that have sought teaching include architects, designers, lawyers and the police.

Structured training for old age psychiatrists has also evolved over the years. The earliest psychogeriatricians in the 1960s and 1970s had little or no specific training. Six months' experience in old age psychiatry is considered valuable for trainees in psychiatry and in

general practice. Specialized training for career old age psychiatrists is during the last three years of a six-year psychiatry training scheme. There is a competency-based curriculum³⁴, and at least two years (full-time equivalent) old age psychiatry in recognized training posts are usually required.

CLINICAL INNOVATION

The demise of the vast Victorian mental hospitals, the coming of community care, more liberal mental health legislation and new effective psychopharmacology have all helped to shape the progress of psychiatry since the 1950s. The psychogeriatricians have consistently fought to prevent older people being left behind younger people in new developments. Important classic texts of innovation in old age psychiatry such as *In the Service of Old Age* by Tony Whitehead (1971)³⁵ deserve particular mention, as do the reports in the 1960s and 1970s of abuses in the unfashionable sectors of care. The Ely Hospital Report (1969)³⁶ was also instrumental in bringing about the Hospital (later Health) Advisory Service (HAS), which advised on the neglected areas of the health service. The HAS was a valuable ally of the early old age psychiatrists, encouraging and spreading good practice. Its first director became an old age psychiatrist upon demitting office³⁷.

Home assessment and support by consultants and other team members was the norm: in some services this is still the usual first point of contact. Initial assessment at home was introduced in the 1960s, in order to evaluate, in the light of knowledge of the home setting, who could be helped without hospital admission, or who might need a medical or a surgical bed rather than psychiatric help. Often the entire management of the patient could be undertaken in the patient's home. Home assessment and treatment is valued by patients, carers and staff, and it helps to build a close working relationship with the local community, and is popular with medical students.

The importance of support for carers of people with dementia has long been recognized. Respite admissions³⁸, social services day care, help with personal care at home and the Admiral Nurse service established in 1994 (www.fordementia.org.uk/admiral.htm) are important in delivering such support.

Psychotherapy, including family therapy with old people and their adult children, dates from the 1960s³⁹ but is still not widespread, despite pockets of enthusiasm⁴⁰. In a very few places psychiatric intensive care units, in particular providing care for elderly men with dementia and disruptive behaviours, have evolved, such older people being excluded from similar services for younger people⁴¹. Elsewhere, intensive home treatment teams are appearing for even those with severe mental illness such as would traditionally require admission.

Old age psychiatry day hospitals date from the 1950s onwards. They were often a substitute for long stay care for people with chronic mental illness living at home or with their family. More recently they have developed to offer assessment, treatment, rehabilitation and support such as might be beyond the capacity of a social care day centre. They enable some with particularly disruptive behaviours unmanageable by a social care day centre to remain in the community⁴².

More recently as 'ethnic minority' populations have aged, understanding cultural and religious customs and attitudes to mental illness and ageing has become important in many local communities.

Other disciplines have developed in parallel to old age psychiatry. The British Psychological Society, for example, established a special

Table 2.1 Core features of a service in 2009

Core features are likely to include:

Community: assessment, diagnosis, treatment, rehabilitation

Inpatients: acute assessment and continuing care

Day hospital

Memory service

Support for carers

Liaison service to geriatric, medical and surgical wards

Other:

planning

teaching

research

liaison with related professions and organizations

advocacy for patients

advice on medico-legal matters, e.g. mental capacity

interest group for psychologists working with older people in 1980 (www.psige.org/index.php).

Without evaluated creativity, we would not have the rich array of services that, despite constraints of limited funding, serve our patients, their relatives and carers. But by no means every service for older people yet has all the components described above (see Table 2.1).

LONG STAY CARE

Up to the 1980s, most long stay care for dementia, along with that of aged people with chronic psychosis, took place in hospitals. Local authority residential homes were intended to care for frail old people, but with the passage of time they too increasingly became facilities for demented people, but lacking nursing skills and facilities appropriate to their residents' needs. During the Thatcher era of the 1980s, long stay care in hospitals was replaced by care in commercial, or, less often, charitable homes. Surveillance of standards in multiple dispersed units became very difficult. Third party inspection and definition of 'minimum standards' was instituted by the Blair government⁴³. Education and training of care home staff, long virtually absent, is now becoming more prevalent. But 'scandals' in the care of old people continue, and although they often achieve publicity, they generally evoke less indignation and less remedial action than similar scandals in child care. Fortunately, architects and designers often now devote special skills to the needs of old people.

THE FUTURE

Old age psychiatrists, like workers in other health specialties, practise within the context of the structure and culture of society. At the time of writing we enter a recession, with uncertainty about the future, but with ever more evidence of the effectiveness of our interventions.

There are more government initiatives. The *National Dementia Strategy*, emphasizes raising awareness, early diagnosis and intervention, and improving quality of care in dementia, and is welcome on that account. However, the government's initial financial backing for the strategy amounts to less than 1% of the total annual cost of dementia care. It is hard to believe that this will make any significant impact. In addition it states, 'Decisions on funding for subsequent years will only be made once we have had the opportunity to consider

the results from the initial demonstrator sites and evaluation work. There is no expectation therefore that all areas will necessarily be able to implement the Strategy within five years⁴⁴. This resonates with previous policies advocating good practice, which are neither mandatory nor adequately funded.

A new Mental Capacity Act seeks to provide a statutory framework to protect vulnerable people who are not able to make their own decisions⁴⁵. There is also new legislation relating to 'deprivation of liberty', significantly affecting people with dementia who lack capacity to decide on their place of care, to determine whether and how they can be confined to a care home or hospital in their best interests. The new Equality Bill should prevent discrimination in services on the basis of chronological age⁴⁶. However, it also carries the paradoxical risk that a separate service for old people may be regarded as discriminatory. Challenges to our special services have long arisen from this viewpoint, and we must continue to show that special services for an inherently low status and thus usually neglected group make for better care, and to point to the reasons why.

Legal and medical changes, and changes in society, will raise new questions, but the 1970s adage for an old age psychiatrist will continue to be 'occasional militancy . . . to gain for the elderly a fair share of scant resources, to put them to best use, to make do with too little while wheeling, dealing, and fighting for more'⁴⁷.

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Commentary on 'In the Beginning' by Felix Post

Claire Hilton

Central and North West London NHS Foundation Trust, Harrow, UK

INTRODUCTION

Felix Post was probably the first dedicated old-age psychiatrist anywhere in the world. 'In the Beginning' is his autobiographical account of the earliest days of old-age psychiatry in Britain. Such accounts are valuable primary sources for understanding the development of the specialty. We are now reaching a point in time when our earliest pioneers like Felix Post (1913–2001) and Martin Roth (1917–2006) have died. It is important that we remember the contributions of our teachers from the past who have set the foundations for our specialty, just as Phillipe Pinel, Emil Kraepelin, Sigmund Freud and many others are celebrated for their contributions to the mental well-being of mainly younger people.

This short chapter by Felix Post has been described as 'pure Felix'. It characteristically reveals his humility and modesty, and his praise of others, attributing little achievement to himself. A brief biographical note and commentary are therefore warranted to set it in context.

'IN THE BEGINNING' BY THE LATE FELIX POST

In 1943, after a year's early training as one of the war-time refugees of the Maudsley Hospital, Professor Aubrey Lewis passed me on to Professor D.K. Henderson and the Royal Edinburgh Hospital for Nervous and Mental Diseases, where I initially worked in the private department. During one of his rounds, Henderson said to me: 'Post, do you see all these old people here? Why don't you write 'em up?' This I obediently did, and my article appeared in the *Journal of Mental Science*ⁱ. The article started by demonstrating that the admission rate of patients over 60 to the Royal Edinburgh Hospital had risen between 1901 and 1941 more steeply than the proportion of this age group in the Scottish population. Interestingly, at this early date, I had found no difficulties in the differential diagnosis of my colleagues' and my own patients. There were 22 senile, arteriosclerotic and presenile dementia patients, 20 manic–depressive patients, 25 patients suffering from involutional or senile melancholia and 51 patients with schizophrenia. Assuming that the functional psychoses were the concern of general psychiatry, the rest of the paper dealt with the dementias and with an attempt to link the type associated with delusions and hallucinations to earlier personality characteristics. I noted that a high proportion of dementia admissions had been precipitated by terminal confusional states, and that of 111 patients admitted over the preceding four years with organic psychoses, only

23 were still occupying beds. I made the false prediction that in the future the main burden of the hospital services would be represented by the chronicity and survival of melancholic and paranoid patients. I did not anticipate that electroconvulsive therapy (ECT) and antidepressive drugs, while producing lasting recoveries in only 25% of cases, would make at least temporary discharge from inpatient care possible in most cases.

Aubrey Lewis was more farsighted. He had published, with a psychiatric social workerⁱⁱ a paper describing the psychiatric and social features of the patients in the Tooting Bec Hospital for Senile Dementia, London, UK, and in 1946 predicted, in the *Journal of Mental Science*ⁱⁱⁱ that ageing and senility would become a major problem of psychiatry.

After army service, I consulted Lewis about possible positions and he recommended me for the post of assistant physician at the Maudsley Hospital. I flattered myself that in me Lewis had seen a future brilliant psychiatrist, but was soon to be disillusioned. Even before the Bethlem Royal and Maudsley Hospitals were united in 1948, Lewis had conceived the idea of using some of the Bethlem beds to establish a unit for patients over the age of 60. After a heated discussion with the Bethlem matron, Lewis obtained agreement for the admission of senile patients to a hospital which, like the Maudsley, had previously admitted only patients thought to be recoverable. Uncovering his batteries, he asked me to take on the development of this Geriatric Unit. Once again, I obeyed (to say without enthusiasm would be an understatement) and, right up to my retirement, I continued also to run a unit and outpatient clinic for younger adults.

A report in the *Bethlem Maudsley Gazette*^{iv} demonstrated that both the Bethlem staff and I had 'caught fire'. The article started with a tribute to Professor Aubrey Lewis and his almost revolutionary idea of including experience in geriatric psychiatry within postgraduate training. The article went on to describe how patients over 60 had gradually infiltrated the Bethlem wards to emerge as a unit for 26 women and 20 men. The two wards were staffed by the same number of senior and junior nurses as the other adult wards, with two trainee psychiatrists changing every six months to other departments. There was one psychiatric social worker, later usually assisted by a trainee. The occupational therapy department had collaborated with the nursing staff to devise and carry out a daily occupational programme as well as socializing activities. The psychiatric social worker ran a weekly afternoon of handicrafts, tea and talk near the Maudsley, where throughout my tenure I conducted a weekly follow-up and

supportive clinic. The first year during which the unit had been in full swing was 1952, and it was recorded that during that year there had been 3.00 admissions to each geriatric bed compared to 3.74 admissions to each general psychiatric place. Patients who had been dementing, but whose home care was no longer possible had been excluded from admission, though not rigidly, as well as patients with recurring illnesses that had been adequately treated at the Bethlem-Maudsley or other hospitals. Of 133 patients, nine died, only four had to be transferred to their regional mental hospitals, seven were resettled in homes for the elderly, while 113 could be returned to family care. One year after discharge, information was successfully obtained about 121 of 124 cases. Seven patients had died, including one suicide of a woman who had discharged herself. Thirty ex-patients had to be readmitted to our or other hospitals, 35 were still outside hospital but by no means symptom-free, but 45 patients would be classified as recovered. These relatively favourable results were due to 89 patients having suffered from affective illnesses: 24 had symptoms associated with brain damage, 10 were mainly paranoid and 10 were regarded as having psychoneurosis. In spite of 4–6 weeks of conservative management 52 patients had to be given ECT. I concluded the article by pointing to research needs and by opining that with 30–40% of patients admitted to British mental hospitals being over the age of 60, training in the special problems of this age group was essential for all entrants to general psychiatry.

The history of the beginning would be incomplete without a brief account of further developments. My little textbook (rightly out of print) and publications on the long-term outcome of affective, paraphrenic and schizo-affective illnesses were largely my own work, but many of the junior psychiatrists made contributions and they and clinical psychologists, as well as social workers, instigated their own researches. Many later made a name for themselves, and some became leading psychogeriatricians. Among them were Tom Arie, the late L.K. Hems, David Jolley, Robin Jacoby, David Kay, Kenneth Shulman and, last but certainly not least, Raymond Levy. After the Bethlem-Maudsley had accepted a district commitment and the admission of involuntary (sectioned) patients, Raymond Levy and my successor, Klaus Bergmann (not a Bethlem trainee), managed to move the Geriatric Unit to the Maudsley, so much closer to the patients' family homes. Raymond Levy succeeded in establishing an Academic Department of Old Age Psychiatry, which has continued to conduct research into the dementias of late life, that most important subject, previously neglected on account of admission restrictions before the hospital abandoned its ivory tower to accept a district commitment. With similar developments elsewhere, psychogeriatrics became a world movement, and Sir Aubrey Lewis would be pleased.

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COMMENTARY

Felix was a refugee from Nazi Germany¹. He enrolled at St Bartholomew's Hospital in 1934, qualifying in 1939. He entered medicine in an era when it was widely assumed that older mentally ill people were 'senile' and therefore nothing could be done for them.

Felix refers to his 1944 paper². He commented on his 'false prediction' for older people requiring long-stay care in hospital, that those with chronic functional illnesses would numerically exceed those with organic illnesses. However, he did not emphasize the real significance of his paper, his observations that 'Old age alone does not produce mental illness', that appropriate diagnoses can be made, and that a multidisciplinary approach is important in treating older people. The possibility of differential diagnosis from a hopeless mass of mental symptoms in old age was not widely recognized until Martin Roth's classic paper in 1955³. Felix was a decade ahead. His conclusions were radical. Felix's paper caught the attention of Professor Aubrey Lewis (1900–1975); he referred to it in his own landmark paper⁴; they shared a common, new and challenging belief that something *could* be done to treat elderly mentally ill people.

Lewis had three contemporaries writing constructively on mental illness in older people. Two were relatively senior refugee psychiatrists: Willi Mayer-Gross⁵ and Erwin Stengel⁶. The third, Felix, was earmarked by Lewis for a clinical role with older people. However, Felix had no intentions of becoming a psychiatrist, let alone one working with older people. But he was aware that refugee doctors were having difficulty in securing senior appointments, especially in traditional elitist teaching hospitals. Lewis offered him a post in 1947 at the Maudsley Hospital, London, a psychiatric teaching hospital. Henceforth, he regarded himself as owing Lewis a huge debt, and thus when Lewis asked him to be consultant on the new Geriatric Unit he could not refuse. Felix's ambivalence to working there stemmed from the prevailing belief that nothing could be done therapeutically to help the old and mentally ill⁷, despite his own published work.

Lewis's objective was to make the Bethlem-Maudsley Hospital a great centre of postgraduate psychiatric teaching and research, of which mental illness of older people would be part⁸. Once established, the Geriatric Unit for functionally ill old people was sufficient for the teaching purposes envisaged by Lewis. With this objective fulfilled, Lewis and his colleagues offered Felix no further support for developing additional services for older people. 'In the Beginning' rightly attributes the founding of the Geriatric Unit to Lewis, but it would be inaccurate to attribute any further developments to him. The rest should be Felix's accolade.

Felix also modestly reported the outcome of treatment of his first inpatients in 1952 as 'relatively favourable'⁹. However, his results could perhaps better be described as 'spectacular'. This is for two reasons. First, at that time most mentally ill old people requiring mental hospital admission would have been admitted to long-stay wards without any assessment, let alone treatment, for their apparent all encompassing label of 'senility'. The expectation of any recovery was extremely low. Second, the only effective therapeutic tools were electroconvulsive therapy (ECT) and psychotherapeutic approaches; antidepressants, antipsychotics and mood stabilizers were yet to be introduced. Sadly, however, this outcome study was published in a journal with only a small circulation; had it been published in a more widely read journal it might have had a greater impact. For Felix himself, however, such results began to produce a sense of 'therapeutic optimism'¹⁰.

Felix also referred to 'my little textbook (rightly out of print)'. This is a valid statement, but fails to reflect on the importance of the 'little textbook', *The Clinical Psychiatry of Late Life*¹¹. It was the first book of its kind to emphasize an evidence-based approach to actively treating older mentally ill people. Highly readable, its philosophy remains at the foundations of good clinical practice today. It ends with the words:

Sometimes, we may effect cures; frequently, we may be able to ameliorate the patient's condition; we shall always endeavour to give him and his family sympathetic support... *Quelquefois guérir; soulager souvent; consoler toujours*.

Why, one may ask, did so many of Felix's junior doctors go on to become leading psychogeriatricians? It was not chance, but likely to be related to his inspiring and enthusiastic teaching. Felix's personal career experience, moving from ambivalence to optimism to conveying his enthusiasm to others raises another contemporary lesson: we need to engage our medical students and junior staff and let them experience what can be done in order that they may carry with them the knowledge and ideals of the specialty, and possibly enter the field themselves. Felix's widespread influence lay largely in his clinical acumen, his meticulousness, his wisdom and his teaching skills¹².

Felix's autobiographical sketch ends with the words 'psychogeriatrics became a world movement, and Sir Aubrey Lewis would be pleased'. Lewis would undoubtedly have revelled in such lasting recognition, and hopefully the more unassuming Felix Post would also be pleased to have his legacy remembered.

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Normal and Abnormal Ageing

Changes in the Macrostructure and Microstructure of the Ageing Brain

Natalie M. Zahr¹, Adolf Pfefferbaum² and Edith V. Sullivan¹

¹Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, CA, USA

²Neuroscience Program, SRI International, Menlo Park, CA, USA

MACROSTRUCTURAL CHANGES IN NORMAL AGEING DETECTED WITH CONVENTIONAL MRI

Conventional brain structural magnetic resonance imaging (MRI) produces images of protons, with contributions primarily from water and some from fat. Tissue contrast is possible because of the fundamental differences in water content in the primary tissues of the brain: white matter consists of about 70% water, grey matter 80% and cerebrospinal fluid (CSF) 99%. Tissue contrast also depends on differences in the degree to which water is bound and differences in the local environment. By judicious choice of imaging acquisition parameters that yield high conspicuity between grey and white matter (e.g. Figure 4.1a), segmentation of brain tissue is possible. Segmentation provides the basis for volumetric and morphological quantification of brain structure^{1,2}. In addition to manual delineation of specific structures, methods for quantitative survey of the brain include

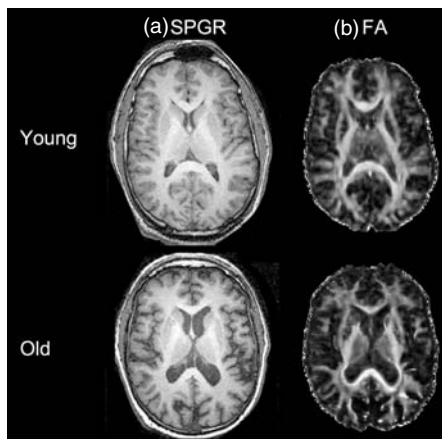


Figure 4.1 (a) Structural magnetic resonance imaging (spoiled gradient recalled, SPGR), and (b) diffusion tensor imaging (fractional anisotropy, FA) images from a young (32 year old) and an elderly (73 year old) male volunteer. SPGR images exemplify those that yield conspicuity between grey and white matter permitting brain tissue segmentation. Fractional anisotropy images facilitate fibre tracking

voxel-based morphometry, as is widely used with spatial parametric mapping (SPM)^{3,4}, parcellation^{2,5} and deformation morphometry^{6–8}. The achievement of quantitative analysis was an essential step for rendering MR images useful in the quest for reliable identification of age-related macrostructural change.

In vivo structural MRI reveals age-related increases in the volume of CSF-filled spaces primarily at the expense of cortical grey matter (cross-sectional^{9–14}, longitudinal^{15–19}).

Despite evidence for widespread thinning of the cerebral cortex as a feature of normal ageing^{16,20,21}, specific grey matter structures of the brain exhibit differential patterns of ageing. A preponderance of data indicates an excessive vulnerability of the frontal lobes, and in particular the prefrontal cortex, as documented cross-sectionally^{22–25}. Other grey matter structures demonstrating cross-sectional decline in volume with age include, but are not limited to, segments of the temporal^{20,25} and parietal cortices²⁰, thalamus^{12,26}, and cerebellum^{11,21,27}. Longitudinal studies, although less frequently reported, support cross-sectional results by revealing disproportionate effects of age on frontal grey matter regions^{15,17,28}, entorhinal^{28,29}, temporal^{17,28}, parietal¹⁷ cortices, and cerebellum²¹. Some³⁰, but not all^{27,31} MRI studies of subcortical structures report little shrinkage of basal ganglia structures. Similarly, although some reports are equivocal^{16,28,32}, it is generally accepted that hippocampal volume shrinks little with age^{20,33,34}. That hippocampal volume shrinkage is not a reliable marker of healthy ageing makes it a robust marker of age-related diseases affecting this structure, notably, Alzheimer's disease.

The relevance of structural MRI findings to age-related decline in function is underscored by correlations with selective behaviours. For example, smaller prefrontal volume predicts poorer performance on the Wisconsin Card Sorting test³⁵ and other tasks involving inhibitory control^{36,37}. Deficits in the working memory that occur in normal ageing correlate with frontal system volume³⁸, whereas episodic memory deficits that occur in Alzheimer's disease correlate with medial temporal lobe/hippocampal volume^{39–41}. Such findings support a double dissociation between normal ageing and Alzheimer's disease: frontal brain volume reductions and executive dysfunction mark normal ageing, whereas volume reductions in the medial temporal lobe/hippocampus and the corresponding memory deficits indicate Alzheimer's pathology^{20,42,43}.

MICROSTRUCTURAL CHANGES IN NORMAL AGEING DETECTED WITH DTI

Whole-brain white matter volume shrinkage is small, estimated at no more than 2% per decade²⁷ (but see ^{31,44}). Yet postmortem investigations, in contrast to macrostructural approaches, have provided fruitful leads to age-related changes in white matter by revealing microstructural white matter compromise⁴⁵ including degradation of microtubules, myelin and axons^{46–48}. *In vivo*, white matter microstructure is detectable with DTI, which has successfully revealed evidence of regional white matter disruption in normal ageing even in regions appearing normal on bulk volume imaging.

Quantification of DTI Data

Water molecules in the brain are in constant Brownian motion. Although movement of water protons affects conventional structural imaging to some degree, DTI allows quantification of this microscopic movement *within* each voxel, providing a depiction of local water molecular movement in terms of the preferred orientation of the motion. Along a white matter fibre, the path of a water molecule is constrained and this movement is called ‘anisotropic’, because diffusion along the long axis of a fibre (axial diffusion) is greater than diffusion across the fibre (radial diffusion⁴⁹). Conversely, regions with few or no constraints imposed by physical boundaries such as CSF in the ventricles allow water movement to be random in every direction; this is therefore ‘isotropic’. Disruption of white matter microstructure detectable with DTI can reflect compromise of cytoskeletal structure, myelin or axon density^{50,51}.

DTI quantification requires computation of a tensor, a mathematical description of a three-dimensional ellipsoid depicting the magnitude and orientation of diffusion in individual voxels. The tensor is associated three eigenvalues, with three corresponding orientational vectors (eigenvectors, $\lambda_1, \lambda_2, \lambda_3$), describing the diffusion ellipsoid by its major axes. The eigenvalue average, or trace, reflects the magnitude of diffusion, referred to as mean diffusivity or the apparent diffusion coefficient. The extent to which one eigenvalue, λ_1 , dominates the other two, λ_2 and λ_3 , determines the degree of anisotropy, that is, the degree of orientational preference within a voxel, typically measured as fractional anisotropy, ranging between 0 and 1 on a normalized scale (Figure 4.1b⁵²). The largest eigenvalue, λ_1 , is the longitudinal or axial diffusivity, λ_L , and reflects axonal integrity, whereas λ_2 and λ_3 quantify transverse or radial diffusivity, $\lambda_T = (\lambda_2 + \lambda_3)/2$, and reflect myelin integrity^{49,53}. For both clinical and research studies, most DTI data sets are reduced to an anisotropy image and a diffusivity image. (For more information about DTI, see⁵⁴.)

Regional Quantification of DTI Data

A variety of approaches have been developed for quantification of DTI data; each has strengths and weaknesses that should be considered when critically evaluating published reports. Approaches for regional quantification of the DTI metrics of anisotropy and diffusivity include manually placing small, geometric samples (cubes, ovals, circles) onto selective white matter bundles, manually identifying anatomically based regions of interest (ROI, e.g. midsagittal corpus callosum), application of whole-brain analysis using SPM or other voxel-based morphometric methods, or tract-based spatial statistics (TBSS⁵⁵). Geometric ROIs have the advantage of yielding rarefied

samples of white matter with minimal effects from partial voluming (i.e. inclusion of grey matter, CSF or both) but the potential disadvantage of under-representing the condition of the full extent of the fibre system under study. Manual identification of the entire fibre tract has the advantage of providing an anatomically based sample of the target fibre with the possibility of examining subdivisions for regional variation; a disadvantage can be its susceptibility to partial voluming artefact because of the extended region sampled⁵⁶. Voxel-based morphometry is attractive because it provides an automated, whole-brain survey of fractional anisotropy or diffusivity, but more often than not, has the under-appreciated cost of inadequate registration⁶. Such misregistration can disproportionately bias results and conclusions drawn from data, especially of the elderly⁵⁷, who have dilated CSF-filled spaces invading targeted white matter samples⁵⁸. TBSS is another survey approach that does not actually track fibres but is used to quantify the whole-brain fractional anisotropy skeleton⁵⁹.

AGEING EFFECTS ON DTI METRICS

With advancing age and senescence, a consensus maintains a decline in fractional anisotropy in brain white matter^{56,60–65} (but see ^{66,67}). Furthermore, consistent evidence supports an anterior–posterior gradient of fractional anisotropy decline with age^{57,58,60,61,65,68–74} that has been confirmed in a monkey model of ageing⁷⁵. TBSS likewise substantiates an anterior–posterior gradient, namely by identifying lower fractional anisotropy values in the frontal, parietal and temporal lobes, corpus callosum (particularly the genu and body) and the internal capsule⁷⁶.

In complement to white matter fractional anisotropy decline in ageing, diffusivity in white matter increases^{58,65,67,77–80}. As with fractional anisotropy, profile analysis reveals that the primary locus of the age effect is in anterior white matter⁸⁰. This pattern of age-related decline of fractional anisotropy and increase in diffusivity mirrors postmortem observations with predominant age-related findings in anterior white matter systems^{45,81}.

QUANTITATIVE FIBRE TRACKING IN AGEING

The degree to which the diffusion orientation of a voxel is similar to its neighbours, or in other words, coherence of diffusivity measures between voxels^{82,83}, serves the conceptual basis for quantitative fibre tracking^{55,84–87}. Connectivity and coherence between different brain regions on vector and fibre tracking maps is readily apparent on visual inspection⁸⁸. Methods for quantitative analysis of structural connectivity of white matter include fibre-tract trajectories^{89–91} and maps of the degree of ‘alignment’ among neighbouring vectors, on a voxel-to-voxel basis, resulting in a measure of intervoxel coherence⁸². Advantages of quantitative fibre tracking over focal ROI analysis include the ability to measure the entire extent of a fibre tract and to characterize its integrity along its full extent.

Quantitative fibre tracking confirms focal DTI measures of an anterior-to-posterior pattern of disruption of white matter integrity^{92,93} as, for example, the elderly have lower fractional anisotropy and higher diffusivity than the young in anterior but not posterior sectors of the fibres coursing through the corpus callosum (Figure 4.2)^{94–96}. Recent work also supports a superior–inferior gradient of ageing effects on white matter (Figure 4.3)^{97–99}, whereas pontocerebellar and cerebellar hemisphere white matter tracts are relatively preserved⁹⁷.

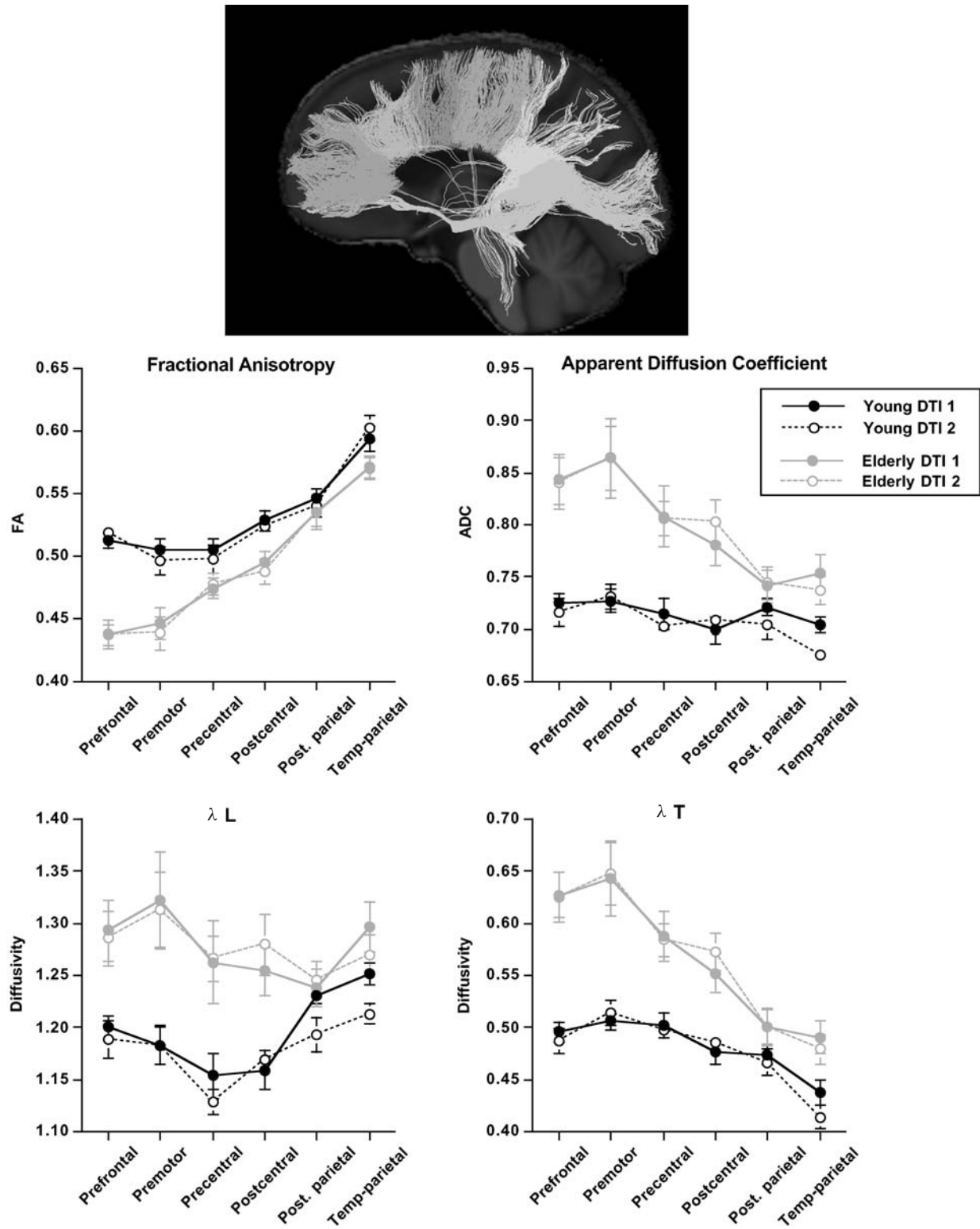


Figure 4.2 Top sagittal image: Example of fibre tracking of the corpus callosum of a 23-year-old healthy woman. The colours represent six different fibre bundles based on previously described divisions¹⁴⁸ identified with fibre tracking based on diffusion tensor imaging (DTI)-derived fractional anisotropy. From anterior (far left) to posterior (far right), the bundles are deemed prefrontal, premotor, precentral, postcentral, posterior parietal, and temporal-occipital. Bottom data figures: Mean $\pm$ SE of the six callosal sectors for the young and elderly groups at MRI sessions two years apart of the four principal metrics of DTI: fractional anisotropy, apparent diffusion coefficient (ADC), λ_1 and λ_t . The elderly group had lower fractional anisotropy and higher diffusivity than the young group at both scanning sessions, and the group differences were greatest in anterior sectors. Reproduced with permission from Sullivan *et al.*¹⁰⁵

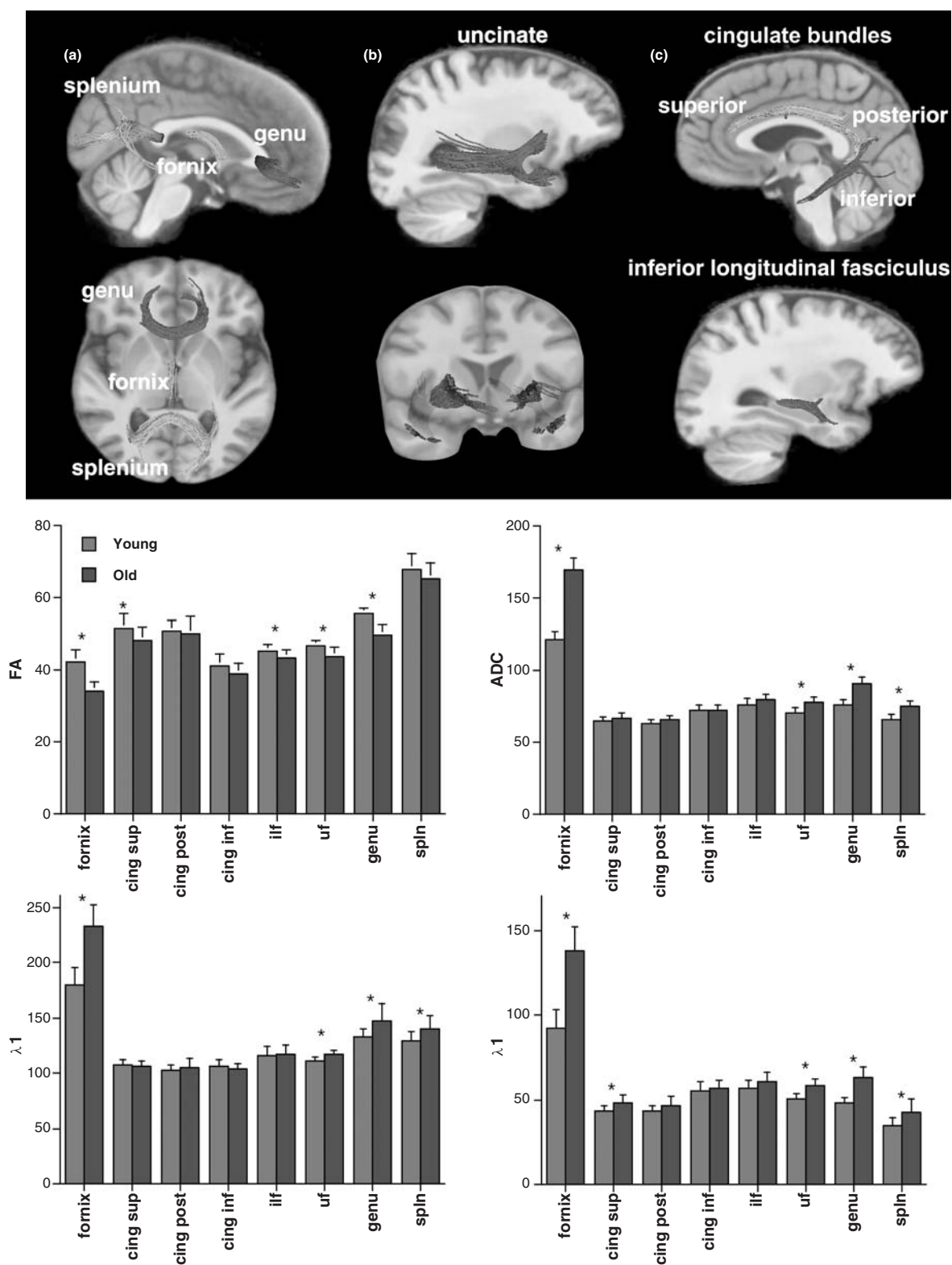


Figure 4.3 Images: Fibre tracts were identified on the group-average fractional anisotropy image in common space. (a) Sagittal (top) and axial (bottom) views of the genu, splenium and fornix. (b) Sagittal (top) and coronal (bottom) views of the uncinate fasciculus. (c) Sagittal (top) view of the cingulum (superior, posterior, inferior) and inferior longitudinal fasciculus (bottom). Bar graphs: Mean $\pm$ SD for fractional anisotropy, apparent diffusion coefficient (ADC), λ_1 and λ_t for young (grey) and elderly (white) subjects for each fibre bundle. * $P \leq 0.05$ t-test. Modified from Zahr *et al.*⁹⁹

LONGITUDINAL STUDIES OF AGEING BRAIN MICROSTRUCTURE

Longitudinal studies of normal, healthy men and women across the adult age range document normative age-related, DTI-detectable changes in brain white matter that are requisite for interpreting DTI data from individuals with neuropsychiatric disorders and other conditions affecting the brain. However, longitudinal studies have their own problems with respect to measurement reliability within and across research centres, selective attrition, and hardware and software system modifications and drift¹⁰⁰. For example, a study of five normal adults imaged five times each resulted in 5% across-subject variation and a mean variation of 2.3 ± 1.2 SD% in diffusivity⁷⁸. Another study measured the reliability of global and regional fractional anisotropy and diffusivity measurements in ten healthy young adults, imaged three times on two different 1.5-T scanners made by the same manufacturer¹⁰¹. When reliability was measured on a voxel-by-voxel basis or on a slice-by-slice basis, fractional anisotropy and diffusivity values were equivalently and significantly higher within than across scanners. In addition to reliability of a common measurement approach, substantial differences can arise when different analysis schemes are applied to the same data set¹⁰².

Longitudinal DTI studies of healthy ageing are only now emerging. The few studies reporting longitudinal results in normal ageing do so secondarily, in that the target study groups were individuals with neurological conditions, including head injury¹⁰³ and amyotrophic lateral sclerosis¹⁰⁴; in neither control group were age-related declines in fractional anisotropy or increases in diffusivity detected. One small prospective study followed eight young and eight elderly individuals over two years¹⁰⁵ but found no evidence of change in any of the six sectors of the corpus callosum examined; instead, the measurement was highly reliable across the interval (see Figure 4.2).

BRAIN WHITE MATTER STRUCTURE–FUNCTION RELATIONSHIPS

The functional ramifications of the DTI metrics have been regularly verified with observations of correlations between regionally specific low fractional anisotropy or high diffusivity and poor cognitive^{61,62,71–73,106,107} or motor⁶⁸ test performance in humans and also a monkey model of ageing⁷⁵. Lower whole-brain fractional anisotropy and higher mean diffusivity correlated with working memory performance^{106,108}. The alternating finger-tapping task, a test of interhemispheric information transfer, revealed a relationship between splenium and parietal pericallosal white matter fractional anisotropy and finger-tapping output that was selective to the alternating condition, requiring interhemispheric motor coordination, and not unimanual conditions, free of transcallosal information exchange⁶⁸. Task switching^{61,109} and lower scores on tests of executive functions^{63,109} correlated with low fractional anisotropy and greater diffusivity in anterior brain regions; lower verbal fluency scores correlated with lower fractional anisotropy in central samples of white matter⁶¹.

Functional correlates of regional fibre tracking are also emerging. Correlations between fibre tracking quantification and the Stroop color-word reading were noted⁹⁴. A large, multifactorial battery of neuropsychological tests reduced to three factor scores revealed that problem solving and working memory factor scores correlated with indices of callosal genu and fornix integrity, whereas the motor factor score correlated with a widespread set of fibre systems, likely

reflecting the multiple brain loci required to execute the tasks, which included speed, dexterity and choice reaction time (Figure 4.4)⁹⁹.

LIMITATIONS OF DTI

DTI studies indicate widely varying fractional anisotropy across brain regions, with lower anisotropy and higher diffusivity in older than younger healthy adults, that is prominent in the anterior supratentorial white matter but minimal to none in posterior cortical and corticospinal tracts. A caveat to this generalization is that selective deletion of uniformly orientated white matter fibres from a tissue sample of crossing fibres, as can occur with Wallerian degeneration, can cause abnormally high anisotropy¹¹⁰. Therefore, interpretation of fractional anisotropy results requires guidance by knowledge of the underlying regional architecture, especially white matter¹¹¹ and supplemented with non-human primate studies, affording the opportunity for *in vivo* examination and postmortem verification of imaging results (cf.⁸⁸).

Furthermore, the diameters of axons, for example in the corpus callosum ranging from 0.4 to 5 μm , with most less than 1 μm , means that a cross-section of the genu of the human corpus callosum contains approximately 400 000 fibres per mm^2 and a single DTI voxel using relatively high resolution ($2 \times 2 \times 2 \text{ mm}^3$) for current standards could contain 1.6 million fibres in a cross-section¹¹². Consequently, caution must be used when interpreting the anatomical meaning of observations made with radiological measures, which are coarse on the size scale of the underlying fibres.

Finally, the diffusion-weighted signal can also be influenced by iron accumulation with age, and the resulting effect is different among deep grey matter structures and white matter and needs to be considered, especially when using DTI to characterize structures known to accumulate iron (*in vivo*¹¹³, postmortem¹¹⁴) or in conditions, such as stroke, that produce high ferritin deposition (cf.¹¹⁵).

OTHER STRUCTURAL MAGNETIC RESONANCE OBSERVATIONS IN AGEING

Convergent postmortem¹¹⁴ and *in vivo* data indicate that deep grey matter brain structures accumulate ferritin at different rates throughout adult ageing^{113,116,117}. Abnormal iron accumulation has been reported in neurological conditions involving the basal ganglia, including Parkinson's disease, multiple sclerosis and Huntington's disease (reviewed in: ^{113,118–122}), and suggests that iron burden contributes to age- and disease-related functional decline^{123,124}.

Iron can be measured *in vivo* with MR imaging because of iron's effect on signal intensity, causing signal darkening on T2* and T2-weighted images that is greater with increasing magnetic field strength. By estimating the transverse relaxivity increase across field strengths, the MR field-dependent relaxivity increase (FDRI) can be calculated^{113,125,126}. For example, acquisition of spin-echo data with a constant TR and multiple echoes at 1.5-T and 3.0-T allows the computation of R2 (the inverse of T2) at each field strength with the difference between R2s divided by the field strength difference producing FDRI in units of s^{-1}/T (Figure 4.5a).

In addition to affecting relaxivity, local iron influences MR gradient-echo image phase, which forms the basis for another method for iron quantification, susceptibility-weighted imaging (SWI) (Figure 4.5b)¹²⁷. The paramagnetic properties of tissue ferritin cause local field inhomogeneity that can also be quantified by examining the phase of the computed spins. The ferromagnetic

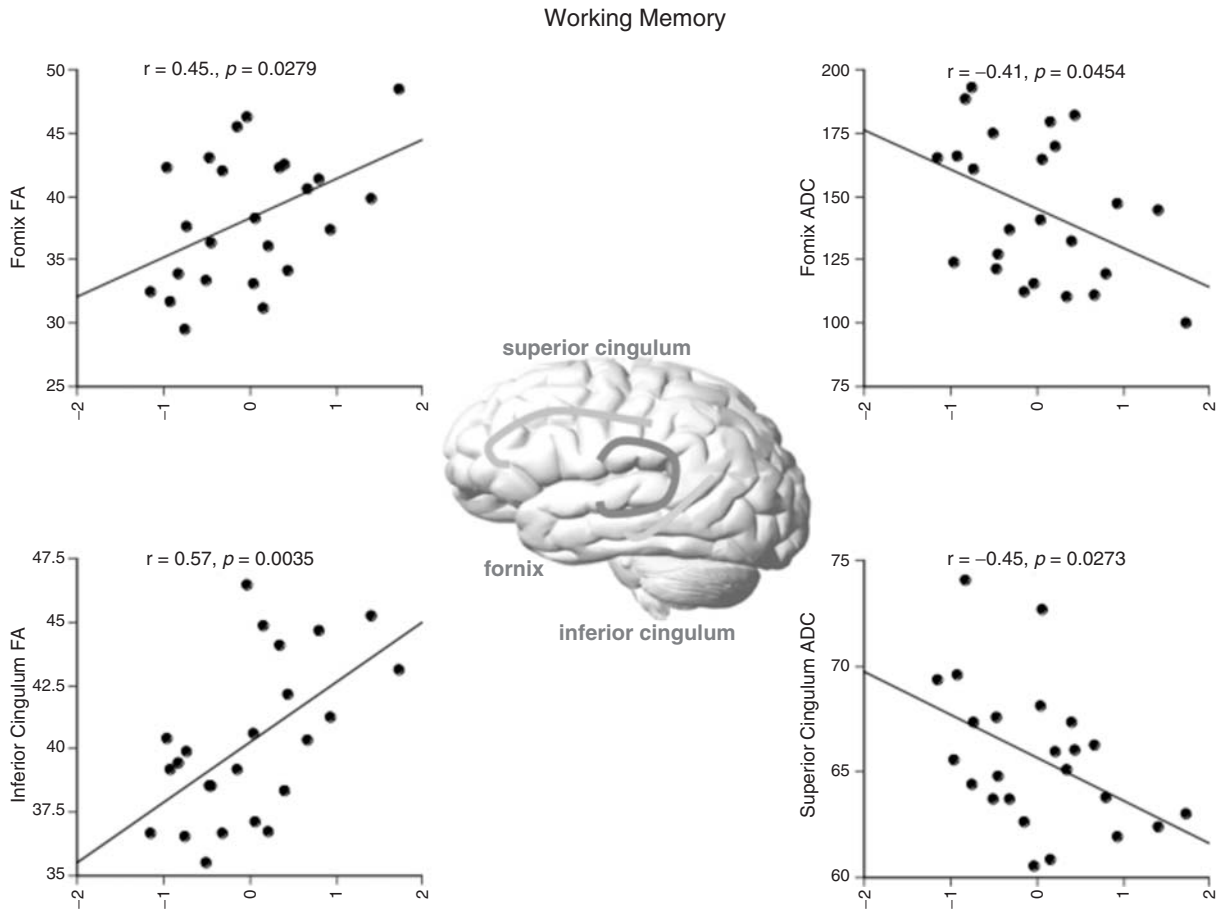


Figure 4.4 Correlations (Spearman rank and Bonferroni corrected) between a working memory domain isolated using principal component analysis and diffusion tensor imaging (DTI) metrics (fractional anisotropy and apparent diffusion coefficient) by tract. Modified from Zahr *et al.*⁹⁹

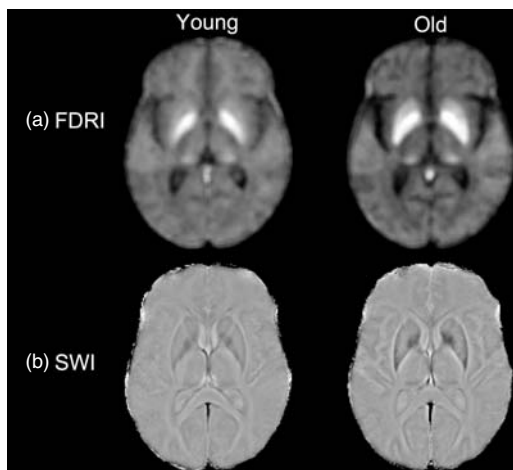


Figure 4.5 Group averages for 11 younger (mean = 24 years old, 5 men, 6 women) and 12 older (mean = 74 years old, 6 men, 6 women) participants for (a) field-dependent relaxivity increase (FDRI) and (b) susceptibility-weighted imaging (SWI) techniques for measuring brain iron. Greater iron concentration yields higher (brighter) FDRI signal but lower (darker) SWI signal. Modified from Pfefferbaum *et al.*¹²⁶

property of iron causes protons to accrue more negative phase in iron-rich tissue. At optimal acquisition parameters, the more iron in a voxel, the lower will be the measured phase¹²⁷.

FDRI and SWI document increasing iron deposition with age in deep brain structures such as the caudate and putamen, globus pallidus, red nucleus, substantia nigra and thalamus^{113,119,126,128}. In a recent comparison study between FDRI and SWI, both methods detected high globus pallidus iron concentration independent of age and significantly greater iron in putamen with advancing age¹²⁶.

Further senescent changes in brain tissue composition and emblematic of tissue degradation are the increases in presence and volume of white matter hyperintensities (WMHs) (e.g.^{129–131}), typically visible in T2-weighted and fluid-attenuated inversion recovery (FLAIR, Figure 4.6) images. WMHs are associated, for example, with hypertension, stroke, traumatic brain injury and respiratory dysfunction^{132–134}. The current controversy regarding WMHs aetiology is whether a common pathophysiological mechanism underlies the formation of periventricular and deep white matter lesions^{134–136}. It is thought that demyelination or ependymal lining damage commonly occurs periventricularly, whereas rarefaction of myelin or cavitations from fibre loss, concomitant of ischaemic damage or arteriosclerosis, commonly occurs in deep white matter¹³⁰. Depending on the location of WMHs, different types of functional decline can ensue^{136,137}.

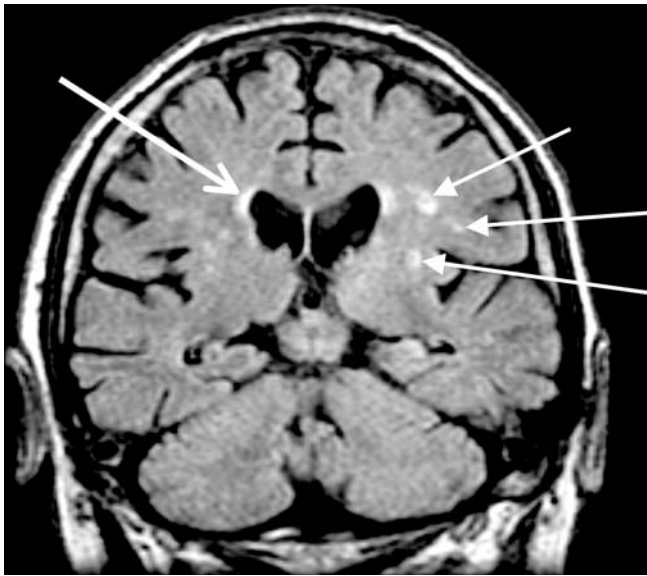


Figure 4.6 Coronal image from a healthy elderly adult volunteer (72 years old) displaying white matter hyperintensities in deep (closed arrows) and periventricular (open arrow) regions of the brain

CONCLUSION

The twentieth century has seen a dramatic increase in life expectancy in developed countries. Estimates from the Health and Retirement Study, sponsored by the US National Institute on Ageing, indicate that ~10% of individuals aged 70 and older in the United States suffer moderate to severe cognitive impairment that rises to ~20% by age 85 years¹³⁸. Therefore, expanding longevity coupled with declining CNS function will dictate the need for continued development of clinically practical and sensitive imaging modalities to assist in the differential diagnosis of age-related diseases.

Advances in neuroradiology have contributed to the neuroscience of normal ageing and to characterizing morphological and tissue changes that occur in the brain with age. Among these is the identification of previously underappreciated occurrence of decline in white matter integrity. The *in vivo* interrogation of the brain has also highlighted the dramatic, involutional brain tissue shrinkage and replacement with CSF, less apparent at the autopsy table as the brain collapses in on itself when removed from the skull¹³⁹.

Finally, a principal aim of this paper was to emphasize neuroradiological concomitants of apparent normal ageing, thereby providing an essential context in which to interpret radiological evidence for neurodegenerative diseases and other conditions of brain insult. Careful history taking and clinical description of presumed healthy men and women have proved essential in identifying factors that underlie departure from normality²⁸ or are categorized as 'normal variants'¹⁴⁰. Factors increasing in prevalence with age and affecting brain tissue and potentially function include hypertension¹⁴¹, cerebrovascular disease^{135,142}, and iron deposition¹¹³. DTI can be more sensitive than conventional MRI for detection of subtle and perhaps prodromal changes in tissue that occur with age (cf. ^{126,143,144}), including those characteristic of stroke^{145–147}. Use and quantification of tractography may also enable monitoring white matter fibre regrowth¹⁴⁸ following trauma, disease or recovery from alcohol and drug dependence and to test models of white matter recovery in normal ageing, trauma and disease.

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Functional Imaging of the Ageing Brain

Robert Perneczky, Christian Sorg and Hans Förstl

*Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar,
Technische Universität München, München, Germany*

INTRODUCTION

Modern imaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and single photon emission tomography (SPECT) provide the groundwork to test mechanistic hypotheses derived from basic neuroscience studies in healthy individuals and patients with neurological and psychiatric disorders. Apart from these scientific applications, functional imaging studies can also provide important diagnostic information in the field of geriatric psychiatry. Therefore, functional imaging scans are recommended by diagnostic guidelines to resolve certain differential diagnostic issues¹, and costs are also reimbursed for these special cases in selected countries (e.g. Medicare Coverage Criteria for FDG-PET for Alzheimer's disease, <http://nps.cardinal.com/nps/PETFFoundations/documents/PETADCovFinal.pdf>). In addition to its benefits for the diagnosis and differential diagnosis of neurological and psychiatric disorders, functional brain imaging has also been shown to increase the confidence of experts in their clinical diagnosis. For example, Foster *et al.*² reported that visual rating of ¹⁸F-fluoro-2-deoxy-glucose (FDG) PET scans after a short training period was more reliable and accurate in distinguishing Alzheimer's disease from frontotemporal dementia (FTD) than clinical assessment on its own. This was particularly true when the raters were uncertain with their clinical diagnosis. Hence, FDG PET is able to add important diagnostic information that appropriately improves diagnostic confidence.

Biomarkers including functional imaging are also gaining importance for the evaluation and monitoring of treatment effects. Modern, sensitive techniques are able to detect subtle brain functional changes resulting from therapeutic interventions, even if the therapeutic effect is not immediately mirrored by clinical improvement. This could lead to the identification of treatment responders in very early treatment phases³ or before the actual treatment period has even started. Furthermore, for some potentially preventive treatments to have their greatest impact, patients need to be identified at the presymptomatic stage. This means that individuals with an increased risk for a certain disease, but who do not yet show any clinical signs, need to be identified. Persons at risk for Alzheimer's disease, for example, can already be identified on the basis of brain metabolic deficits in their FDG PET scans before first symptoms, such as forgetfulness, appear⁴.

This chapter provides an overview of a selection of functional imaging techniques and brain functional changes associated with

ageing, some prevalent neurodegenerative and psychiatric disorders, and those due to treatment. Important clinical aspects and future research perspectives will be discussed.

FUNCTIONAL IMAGING TECHNIQUES

Functional neuroimaging is broadly defined as techniques that provide measures of brain activity. Commonly used techniques are electroencephalography (EEG), magnetoencephalography (MEG), PET, SPECT and fMRI. Here we focus on PET and fMRI, which primarily aim at the regional mapping of mental processes. These techniques measure metabolic and haemodynamic brain processes closely linked with neuronal activity. PET and fMRI allow both the detection of regional activity changes in response to experimentally presented stimuli or cognitive tasks and the detection of synchronous co-activity changes across brain regions in response to stimuli or during rest. In this section we review the biological basis of functional neuroimaging signals, then we describe the physics of PET and fMRI signals, and finally we discuss two basic principles underlying functional neuroimaging data analysis: functional specialization and functional integration.

Behaviourally evoked changes in blood flow are at the heart of functional neuroimaging⁵. Blood flow changes reflect metabolic changes, which in turn reflect changes in neuronal activity. From a metabolic point of view neuronal activity is dominated by transmitter recycling. Eighty per cent of brain energy is used for glutamate recycling. Central to glutamate recycling are aerobic glycolysis and oxidative phosphorylation. These activity-dependent processes with their main substrates H₂O, O₂ and glucose provide the basis for¹⁵ O-H₂O-PET, FDG PET, and blood oxygen level-dependent (BOLD) fMRI.

Oxygen-15 and fluorine-18 are isotopes with short half-lives that are introduced into the body incorporated into H₂O and glucose. As the tracers decay, emitted gamma rays are detected by the PET scanner and used for image construction. The spatial resolution is about 1.5 cm and the temporal resolution is about 60 s; both values strongly influence the experimental design of neurocognitive paradigms. The fundamental signal for BOLD fMRI comes from hydrogen atoms mainly bonded to H₂O within the brain. In the presence of a static magnetic field, these hydrogen atoms absorb energy that is applied at a characteristic radio frequency. After radiofrequency excitation,

hydrogen atoms emit energy at the same radiofrequency until they gradually return to their equilibrium state (resonance phenomenon). The MRI scanner measures the emitted radiofrequency energy. The measured radiofrequency signal decays over time, influenced by distinct factors, including the presence of inhomogeneities in the magnetic field. BOLD fMRI techniques are designed to measure primarily changes of inhomogeneity within a small volume of tissue that result from changes in blood oxygenation. Deoxy- and oxyhaemoglobin (Hb-CO₂, Hb-O₂) have different magnetic properties; Hb-CO₂ is paramagnetic and introduces an inhomogeneity into the nearby magnetic field, whereas Hb-O₂ is weakly diamagnetic with little effect. Hence, an increase in the concentration of Hb-CO₂ causes a decrease in image intensity, and a decrease in Hb-CO₂ causes an increase in image intensity (BOLD effect). The spatial resolution of BOLD fMRI is about 0.5 cm and temporal resolution about 1–4 seconds.

There are two key topics in the analysis of functional imaging data, reflecting the long-standing debate in neuroscience about functional specialization versus functional integration in the brain⁶. The first is brain ‘mapping’, where three-dimensional images of neuronal activation are generated showing which parts of the brain respond to a given sensory stimulus or cognitive task. This is also known as the study of functional specialization and generally proceeds using some form of statistical parametric mapping (SPM) based on a voxel-wise analysis. A classic example here is the identification of human V4 and V5, the areas specialized for the processing of colour and motion. The second topic is ‘functional integration’, where models are used to analyse how different brain areas interact. A classic example is the use of models to find increased connectivity between dorsal and ventral visual streams after subjects learn object–place associations. A large number of statistical techniques are used to detect interregional connectivity (e.g. independent component analysis, support vector machine, dynamic causal modelling).

AGE-RELATED FUNCTIONAL CHANGES

Brain Functional Decline

‘Normal ageing’ is associated with numerous biological deteriorations in the human body, which also include brain functional changes. However, ‘normal ageing’ is a rather fuzzy concept and it is sometimes difficult to separate age-related and disease-related brain changes. All the same, with age the brain undergoes both structural and functional changes that underlie subjective complaints. The pre-frontal cortex shows the most prominent functional deterioration in most studies, whereas other regions including the anterior hippocampus, the thalamus and the posterior cingulate cortex are affected to a much lesser extent⁷. These results support the theory that the first areas to emerge phylo- and ontogenetically are the most resistant to age effects and the last to emerge are the most vulnerable. Furthermore, the relative functional preservation of brain structures during ‘normal ageing’ that are affected early in Alzheimer’s disease, such as the hippocampus and the posterior cingulate cortex⁸, seems to mark the parting of the ways between ageing and brain disease. This is also supported by the finding that cognitively normal elderly individuals with a pathological brain metabolic pattern are more likely to experience memory decline⁹ and are at elevated risk of developing symptoms of Alzheimer’s disease¹⁰. Also in line with these findings, Alzheimer’s disease-like brain functional patterns are also found in cognitively normal elderly individuals with an increased genetic risk for Alzheimer’s disease (i.e. carriers of the

apolipoprotein E allele $\epsilon 4$ (*APOE4*)¹¹). Alzheimer’s disease-like changes are already present at even younger ages in pre-symptomatic individuals from families with known early-onset autosomal dominant Alzheimer’s disease-carrying mutations in the *PRESENILIN1* gene¹². Interestingly, a maternal history of Alzheimer’s disease also predisposes cognitively normal individuals to progressive metabolic deficits in Alzheimer’s disease-vulnerable brain regions, which may be related to a higher risk of developing the disease⁴. Although the exact causes of these abnormalities are not yet known, these results suggest the involvement of maternally inherited predisposition to brain metabolic failure, possibly connected to mitochondrial DNA. The facts that mitochondrial DNA is entirely maternally inherited in humans, and diseases associated with mitochondrial DNA mutations often present as sporadic disorders, support this hypothesis.

Adaptation and Compensation

Age- and disease-related changes are not only associated with functional deterioration but also with counteractive measures. Accessory neural networks are activated to solve increasingly difficult tasks (adaptation). Similar mechanisms are deployed if a task cannot be solved by the usual means because of damage to the brain regions normally involved due to age-related changes or neurodegeneration (compensation)¹³. To offset brain functional deterioration, networks and cognitive patterns less susceptible to interference are activated; furthermore, additional networks not involved in young healthy individuals for the same task are recruited. These activity adjustments are exemplified by two well-described phenomena. The PASA (posterior-anterior shift in aging) phenomenon describes one possible reaction of the human brain to age-associated cognitive impairment. An increased activation of pre-frontal areas in conjunction with a decreased activation of occipital areas is found for the same cognitive paradigm in elderly individuals compared to healthy young persons. The degree of this activity shift is positively associated with task performance¹⁴. The HAROLD (hemispheric asymmetry reduction in older adults) phenomenon, on the other hand, delineates a reduction of hemispheric asymmetry in elderly individuals¹⁵; compared to young individuals, elderly persons tend to activate additional contralateral and to deactivate ipsilateral brain regions for the same cognitive task. Again, task performance positively correlates with the degree of the activity change. Taken together, PASA and HAROLD are good examples of the three possible mechanisms of cerebral activity changes associated with efficient information processing during ageing: (i) increased activation of brain regions already involved at the same task difficulty level in young individuals; (ii) activation of additional networks in other brain regions; (iii) more efficient deactivation of interfering networks.

FUNCTIONAL CHANGES IN NEURODEGENERATIVE DISORDERS

Neurodegenerative disorders are associated with distinct brain functional patterns. These patterns help to separate different disorders and to identify patients at oligosymptomatic stages.

Mild Cognitive Impairment and Alzheimer’s Disease

In Alzheimer’s disease functional brain damage is typically found in the hippocampus, and the pre-frontal, temporoparietal and posterior

cingulate association cortices^{8,16}. The hippocampus and the posterior cingulate cortex seem to be affected in very early disease stages; metabolic deterioration of these two regions is already present in patients with mild cognitive impairment (MCI)^{17,18}. Furthermore, an FDG PET suggestive of Alzheimer's disease in patients with MCI is a strong predictor for progression to dementia, especially in the presence of other risk factors such as an *APOE* $\epsilon 4$ allele¹⁹. The degree of posterior cingulate cortex hypometabolism is also positively correlated with clinical disease severity in MCI²⁰. However, several studies show that there is no linear association between brain damage and clinical symptoms, and that individual characteristics related to cognitive reserve modify the association between neurodegenerative damage and clinical signs^{21–23}. Therefore, clinical symptoms tend to be less severe in individuals with higher estimated cognitive reserve than would be predicted by the amount of their brain damage.

Frontotemporal Lobar Degenerations

The clinical syndromes FTD, semantic dementia (SD) and non-fluent progressive aphasia (NFPA) have distinct morphological and functional imaging correlates. Furthermore, associations between specific clinical symptoms and focal functional brain pathology can be established. For example, metabolic reductions in brain regions related to micturition can be found in patients with FTD who suffer from urinary incontinence in contrast to those patients who do not experience this distressing symptom²⁴.

In FTD, bi-hemispheric functional brain pathology, which predominantly affects the pre-frontal cortex, the anterior cingulate cortex, the caudate nucleus and the insula, is already present in early clinical stages²⁵. As the disease progresses, the functional pathology crosses the boundaries of the pre-frontal cortex and spreads to temporal and parietal regions²⁶. Davies *et al.*²⁷ recently reported a group of patients with FTD without any structural brain changes that seem to have a better prognosis. However, brain functional alterations and the clinical relevance of this finding have yet to be explored. It is interesting to note that the degree of functional brain pathology is also influenced by genetic characteristics²⁸ and cognitive reserve^{29,30}. In SD, initially asymmetric, in most cases left-sided, functional lesions of the temporal cortex, more specifically the temporal pole, are found²⁵. It was recently shown in a follow-up study that the metabolic deficit only worsened in the anterior cingulate cortex after 15 months; this limited worsening was, however, associated with a considerable clinical decline³¹. In NFPA, the asymmetric functional deficit is predominantly located in the left temporal and insular cortex, the caudate nuclei and the thalami^{32–34}. However, right hemispheric functional pathology was reported in left-handed patients³⁵ (Figure 5.1).

Lewy Body-Associated Disorders

Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) probably both belong to a spectrum of Lewy body-associated disorders. This notion is supported by a similar pattern of functional cerebral pathology, which includes brain regions also affected in Alzheimer's disease, such as the pre-frontal, temporoparietal and posterior cingulate cortex, and additional areas in the visual association cortex^{36,37}. In a direct comparison, patients with DLB had a significant metabolic reduction in the anterior cingulate cortex compared with patients with PDD³⁶. Associations between focal metabolic deficits and typical neuropsychiatric symptoms were reported, for

example between right pre-frontal metabolism and delusions³⁸, and metabolism in visual association areas and visual hallucinations^{39,40}. Furthermore, the impairment of daily activities was also linked to focal functional brain pathology^{41,42}.

FUNCTIONAL CHANGES IN PSYCHIATRIC DISORDERS

Next we review some studies in major depression and in schizophrenia using fMRI and FDG PET. Since explicit neuroimaging studies exploring the effect of age on major depression and schizophrenia are rare, we focus here on some recent imaging studies in major depression and schizophrenia, providing some new insights in disease mechanisms and demonstrating the potential of neuroimaging techniques for a better understanding of disease-related symptoms by altered brain processes. For both disorders changes in the default mode network (DMN) will be of special interest. The DMN comprises the medial pre-frontal cortex, the posterior cingulate cortex, and the lateral parietal cortex (for review see⁴³). Areas of the DMN show elevated metabolism at rest, they are functionally connected by synchronized co-activity at rest and they consistently deactivate across a wide range of attention demanding, goal-directed behaviours; since DMN activation is related to self-referential functions such as remembering the past, planning the future or perspective taking of the mental state of others, deactivations during goal-directed behaviour are suggested as an attenuation of self-referential processes in order to improve goal-oriented attention⁴³.

The first finding pointing at a potential role of the DMN in major depression was reported by Greicius and colleagues⁴⁴; the authors observed increased synchronized co-activity of the medial pre-frontal cortex within the DMN in major depression during rest. Examining the relevance of this result, Sheline *et al.*⁴⁵ found that in major depression medial pre-frontal regions of the DMN exhibited failure to deactivate during both looking at negative stimuli and appraising them. Patients with major depression and healthy controls were instructed to look at pictures inducing negative emotions in a passive mode and to appraise them actively (making a negative picture positive by depersonalizing it such that it does not pertain to the viewer or that the picture is not real). For the passive viewing and the active regulating condition patients and controls demonstrated reduced activations compared to the baseline state (i.e. deactivations) in the DMN. However, compared with controls, depressed patients' deactivations were less distinctive in several areas of the DMN, notably in the medial pre-frontal cortex. This result suggests that patients with major depression might have problems in reducing self-referential processes both during emotion-related activity and also during subsequent emotion regulation.

In a similar design to that of Sheline *et al.* Grimm and colleagues⁴⁶ found that the degree of deactivation failure correlated with the severity of depressive symptoms and reported hopelessness. These results together point at the prominent role of the DMN in major depression: the DMN seems to be critically involved in some key deficits of major depression such as emotion regulation or increased self-focused cognitions.

Several recent studies have revealed substantial changes within the DMN of patients with schizophrenia. Garrity and colleagues⁴⁷ found reduced synchronized co-activity within superior parts of the posterior cingulate cortex and the precuneus and increased co-activity within the inferior posterior cingulate cortex and the

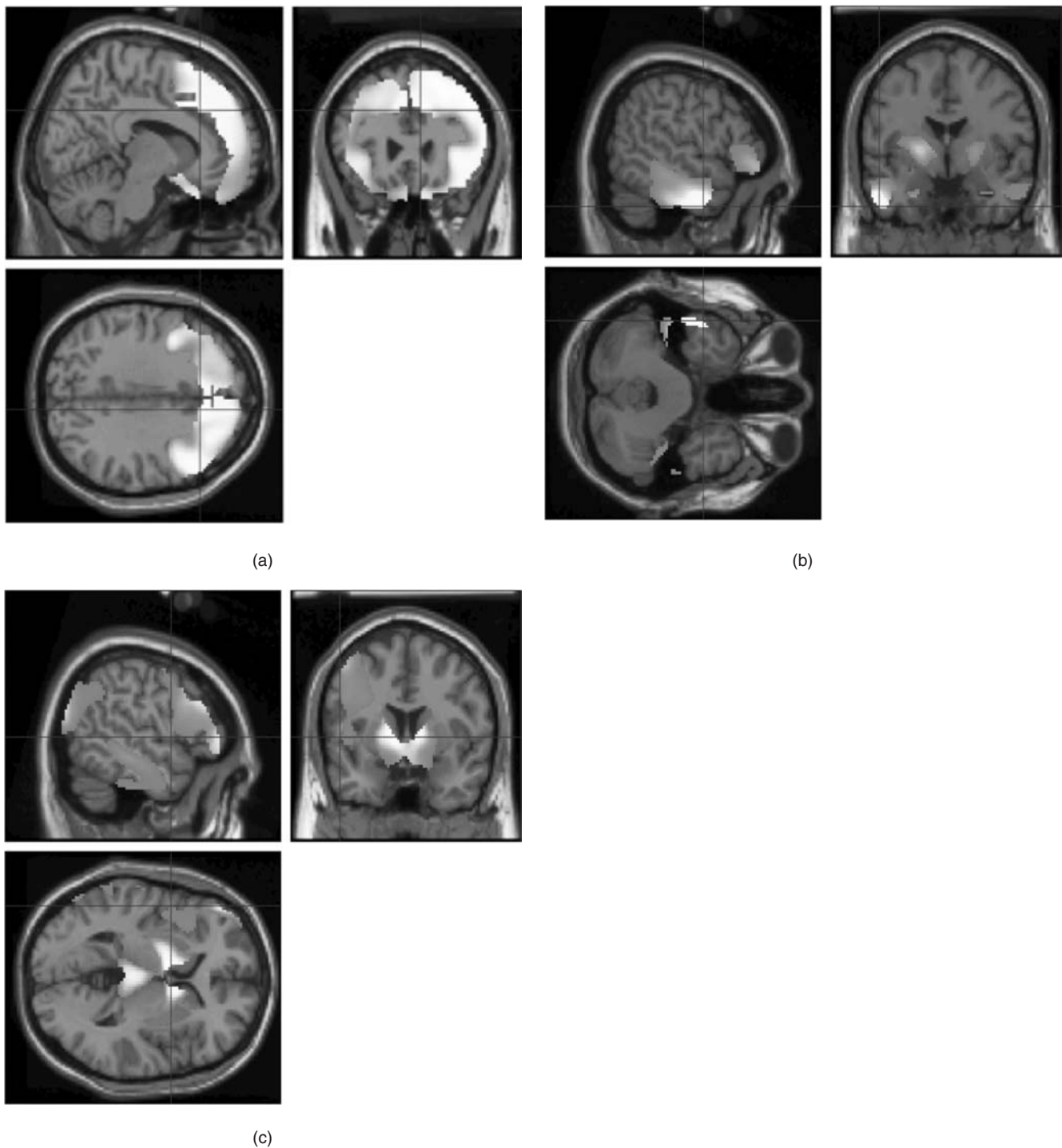


Figure 5.1 Reductions of regional cerebral glucose metabolism in ^{18}F -fluoro-2-deoxy-glucose positron emission tomography (FDG PET) studies of patients with (a) frontotemporal dementia, (b) semantic dementia and (c) progressive non-fluent aphasia compared with healthy control subjects (sagittal, axial, and coronal slices; areas with reduced metabolism are displayed in colour). *A full colour version of this figure appears in the colour plate section*

medial pre-frontal cortex in patients with schizophrenia during an auditory oddball attention task. In particular, increases in co-activity (i.e. functional hyperconnectivity) were correlated with positive symptoms. Looking at a potential relation between hyperconnectivity within the frontal DMN and already known hyperactivation of areas

within and outside of the DMN in schizophrenia, Whitfield-Gabrieli *et al.*⁴⁸ instructed patients with early schizophrenia, first-degree relatives of patients with schizophrenia, and healthy control subjects to perform a working memory task during fMRI. They found gradually reduced deactivations of the medial pre-frontal cortex

across patients with schizophrenia, relatives of patients and controls with deactivations correlating with the cognitive performance. In the patient group deactivations were related to the severity of positive symptoms. Both patients and relatives hyper-activated in the dorsolateral pre-frontal cortex. With regard to functional connectivity, synchronized co-activity of the medial pre-frontal cortex during rest was highest in patients and lowest in controls. This hyperconnectivity of the medial pre-frontal cortex was related to both the hyperactivity of the dorsolateral pre-frontal cortex and the deactivation of the medial pre-frontal cortex, indicating an association between hyperactivation and hyperconnectivity in schizophrenia.

Hyperactivation of the DMN may blur the boundary between internal, self-focus-based thinking and external world-focus-based perceptions. Since many symptoms of schizophrenia involve an increased sense of self-relevance in the world or a smearing of internal reflection and external perception, hyperactivity and hyperconnectivity of the DMN may contribute to these critical symptoms of schizophrenia.

TREATMENT EFFECTS ON BRAIN FUNCTION

Including functional neuroimaging in clinical trials and clinical treatment monitoring procedures may identify neurochemical and anatomic differences between treatment responders and non-responders. These differences may serve as biomarkers for the prediction of treatment response and provide valuable information for treatment development by identifying mechanisms of treatment resistance.

Treatment Effects in Dementia

In Alzheimer's disease, cholinergic treatment with donepezil was associated with a stabilized regional cerebral blood flow in treatment responders, whereas blood flow declined in non-responders in a study by Nobili *et al.*⁴⁹. Similar treatment effects of donepezil were also shown in patients with cognitive impairment after traumatic brain injury⁵⁰. The binding of donepezil to acetylcholinesterase can also be directly measured *in vivo* with PET, allowing quantitative analyses of acetylcholinesterase and direct investigation of the pharmacokinetics of donepezil in the human brain⁵¹. Okamura *et al.*⁵² reported that up to 60% of acetylcholinesterase donepezil-binding sites were occupied after the oral application of 5 mg donepezil. Cholinergic treatment with galantamine also caused sustained inhibition of acetylcholinesterase activity in patients with Alzheimer's disease; this effect was associated with attentional rather than memory improvement⁵³. Brain functional changes were also demonstrated for drugs targeting transmitter systems other than the cholinergic system. Fellgiebel *et al.*⁵⁴, for example, reported clinical and brain metabolic improvements in a patient with FTD under treatment with aripiprazole, a newer antipsychotic with partial agonistic properties at serotonin 5-HT_{1A} and dopamine D₂ receptors, and partial antagonism at serotonin 5-HT₂ receptors. This study also suggests that common functional imaging techniques can be used to provide neurobiological evidence for the clinical effects of different psychotropic drugs.

Treatment Effects in Geriatric Depression

Most studies on antidepressant interventions in unipolar depression, including antidepressant drugs³, total sleep deprivation⁵⁵,

psychotherapy⁵⁶ and electroconvulsive therapy⁵⁷, focus on mid-life individuals. The available data in geriatric depression are limited. Nobler *et al.*⁵⁸ reported that after treatment with nortriptyline or sertraline, the study group as a whole did not show any blood flow changes; furthermore, there were no global blood flow differences between treatment responders and non-responders. However, the blood flow pattern differed significantly between treatment responders and non-responders: responders showed regional blood flow reductions in the pre-frontal and anterior temporal cortices. Brain metabolic reductions in the anterior cingulate cortex and the amygdalae were observed under chronic citalopram treatment by Liotta *et al.*⁵⁹; the reductions were greater in responders than in non-responders. Wu *et al.*⁶⁰ showed that improvement under treatment with sertraline and after sleep deprivation was associated with a metabolic decrease in the orbitofrontal cortex, whereas clinical worsening was related to a metabolic increase in the dorsolateral pre-frontal cortex. Early metabolic decreases of the right cingulate gyrus after total sleep deprivation in combination with sertraline treatment were furthermore associated with clinical improvement⁶¹. However, these synergistic effects of antidepressant drug and sleep deprivation could not be replicated in a randomized, placebo-controlled study by the same group⁶². Taken together these results suggest that the state of severe depression is associated with increased functional activity, the reduction of which through different antidepressant therapies is linked to clinical improvement.

CLINICAL APPLICATION AND FUTURE PERSPECTIVES

Functional Neuroimaging in Clinical Practice

Structural imaging of the brain is an integral diagnostic procedure in psychiatry. It can provide indispensable information on possible organic aetiologies of psychiatric disorders, sometimes with immediate therapeutic consequences; furthermore, structural imaging can also support the clinical diagnosis in geriatric psychiatry, such as in the case of marked mediotemporal atrophy in Alzheimer's disease⁶³. However, functional imaging techniques are experiencing increased popularity in the search for more sensitive and specific biomarkers for distinct psychiatric disorders. For a limited number of indications, functional imaging studies are already recommended by diagnostic guidelines. These indications include the assessment of regional cerebral blood flow or metabolism by means of PET or SPECT imaging for the differentiation of Alzheimer's disease and other neurodegenerative dementias such as FTD. Functional imaging should, however, never replace structural imaging; functional imaging should rather be used to provide complementary information in uncertain clinical cases. The added clinical value of functional imaging in several psychiatric and neurological disorders, including major depression and schizophrenia, is still to be determined. The identification of responders and non-responders in early treatment phases or even before starting a treatment would be especially desirable. Furthermore, novel imaging procedures such as resting state fMRI (rs-fMRI) could not only help to clarify the brain functional basis of neurodegenerative and psychiatric disorders but also serve as non-invasive biomarkers for the diagnosis and differential diagnosis in geriatric psychiatry⁶⁴.

Future Perspectives

Representing a new tool of functional neuroimaging research with some potential for reaching clinical relevance in psychiatric disorders, rs-fMRI focuses on changes of functional interactions between

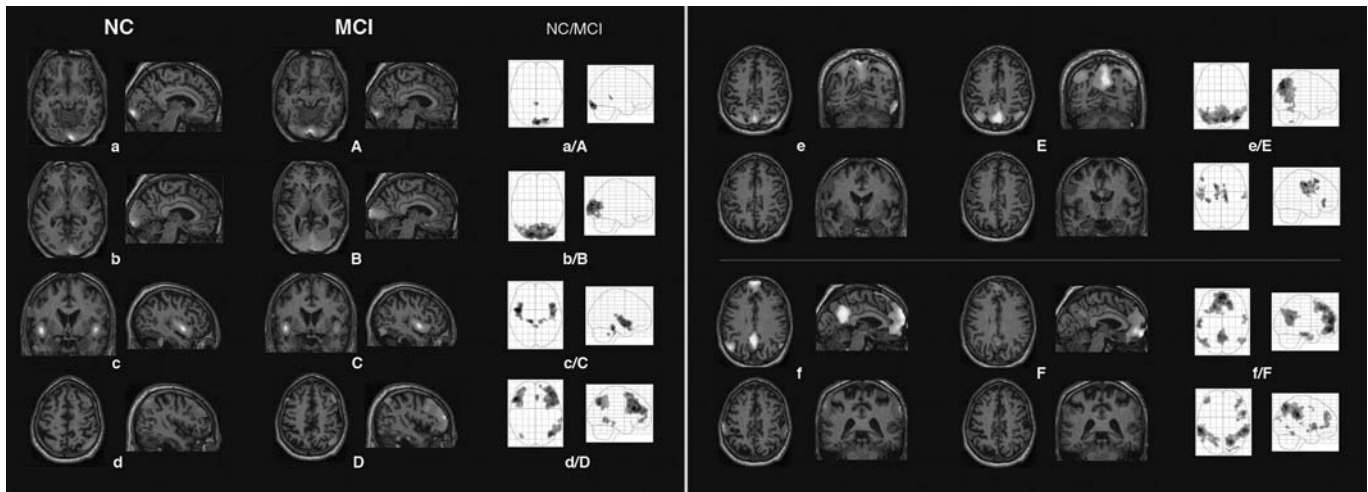


Figure 5.2 Brain networks characterized by synchronized co-activity during rest in normal controls (NC) and patients with mild cognitive impairment (MCI) detected by 4 min of resting state functional magnetic resonance imaging (fMRI). Brain networks correspond with networks found during characteristic cognitive task conditions such as seeing or attending. Selectively in both networks of part f/F patients had reduced co-activity compared with controls: the default mode network and an attention network



Figure 5.3 The functional connectivity at rest within the default mode network (DMN) correlates with psychopathology in patients with schizophrenia. Psychopathology reflects positive symptoms (composite Scale for the Assessment of Positive Symptoms (SAPS) score of positive symptoms); connectivity reflects whole brain functional connectivity with seed in the medial pre-frontal cortex. Adapted with permission from data published in Whitfield-Gabrieli *et al.*⁴⁸

brain areas. Since it is performed at rest, rs-fMRI only needs minimal compliance of patients during imaging, making it appropriate for clinical purposes. Because it focuses on interactions between brain areas, rs-fMRI detects functional changes characteristic of several psychiatric disorders (Figures 5.2 and 5.3)⁶⁵.

In addition to this new brain mapping tool, several other new approaches aim at the integration of distinct structural and functional imaging parameters. Of particular note, machine learning-related methods such as support vector machines and various clustering procedures have been used. The basic idea of these approaches is to identify distinct patterns that are specific for a set of patients⁶⁶. However, further research is warranted to explore the real potential of these newer methods.

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Neurophysiology of the Ageing Brain

Paolo Maria Rossini and Laura Parisi

Clinica Neurologica University Campus Bio-Medico, Rome, Italy

INTRODUCTION

The few individuals who reach very old age are called 'longevity outliers'. This particular group represents the fastest growing age group worldwide. For instance, the number of centenarians increases steadily in the US population and their numbers are expected to grow to more than 400 000 in the next 30 years¹.

Awareness of age-related diseases such as dementia has prompted considerable interest in the study of the ageing human brain to trace a clear boundary between physiological and pathological ageing, to carry out primary prevention on populations at high risk of developing dementia, to achieve secondary prevention and to apply eventual disease-modifying therapy to at-risk subjects. Results from these types of studies could be used to plan political and public health interventions. Recent investigations have prompted advancement in biochemical, structural, functional and neurophysiological fields.

Ageing is a physiological dynamic process due to a specific property of the central nervous system (CNS) known as neuronal plasticity. The concept of 'plasticity' applied to neurobiology typically denotes the *potential for change* in addition to the mechanisms of self-repair and/or of reorganization of neural connections. Neural plasticity underlies learning as well as endogenous brain function repair², including synaptic efficacy and *synaptic redundancy*; on this basis the functional status and distribution of a network depends on the balance between neural excitation and inhibition, with some areas appearing silent or 'masked' by a mechanism of active tonic inhibition, the latter being prone to alteration or removal, causing a rapid change of the functional network, a process termed 'unmasking'³. Additional mechanisms include *long-term potentiation* (LTP) and *long-term depression* (LTD), which contribute to the functional strengthening or weakening of existing synapses by which information is stored in the CNS. LTP has been regarded as the prototypic mechanism of modified synaptic efficacy, and it can differently occur via modification of the input to a postsynaptic cell, the concomitant synchronous input to the synapse from another cell, or postsynaptic depolarization. LTD stems from Na⁺ or Ca²⁺ channels at least for short-term changes, while LTP-like mechanisms include glutamate-dependent NMDA receptor activation for long-term changes, a process that can be antagonized by GABA inhibition⁴. Another plasticity-related process is neuronal sprouting and formation of new synapses influenced by local neurotransmitter,

neurotrophic factors and synaptic protein synthesis⁵. In particular, dendrites and related spines with synaptic connections undergo continuous remodelling most likely also modulated by interaction with neighbouring astrocytes⁴.

Postmortem examinations show that brain ageing is characterized by the formation of neurofibrillary tangles and senile plaques in both cognitively intact individuals and patients with dementia, namely Alzheimer's disease¹. The ubiquitous presence of these lesions and the steady increase of the prevalence of dementia up to 85 years have strongly supported a continuum between normal and pathological brain ageing.

Ageing is a physiological process that occurs asynchronously in different areas of the brain, its rate being also dependent on the style of life. The differential age-related changes produced in several regions of the brain in the anatomy of neurons, volume tissue, density and dynamics of several neurotransmitters give support to this suggestion⁶.

From a macroscopic point of view, brain ageing becomes evident by atrophy. In 1955 Brody estimated that the neuronal loss was about 40%. In 1986 Braak and Braak specified that during the ageing, especially pyramidal cells of frontal lobes die. Some studies suggest that the *primum movens* is a functional and then a structural modification of synapses⁷. It is followed by a modification of the dendritic tree and then by the neuronal death, today known as *apoptosis*. Particularly, the hippocampus seems to be one of the most vulnerable structures in brain ageing.

Functional modifications precede the structural ones, so it is hoped that by integrating structural techniques with the functional ones it will be possible to better investigate brain ageing. Moreover, modern neurophysiological techniques (transcranial magnetic stimulation, TMS; electroencephalography, EEG; magnetoencephalography, MEG; event-related potentials, EPRs) could be helpful for this purpose, being of low cost and non-invasive⁸. Modern techniques of functional neurophysiological imaging allow investigation with high accuracy of the cortico-cortical 'connectivity' that is the base for synchronization and functional binding. These phenomena allow neuronal populations, even at a distance, to contribute to a specific task or to process a specific input working together only for a few milliseconds. Analysis of EEG and MEG signals and TMS techniques gives us worthwhile information about that.

TRANSCRANIAL MAGNETIC STIMULATION

TMS is a brief and intense magnetic field, created by a strong electric current circulating within a coil resting on the scalp; it penetrates human tissue painlessly and, if the current amplitude, duration and direction are appropriate, it induces in the brain (or in spinal roots, or in nerves) electric currents that can depolarize neurons or their axons. TMS can demonstrate causal relationships between the stimulated area and behaviour. It can be used to interfere with the neuronal activity underlying sensory processing, motor planning or execution, attention and visual processing or awareness, different forms of declarative and non-declarative memory, reasoning, mathematics, language and consciousness. This temporary disruptive effect of TMS on cortical function is often referred to as a 'virtual lesion' and is likely to occur because the stimulus transiently synchronizes the activity of a large proportion of neurons under the coil, thus inducing a long-lasting, generalized inhibitory postsynaptic potential that reduces cortical activity for the next 50 to 200 milliseconds, depending on stimulus intensity and duration. Moreover, repetitive TMS (rTMS) can produce changes – outlasting the period of stimulation – in cortical excitability⁹.

rTMS studies are increasing knowledge about correlation between anatomic structures and their functions. For example, they showed that dorsolateral prefrontal cortex (DLPFC) is implicated in working memory and in verbal episodic memory tasks.

Lesions of frontal lobes cause a reduction of learning and memory abilities but they do not cause the same memory loss as bilateral hippocampal lesions do. So, it has been demonstrated that prefrontal cortex (PFC) is involved in episodic memory tasks and that during encoding or retrieval, there are different areas of PFC that are activated with different *patterns*. It has been demonstrated that left PFC is involved in encoding processes; instead right PFC is involved in retrieval processes. This theory is known as hemispherical encoding retrieval asymmetry (HERA)^{9–11}. Nowadays, it is known that the HERA model is not so absolute but that there could be variations due to the nature of the presented stimuli, the strategies of memorization used and the grade of difficulty of the task. Recently, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have demonstrated that PFC activity tends to be less asymmetric in older than in younger adults (hemispheric asymmetry reduction in older adults, HAROLD). This change may help counteract age-related neurocognitive decline (compensation hypothesis) or it may reflect an age-related difficulty in recruiting specialized neural mechanisms (dedifferentiation hypothesis)^{12,13}. Functional neuroimaging techniques could not be used to study whether the loss of asymmetry during ageing reflects compensatory mechanisms or dedifferentiation processes; in fact, they show only the activation of a specific area during a task, but this activation could be related to the performance of the task without being the cause. Instead, this issue was addressed by using rTMS to assess causal relationships between performance and stimulated brain regions. Rossi *et al.* studied the effects of rTMS applied to the left or right DLPFC simultaneously with the presentation of memoranda on visuo-spatial recognition memory task, in a population of healthy subjects divided into two classes by age (<45 and >50 years). In the younger subjects, rTMS of the right DLPFC interfered with retrieval more than left DLPFC stimulation. The asymmetry of the effect progressively vanished with ageing, as indicated by bilateral interference effects on recognition performance. Conversely, the predominance of left DLPFC effect during encoding was not abolished in the older subjects, thereby indicating its causal role

for encoding along the life span. Findings with rTMS suggest that the bilateral engagement of the DLPFC has a compensatory role on episodic memory performance across the age span¹³.

CORTICAL EXCITABILITY

Physiological ageing is associated with more complex activations of the motor system to compensate for the reduced skill in motor performance^{14,15}. Therefore, TMS variables can provide useful clues to investigate causally subclinical changes of cortical excitability at the motor cortex level. Unfortunately, studies do not show converging findings, probably as a result of technical and experimental differences among them^{13,16–18}. Apart from assessing cortical excitability, TMS can be used to measure intracortical facilitatory and inhibitory mechanisms resulting from the balance among neurotransmitters, and dynamic synaptic adaptations to progressive neuronal loss. Motor threshold is generally reduced in Alzheimer's disease compared to healthy age-matched controls and is similarly reduced in subcortical ischaemic vascular dementia^{16,19,20}, even if several reports have not found reduction of motor thresholds^{21,22}, with one study noting increased rather than decreased motor thresholds in Alzheimer's disease²³. Global cortical hyperexcitability while the brain is 'at rest' in Alzheimer's disease is a consistent result²², which seems to occur independently of GABAergic and cholinergic cortico-cortical mechanism dysfunction as reduced motor thresholds and intracortical inhibition (ICI) and short-latency afferent inhibition (SAI) are uncorrelated. Since TMS does not provide specific pathophysiological information but is sensitive to the 'global weight' of several neurotransmitters as well as subcortical and cortical motor inputs, interpretation of cortical hyperexcitability in Alzheimer's disease is not yet possible.

The majority of these TMS results indicate that the cortex of Alzheimer's disease patients is hyperexcitable, and that such hyperexcitability may offer clues for the differential diagnosis from other dementias in which the cholinergic deficit is not predominant. An intriguing issue that can be addressed by TMS is the study of cortical reorganization of the motor output in Alzheimer's disease. Indeed, motor cortex physiological organization is early involved in Alzheimer's disease, despite the lack of clinically evident motor deficits, which only appear later²⁴. This observation is not surprising considering that the motor cortex, through muscarinic receptors and cholinergic terminals, receives a major input from the nucleus basalis of Meynert²⁵. Mapping of motor output in mild Alzheimer's disease patients asymptomatic for motor deficits has demonstrated frontal and medial shift of the cortical motor maps for hand muscles. In healthy controls the centre of gravity of motor cortical output is coincident with the site of maximal excitability (hot spot²⁶), whereas in Alzheimer's disease patients it shifts towards frontal and medial regions in the absence of changes in the hot spot²². An altered synaptic plasticity in Alzheimer's disease also has been demonstrated by applying brief trains of high-frequency rTMS to motor cortex and recording motor-evoked potentials (MEPs) from the contralateral hand muscles. This procedure can induce a progressive increase in MEP size in normal age-matched controls, but it produces opposite changes in Alzheimer's disease. This finding was interpreted as an altered short-term synaptic enhancement in excitatory circuits of the motor cortex. Additional assessment of these findings will be required by evaluating Alzheimer's disease patients after different pharmacological treatments (e.g. cholinergic versus drugs acting on NMDA glutamate receptors).

In summary, TMS assays of cortical disinhibition in Alzheimer's disease as a dysfunction of a single neurotransmitter in a single neural circuit or as the net effect of a complex involvement of more than one neurotransmitter system in several brain areas likely reflects a single facet of a pathological mosaic. A lasting preclinical condition under the attack of pro-degenerative agents could produce the Alzheimer's disease brain as alternative strategies of functioning belonging to the brain reserve even for the execution of simple motor tasks^{15,22}. The emerging evidence indicates that the 'stressed synapses' may acquire a different function both in terms of effects and of utilized neurotransmitter and may be strongly dependent on the sampling time of the tested patients²⁷.

rTMS could be useful to improve cognitive performance in healthy subjects or in patients with mild cognitive impairment (MCI). These effects include selective shortening of picture naming²⁸ and action naming without changing verbal reaction times for naming objects²⁹, improving subjects' speed at finding the solution to a reasoning puzzle³⁰, and improving performance on a choice reaction task³¹. It can be hypothesized that rTMS – by shifting the level of cortical excitability – might allow either more or less access (by interfering, for example, with the functioning of local inhibitory circuits) to brain networks relevant to the experimental task. These effects might vary depending on the timing of the TMS stimulation and on the hierarchical role of the brain area stimulated within the whole functional network underpinning the function under investigation.

These findings reflect the potential of rTMS to recruit compensatory networks that underlie the memory-encoding process and suggest that rTMS is capable of transient and positive rehabilitative influences on brain function^{9,32}.

EEG/MEG RHYTHMS

Advanced EEG analysis techniques together with analysis of MEG signals contribute to the investigation of brain ageing. Among EEG analysis techniques, the most worthy are the surface Laplacian transformation or coherence analysis of EEG, which can illustrate changes in specific oscillatory frequencies over time and can provide quantitative measurements of individual rhythm³³. Moreover, the low resolution electromagnetic topography algorithm (LORETA) technique computes three-dimensional linear solutions from multi-channel input to localize generators *in* the brain from the EEG field distribution on the scalp by employing a three-shell spherical head model of the scalp, skull and brain compartments³⁴. LORETA solutions consist of voxel z-current density values that are used to predict EEG spectral power density at scalp electrodes. A normalization method yields current density at each voxel for the power density averaged across all frequencies (0.5–45 Hz) and voxels of the brain volume.

Instead, MEG is a non-invasive technique that permits spatial identification of neuronal activation from spontaneous cerebral or external stimulus presentation. MEG signal characteristics are not influenced by extracerebral tissue layers (i.e. meninges, skull, scalp, muscles). MEG signals originate from current flow of tangential dipoles in cortical gyri and sulci^{35,36}. The signals reflect the spatial and temporal production of a dipolar source modelled as an equivalent current dipole (ECD). This method provides three-dimensional localization of dipolar field distributions over the scalp with time resolution of milliseconds. Hence, MEG signals can directly estimate the number of active neural pools and provide accurate measures of the intracellular currents in a limited shallow brain region below the recording sensor without influence from volume conduction.

Resting EEG changes across physiological ageing, with gradual changes in spectral power profile indicating a pronounced amplitude decrease of alpha (8–13 Hz) and a global 'slowing' of the background EEG, with increases in power and topographic location in the slower delta (2–4 Hz) and theta (4–8 Hz) frequency ranges^{37–39}. Ageing effects on parieto-occipital alpha rhythms reflect the activity of dominant oscillatory neural network modulated by thalamo-cortical and cortico-cortical interactions facilitating/inhibiting the transmission of sensorimotor information and the retrieval of semantic information from cortical storage^{40,41}. Low-frequency alpha is primarily related to the subject's global attentive readiness, whereas high-frequency alpha reflects the oscillation of neural systems for the elaboration of sensorimotor or semantic information³⁹. Over the course of age, alpha power decreases combined with changes in cholinergic basal forebrain system and in the excitatory activity in the cholinergic brainstem pathway⁴². Despite the relative consensus on alpha decrease, there is no general agreement on the modulation of delta and theta activity in brain ageing⁴³.

Resting EEG changes in pathological brain ageing. When compared to healthy normal elderly (Nold) subjects, Alzheimer's disease patients exhibit high power for delta and theta and low power for posterior alpha (8–12 Hz) and/or beta (13–30 Hz) frequencies^{44–47}. EEG abnormalities were associated with altered regional blood flow/metabolism and with impaired global cognitive function as evaluated by Mini-Mental State Examination (MMSE)^{48,49}.

MEG also has provided contributions to the understanding of the cortical rhythms in pathological ageing. Parieto-temporal delta and theta sources enhanced in power in Alzheimer's disease compared to Nold subjects in association with hippocampal atrophy⁵⁰. Furthermore, Alzheimer's disease subjects demonstrated a decrease of alpha sources in parieto-occipital region possibly compensated by an increase of temporal alpha sources⁵¹. Finally, cortical theta and alpha rhythms as revealed by MEG have discriminated the severity level of Alzheimer's disease and distinguished it from Lewy body dementia.

EEG power *per se* does not capture one of the main features of Alzheimer's disease, namely the impairment of functional neural connectivity. It has been reported that Alzheimer's disease patients present an abnormal linear coupling of EEG rhythms among cortical regions, as revealed by spectral EEG coherence^{52–56}, suggesting a linear temporal synchronicity of coupled EEG rhythms from simultaneously engaged neural sources. Such findings imply that functional coupling of cortical rhythms is modulated by cholinergic systems, and that a decrease of cortical EEG coherence may be a fine-grained marker of Alzheimer's disease, since it is characterized by defective basal forebrain cholinergic inputs to cortex and hippocampus⁵⁷. Most EEG studies of Alzheimer's disease have reported a prominent decrease of alpha band coherence^{52,54–56,58–60}. This result also has been found to be associated with ApoE genetic risk, which is hypothesized to be mediated by cholinergic deficit⁵². However, delta and theta band coherence changes in Alzheimer's disease are not homogeneous, as some studies demonstrate a decrease of slow-band EEG coherence, whereas others find an increase^{56,61}.

MCI subjects present an intermediate magnitude of low-frequency alpha (8–10.5 Hz) activity from parietal, occipital and limbic areas, compared to mild Alzheimer's disease and normal elderly⁶². Increase of slow EEG power coupled with a decrease in alpha activity is linked to cognitive performance decline in MCI patients compared to Nold. More importantly, the magnitude of these sources is correlated negatively with MMSE scores across subjects of the three groups, suggesting that EEG evidence of alpha power decrease in MCI compared to normal subjects is related to behavioural cognition^{60,63–65}.

The relative decrement of posterior low-frequency alpha sources in MCI may be related to an initial selective impairment of the cholinergic basal forebrain, which could induce a sustained increase of the excitatory activity in the cholinergic brainstem pathway⁴². As a consequence, the increased excitability of thalamo-cortical connections would desynchronize the resting alpha rhythms and enhance the cortical excitability as seen in Alzheimer's disease. Hence, changes of low-frequency alpha power in MCI and mild Alzheimer's disease suggest a progressive impairment of the thalamo-cortical and cortico-cortical systems that govern visual attention. This hypothesis is consistent with clinical findings of increasing deficits of visuo-spatial abilities in MCI and mild Alzheimer's disease. Similarly, limbic sources imply a progressive impairment of thalamo-cortical and cortico-cortical systems regulating attention tone for memory functions.

Quantitative EEG is able to predict with a good approximation MCI progression to Alzheimer's disease in a short run; this was demonstrated by Rossini *et al.*⁶⁶, who investigated whether combined analysis of EEG power and coherence provides early and reliable discrimination of MCI subjects who will convert to Alzheimer's disease after a relatively brief follow-up.

EEG and MEG rhythms can change over time in relation to a specific event. Event-related desynchronization (ERD) and event-related synchronization (ERS) of EEG or MEG rhythms describe neuroelectric events preceding and following a task execution³⁹. ERD/ERS is defined as reduction/increase in EEG power during event (sensory, motor, cognitive) when compared to baseline at a certain frequency band. Alpha band hyper-reactivity in Alzheimer's disease as indexed by increased alpha ERD suggests an abnormal increase of the cortical excitation or disinhibition even during simple cognitive demands. Such findings agree with previous functional neuroimaging studies on memory, which demonstrated a stronger allocation of cortical resources in Alzheimer's disease when compared to Nold subjects^{66,67}. In addition, they are consonant with other findings of abnormal central rhythms when processing sensory stimuli or performing voluntary movements and with hyper-reactivity of Alzheimer's disease primary motor cortex as revealed by TMS^{15,68}.

Artificial neural networks (ANNs) are a useful tool in early diagnosing of dementia; they elaborate in an innovative way EEG signals. Starting from a standard EEG recorded with the international 10–20 system, it is a low cost and non-invasive procedure, it is widespread and it does not require highly qualified staff at the moment of recording. It has been shown that a correct automatic classification of MCI and Alzheimer's disease subjects can be obtained extracting spatial information content of the resting EEG voltage by ANNs with an accuracy greater than 92%⁶⁹. Moreover, the classification of the individual Nold and MCI subjects, with this tool, could reach a sensitivity of 95.87% and a specificity of 91.06% (93.46% accuracy)^{70,71}. ANNs could be a worthy tool to improve screening of high-risk population one day.

CONCLUSION

Doubtless the only approach to trace a narrow line between physiological and pathological ageing is integrating genetic, biological, structural and functional variables. The latter change early, so measurement of functional variables could be helpful for early diagnosis. Neurophysiological tools that are low cost, non-invasive and widespread could be useful for large-scale screening and follow-up of populations at high risk of developing dementia. One of the most exciting challenges is to improve them.

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Potential Regeneration of the Ageing Brain

Stephen B. Dunnett

School of Biosciences, Cardiff University, UK

The brain does not spontaneously regenerate. As long ago as 1928, Cajal recorded that ‘once development was ended, the founts of growth and regeneration of axons and dendrites dried up irrevocably. In adult centres ... everything may die, nothing may be regenerated’¹. Although it remains the case that the damaged mammalian central nervous system (CNS) does not in general generate new nerve cells in response to disease or injury, the intervening 70 years have identified a considerable plasticity of axons to remodel nerve connections and a limited degree of neurogenesis that opens new opportunities for promoting regeneration and repair in the damaged, diseased or ageing nervous system (see Figure 7.1).

ADAPTIVE PLASTICITY

Even if lost cells are not replaced, spared neurons and fibres retain a considerable degree of plasticity to adapt to lost connections by adaptive biochemical compensation both at the presynaptic level – for example by changes in cell firing, transmitter synthesis, release and reuptake – and postsynaptically, by changes in receptor density, receptor sensitivity and post-synaptic signalling (Figure 7.1C)^{2,3}.

COLLATERAL SPROUTING

The first clear evidence that Cajal’s dictum was overly pessimistic in relation to the mammalian CNS came from the demonstration that if a septal cell loses some of its normal axonal inputs then other afferent axons can sprout into the vacated spaces to form new synaptic connections with the target cell⁴. If the new inputs are from a different source they are by and large not functional. However, collateral sprouting of spared fibres of the same systems do appear to be able to sustain functional recovery in a number of model circuits of the brain (Figure 7.1D)^{3,5,6}.

REGENERATIVE SPROUTING

A major problem for extensive axonal reorganization in the adult brain is that although axons can undergo a degree of local sprouting, they do not typically retain the developmental capacity for long-distance growth through the CNS to distant targets (Figure 7.1E)^{3,7}. Long-distance growth of axons can nevertheless be promoted by providing an alternative substrate for growth such as Schwann cells from the peripheral nervous system (PNS) which can be used to bridge a

gap caused by a lesion cutting a pathway, or be implanted as a track along which new axons can grow (Figure 7.1H)⁸.

NEURAL TRANSPLANTATION

When essential populations of neurones are lost they may be replaced by transplantation. The techniques are now well established for transplantation of embryonic cells derived from the CNS into the brain of adult or aged experimental animals (Figure 7.1G), and such grafts have been demonstrated to survive, repopulate areas of denervation, replace deficient innervations, and restore lost functions in a wide variety of model systems^{9,10}. There is now compelling clinical evidence that such grafts can provide a substantial alleviation of symptoms in Parkinson’s disease¹¹, and clinical trials are now underway in Huntington’s disease, spinal cord injury and stroke^{12–14}. It remains a matter of speculation whether neuronal transplantation can alleviate the more diffuse and widespread degeneration associated with ageing and the dementias.

TROPHIC SUPPORT

Neuronal connections are dependent upon trophic support from their targets, and neurodegenerative diseases of ageing may in part be attributable to a decline in growth factor support¹⁵. Thus, an alternative approach to prevention of progressive neurodegeneration, and to induction and guidance of regenerative axon growth, is to apply or replace identified trophic factors explicitly. For example, dopaminergic neurones, which decline in several neurodegenerative diseases of ageing, are dependent upon trophic factors (including brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF)) for trophic support. Chronic infusion of GDNF into the striatum or midbrain can inhibit progressive lesion and age-related atrophy of midbrain dopamine neurones and block the functional decline in motor abilities (Figure 7.1F) both in experimental animals¹⁶ and in man¹⁷. A similar strategy involving chronic central infusions of nerve growth factor (NGF) has been attempted in a pilot experiment in Alzheimer’s disease with only modest success¹⁸. A major issue to be resolved is how to deliver large trophic factor molecules – which do not cross the blood–brain barrier – to defined targets in the brain; the most powerful experimental techniques to date involve either implantation of cells that are engineered to secrete the particular trophic factor molecule (Figure 7.1G)¹⁹ or direct *in vivo* gene transfer (Figure 7.1F)^{20,21}.

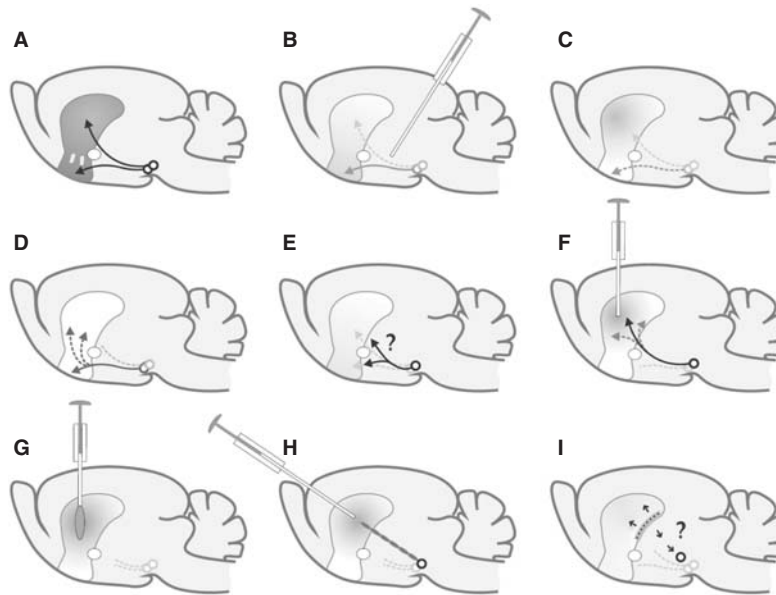


Figure 7.1 Schematic illustration of examples of regeneration and repair in the nigrostriatal system of rats **A.** Normal dopaminergic projections to the striatum arising from dopamine neurons in the ventral mesencephalon. **B.** Toxin 6-OHDA injections into the nigrostriatal pathway deplete striatal dopamine, typically more extensively in the dorsal neostriatum than in the ventral striatum. **C.** Compensatory adaptation of striatal receptors and biochemical turnover from residual spared. **D.** Compensatory collateral sprouting of ventral afferents following complete lesions of dorsal striatum. **E.** Long-distance regenerative axon growth from ventral mesencephalon typically is not a feature of nigrostriatal damage. **F.** Chronic delivery of growth factors such as GDNF by infusion or *in vivo* gene transfer can protect damaged axons and promote axon regeneration within the neostriatum. **G.** Implantation of ventral mesencephalic cells can restore dopaminergic innervation of the denervated striatum. **H.** Implantation of bridge grafts, e.g. of GDNF-secreting glial cells, can provide a substrate for long-distance axon regrowth from the ventral mesencephalon. **I.** Although adult neuron stem cells in the subventricular zone can provide functional cell replacement in dentate gyrus and olfactory bulb, evidence for a similar capacity for cell replacement in the striatum or ventral mesencephalon is weak

ADULT NEUROGENESIS

It was believed until recently that all neurones of the mature nervous system are born in early development so that once lost they are not replaced. It is now clear that there exists in the adult human brain a small population of resting 'neuronal stem cells' with the capacity both to undergo further cell division and to differentiate into both neurones and glia²². This opens the hope that such cells may be recruited for repair, either by isolation, expansion and differentiation into defined neuronal cell types *in vitro*, and reimplantation, or by finding the means to induce their spontaneous division, migration to areas of cell loss, and local differentiation into appropriate neuronal phenotype to replace lost target cells *in vivo* (Figure 7.1I). However, claims that endogenous adult stem cells can underlie recovery of function in the adult brain remain largely unsubstantiated, and substantial technical and theoretical problems remain in translating such procedures into applications for repair in human ageing.

CONCLUSION

Although the repair of neuronal damage associated with neurodegenerative disease and normal ageing remains experimental, rapid advances are being made in the techniques for inhibiting degeneration, promoting regenerative growth and replacing lost populations of cells. The pessimism that has for long surrounded the poor prognosis of brain damage in ageing and disease is being transformed to an optimism that these novel experimental approaches may find direct

clinical application in the neurodegenerative diseases of ageing. Nevertheless, formidable technical problems still need to be overcome to transform theoretical prospects into practical therapies.

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Neuroendocrinology of Ageing

Marcus Simmgen

Thomas Addison Unit, St George's Hospital NHS Trust, Blackshaw Road, Tooting, London, UK

INTRODUCTION

The subject of neuroendocrinology is the interface between the nervous and endocrine systems within the brain. Their structural and functional interaction is bi-directional; that is, neuronal activity modulates endocrine secretion and, in turn, hormones influence brain function. Both neurons and endocrine cells transmit signals to distinct target cells by releasing a chemical mediator that is recognized by specific receptors. There is overlap, as some secreted substances serve as both neurotransmitter and hormone, for example arginine vasopressin (AVP, also called antidiuretic hormone, ADH) or vasoactive intestinal peptide (VIP). Virtually all neurotransmitting systems are involved in the neuroendocrine interaction, and jointly they regulate metabolic homeostasis, growth, development and reproductive function and they influence behaviour, learning, emotional and mental state.

Within the brain, the anatomical sites of closest interaction between the two systems are the hypothalamic-pituitary unit and the pineal gland. Peripherally, endocrine secretion is controlled either by direct innervation through autonomic secretomotor fibres or, indirectly, through the regulation of blood flow.

The endocrine effects on the CNS are widespread: the limbic system structures of hippocampus, amygdala, hypothalamus and cingulate gyrus, as well as the pre-frontal cortex and various other parts of the brain, are responsive to endocrine signals that may alter their morphology or functional behaviour.

The neuroendocrine interface is also linked closely to the body's immunological responses, and the increasingly complex interactions have been described as a neuroendocrine-immune network. Significant immunological changes occur during the ageing process, in part as a consequence of these interactions; however, these aspects are beyond the scope of this chapter.

As in other regions of the brain, the number and function of certain hypothalamic neurons and neuroendocrine cells declines during senescence, while other cell populations remain intact or even hypertrophy^{1,2}. Circadian rhythms of secretion undergo a phase shift or become less pronounced and increasingly irregular³. Some endocrine axes undergo a significant physiological decline in their activity as a consequence of altered central regulation, loss of peripheral endocrine secretory capacity, tissue responsiveness or post-receptor signalling changes. While the menopause is an established life event for women, the effects of the gradual decline of male sex hormone levels (sometimes termed 'andropause'),

of adrenal androgen production ('adrenopause') and of growth hormone ('somatopause') on healthy ageing are still the subjects of ongoing debate and research. In senescence, there are changes in body composition, loss of muscle strength, reduction in endurance and frequently a decline in cognitive, emotional and psychological function. Various hormonal changes contribute to these developments, and the chapter is arranged by endocrine axis and peripheral hormone. A brief overview of its physiology and CNS-related regulation is followed by a description of the changes occurring during senescence, and the implications for the ageing person.

ADENOHYPOPHYSIS

The anterior, glandular lobe of the pituitary gland is derived from pharyngeal ectoderm rather than from neuroectoderm. It achieves a close functional relationship with its regulatory neurons through the capillary portal circulation that exists between the median eminence of the hypothalamus and the adenohypophysis. Releasing and inhibiting hormones thus reach the anterior pituitary gland to exert control over its secretion of hormones with a tropism for the peripheral endocrine glands. All anterior pituitary hormones are released in a pulsatile manner. While they provide feedback inhibition at hypothalamic neurons (short loop), the peripheral hormones exert negative feedback at pituitary and hypothalamic level to ensure stable plasma levels (long loop). The pituitary generally reduces in size during senescence⁴.

Somatopause

Growth hormone is synthesized by the somatotroph cell population of the anterior pituitary gland and released in pulsatile bursts with a peak after the onset of sleep. Two hormones are known to stimulate growth hormone synthesis and secretion: growth hormone-releasing hormone (GHRH) and ghrelin, both of which are produced in the hypothalamic arcuate nucleus. The former acts via its cognate GHRH receptor (GHRHR), and the latter via the growth hormone secretagogue receptor (GHSR). In addition, a range of other factors exert control over growth hormone release; such as metabolic substrates, physiological stimuli (sleep, exercise or stress) and certain neurotransmitters. Somatostatin, a hormone produced in the hypothalamic anterior paraventricular nucleus (PVN) inhibits growth hormone release, and the overall output effectively reflects an integration of all these stimuli.

Under the influence of growth hormone, primarily the liver produces insulin-like growth factor 1 (IGF-1), which mediates many of the effects of growth hormone on target tissues. Metabolic effects of growth hormone are: increased muscle mass and strength, reduced fat mass, increased bone density and improved cholesterol levels⁵.

Growth hormone levels peak in adolescence and decline by 14% each decade, a process that is further accelerated in postmenopausal women. The amplitude of nocturnal growth hormone pulses falls and may disappear⁶. Since physiological ageing is associated with an increase in body fat and a reduction in muscle mass, as well as with a fall in bone density, there are similarities with adult growth hormone deficiency, and the term 'somatopause' has been used for this. A trial of supplementary growth hormone in a cohort of ageing men showed significant improvement in these parameters⁷. After 12 months of administration, however, side effects of carpal tunnel syndrome, gynaecomastia and hyperglycaemia became evident⁸. A meta-analysis concluded that, while growth hormone replacement was beneficial in growth hormone deficiency, supplementation in an otherwise healthy elderly person showed no evidence for improvements in maximal oxygen consumption, bone mineral density, lipid levels and fasting glucose and insulin levels. There was no suggestion that growth hormone prolonged life. Since there is also a theoretical risk of increased neoplastic disease, there are no grounds to advocate growth hormone supplementation in healthy ageing⁵.

As an alternative, small molecules have been developed to act at the GHSR as a long-acting oral ghrelin analogue⁹. One trial was reported after one year to have achieved enhanced growth hormone pulsatility, restored IGF-1 values to juvenile levels, increased fat-free body mass and marginally lowered LDL-cholesterol. Observed side effects were a mild increase in fasted glucose, insulin resistance, cortisol levels and a weight gain of 2.7 kg vs. 0.8 kg in the placebo group¹⁰. Another compound improved lean body mass and functional strength, balance and coordination. Side effects were deterioration in parameters of insulin resistance, fatigue and insomnia¹¹. Neither drug has reached the market.

Prolactin

Prolactin is structurally related to growth hormone, and its secretory regulation is unusual in that the pituitary lactotroph cells are under tonic inhibition by dopamine-producing hypothalamic neurons. Circulating prolactin levels comprise of a combination of basal and pulsatile release¹². Prolactin levels rise in response to sleep to peak in the early hours¹³, and secretion is increased by stress and other stimuli. In men and non-pregnant women, prolactin concentrations gradually decline with advancing age. Frequent nocturnal sampling showed this to be a result of falling basal prolactin secretion that is associated with a reduced lactotroph cell mass or responsiveness, and also to be due to a reduction in hypothalamic stimuli for pulsatile bursts¹⁴. In ageing rats, the circadian rhythm of prolactin secretion loses the ability to adapt to changes in the light-dark cycle¹⁵.

In a large observational study of a cohort of middle-aged men (52 ± 12.9 years) attending for sexual dysfunction, the lowest quartile of prolactin concentrations was associated with increased risk for metabolic syndrome, atherogenic erectile dysfunction, premature ejaculation and anxiety. There also is evidence for immunomodulating properties of prolactin since, in mice, prolactin deficiency caused impaired lymphocyte function by reducing cytokine-induced macrophage activation¹⁶. However, the clinical relevance of reduced prolactin levels in senescence is unclear and no trials of replacement therapy in ageing humans have been conducted.

Menopause

The female cycle is under complex regulation by luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are produced by the gonadotroph cell population of the anterior pituitary gland. Both are released in pulsatile fashion under control by hypothalamic gonadotrophin-releasing hormone (GnRH). In addition to the daily high-frequency pulsatility, their secretion is cyclical over the period of a lunar month. Complex feed-forward and feedback regulation between the hypothalamus, the pituitary gonadotroph cells and the ovary leads to the menstrual cycle during a woman's fertile years. Oestrogen is produced mainly in the granulosa cells of the developing ovarian follicle from an androgenic precursor and is the main female sex steroid hormone.

Follicular depletion, however, is not the sole reason for the menopause. Studies in rats demonstrated that prior to any cycle irregularities there was an early decline in GnRH-neuron response and a consequently reduced LH surge in response to oestrogen around the time of ovulation. Thus the functional loss begins centrally at the level of hypothalamus and pituitary which, together with the changes at ovarian level, leads to the menopause¹⁷.

With the loss of follicular activity, which usually occurs around the mid-sixth decade of life, a rapid fall of oestrogen levels ensues and FSH and LH levels rise due to absence of feedback inhibition. Consequences of a lack of oestrogen are manifold: Atrophy of oestrogen-responsive tissues, rapid loss of bone mass, adverse changes to the lipid profile with increased atherogenic risk, depressive mood swings, lack of concentration, anxiety and loss of libido. Vasomotor symptoms of hot flashes not only impair quality of life, but also represent altered blood vessel physiology that is associated with increased cardiovascular risk¹⁸. Since the reduction in oestrogen leads to a narrowing of the 'thermoneutral' zone of temperature regulation in the hypothalamus, small changes in core body temperature can trigger symptoms¹⁹.

Oestrogen-containing hormone replacement therapy (HRT) can ameliorate vasogenic menopausal symptoms and delay biochemical changes. To avoid a concomitant excess risk of cardiovascular events, HRT should be taken early²⁰ and for a limited period only to minimize the additional hazard of thromboembolism and breast cancer²¹. Contrary to expectations, HRT in elderly women did not preserve cognitive ability but was associated with an increased risk of dementia and global cognitive decline that correlated with a reduction in hippocampal, frontal lobe and total brain volumes²². It should be noted, however, that some of the noted CNS effects might be (i) specific to the hormone molecule used in the quoted studies, (ii) related to the late timing of HRT, and (iii) due to elevated levels of LH itself, rather than related to oestrogen deficiency²³.

Andropause

Testosterone, the predominant male sex steroid hormone, is produced by testicular Leydig cells under the influence of LH and FSH. As in women, both gonadotrophins are released in pulses from the anterior pituitary gland under GnRH control. Testosterone levels in men follow a diurnal rhythm with peak concentrations occurring in the morning. At puberty, bioavailable testosterone levels begin to rise; they peak around the third decade of life and gradually fall thereafter at an annual rate of 1.3%²⁴. Circulating testosterone binds to sex-hormone-binding globulin (SHBG) and, with less avidity, to albumin. Thus the availability of free testosterone reduces as SHBG levels rise

with age by 1.2% per annum. Leydig cell attrition, reduced steroid synthetic activity and a lower responsiveness to LH are the main testicular factors contributing to this decline²⁵. The circadian variation in testosterone also declines with age. The term 'andropause' has hence come into use as a male equivalent to the menopause, even though the decline in sex hormone levels is gradual in men compared to the relatively sudden reduction in women.

Reduced testosterone availability exerts major metabolic effects on metabolism and thus lowers muscle mass and strength, raises body fat content and negatively affects bone health, libido and reproductive function, as well as mood and cognition²⁶. As in menopausal women, the elevation of LH has been implicated in the pathophysiology of Alzheimer's disease in men, as low testosterone concentrations were correlated with increased amyloid-beta protein levels²⁷. While a significant proportion of ageing males over the age of 65 years have reduced levels of testosterone, there was wide variability within a large cohort of community-dwelling men and serum concentrations were a poor indicator of symptoms^{28,29}. A recent consensus statement therefore emphasized the need for correlation of clinical symptoms with testosterone levels, the lack of cardiovascular and bone fracture outcome data and the need for surveillance for prostate carcinoma, among others, in case of replacement therapy³⁰.

Thyroid Axis

The hormones thyroxine (or tetra-iodo-thyronine, T4) and tri-iodo-thyronine (T3) are synthesized and secreted by thyroid follicular cells. Only a small proportion of T4 is converted to T3 prior to its release from the thyroid; almost all of the remainder undergoes mono-deiodination in peripheral tissues. T3 has greater biological activity than T4 and a shorter half-life. Plasma levels of both hormones are regulated by thyroid-stimulating hormone (TSH, also called thyrotrophin) that is released by the thyrotroph cells of the anterior pituitary gland, which in turn are under hypothalamic thyrotrophin-releasing hormone (TRH) control.

Virtually all tissues possess receptors for the thyroid hormones, through which the latter regulate the basal metabolic rate, tissue function, protein, fat and carbohydrate metabolism, as well as influence mental function and psychological well-being. The prevalence of thyroid autoantibodies significantly increases with age and, if primary thyroid dysfunction is present (subclinical or overt hypo- or hyper-thyroidism), cognitive function is almost invariably affected³¹. Such conditions clearly merit thyroid hormone replacement or suppressive therapy, respectively. In primary hypothyroidism, the pituitary thyrotroph cells appear to lose their responsiveness to low thyroid hormone levels, as the TSH response was significantly reduced at ages over 80 years³².

In a large, thyroid disease-free population, however, senescence *per se* led only to a minor increase in TSH levels, which remained well within the normal range³³.

Adrenocortical Axis

The hypothalamic–pituitary–adrenal (HPA) axis is central to the adaptive stress response that follows an initial, catecholamine-mediated 'fight-or-flight' reaction. Cortisol is released from the adrenal cortex following stimulation by adrenocorticotrophic hormone (ACTH, also called corticotrophin), which is produced by the corticotroph cell population of the anterior pituitary gland. Corticotrophin-

releasing hormone (CRH), from hypothalamic neurons residing in the PVN, regulates ACTH secretion in a diurnal pattern.

Cortisol is the main glucocorticoid in humans. It induces insulin resistance and raises blood glucose levels, causes protein and bone catabolism and an elevation in blood pressure. It also dampens the immune response. While a short-term stress response is necessary to deal with the challenges to the body's homeostasis, this reaction must itself be regulated. The hippocampus expresses glucocorticoid receptors and exerts inhibitory control over HPA axis activation, thus limiting the stress response³⁶. The physiological day-to-day stress adaptation has been termed 'allostasis'³⁴, with its regulatory failure leading to an 'allostatic load'³⁵. The hippocampus expresses glucocorticoid receptors and exerts inhibitory control over HPA axis activation, thus limiting the stress response³⁶.

The adrenal capacity for cortisol production is not affected by ageing, although its circadian rhythm is blunted and basal activity increased³⁷. However, with advancing age the negative-feedback sensitivity reduces at hippocampal level and the HPA axis activity increases³. In both sexes, mean cortisol levels increased by 20–50% between the ages of 20 and 80 years³⁸. Magnetic resonance imaging showed that the volumes of hippocampus and anterior cingulate gyrus were inversely correlated with baseline ACTH levels, and that older subjects demonstrated a slower decrease in ACTH in response to an infusion of cortisol than younger volunteers³⁹. The stress-induced remodelling of the hippocampus and the resulting rise in glucocorticoid levels thus increases the allostatic load, with negative results for a range of metabolic parameters and the immune system that is associated with ageing⁴⁰.

Furthermore, the hippocampus and related limbic structures of the amygdala and pre-frontal cortex are of key importance for learning and memory function, including emotional learning and processing. Persistent elevation of glucocorticoid levels is involved in the emotional memory disturbances found in depression and posttraumatic stress disorder⁴¹.

Adrenopause

Dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) are abundant androgenic steroid molecules that serve as precursor molecules for other androgens and oestrogen. DHEA is produced by the adrenal cortex and also serves as a neurosteroid⁴². ACTH regulates its secretion and, in contrast to cortisol and aldosterone, DHEA levels physiologically decline with ageing from the third decade onwards by around 2% annually^{43,44}. At the age of 80 years, DHEA concentrations are approximately 20% of those of younger controls⁴⁵.

Observational studies have associated low DHEA levels with cardiovascular disease, low bone density, type 2 diabetes, low mood and Alzheimer's disease. However, no causal relationship has been established⁴⁶.

DHEA replacement therapy is the focus of research for its potential anti-ageing properties in otherwise healthy older subjects. So far, however, no firm therapeutic indication has emerged^{43,47}.

NEUROHYPOPHYSIS

The posterior, neural lobe of the pituitary gland contains axonal projections of neurons from the supraoptic (SON) and paraventricular (PVN) hypothalamic nuclei. Axoplasmic flow transports arginine-vasopressin (AVP) and oxytocin to the neurohypophysis for storage.

The nuclei receive cholinergic and noradrenergic innervation and hormone secretion is triggered by a rise in plasma osmolality, reduction in circulating fluid volume, nausea, pain or emotional stress. While the AVP receptor V2 is mainly expressed in the kidney, V1a and V1b receptors are widely distributed within the brain⁴⁸.

Arginine-Vasopressin

AVP is central to the maintenance of fluid and osmolality homeostasis throughout life. Basal AVP levels in men were higher in older subjects and showed less responsiveness to fluctuations in osmolality compared to young volunteers. Reduced satiation to water consumption after induction of thirst by infusion of hypertonic saline was demonstrated by altered blood flow in the anterior mid-cingulate cortex on positron emission tomography⁴⁹. The renal tubules become less responsive to AVP in ageing humans and rodents. In the rat, the reduced urine-concentrating ability was found to be due to a down-regulation of the V2 receptor, while AVP levels remained normal⁵⁰.

In addition to its function in fluid homeostasis, abnormal plasma AVP levels have been implicated in a range of mental disorders. Elevated concentrations of AVP have been noted in depression, posttraumatic stress disorder, acute schizophrenia and other mental illnesses⁴⁸. In depressed patients with Alzheimer's disease, however, the content of AVP and oxytocin mRNA in SON and PVN was unchanged compared to controls, and there was no correlation with depression⁵¹. In rodent models and (confirmed in part) in humans, AVP has also been determined to modify memory and social behaviour such as aggression and affiliation⁵².

Oxytocin

Oxytocin plays no significant physiological role in senescence. Basal levels and the response to hypoglycaemia-induced stress remained comparable in older compared to young men⁵³.

PINEAL GLAND

The pineal gland is situated within the roof of the third ventricle above the Sylvian aqueduct. In fish and amphibians the equivalent structure is light sensitive, whereas in humans the pineal gland receives input from the hypothalamic suprachiasmatic nucleus (SCN) that, in turn, is connected to the retina via non-visual photosensitive pathways. The SCN functions as the master clock for circadian rhythmic activity, which is further entrained by external zeitgebers.

Melatonin

The pineal gland synthesizes and secretes melatonin predominantly during periods of darkness and thus conveys a biological diurnal rhythm as well as an annual seasonal rhythm to the body.

While daytime melatonin production remains virtually unchanged throughout life, nocturnal secretion of melatonin peaks in early childhood and thereafter continuously declines with age. After the age of 60 years, peak peripheral night-time melatonin concentrations fall to 40 pg/ml, compared to 160 pg/ml at the age of 10 years. Background daytime levels are in the order of 30 pg/ml⁵⁴.

The SCN and the hypothalamus express a high density of MT1 receptors, allowing for chronobiological feedback to the central clock. In senescence, the circadian rhythm becomes weaker, sleep

disturbances more common and there is an associated increasingly irregular diurnal melatonin secretion. The reduced number and density of MT1 receptor-expressing neurons that was found in the SCN of older subjects compared to young controls can, in part, explain this. In the last stages of Alzheimer's disease the prevalence of these neurons was further reduced⁵⁵.

Melatonin has non-sedative sleep-inducing properties, and trials of prolonged-release melatonin administration to patients with insomnia aged 55 years and older have shown to improve sleep quality, morning alertness and psychomotor performance. The supplement was administered for three weeks and no withdrawal or rebound symptoms were observed^{56,57}.

CONCLUSION

Complex neuroendocrinological changes occur during the healthy ageing process at hypothalamic, hypophyseal and target endocrine tissue level. There is increasing evidence that altered neuronal function with irregularities in biological rhythm and decreased secretory responsiveness leads to the significant reduction in availability of several peripheral hormones³. Declining levels of sex steroids, growth hormone, adrenal androgens and melatonin secretion contribute to significant adverse changes in body composition and endurance, cardiovascular risk profile, bone strength, sexual physiology, circadian rhythms, cognition and emotional and psychological well-being. Attempts at restoring youthfulness through the replacement of physiologically declining hormones have so far concentrated on time-limited, perimenopausal therapy with low-dose oestrogen. However, promising molecules to improve the growth hormone axis and the melatonin-mediated sleep-wake cycle are being tested. As senescence is a multifactorial process in which other morbidities and drug therapy frequently play a major part, any neuroendocrine changes should naturally not be viewed in isolation. Furthermore, whether a physiological change in life is perceived as being pathological and warranting treatment must be considered within the individual's social, environmental and lifestyle context. An optimistic outlook has the potential to prolong life considerably⁵⁸.

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Genetic Aspects of Ageing

Ben Pickard¹ and Douglas Blackwood²

¹*Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS), University of Strathclyde, UK*

²*Division of Psychiatry, University of Edinburgh, UK*

INTRODUCTION: LIVING LONGER VERSUS CHEATING DEATH

That there may be specific biological processes determining life span is an intriguing concept, and one which has attracted interest from both the academic and commercial sectors. Such interest has often focused on the simple numerical indicator of life span but this can often be at odds with the clinical perspective that centres on quality of life for the elderly. In this chapter we will review the latest findings and current ideas in the fields studying the biological process of ageing, its evolutionary underpinning and the genetic factors intertwined with environmental exposure that determine our life span. There is also a semantic issue of whether a discussion of ageing should include factors contributing to longevity if they merely afford protection against the dominant degenerative disorders or serious illnesses of the elderly or only concentrate on mechanisms that actively delay the ageing process¹. Plainly, these two aspects of ageing are inextricably linked but from a research point of view, and in the context of genetic models, only the latter offers fundamental insights into the process.

AGEING GENETICS, HERITABILITY AND EVOLUTIONARY INFLUENCES

Danish epidemiological studies have reported that the heritability of human longevity is approximately 25%^{2,3}: a figure similar to that for lower organisms. Thus there exists scope for the genetic dissection of the phenotype and a substrate for the processes of evolution to act on⁴. In its purest form, evolution requires that advantageous genetic variation is favoured and increases its frequency in the population through the process of natural selection. This is mediated through its ability to increase a carrier individual organism's 'fitness' and thus its ability to reproduce at a greater than average level. It can be appreciated that this raises fundamental conceptual issues in the context of the genetics of longevity. Female reproductive fitness, in particular, occupies only a proportion of the modern human life span and so it could be hypothesized that gene variants influencing life span in the age range from 55–85 years would be under minimal selection compared to those dictating survival within the 15–45-year age range. It has also been argued that, for some species, individuals living beyond reproductive age are counterproductive to species survival – they are a drain on limited resources and thus compete with actively reproducing individuals. Selection pressure for a

biologically programmed 'cap' on life span might avoid this conflict. A second argument against a clear genetic contribution to human longevity would be the vast period of human existence on Earth for which 45 years was 'old age'. In the case of humans, long life spans are a modern phenomenon – average life expectancy dropped in the transition from 'hunter-gatherer' (Mesolithic Stone Age) to agrarian (Neolithic Stone Age) lifestyles⁵ and did not significantly exceed the median life span of approximately 30–35 years until recent centuries. The implications are that not only does a long life harm fellow members of one's species, it also has no evolutionary outlet in the form of increased reproductive fitness. The genetics of ageing is left evolutionarily 'rudderless' in these circumstances.

However, two hypotheses offer an alternative view, supporting an evolutionarily 'visible' role for ageing. Firstly, the adoption of agriculture inevitably led to community living and increased social complexity. These social organization developments might be manifest in the altruistic role of the elderly in supporting the community – perhaps through leadership, childcare or other division of labour favourable for group survival. The impact of cultural effects (a form of environment) on ageing can never be entirely separated from genetics in the study of ageing in particular and will be covered in more detail below. Secondly, and perhaps more biologically tractable, is the argument that the genetic variants altering later life survival also play a role in earlier life fitness and are thus relevant to reproductive potential.

Finally, it is also worth considering the corollary of the sudden upturn in life span in recent human history – it has exposed humans to the consequences of genotypes that were never previously expressed for so long. For example, gene variants increasing susceptibility to Alzheimer's disease might be the result of random mutational drift or positive selection for their benefit in the young, but it is only now that they have been exposed to the environment of the ageing brain and consequently deemed pathological.

AGEING BIOLOGY: CLUES FROM HUMAN SYNDROMES

The fact that well-characterized human disorders of premature ageing (progeria) exist suggests that there are real biological processes at work, and ones which are tractable to genetics research. Individuals with progeroid disorders present with a spectrum of phenotypes which closely resemble natural ageing but these occur in young

adulthood or even childhood. A multitude of mutations in two particular genes, *WRN* and *LMNA*, account for the majority of these cases. Werner syndrome (WS) is perhaps the best studied of these and is caused by mutations in the *WRN* gene which encodes a helicase/exonuclease protein that functions during the critical processes of active nuclear DNA functioning such as replication, recombination and repair – when potentially pathological errors can be introduced into our DNA. Thus, the consequences to genomic integrity in WS patients are an accelerated version of those hypothesized to occur in normal individuals as a result of a lifetime of environmental exposure and mutation accumulation. The phenotypes are similar too, ranging from osteoporosis, cataracts, type II diabetes, atherosclerosis and cancers (particularly mesenchymal sarcomas) such that WS patients tend to die in their 50s as a result of complications arising from these conditions. Interestingly, the phenotypic spectrum of WS doesn't seem to include the neurodegenerative conditions such as Alzheimer's disease. It is tempting to speculate that these particular disorders are due to the accumulation of protein aggregates (plaques and tangles), i.e., protein attrition rather than genomic DNA attrition.

Mutations in the lamin A gene, *LMNA*, encoding a nuclear intermediate filament protein involved in the packaging of nuclear chromatin, cause 'atypical' WS, or in extreme cases involving a particular *LMNA* splice mutation, the severe and very early-onset Hutchinson–Gilford progeria syndrome (HGPS). A number of other rare progeroid syndromes exist and, of these, Cockayne syndrome type 1 (CS) is the only other one discussed here. This is caused by mutations in the transcription-coupled nucleotide excision repair genes, *CSA* and *CSB*, which also contribute to the cell's battle against genomic damage.

The genes emerging from these human conditions unequivocally point to the maintenance of genomic integrity as a vital process in ageing, involving the concerted action of several different systems to achieve it. Mutations in these systems seem to result in either progerias or cancer syndromes, or occasionally both (e.g. WS). It has been suggested that these alternative outcomes result from the specific responses to DNA damage initiated by the various systems: repair, apoptosis or senescence⁶.

AGEING BIOLOGY: CLUES FROM LOWER ORGANISMS

The validity of certain mouse models of ageing has sometimes been questioned for the very reasons discussed previously – distinguishing genuine progeroid features from a numerically shorter life span due to pathological state⁷. Therefore, the presence of features such as kyphosis, as an indicator of an osteoporotic state, stereotypical fat deposition and atrophy of the epidermis are often employed as benchmarks of true ageing models. The progeroid conditions in humans point towards accumulating DNA damage as a mechanism of ageing and the increased life span of mice over-expressing the antioxidantizing protein thioredoxin seems to confirm the importance of this process. However, other transgenic mouse models with modulated life spans suggest that additional contributory mechanisms are at play. Historically, it has been suggested that cellular, organ and organismal ageing are affected by the rate of cell proliferation and apoptosis. This has manifested itself in such concepts as the Hayflick limit⁸ whereby oxygen levels encountered and cell divisions undergone are recorded by each cell using the gradual shortening of the telomere sequences located at the ends of chromosomes as an internal clock. At a defined telomere threshold length the cell enters a state of protective

self-induced senescence, thus reducing the potential for DNA damage to be manifest as oncogenic cellular changes.

Indeed, a number of mouse mutations linked with altered life span involve proteins that can be classified as regulators of mitosis and cellular proliferation (e.g. p53, Brca1 and p21^{WAF1}) and these have been reviewed elsewhere⁹. Alternatively, other mouse models centre on the signalling pathways modulating and modulated by growth hormone, insulin and insulin-like growth factor such as the Ames dwarf and Laron mouse strains. Mice deficient for the *Klotho* gene product, encoding a hormone that inhibits the action of the insulin/IGF-1 pathway, show a progeria phenotype whereas *Klotho* over-expressing mice are longer lived. Finally, *SIRT1*, a member of the sirtuin class of genes, downregulates the production of insulin and IGF-1 thus promoting increased life span. These mouse models, particularly the dwarf strains, and other observations point to a correlation between longevity and body size within a species. It has been reported that shorter humans have on average a greater life span – this is even despite the observation that taller individuals are generally protected against atherosclerosis. The speculation is that body size is closely related to 'cellularity', or the number of divisions during the growth process. This in turn is a reflection of the proliferative potential of an individual's cells as discussed above. The correlation is clearly not a simple one as those with progeroid syndromes are often of short stature. Moreover, the role of the growth hormone/insulin pathway in aspects of cell proliferation, growth, DNA repair and caloric intake (discussed below) means that these processes are all interconnected at some level in their contribution to the rate of ageing.

Naturally, many mouse strains deficient in aspects of genomic repair have been generated given the seeming importance of this process in ageing. One intriguing and counterintuitive result comes from the study of *Csb*, *Xpa* and *Ercc1* mouse mutants and combinations thereof. These mice show definitive progeroid symptoms but also display a downregulation of the insulin/IGF-1 signalling pathway. Normally, such downregulation is protective and life prolonging as discussed in detail below, but in these instances it appears to be an innate compensatory mechanism responding to increased levels of genome instability.

It may be the case that ageing is such a fundamental property of life or the environmental insults so similar that organisms from across all taxa have adopted the same molecular machinery to counter it. In this way there are a growing number of studies which seek to address human ageing through the study of yeast, nematode worm and fruit fly in addition to the mouse. McCarroll *et al.* pursued this approach to the genetics of ageing by employing cross-species profiling of gene expression changes correlated with age¹⁰. What they observed was a shared set of age-responsive gene expression changes between the nematode *C. elegans* and the fruit fly *D. melanogaster*. Genes involved in oxidative metabolism (such as respiratory chain proteins, ATP synthase and citric acid cycle proteins) and active molecular transport were significantly reduced with age. However, the timing of these changes suggested that this was part of an active programme rather than solely a response to environmental attrition. For instance, in both species, experimentally reducing oxidative stress had the greatest effect on life-span extension during early adulthood. Conversely, modulating the insulin/IGF-1 system had a more pronounced effect on life span in the middle-aged organism. We can interpret these findings to mean that the body has set in place metabolic strategies to pre-empt and minimize the damage associated with ageing. As the authors suggest, a greater appreciation of human health-affecting behaviour in early adulthood might yield benefits in later life.

The same laboratory pursued the role of the *insulin/IGF-1* and *daf-2* (insulin/IGF-1 receptor) pathway that was already known to affect life span in *C. elegans*¹¹. Using mutant strains and RNAi methodologies, they showed through microarray screens that the FOXO transcription factor *daf-16* is required to mediate this signalling pathway: *daf-2* deficiency releases *daf-16* from repression and allows it to activate its downstream target genes. Interestingly, the insulin/IGF-1 signalling system has close parallels in mammals – a mammalian orthologue of *daf-16* exists, *FOXO3A*, that is regulated by the IGF-1 pathway effector and ageing gene, *p66^{SHC}*. In the *C. elegans* experiment, sets of *daf-16* upregulated and downregulated genes were identified in longer living mutant strains. In the former group, the genes encoding for stress response and antioxidant genes such as *superoxide dismutase 3* and a *metallothionein* gene were identified together with lipid hormone metabolism and antimicrobial genes. In mammals, *FOXO3A* seems to additionally upregulate components of the genome maintenance pathway. In the latter, downregulated, group of genes were examples of metabolic genes, ubiquitination genes and genes of the vitellogenin structural egg yolk protein group. In the light of the earlier discussion regarding whether longevity is the result of active life extension or avoidance of death, it is interesting to see examples of both mechanisms (antioxidant/metabolic inhibition vs. antimicrobial) represented in the gene lists.

REACTIVE OXYGEN SPECIES, CELLULAR DAMAGE AND GENETICS

The damage to DNA and other cell macromolecules is caused by the reactive oxygen species (ROS) produced as a result of the energy-generating oxidative phosphorylation occurring within the mitochondria in each of our cells¹² – a small proportion of the oxygen consumed in this process is released as reactive superoxide species. Because mitochondria themselves possess a genome (encoding some of the components of the oxidative phosphorylation machinery) located near the source of the ROS, it has been suggested that it is very likely to be subject to high levels of damage (mutation accumulation) as the organism ages. Mitochondrial mutations would potentially cause feed-forward degeneration: a reduction in oxidative phosphorylation efficiency causing an increase in ROS production and, therefore, further propensity for cellular damage. Ageing not only results in the accumulation of mutations in the mitochondrial genome but it also permits the mutated genomes to accumulate within each cell (each cell has anywhere between 10s and 100s of mitochondrial genomes). At some point, a threshold will be crossed where the accumulating mitochondrial deficits impinge on cell function – and it can be appreciated that if such cells are part of the proliferating stem cell niche then either the dissemination of the deficit could be accelerated within a tissue or the proliferation process inhibited by the reduction in oxidative phosphorylation leading to a decrease in tissue regeneration¹³. It is now well documented that multiple organ systems are compromised by mitochondrial failure¹⁴. Perhaps due to their high energy demands, the central and peripheral nervous systems appear particularly susceptible to mitochondrial dysfunction which manifests itself in the form of neuropathies and dementia. Nevertheless, pathologies of the heart, lungs, musculature, pancreas and thymus have also been linked to mitochondrial failure in humans. Two studies have shown particularly clear age-dependent accumulation of definitively pathological mitochondrial mutations in the substantia nigra – a region of the brain implicated in the aetiology of Parkinson's disease in the elderly. The causal link with

illness is not straightforward, however, as the mutation prevalence appears to be equal in aged individuals with or without Parkinson's disease^{15,16}. Mitochondria, like nuclei, have dedicated mechanisms for repairing damaged DNA and thus mouse models have been generated that lack one of the repair proteins encoded by the *Polg1* gene. These mice have greatly increased levels of mitochondrial mutations and show a decreased life span associated with typical ageing phenotypes such as osteoporosis and weight loss^{17,18}.

A GENE–ENVIRONMENT INTERACTION BETWEEN CALORIC INTAKE RESTRICTION AND LONGEVITY

A longstanding direction for ageing research is based on the observation that a reduction in caloric intake results in not only an increase in life span but also an increase in general health including a reduction in illnesses of old age¹⁹. These studies seem to hold true across a wide range of species from yeast, *C. elegans* and *D. melanogaster* through to mouse and monkey. In terms of reproductive fitness, however, dietary restriction actually reduces fecundity. This suggests that variants leading to reduction in food uptake or slowed metabolism are unlikely to be favoured by genetic selection processes as they will be outcompeted by variants promoting an 'eat fast–die young' strategy that produces greater numbers of offspring.

Dietary restriction seems to exert its effect on life span through a number of mechanisms. These can be essentially divided into two classes: those that alter intracellular pathways governing metabolism and survival and those that counteract the production of the harmful reactive oxygen species that are a byproduct of the oxidative phosphorylation pathway²⁰.

As detailed earlier, metabolic control through the insulin and insulin-like growth factor pathway is implicated in ageing and this is highlighted by its role in the response to dietary restriction. In times of freely available nutrition, insulin signalling results in the phosphorylation and subsequent degradation of Forkhead transcription factors (*daf-16* in *C. elegans* and *FOXO3A* in mammals). However, when food is limited, these transcription factors are able to enter the nucleus where they activate a set of genes which are thought to mediate a change in organismal strategy geared towards survival or even hibernation-like states. New insights from *C. elegans* are rapidly filling in the gaps at the 'top' part of the pathway translating caloric restriction into longevity. The *eat-2* gene encodes a nicotinic acetylcholine receptor subunit which is involved in the innervation of musculature required for eating. Mutants for this gene mimic the dietary restriction phenotype of increased longevity because of mechanical difficulties in eating. This reduced ageing phenotype is absent, however, in the presence of a second mutation in *wwp-1*, which breaks the link between dietary restriction, altered metabolism and life extension. The *wwp-1* and *ubc-18* genes encode interacting E3 and E2 subunits, respectively, of a ubiquitin ligase complex that targets other proteins for destruction. Current research suggests that components of the TOR pathway (a sensor of amino acid nutrition) and PHA-4 protein (FOXA, a transcription factor that overlaps functionality with *daf-16/FOXO*) may be such targets, ultimately leading to the activation of the life-prolonging metabolic state²¹. TOR signalling has received considerable interest recently because a large-scale study of dietary supplements affecting ageing in mice showed that a TOR inhibitor, rapamycin, significantly extended life span²² even when administered to aged mice. Rapamycin, already used as a cancer treatment, has immunosuppressant activity meaning that it is unlikely to be used as the first anti-ageing therapy.

However, direct suppression of the pathways targeted by TOR (translation of mRNAs into protein and the breakdown and recycling of cellular components through the process of autophagy) might provide more specific and less harmful therapeutic options.

Two principal conclusions can be made by the reader of longevity research literature. Firstly, the various pathways described above exhibit significant cross-talk at several levels. This cooperation is required to ensure detection and integration of all relevant nutritional/environmental signals and to coordinate responses across metabolic, cell cycle and genomic repair systems. Secondly, this is perhaps the clearest example of gene–environment interaction. It will be interesting to see how quickly this research moves from ‘bench to bedside’, either in the form of proactive and preventative health education policies or in the search for drug therapies mimicking the beneficial effects of dietary restriction.

Finally, we may speculate on the efficiencies of evolution such that the biological processes used by unicellular organisms to withstand primordial boom-and-bust conditions have been molecularly conserved but now reworked as homeostatic mechanisms impacting on cellular proliferation, fecundity and, ultimately, life span.

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The Clinical Pharmacology of Ageing

Brian Clarke and S. H. D. Jackson

Department of Clinical Gerontology, Kings College Hospital, London, UK

INTRODUCTION

The proportion of the world's population over the age of 60 years doubled in the last century and will increase two- to threefold in the first century of this millennium¹. This population has a higher prevalence of chronic illnesses including cardiovascular diseases, cancers, osteoporosis, diabetes, Parkinson's disease, dementia and many other conditions. An increasing body of research is adding further prescribing indications for diseases that occur in the elderly population. This, along with the increasing size of the population, means that the numbers of prescriptions for elderly patients are increasing. Depending on the age group between 60% and 80% of elderly people are taking medication and between 20% and 30% of these patients are taking at least three drugs². It is also estimated that although those over 75 years account for 14% of the population, they receive 33% of medication prescribed³.

An appreciation of the physiology of the ageing process and how it affects an individual's response to, and handling of, drugs (and drug combinations) is essential to ensure safe prescribing for this vulnerable population⁴. The ageing process can be described as the consequences of the sum of local effects at the cellular and molecular level. A feature of cellular ageing is the disruption of regulatory processes between cells and organs with consequent failure to maintain homeostasis. There is also time-related loss of functional units (the smallest structures still capable of performing the specific physiological activity characteristic to the organ involved) such as nephrons and neurons⁵. These age-related physiological changes affect all organ systems in the body, they significantly affect how the ageing body handles and responds to pharmacological agents and hence need to be considered when prescribing. Chronic illness in older age and related organ dysfunction can compound these ageing-associated changes.

In this chapter we describe the age-associated changes in physiology and consequent changes in pharmacokinetics and pharmacodynamics and their implications for prescribing in elderly patients.

PHARMACOKINETICS AND THE AGEING PROCESS

Pharmacokinetics is the description of how the body handles drugs after administration. It incorporates the liberation, absorption, distribution, metabolism and excretion of drugs and their metabolites. These processes may be affected by the physiological changes associated with ageing resulting in changes in the pharmacokinetics of drugs.

Absorption

Following administration, a number of factors affect a drug's entry into the circulation. These include properties such as particle size, molecular weight, charge, solubility and pK_a (the pH at which 50% remains in an un-ionized, lipid-soluble state). Most drugs are weak acids or bases and are present in solution as both ionized and non-ionized species. Non-ionized drugs are lipid soluble and diffuse easily across the cell membrane. Following liberation some absorption may take place in the stomach, depending on the pK_a of the drug and the pH of the stomach. Gastric acid secretion decreases with normal ageing, confounded by the widespread use of proton pump inhibitors and, to a lesser extent, H₂ receptor antagonists, as well as eradication of *Helicobacter pylori*⁵. Drugs requiring an acidic environment to become ionized will be affected most (e.g. iron compounds). However, for most drugs the large surface area of the small bowel makes it the main site of drug absorption. With ageing, although many drugs show no change in absorption, there is slightly reduced small bowel absorption of some substances (including iron, calcium and sugar). There is slower colonic transit time with age, and an associated decrease in peristalsis, largely due to a loss of neurons involved in control of the gastrointestinal tract¹. Passive intestinal permeability is probably unchanged in old age for most substances. However, active transport of other agents such as vitamin B12 is impaired. The effects of these age-related changes would influence primarily those drugs with low permeability and low solubility, e.g. cephalexin. Agents such as benzodiazepines and lithium are readily absorbed. Some agents such as neuroleptics can be esterified with long-chain fatty acids to yield depot formulations that are only slowly absorbed from the site of peripheral injection, e.g. flupentixol where the elimination half-life ($t_{1/2Z}$) can be prolonged from 6 hours to 36 hours by use of an intramuscular depot preparation.

Distribution

The volume of distribution (V), also known as apparent volume of distribution, is a pharmacological term used to quantify the distribution of a medication between plasma and the rest of the body after oral or parenteral dosing. It is defined as the volume in which the amount of drug would need to be uniformly distributed to produce a given plasma concentration. Put another way it refers to the fluid volume that would be required to contain all of the drug in the body at the same concentration as that in the blood or plasma. A drug

with a high V (e.g. morphine –300 litres) implies extensive distribution outside the blood or plasma to other tissues such as fat or muscle. The V is dependent on lipophilicity and the ability of the drug to bind to plasma proteins such as albumin (acidic drugs) and α 1-acid glycoprotein (basic drugs) thus holding drug in the blood compartment and reducing V ^{6,7}.

An initial phase of distribution reflects cardiac output and regional blood flow, to well-perfused organs (heart, liver, kidney and brain). A second phase, involving a larger fraction of the body mass, to muscle, skin, viscera and fat can take several minutes to hours to reach steady state. Drugs accumulating in a given tissue, such as fat, may serve as a reservoir that prolongs drug action in that same tissue or at a distant site⁷.

With ageing there is a decrease in lean body weight, muscle mass and body water and an increase in body fat per kg of body weight. As a result, lipid-soluble drugs such as benzodiazepines, morphine, neuroleptics and amitriptyline have an increased V due to the higher proportion of body fat. With ageing the higher V for such lipid-soluble drugs, (along with reduced clearance) will result in prolonged elimination half-life and hence drug effects. For water-soluble drugs, V will fall hence higher concentrations will be reached after initial administration. Loading doses of water-soluble drugs should, therefore, be reduced in elderly patients unless the drug also binds to muscle such as digoxin when the muscle mass would be a relevant consideration.

Protein Binding

Many drugs are protein bound to a varying degree. Bound drugs are inactive. An unbound drug is free to mediate its effect. The binding is usually reversible. Most acidic drugs (diazepam, phenytoin, warfarin) bind to albumin. Basic drugs such as lidocaine and tricyclic antidepressants bind to α 1-acid glycoprotein. With healthy ageing there is no substantial change in plasma proteins, however, intercurrent illness can result in a drop in albumin and an increase in α 1-acid glycoprotein (an acute phase protein)⁵. Chronic disease tends to accelerate the age-related decline in serum albumin. This can produce clinically significant increases in the free fraction of very heavily protein-bound drugs such as ibuprofen (99.5% bound)⁵. Other highly protein-bound drugs include benzodiazepines (>90%) and many antipsychotics (>90%). Lithium, however, is not protein bound and is excreted unchanged rather than being metabolized.

Clearance – Hepatic

Hepatic metabolism of drugs is dependent on the ability of the liver to extract drugs from the blood passing through the organ. Lipophilic drugs are metabolized into more hydrophilic compounds to facilitate elimination, particularly through the urine. However, in some cases metabolites are biologically active or even toxic. Thus risperidone is metabolized to an active metabolite (9-OH risperidone) which has a $t_{1/2}$ of 22 hours versus the parent drug $t_{1/2}$ of 4 hours. Similarly, diazepam is metabolized to an active metabolite (desmethyldiazepam) and amitriptyline is metabolized to nortriptyline. Both active metabolites have a longer $t_{1/2}$ than the respective parent drugs. In the liver, phase I metabolism introduces a functional group onto the parent compound, generally resulting in loss of pharmacological activity. Phase I reactions are located primarily on the endoplasmic reticulum and are performed largely through the cytochrome P450 system of enzymes. This family of enzymes

oxidize, hydroxylate or hydrolyse the drug substrate^{6,7}. Several studies have shown an age-related decline in the clearance of drugs by phase I metabolism, probably reflecting a reduced hepatic mass (and, for high clearance drugs, blood flow), as enzyme activity is preserved⁵. Induction or increased synthesis of the cytochrome P450 enzymes induced by drugs, such as phenytoin, isoniazid, glucocorticoids and alcohol, may decrease the bioavailability of parent drug compounds.

Inhibition of drug biotransformation enzymes, commonly by depletion of necessary co-factors, results in elevated levels of parent drugs. This can lead to increased pharmacological effects and an increased incidence of drug-induced toxicity. Inhibition of different isoforms of cytochrome P450 enzymes can be seen with erythromycin and ketoconazole (CYP450 3A4); SSRIs (CYP450 2D6). For two of these enzymes, CYP4502D6 and CYP4502C19, genetic polymorphisms exist that lead to poorly functioning enzymes causing individuals to be poor metabolizers. Thus when prescribing drugs metabolized by these enzymes where the therapeutic window is narrow, prescribing should be on the basis the patient is a poor metabolizer. For example when prescribing haloperidol starting doses should be those appropriate to poor CYP2D6 metabolizers.

Many pharmacokinetic drug interactions occur at the level of hepatic metabolism. For example the inhibition of clozapine and chlorpromazine metabolism by cimetidine.

Phase II reactions are conjugations. They are performed in the cytosolic compartment. Glucuronidation is the most important of the conjugation reactions. The increased water solubility of the glucuronide conjugates promotes their elimination in the urine or bile. Examples of drugs metabolized this way are benzodiazepines and morphine. The two main metabolites of morphine are morphine-3-glucuronide and the active metabolite morphine-6-glucuronide. Although they are formed in the liver they are excreted renally and hence accumulate in chronic kidney disease. Much less effort has been directed at the investigation of the effects of ageing on the conjugative mechanisms. In general, however, studies have not reported a major effect of ageing on the pathways of conjugation.

Clearance – Renal

Excretion of drugs and metabolites in the urine involves three processes: glomerular filtration; active tubular secretion; and passive tubular reabsorption. With ageing, renal mass decreases, as does glomerular filtration rate (GFR). There is also a reduced ability to concentrate urine and a reduced thirst during water deprivation.

GFR decreases at an average rate of 1 ml/min/year after middle age, and is often considered the most important pharmacokinetic change in older age. A normal GFR in a young adult is 120 ml/min depending on body size. Reduction in GFR with age affects the clearance of many drugs such as water-soluble antibiotics, diuretics and lithium and some non-steroidal anti-inflammatory drugs. Declining renal function cannot be quantified by measuring serum creatinine alone as creatinine production is a reflection of muscle mass, which declines with age. Clinically significant reduced renal function may be present with a serum creatinine still within the normal range. GFR can be calculated using several equations. The Cockcroft–Gault (CG) equation uses age, weight, gender and serum creatinine⁸:

$$\begin{aligned} \text{GFR (ml/min)} \\ = 1.23 \times \frac{(140 - \text{age})(\text{years}) \times \text{weight (kg)} \times (0.85 \text{ if female})}{\text{Creatinine } (\mu\text{mol/L})} \end{aligned}$$

The Renal National Service Framework recommends that all laboratories report a formula-based estimation of GFR when serum creatinine is requested in adults⁸. The Modification of Diet in Renal Disease (MDRD) study equation (based on serum creatinine, age, gender and ethnic group) is widely used. The MDRD formula has the advantage of not requiring a weight, and can therefore be issued by the laboratory at the same time as a creatinine result is reported, however, it takes no account of muscle mass other than via age. Cockcroft and Gault estimates tend to be lower than MDRD estimates. The adjustment of drug dosing in becomes particularly relevant where drugs are substantially or entirely excreted by the kidney. Routine pre-prescribing estimation of GFR is an essential adjunct to good prescribing in this vulnerable group. Given that the MDRD estimated GFR is now routinely provided this is the method of choice.

Where there is a narrow therapeutic index, significant toxicity can occur if doses are not adjusted downwards to account for renal impairment and subsequent reduced excretion. Examples include lithium, aminoglycosides and digoxin. Lithium toxicity is manifest as neuromuscular excitability, coarse tremors, fascicular twitching, motor agitation, delirium, nausea and even seizures if severely toxic. It is the most dialysable toxin known due to its low molecular weight. Indications to dialyse include high lithium concentrations ($>4 \text{ mEq/L}$), or a concentration $>2.5 \text{ mEq/L}$ in a markedly symptomatic patient.

The presence of causes of chronic kidney disease such as hypertension and diabetes will potentiate the age-associated decline in renal function. It is especially important to review regularly drug therapy in frail older patients who may have, along with other known cardiovascular morbidities, undetected significant renal dysfunction.

Elimination Half-Life

The elimination half-life ($t_{1/2}$) is the time it takes for the plasma concentration to be reduced by 50% during the elimination phase. This is distinct from the absorption half-life ($t_{1/2\text{abs}}$) or distribution half-life ($t_{1/2\text{d}}$). It is a function of both volume of distribution and clearance, where clearance is the nominal volume of blood that is cleared of drug per unit time:

$$t_{1/2} = V / Cl$$

where $t_{1/2}$ = elimination half-life; V = volume of distribution; Cl = clearance

The $t_{1/2}$ provides a good indication of the time required to achieve steady state after a drug is started, and also an estimate of the time required to remove a drug from the body, and of appropriate dosing intervals. It takes approximately five half-lives to reach steady state during chronic dosing and a similar time to remove the drug when dosing is stopped. Thus for amiodarone with a $t_{1/2}$ in excess of two months in elderly patients, it would take at least 10 months to reach steady state or to remove the drug from the body. For lipid-soluble drugs, the elimination half-life increases with age, due to both reduced clearance and increased V ^{6,7}. For water-soluble drugs such as lithium the reduced volume of distribution partially offsets the effect of reduced clearance on $t_{1/2}$.

Renal tubular interactions are a common cause of pharmacokinetic drug interactions. For example renal tubular reabsorption of lithium is increased by thiazide and loop diuretics. This leads to reduced clearance of lithium and hence rising concentrations. Thus therapeutic drug monitoring can help manage such interactions unlike pharmacodynamic interactions (see below).

Bioavailability and First-Pass Metabolism

Bioavailability is a term used to describe the fractional extent to which an unchanged drug reaches the systemic circulation from its original site of administration. This takes into account the absorption, hepatic metabolism and biliary excretion of a drug that may occur before an oral drug reaches the systemic circulation.

Drugs that undergo substantial first-pass metabolism in the liver are avidly extracted from the blood during passage through the presystemic circulation (gut wall and liver), reducing their bioavailability. Ageing is associated with a reduction in first-pass metabolism, probably due to a 20–30% reduction in liver volume with age and a concomitant reduction in liver blood flow. As a result the bioavailability of drugs that undergo extensive first-pass metabolism, such as chlormethiazole, propranolol and labetalol can be significantly increased⁵.

Pharmacodynamics

Pharmacodynamics can be defined as the study of the biochemical and physiological effects of drugs and their mechanisms of action. This includes therapeutic effects and unwanted effects. The effect of ageing may result in increased or decreased effect of a given drug concentration, when compared to the effect of the same concentration in a younger patient. These changes in sensitivity occur independently of any changes in pharmacokinetics that may also exist. Drugs exert their effect by binding selectively to target molecules within the body, these are usually proteins, but are also other macromolecules. The main drug targets are receptors, enzymes, ion channels, transporters (carriers) and DNA. An agonist drug uses a receptor site to activate or enhance a cellular response to that specific receptor. Benzodiazepines, for example, act as agonists at GABA_A receptors. A drug that binds to a receptor target but is unable to elicit a maximal tissue response, in effect demonstrating less intrinsic activity or efficacy, is termed a partial agonist. Buspirone is an example of a partial agonist at 5-HT_{1A} receptors, providing anxiolytic effects without inducing extra-pyramidal side effects. The antipsychotic aripiprazole acts as a partial agonist at dopamine D₂ receptors.

An antagonist binds to a target site and inhibits the action of an endogenous agonist at that site. Mirtazapine is an antagonist at presynaptic α_1 -adrenergic, 5-HT₂ and 5-HT₃ receptors. Most antagonists are competitive, in that they bind reversibly to a site and the effect of the antagonist may be overcome by raising the concentration of the agonist, as an example, many antipsychotics competitively antagonize dopamine receptors.

Other mechanisms of antagonism include irreversible competitive antagonism, whereby raising the concentration of endogenous agonists does not overcome the antagonist's effect: selegiline, for example, irreversibly inhibits monoamine oxidase-B. Non-competitive antagonist drugs do not block receptors, but block the signal transduction process initiated by receptor activation. Pharmacokinetic antagonism reduces free concentration of a drug by reducing its absorption or by accelerating its elimination. A chemical antagonist combines with the drug to neutralize its effect, e.g. protamine sulphate neutralizes the action of heparin^{6,7}.

Receptor activity and expression changes with ageing and the effect of age on drug sensitivities will vary depending on the drug studied. This makes generalizations difficult. However, there is evidence of reduced β -adrenoreceptor function in advancing age, reducing the elderly patients response to propranolol (β -adrenoreceptor antagonist).

and salbutamol (β_2 -adrenoceptor agonist). The responsiveness of α -adrenoceptors on the other hand is preserved with advancing age.

The ageing cardiovascular system also has reduced aortic and large artery elasticity and compliance, leading to higher systolic blood pressure, increased impedance to left ventricular ejection, with resultant tendency towards left ventricular hypertrophy. There is also a reduction in intrinsic heart rate and a reduction in baroreceptor sensitivity.

Orthostatic intolerance increases, as the response to posture change is blunted, leading to increased postural sway and propensity to falls^{5,9}. This can of course be exacerbated by the concomitant use of anti-hypertensives and vasodilating drugs, and by drugs that may cause this as a side effect such as the α -blocker, tamsulosin.

In the brain, cholinergic function decreases with age, thermoregulation is also impaired, especially in frail individuals. There is also reduced shivering and vasoconstriction responses to hypothermia. Frail elderly patients are particularly prone to the adverse effects of neuroleptics, including delirium (anticholinergic effect), extrapyramidal symptoms (D_2 blockade), arrhythmias (prolongation of QT) and postural hypotension (α_1 blockade).

Of significant concern to elderly patients is the increased risk of death and cerebral ischaemia or stroke among those receiving treatment for psychosis or behavioural manifestations of dementia¹⁰. On the basis of 17 placebo-controlled trials of new neuroleptics, involving 5106 patients with dementia-related psychosis, the US FDA reported a 1.6- to 1.7-fold increase in the risk of death associated with all atypical antipsychotics¹¹. The relative risk of stroke or transient ischaemic attack with risperidone is reported as high as 3.3 in this group versus controls¹³. It is, however, the only neuroleptic to have a marketing authorization for short-term use in the management of persistent aggression in patients with moderate to severe Alzheimer's disease.

There is increased sensitivity to the central nervous system effects of benzodiazepines, sedation being induced at much lower concentrations with advancing age. In addition these drugs are associated with an increase in postural sway and consequently falls. Table 10.1 lists some of the more common drug-specific pharmacodynamic changes that are seen with ageing along with some examples where ageing has no effect⁵.

Pharmacodynamic drug interactions are those where drug A changes the effect of drug B without affecting its pharmacokinetics. Examples include the potentiation of the effects of lithium by

calcium channel blockers, the lowering of seizure threshold by tricyclics and lithium reducing the effect of anticonvulsants.

ADVERSE DRUG REACTIONS

Approximately 5–10% of hospital admissions are related to managing drug-toxicity effects. Adverse drug reactions (ADRs) are common in elderly patients – it has been estimated that ADRs are the fourth to sixth leading cause of death. When adverse reactions occur in elderly patients, they are more likely to be severe and are less likely to be reported or recognized¹. ADRs can be described as dose related, in that they are predictable based on the drug's pharmacological properties. Alternatively they may be idiosyncratic and not predictable on the basis of the pharmacological properties of the drug. These are often of an unknown mechanism and more likely to be more serious than dose-related ADRs (e.g. anaphylaxis)^{1,13}. Recent data suggest that half of all disability or premature deaths from medication-related problems are preventable through prescribing vigilance and monitoring³.

The presence of multiple drug treatments has been identified as an important factor associated with ADRs – the more medication the greater the chance of an ADR. However, ageing can be associated with an increased risk of adverse effects due to changes in pharmacodynamics independent of pharmacokinetics and multiple drug prescriptions. Non-steroidal anti-inflammatory drug (NSAID)-induced adverse events such as gastrointestinal haemorrhage and perforation increase with age, as does NSAID antagonism of antihypertensive therapy.

POLYPHARMACY VERSUS APPROPRIATE PRESCRIBING

The art of prescribing for the elderly patient is a balance between the conflicting demands of research evidence, practical considerations and patients' wishes. Polypharmacy can be defined as the concurrent use of multiple drugs (variously defined as the use of five or more drugs). It is no longer a useful term as it fails to encompass the omission of treatments for which there are clinical indications. Appropriate prescribing has been used to describe various aspects of medicines such as formulation and packaging, but should also be used to cover overuse, underuse and misuse of treatments. This term therefore describes not only the omission of medicines not indicated but also the use those that are indicated¹⁴. The National Service

Table 10.1 Selected pharmacodynamic changes with ageing

<i>Drug</i>	<i>Pharmacodynamic effect</i>	<i>Age-related change in sensitivity</i>
Adenosine	Heart-rate response	↔
Diazepam	Sedation, postural sway	↑
Diltiazem	Acute and chronic anti-hypertensive effect	↑
Diphenhydramine	Postural sway	↔
Enalapril	ACE inhibition	↔
Furosemide	Peak diuretic response	↓
Heparin	Anticoagulant effect	↔
Morphine	Analgesic effect, respiratory depression	↑
Temazepam	Postural sway	↑
Warfarin	Anticoagulant effect	↑

↔ = no significant change; ↑ = increase; ↓ = decrease

Table 10.2 Causes of suboptimal drug prescribing

Clinical skills
• Inadequate clinical assessment leading to incorrect diagnosis
• Failure to obtain history of or document previous adverse drug reactions
• Failure to record current medication including over-the-counter medication
• Failure to monitor response to treatment
• Failure to recognize potentially serious drug interactions
• Failure to recognize subtle adverse drug reactions
• Failure to review repeat medication
• Failure to take account of altered pharmacokinetics and pharmacodynamics
• Simple error

Source: Modified from the Royal College of Physicians¹⁶

Table 10.3 Prescription checklist

• What are the patient's views?
• What is the diagnosis (or diagnoses) you are treating?
• What is the main aim of treatment?
• What are the treatment possibilities in this patient? (non-pharmacological potential?)
• How are your preferred drug and its metabolites (if active) cleared?
• Will other disease states affect your choice?
• Will physiological states (e.g. ageing) affect your choice?
• Could one drug treat more than one problem?
• What is the best route and dosage?
• When will you dose titrate?
• What will its duration be?
• What are the potential adverse effects?
• What potential drug interactions are relevant?
• Would discontinuing another drug help?
• What information should you discuss with the patient?

Framework for Older People highlights the need for appropriate prescribing¹⁵. Optimizing prescribing includes developing an awareness of the causes of suboptimal prescribing (Table 10.2) and the use of a prescription checklist to aid decisions (Table 10.3). Certain drugs should be actively avoided in elderly patients including: long-acting oral hypoglycemics as they present a high risk of hypoglycemia; long-acting benzodiazepines due to an increased risk of falls and disorientation; and non-selective anticholinergics as they can impair cognition and have significant peripheral anticholinergic side effects.

CONCLUSIONS

The ageing process is characterized by functional changes in all organ systems and results in reduced homeostatic capacity. These changes affect the pharmacokinetics and pharmacodynamics of many drugs commonly used in this age group. The high prevalence of

co-morbidities and consequent high number of concomitant prescribed drugs are major factors in the development of ADRs. The reduced functional reserve associated with ageing is also responsible for an increased vulnerability to the effects of prescribed drugs and ADRs. A knowledge and appreciation of these processes, and their consequences, is necessary to ensure appropriate and safe prescribing in this age group.

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Cognitive Gerontology

Patrick Rabbitt

Neurocognitive Development Unit, School of Psychology, University of Western Australia, Australia

'Cognitive gerontology' is the study of changes in mental abilities and behaviour in old age and so also of changes in the brain and central nervous system that cause them. It developed alongside the rapid growth in academic psychology during the 1950s, promoted by the respect, and the access to funding that investigators, who then termed themselves 'human experimental psychologists', had gained by work on military applications during World War II. Leading figures of that decade were James Birren in the USA and Alan Welford in the UK. Welford was trained in applied experimental psychology and in ergonomics by Sir Frederick Bartlett. His book, *Ageing and Human Skill* (1958), summarizes his research with gifted colleagues in the Cambridge UK Nuffield Unit¹. This was funded to discover how the contributions of older workers to the post-war economy might be optimized by appropriate training, systems and equipment. Present sensitivity to the imminent demands of ageing populations makes these key aims of current cognitive gerontology. Birren, was convinced by his work with the distinguished psychophysicist, 'Smitty' Stevens that the study of perceptual systems and response times must be the most direct way to use behavioural evidence to deduce changes in the central nervous system. He greatly broadened this view when he became director of the Section on Aging in the National Institutes of Health in Bethesda, MD, where his congenial personality facilitated collaborations that confronted him with medical, biological, epidemiological, demographical and social concomitants of old age. His friend Nathan Shock had begun at Baltimore the first, longest and most thorough longitudinal study of physiological, medical social and psychological changes in a large sample of older people². From Shock's experience Birren learned to appreciate the separate and interacting effects of these factors in contributing to the enormous variability between individual trajectories of ageing – points missed by colleagues with backgrounds solely in 'mainstream' psychology who, because neurophysiological data was then unobtainable, typically borrowed from 'mainstream cognitive psychology' experimental paradigms originally designed to test functional models of mental abilities in young adults. The study of age changes in mental abilities potentially offered a timely challenge to the models then current in mainstream cognitive psychology which, at that time, represented unrealistic 'steady-state' systems that described neither individual differences nor processes of change within them. This challenge was not met until the late 1990s, when unanticipated results from brain imaging and electrophysiology began to bring into question models that had been derived solely from behavioural evidence. These new opportunities now allow us more sensibly to address some of the

basic questions for cognitive gerontology: Why do cognitive changes occur? Are they inexorable or can we delay them? What, precisely, are the changes that occur in the brain and central nervous system and how do these affect mental abilities and behaviour? When do changes first begin and how fast do they proceed? Do all individuals age at the same rate or do some age earlier and faster than others? Do all cognitive abilities change at the same or at different rates? Do individuals experience similar or different patterns of changes in their abilities? How does ageing affect our everyday cognitive competence and what can we do to mitigate its effects?

Physiologists had long recognized that because changes in the brain, body and central nervous system occur at markedly different rates in different species and individuals it is not useful to index ageing only by calendar time. They tried to derive algorithms to quantify progress of 'biological ageing' from a variety of different markers of the progress of physiological change³. These algorithms are interesting in actuarial and epidemiological contexts, but have proved less fruitful than study of associations between changes in specific biological subsystems, such as are involved in vision, hearing, touch and motor control and concomitant changes in mental abilities. Sensory changes evidently affect cognitive abilities because losses of visual acuity contrast sensitivity and colour vision⁴, hearing, especially in higher frequencies, tactile sensitivity, smell and taste all degrade the information that we need to perceive and interpret objects and events⁵ and losses of fine motor control impair our ability to respond rapidly and appropriately to our environments⁶. However in addition to these direct effects of information degradation, sensory changes also have other 'knock-on' entrained effects because the additional effort necessary to resolve degraded sense data draws on the limited pool of information-processing resources necessary to interpret and remember what we have seen or heard^{7,8}. Because the time courses of sensory changes correlate robustly with those of declines in mental abilities such as intelligence, decision speed and memory, amounts of sensory losses are very effective biological markers for the extents of cognitive changes^{9,10}. A logical problem in interpreting such associations between changes is key to many issues in ageing studies: because all physiological, neurophysiological and cognitive changes occur over the same periods of time between their progress are inevitable but may be as functionally uninformative as between independent clocks running at different rates. Imaging of brains *in vivo* now resolves this issue, showing that most of the shared variance between sensory and

cognitive changes is accounted for by concomitant gross changes in brain volume and blood flow¹¹ and prevalence of white matter lesions¹².

A further question is what are the basic functional causes of these interdependent changes in general physiology and neurophysiology? Whether, for example, they are the burden of damage from pathologies and accidents that accumulates throughout the lifespan or whether some other processes, distinct from the effects of the sum of all pathologies and acquired physiological damage, that acts on all biological systems, though possibly at different rates, that is possibly genetically programmed, and so can be loosely described as 'biological ageing'. Like most apparent dichotomies in the 'nature/nurture' debate, this is misleading because both endogenous and exogenous factors operate jointly and strongly interact. There is good evidence for a 'medical model' of ageing based on the premise that, even after differences in their calendar ages have been taken into account, the pathologies and 'negative biological life events' that individuals have experienced account for a large proportion of the variance in mental abilities between them. Exceptionally healthy older men retain greater ability than those with poorer health¹³. Mental changes accelerate as death approaches¹⁴ and some terminal pathologies, such as diabetes and infections, are associated with faster 'terminal decline' in cognitive abilities than others¹⁵. Thus, even apart from the incidence of particular neuropathologies such as dementias and cerebrovascular accidents that directly affect brain integrity, a substantial proportion of age-related decline in mental abilities is driven by a variety of pathologies that affect cerebrovascular sufficiency and brain metabolism. It would be useful to have quantitative estimates of exactly how much of that proportion of variance in mental abilities between older individuals, that is associated with differences in their calendar ages, can be accounted for by experience of particular pathologies. Though exact quantitative data are not yet available it seems no longer useful to argue whether cognitive changes are brought about 'mainly' by inexorable processes of endogenous 'normal ageing' or 'mainly' by pathologies and accidents. New technologies such as brain imaging, transient magnetic stimulation and cortical evoked potentials will soon tell us to what extent the amounts and patterns of central nervous system changes differ between individuals, what pathologies, genetic factors or life events may produce faster changes or different patterns and precisely how brain changes affect different mental abilities.

'Cognitive gerontology' is now a science in transition between a legacy of models to interpret a rich archive of behavioural observations and to gain an increasingly better understanding of the relationships of changes in abilities to the ageing brain and central nervous system that reveals these models to be inadequate – as indeed their proposers knew that they would as better neurophysiological evidence accumulated.

Discussion of the behavioural legacy may begin with Jim Birren's conviction that measurements of response times are an exceptionally good tool to investigate age-related cognitive change^{16,17}. This idea had been reinforced by Joseph Brinley's discovery that exact estimates of average decision times for groups of older adults can be closely estimated by multiplying those of young adults by a simple constant¹⁸. John Cerella verified this for reported data from 108 different tasks on which older and younger groups had been compared¹⁹. Tim Salthouse greatly extended the implications of these findings by a further discovery that age-related variance in response times can also account for most of the age-related variance in errors on tests of verbal memory in which decision times are not constrained^{20,21}.

He argued from this that 'general slowing' of the cognitive system not only reflects, but also is the main functional driver of losses in all or most other mental abilities, so that behaviourally measured changes in performance on all, or most, cognitive tasks can be related to changes in a single, very simply measured, index of task performance. This idea became central to discussions for the next 20 years. This was a very powerful theory, but also became uncomfortable because it seemed to leave nothing further to investigate.

Investigators attempted various escapes. Some argued that 'general slowing theory' confused levels of description because behaviourally measured performance indices, such as response times, are distinct logical entities from psychometric statistical constructs such as 'general fluid intelligence' or 'information processing speed' that are computed on the basis of shared variance between performances on different tasks, and that both these entities are distinct from 'neurophysiological system characteristics': the many and various properties of neurones and their mutual interactions that determine their efficiency. Others re-evaluated the implications of the simple linear scaling suggested by 'Brinley plots'²².

Other investigators beyond discussions of simple relationships between task complexity and averages of decision times to propose sophisticated models to account differences between distributions of response times produced by older and younger adults^{23,24}. A third escape from the constraints on discussion imposed by 'general slowing theory' derived from observations that neuronal changes occur earlier and are greater in the frontal and prefrontal and temporal cortex than in other parts of the brain²⁵. This makes it plausible that tasks derived from diagnostic tests for frontal damage, such as inhibition of irrelevant information in perception, planning, 'working' memory or task alternatives, may be especially sensitive to increasing age. Considered across all published studies in which no neurophysiological information is available, have been unclear. This is probably because while it is increasingly apparent that the range and variety of patterns of brain ageing differ widely between individuals behavioural comparisons have been made on small samples often of 20 persons or fewer who have not been selected on imaging data. Nevertheless more sophisticated mathematical analyses do suggest that some differences in distributions of reaction times and errors consistent with the frontal ageing hypothesis can be found, even on relatively small and unselected samples.

The frequency of elderly individuals' complaints of memory inefficiency is second only to that of their complaints about arthritis²⁶. Nevertheless subjective reports of memory problems seem to be associated more with current levels of depression than with objective performance. Models for age-related declines in memory efficiency have been influenced by evidence of 'general slowing'. Craik and Lockhart showed that because the longer people are allowed to inspect and process words the better they can subsequently recall and recognize them, consequently age impairments can, at least partly, be attributed to reduced 'depth of processing' caused by slowing of information processing²⁷. There is also support for the idea that impairment may be specific to some aspects of memory tasks rather than general to all. Craik and Byrd report that age impairs the ability to select critical information to be remembered²⁸. However, discussions of age-related memory losses have been less constrained by the 'general slowing' hypothesis because most investigators have been more concerned with the nature of our memory representations of events and information than with the speed with which these can be established and retrieved. Consequently, a large literature discusses whether old age makes it more difficult to encode and recall some kinds of information rather than others. Differences are reported between verbal and

spatial information, for faces, for proper names, for hymn tunes, and for the sources and context of correctly recalled material. There are also 'natural history' experiments comparing age-differences reports of vividness, detail and accuracy of so-called 'flashbulb memories' of striking public or private events (e.g. see²⁹). Another critical distinction is between memory for information that has been acquired, used and so rehearsed over many years and memory for more recently learned material (e.g. see³⁰). Conceptually related to this distinction between memory for recall of recent and distant information, for more and less frequently rehearsed material and for more and less emotionally charged and striking information are investigations of the numbers of memories that elderly people can retrieve of events from different periods of their lives³¹. Most studies find a scarcity of quantity, but not necessarily of the vividness of memories from childhood. This contrasts with a 'reminiscence bump' of memories relating to adolescence and young adulthood, with a marked decline in memories for the very recent past³¹. One explanation is that the greater efficiency of the central nervous system in youth makes memories of earlier experiences more detailed and durable. Another is that events experienced in youth are, at least when they are experienced, novel, possibly also more exciting and are likely to have been more frequently recalled in subsequent years than the probably more often repeated, and possibly more banal, experiences of late middle age and senescence. Consistent with this idea are findings that, irrespective of the ages of individuals when they experienced them, particularly eventful historical periods such as World War II are especially numerous and vivid, and of course also more often provide material for reminiscence.

This distinction between the ability to recall and to use information and skills acquired over a long lifetime and continually updated by practice and the ability to remember new information and events and to learn new lessons from them is a key issue that differentiates between the study of abilities in old age and in youth. It is best defined in the work of John Horn who distinguished between what he termed 'fluid abilities' that are early impaired by age and 'crystallized' abilities that show relatively little decline³². Fluid abilities are indexed by scores on tests of general intelligence and of the ability to acquire and recall new information and 'crystallized' abilities are indexed by tests of acquired, and subsequently continuously practised, material such as vocabulary and social skills.

Memory studies have also been influenced by the hypothesis that because ageing affects the frontal and temporal lobes of the brain earlier and more severely than other areas, so the selection of relevant from irrelevant information held in memory must be more sensitive to age than other abilities (e.g. see³³). Also associated with the frontal and temporal lobes are the abilities, collectively termed 'prospective memory', to use past information to anticipate what is likely to happen next, to plan how to cope with anticipated events and to retain these plans until they can be appropriately implemented³⁴. A key insight has been that, in old age, the efficiency of prospective memory, as indeed other kinds of memory, depends on the availability of environmental information to support recall.

Studies of cognitive ageing use two methodologies: cross-sectional comparisons between groups of different ages and longitudinal studies in which the same groups are repeatedly assessed. These can very profitably be combined by analyses including both kinds of comparisons³⁵ (see Baltes, 1968). A pervasive difficulty for both is inadvertent selection of participants. Elderly individuals who volunteer for demanding studies are atypically able and well members of their generations and are usually also better educated, more likely to have practised intellectually demanding professions and are usually

also not socioeconomically disadvantaged. Representation of ethnic minorities is also questionable. In more arduous longitudinal studies self-selection of volunteers not only biases initial recruitment but also brings about selective attrition because less healthy and so least able participants withdraw or die leaving a progressively elite group of survivors. So, in longitudinal studies, true rates of cognitive change will be miscomputed unless the incidence of these deaths and dropouts is taken into consideration¹⁴. Another difficulty for longitudinal studies of mental abilities is that if participants are repeatedly given the same, or similar, tests even at intervals of many years, they show significant practice effects. This also leads to potential miscomputations of trajectories of change, more particularly because older and less able individuals, and those who approach dropout or death, experience less improvement from practice than the younger, more intelligent and more healthy. Anstey, Hofer and Luszcz illustrate how some of these issues can be dealt with in an exploration of both cross-sectional and longitudinal examinations of the ways in which correlations between sensory and cognitive variables change over time⁹.

It is becoming questionable whether very large and prolonged longitudinal studies that collect only behavioural data on cognitive change, with additional data on health and demographics, are the most resource-effective way of learning how and why age affects mental abilities. The rapid development of non-invasive brain imaging means that we can now detect changes in the brain and central nervous system over periods measured in months rather than decades that can be related to contemporaneous patterns of cognitive changes within individuals. Thus, even with small samples we can study variability in idiosyncratic patterns of brain changes and correspondingly patterned changes in cognition³⁶. Raz *et al.* provide excellent general discussions of how such studies can be carried out and what they can tell us³⁷. An explosion of studies of relationships between changes in specific brain locations and in particular aspects of cognitive performance includes age differences in the functional neuroanatomy of verbal recognition memory³⁸, the functional neuroanatomy of age related changes in visual attention³⁹, changes in entorhinal cortex and losses of memory function, age-related differences in working memory using real-time fMRI, differences in brain activity associated with age-related changes in memory function and brain changes associated with changes in motor performance.

These relationships between changes in specific brain locations and in specific abilities proceed against a background of global changes affecting all parts of the brain such as increasing prevalence and distribution of white-matter lesions, losses in brain volume and declines in cerebral blood flow that all appear to be associated with declines in information processing rate^{11,12}. This complicates interpretation of cognitive effects of localized brain changes that may be masked or blurred by these global changes that affect all systems, but to different degrees. This may partially explain apparent contradictions between the results of the many studies using behavioural evidence alone to test the sensible hypothesis that earlier and faster 'ageing' of the pre-frontal cortex must result in correspondingly more marked age decrements in abilities such as working memory, planning, attention and executive functions. For example most of the adapted behavioural clinical diagnostic tests for frontal damage tests used to test this hypothesis are scored in terms of the relative speed with which decisions can be made. Since we know that gross brain changes such as white-matter lesion incidence specifically impair processing speed, scores on so-called 'frontal' tasks must evidently reflect some complex combination of local and global effects. It is therefore unsurprising that comparisons between small groups of 30 or fewer individuals

for whom information on brain status is not available should only sometimes find evidence for the 'frontal ageing' hypothesis.

With these cautions, 'cognitive gerontology' is now becoming an exciting science in which a rich body of behavioural data and growing sophistication in understanding brain changes is rapidly transforming our understanding of how and why our mental abilities change, why all of us do not change at the same speed or in the same ways and, hopefully, suggest what we may do about this.

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Chronological and Functional Ageing

David Melzer and Iain Lang

Peninsula Medical School, University of Exeter, UK

INTRODUCTION

Ageing is a surprisingly difficult process to define or measure. In a superficial sense it is everything that happens to an individual over time but, for geriatricians and gerontologists, notions of ageing are tied to physiological deterioration and increasing vulnerability to diseases absent in the young. This notion of ageing is synonymous with 'senescence' and is defined¹ as progressive deterioration during adult life that underlies an increasing vulnerability to challenges and a decreased chance of survival.

The relationship between chronological and functional age has implications for ageing research and public policy. In this chapter we describe more meaningful ways of thinking about human ageing than through the proxy of elapsed time, or chronological ageing.

THE PLASTICITY OF AGEING

Ageing is widely seen as the result of lifelong accumulation of random molecular damage². Damage results in declining function at many levels³, including in mitochondrial function, DNA transcription (through unrepaired somatic DNA mutations) and in the ability of cells to divide and repair tissues. The balance between damage and repair mechanisms determines the amount of unrepaired damage, which manifests as ageing at the cellular and organism level. Secondary responses to damage can then occur, including chronic inflammation, hypothesized as a major element in human ageing⁴.

Ageing processes are surprisingly plastic and variable. This is evident at all levels from the molecular to the societal and global population levels. The most dramatic demonstration of the plasticity of ageing is the finding that hundreds of mutant genes (mainly knockouts) can produce radical life extensions in model organisms⁵. In addition to affecting stress responses and telomeres, endocrine signalling has also emerged as particularly important in these models. In general, the impact of 'longevity' gene manipulation on lifespan becomes progressively smaller on moving up the evolutionary ladder⁶ and relevance to human ageing is speculative.

In addition to genetic manipulation, caloric restriction in laboratory settings also increases lifespan when compared to unlimited feeding^{7,8}. In humans, obesity is a risk for mortality and functioning in older people⁹ but whether there are benefits in radically reducing caloric intakes below those required for maintaining a healthy weight is unclear.

The variability of ageing in humans is apparent both in single organs and in the longevity and functioning of individuals. Analyses of the Baltimore Longitudinal Study of Ageing have shown marked heterogeneity in the rates of decline in function of different organ systems: for example, mean maximum work rate and renal blood flow generally decline far faster than measures of nerve conduction¹⁰. More surprising, individuals show great heterogeneity in patterns of impairment of individual systems, with little indication of typical patterns. In human population studies, it is usual to find people functioning at a higher level than others aged 20 or 30 years younger.

One potential means of identifying an individual's 'true' age is through identifying biomarkers of ageing. The concept of biomarkers of ageing is appealing because it implies biological measures can reflect the rate of ageing and that successful interventions on the ageing process may affect these markers. The American Federation for Aging Research proposed that a biomarker of ageing must¹¹:

- predict the rate of ageing – i.e. it should be a better predictor of lifespan than chronological age;
- monitor a basic process that underlies the ageing process, not the effects of disease;
- be testable repeatedly without harming the person;
- be valid in humans and in laboratory animals.

Markers showing potential include telomere length¹² and p16^{INK4a} expression¹³.

The search for biomarkers of ageing assumes there is an underlying biological state of ageing that can be summed up as a single number but counterarguments regard ageing as a complex, uncoordinated phenomenon that cannot be encapsulated so simply¹⁴. Despite much research effort, most gerontologists accept that no biomarkers of ageing have yet been validated^{11,15}.

FUNCTIONAL HEALTH STATUS

A key aspect of functional ageing or functional health status assesses functioning at the level of the whole older person. Functional health status is related to chronological age, disease and need for care, and understanding the functional aspects of ageing is an important part of geriatric medicine. In the medical model of disease, the clinician gathers symptoms and signs, makes a diagnosis and bases the therapeutic approach on this diagnosis. Complementing this

disease-orientated approach, functional assessment provides an understanding of the impact and consequences of the older person's disease or diseases, giving information on level of independence and prognosis, as well as health care, rehabilitation and social needs.

Since a major impact on functional health comes from disease, a framework that represents the relationship between disease and disability is valuable in developing the concept of functional ageing. The World Health Organization (WHO) originally proposed a theoretical pathway progressing from disease to impairment to disability to handicap¹⁶. An alternative pathway, proposed by Nagi¹⁷ and utilized by the US Institute of Medicine¹⁸, progresses from diseases and conditions to impairment to functional limitation to disability. An effort to operationalize this latter pathway defines 'impairment' as dysfunction and structural abnormalities in specific body systems, 'functional limitation' as restriction in basic physical and mental actions such as ambulating, grasping, and stepping up, and 'disability' as difficulty in doing activities in daily life such as personal care, household management, job and hobbies¹⁹. The importance of identifying external factors that needlessly cause disablement outside the individual is a major theme in the more recent WHO classification systems²⁰.

Means of assessing and reporting functional health status include the following.

Self-Reported Functioning

Physical functioning shows a downwards trend with age and is often assessed through self-report of the ability to perform specific tasks, including self-care activities such as bathing and dressing (activities of daily living), and activities necessary to maintain independence in the community, such as shopping and food preparation (instrumental activities of daily living)^{21–24}. A concern with self-reported functioning is that different individuals and groups may have different thresholds for reporting difficulty or inability to carry out activities²⁵.

Performance Measures

Performance measures of functioning, in which the individual is asked to carry out standardized tasks, offer a way of benchmarking function and comparing over time or across populations²⁶. Self-reported functional status may differ from measured function for a variety of reasons, including differences in the domains measured. Assessing both allows us to combine an objective measure of poor performance with an indication of how much everyday function is affected²⁷. Tests of physical function are used in clinical assessments of older people^{28,29} and can help identify individuals with pre-clinical limitations who are at increased risk of developing disabilities^{30,31}. One established measure is the short physical performance battery, including measures of gait speed, chair stands and tandem balance tests: this score has been widely used in clinical settings for the assessment of mobility limitations³². Other approaches include these measures plus muscle strength and respiratory function³³.

Frailty

Frailty, generally taken to mean multisystem impairment and a high level of vulnerability, has been defined in two ways: as a phenotype; and as a score of age-related deficits or 'frailty index'. The phenotypic approach defines frailty as a clinical syndrome in relation to five criteria: unintentional weight loss (10 lbs or more in the

preceding year); self-reported exhaustion; weakness (grip strength); slow walking speed; and low physical activity³⁴. Using these criteria, individuals are defined as either frail (three or more criteria present) or not frail (fewer than three criteria). The frailty index approach sums the number of age-associated deficits experienced by an individual, including symptoms, signs, diseases and disabilities³⁵ (Rockwood 2007). The resulting score provides an indication of the likelihood that frailty is present, and the index demonstrates characteristic changes with age. Each of these operationalizations of frailty has been validated in multiple populations. Although the two approaches overlap there are substantial differences between them³⁶ and it has been suggested each represents a different form of frailty and a different trajectory of age-related loss of function³⁷.

Cognitive Function

Age-related functional decline has cognitive as well as physical aspects. These often occur together, and they share some risk³⁸ as well as protective³⁹ factors. The care burden associated with dementia, on both a societal⁴⁰ and a household level⁴¹ level, is large. There are major public health concerns about the impact on health and social care services of growing numbers of older people with declining cognitive function and dementia⁴². Among the challenges of dealing with this growing problem is the shortage of effective treatments for dementia, and attention has been drawn to identifying individuals with mild cognitive impairment – that is, those who are not demented but have a memory impairment beyond that expected for age and education⁴³. Cognitive function and dementia are covered in more details in Part IV of this book.

Factors Affecting Functional Health Status

The prevalence of disability in activities of daily living (ADL) in the non-institutionalized population rises steeply with increasing age and is higher in women than men at the older ages⁴⁴ – see Figure 12.1.

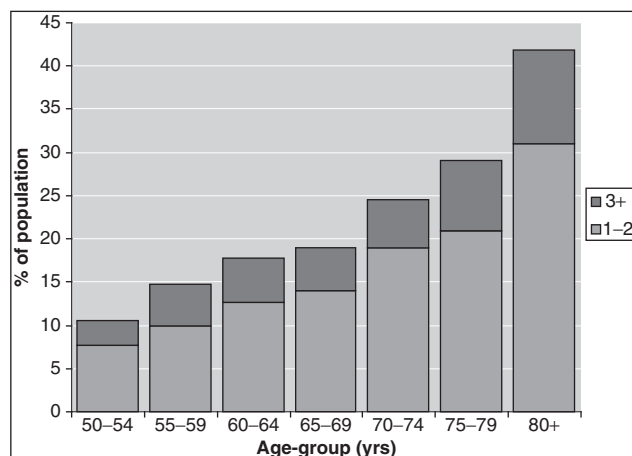


Figure 12.1 Percentage of community-living respondents reporting one to two, and three or more disabilities in activities of daily living. Activities include dressing, walking across a room, getting in and out of bed, eating and using the toilet

Source: Data from the English Longitudinal Study of Ageing (Steel *et al.*, 2004)

The prevalence of ADL disabilities in institutional settings is generally very high. It is important to keep in mind that, although chronological age is strongly related to disability prevalence, many other factors, particularly socioeconomic status, have large impacts on disability that are independent of age^{45,46}. Large differences in functional health status exist between groups, with those in less privileged social positions having higher rates of incidence and prevalence of disability, in both developed⁴⁷ and emerging countries⁴⁸.

Cognitive impairment is a major contributor to functional disability^{49,50}, as are depressive symptoms^{51,52}. A number of potentially modifiable behaviours are associated with physical function or functional decline in later life. These include obesity⁵³, smoking⁵⁴ and low levels of physical activity⁵⁵. The onset of functional disability often occurs relatively early in life: recent studies have identified that up to one in five adults aged 50–64 experiences some problems with walking a quarter of a mile^{56,57}.

LONG-TERM TRENDS IN FUNCTIONAL HEALTH STATUS AND POLICY IMPLICATIONS

An important issue connected to functional ageing is the relationship between length of life and time spent in a disabled state. Life expectancy increased substantially through the 20th century. One consequence of reduced early-life mortality may be that more people survive to ages where they suffer from chronic diseases, leading to increased prevalence of long-term disability and loss of independence. Increases in life expectancy which bring longer periods of life with impaired function are undesirable both for individuals and for societies and a major goal of gerontology is increasing longevity without increasing the number of years spent in the disabled or dependent state.

An important concept in relation to evaluating the consequences of worldwide population ageing is ‘active life expectancy’ or ‘disability-free life expectancy’⁵⁸. Active life expectancy is defined as the average number of years an individual at a given age will survive and remain in the active, or non-disabled, state. Most analyses of active life expectancy define disability in relation to activities of daily living, with active life expectancy calculated using life-table techniques that consider transitions from the active, non-disabled state to a disabled state or death. The original analysis of active life expectancy considered the transitions to both death and disability as irreversible⁵⁸ but recent studies have shown a substantial proportion of disabled persons returns, at least temporarily, to the non-disabled state⁵⁹.

Compression of Morbidity

A related theory is ‘compression of morbidity’⁶⁰, the idea that the burden of lifetime illness may be compressed into a shorter period prior to death. Fries argued that in all species the maximum lifespan is fixed, human beings are quickly approaching this limit, and with a stable life expectancy any postponement of disease and disability would result in a compression of morbidity. He stated the compression of morbidity was inevitable and predicted a decrease in the period people could expect to spend with severe disease and disability. The relationship over time between life expectancy and active life expectancy can be used to assess the occurrence of a compression of morbidity. Three possible scenarios for population morbidity in women are illustrated schematically in Figure 12.2. The total length of the bars in this figure represents life expectancy for Non-Hispanic black U.S. females projected by the Census Bureau for 2050. The

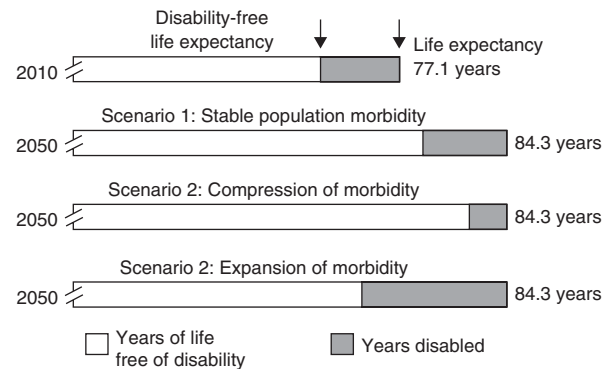


Figure 12.2 Scenarios for change in average burden of population disability level: compression of morbidity and alternatives

length of the unshaded segments of the bars represents active or disability-free life expectancy, and the shaded areas of the bars represent the average number of years in the disabled state. In scenario 1, the onset of disability has been postponed the same number of years as life expectancy has increased, and the number of years spent in the disabled state is unchanged from 2010. In scenario 2, there has been a compression of morbidity. Finally, in scenario 3, although disability-free life expectancy in 2050 has increased compared with 2010, it has not kept pace with increases in life expectancy and there is an expansion of population morbidity.

Active life expectancy is not always easy to assess and debates persist about whether compression of morbidity is taking place. However, trends in disability can be estimated in other ways. It is possible to estimate disability prevalence, which is not equivalent to disabled life expectancy but reflects a cross-sectional picture of the proportion of the population that is disabled. Much attention has been focused on examining longitudinal trends in disability by analysing annual estimates of disability prevalence. In the US, it appeared that in the 1970s the prevalence of age-related disability was rising but in the 1980s rates declined^{61–63} and this trend seems to have continued. A number of studies have reported ongoing year-on-year improvements in the health of the older population^{61,64–66} and reports from other countries, including New Zealand⁶⁷ and England⁶⁸ suggest similar patterns of decline in age-related disability may also be occurring there.

Possible causes of these declines in disability prevalence include environmental changes making daily tasks easier¹⁹, more intensive use of assistive devices⁶⁹ and other social changes, including attitudes to being active in old age. In addition, the proportion of older people who have little education (a potent risk factor for disability) has declined^{63,70}. There is evidence of declining prevalence of some medical conditions in old age, especially cardiovascular disease, and health risk avoidance and improved diagnostic and therapeutic techniques will also have contributed⁷¹.

The future burden of morbidity and disability in the older population is of great concern to those involved in planning, financing and delivering health care and social services. If current rates of disabling diseases such as Alzheimer’s disease and hip fracture remain unchanged, the numbers of older people with these diseases will increase substantially during this century⁷². Understanding the factors that affect functional ageing is critical to reducing the burden of disability and compressing morbidity. Effective interventions are needed to prevent the onset and mitigate the consequences of diseases and conditions that lead to much disability in later life.

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Successful Ageing

Ann Bowling

Department of Primary Care and Population Health, University College London, UK

BACKGROUND

Population ageing and increases in life expectancy in the developed world have led to international interest in how to age 'successfully'. But there is no interdisciplinary agreement on what successful ageing is. The literature reveals that conceptual definitions and measurement of successful ageing vary both within and between disciplines; there is little interdisciplinary cross-referencing. Biomedical models emphasize physical and mental functioning as successful ageing, while sociopsychological models focus on social functioning, life satisfaction and psychological resources. Older people themselves adopt multifaceted definitions of successful ageing^{1,2}. Moreover, research shows that older people consider themselves to have aged successfully, but classifications based on traditional, narrower domain models do not¹⁻³. This suggests that a model of successful ageing needs to be multidimensional, cut across disciplines, and incorporate a lay perspective for social significance. Moreover, there is overlap, and lack of clarity, in the literature between concepts of successful ageing, active ageing and quality of life. Analysis of overlap between lay perceptions of these concepts in surveys using comparable methods showed that lay perceptions of active ageing emphasized striving to *maintain* health, functioning, and wider well-being (e.g. exercising the body and/or mind in order to maintain health and functioning), while lay definitions of successful ageing and quality of life focused on the existence of a state, rather than the striving for its achievement (e.g. the having health and ability *per se*⁴). This distinction is consistent with the literature on active ageing, which portrays quality of life, and also having 'successfully aged', as the end points, although 'successful ageing' can also be viewed as a dynamic process.

An earlier interdisciplinary systematic review of the literature by this author^{1,3} found that the most common definitions of successful ageing were based on theories of social functioning, life satisfaction, psychological resources and biomedical approaches. A small body of literature focused on lay views. The distinction between concepts as either predictor or constituent variables was not always clear. The survey with the highest citations for successful ageing was the MacArthur Foundation studies of successful ageing⁵⁻⁷, which are based on a biomedical model, broadened to include active engagement with life.

SOCIAL FUNCTIONING

Social functioning has been conceptualized and measured in many different ways, including social engagement, social roles, participation and activity, social contacts and exchanges, and/or positive social relationships. The main theoretical approaches relating to successful ageing and social functioning are disengagement, activity and continuity theories, although each suffers from limitations, and all are now outdated (see Bearon for critique⁸).

LIFE SATISFACTION

A smaller number of authors included life satisfaction, well-being or their elements in their conceptual and empirical definitions of successful ageing. Components of life satisfaction include zest, resolution, fortitude, relationships between desired and achieved goals, self-concept and mood, including happiness⁹⁻¹¹. Havighurst¹¹ (p. 305) stated, 'a person is aging successfully if he feels satisfied with his past and present life', thus arguing that life satisfaction is an attribute of successful ageing, although others have argued that it is a condition for its achievement. Feelings of well-being were an outcome indicator of successful ageing in the Berlin Aging Study¹². There is lack of consistency about the status of life satisfaction, in particular, as an indicator or constituent variable.

PSYCHOLOGICAL RESOURCES

Few investigators have included psychological resources as their study definition of successful ageing, and again it was not always clear whether the concepts used were predictor or constituent variables. Psychological models include possession of the resources of personal growth, creativity, self-efficacy, autonomy, independence, effective coping strategies, sense of purpose, self-acceptance and self-worth. These models have been criticized for their emphasis on autonomy, thus marginalizing frail older people¹³.

Baltes and colleagues¹⁴ developed a strong theoretical model based on the need to employ compensatory strategies when facing the dynamic between challenges and depleting reserves: selective

optimization with compensation (SOC). With this model, it is proposed that individuals can contribute to their own successful ageing: when *selected* activities can no longer be performed, strategies are needed to find new ones, and to maximize reserves. There is some supportive evidence from the Berlin Aging Study that people who use these strategies have better well-being than others¹².

Ryff's theoretical model of successful ageing emphasizes a life course approach, and holds that a developmental focus is required^{15,16}. She argues that successful ageing includes 'positive or ideal functioning' and is related to development over the life course. Fisher¹⁷ also emphasized adaptability and coping, and defined successful ageing as an ability to continue to grow and learn by using past experiences to cope with present circumstances and set goals for development.

BIOMEDICAL THEORIES

Biomedical or decline theories generally define successful ageing as the optimization of life expectancy, while minimizing physical and mental deterioration. The MacArthur Foundation in the USA commissioned a major study of successful ageing led by Rowe, which comprised a three-site longitudinal study of adults living in the community aged 70–79 in 1988. It was rooted in Rowe and Kahn's^{5–7} model of successful ageing as absence, or avoidance of, disease and risk factors; maintenance of physical and cognitive functioning; and active engagement with life (with others and in productive activities). They made the distinction between 'usual ageing', which describes normal decline in physical, social and cognitive functioning with age, and 'successful ageing', in which physiological and cognitive functional loss is minimized, there is active engagement with life, and capabilities even enhanced. This only partly recognizes heterogeneity among older people, and criticisms of Rowe and Kahn's model include its narrowness, neglect of life course dynamics, failure to address adaptation to disease, and neglect of those who are incapacitated who cannot age successfully by the criteria used. A small number of studies have used elements of both biomedical and psychosocial approaches.

LAY VIEWS OF SUCCESSFUL AGEING

Lay views are important to investigate in order to ensure that models of successful ageing have social significance, and to minimize the danger that definitions reflect mainstream cultural expectations and norms for the behaviour of older people. Without social significance, policy initiatives to enhance successful ageing are likely to fail.

The systematic review of the literature, and empirical research by this author, illustrated that lay people view this concept multidimensionally, and included the following elements in their definitions: physical health and functioning; mental and cognitive health; psychological well-being and life satisfaction, including happiness; social functioning – relationships, support, activities and productivity; psychological resources, including personality, personal growth, accomplishments, sense of purpose, physical appearance, self-acceptance, coping, positive outlook, sense of humour; spirituality; lifestyles; neighbourhood; financial circumstances and security. It is also perceived as a dynamic concept. Von Faber *et al.*¹⁸ reported, from the Leiden longitudinal study of people aged 85+, that older people defined successful ageing as a process of adaptation rather than as a state of being, supporting psychological rather than biomedical models. Thus, investigations of older people's views of successful ageing

have indicated that they are far more multifaceted than existing models, crossing the boundaries between the physical, psychological and social self. Moreover, research shows that, overall, many older people consider themselves to have aged successfully while biomedical classifications do not categorize them so. Strawbridge *et al.*¹⁹ compared self-ratings of successful ageing among their sample members aged 65–69 from the longitudinal Alameda County Study with Rowe and Kahn's three-factor model. They reported that, while half the sample could be categorized as having aged successfully with their own self-ratings, only 19% could be so categorized with Rowe and Kahn's model. Bowling's further national survey of people aged 50+ living at home in Britain, asked people what they understood by the term successful ageing, then to rate the extent to which they had aged successfully². Two-thirds of respondents defined successful ageing in terms of having good health and functioning; almost half defined it psychologically. Others defined it mainly in relation to social roles and activities, social relationships, neighbourhood and local community. About four in ten (39%) respondents rated themselves as ageing successfully 'Very well', and a further 37% as 'Well', as opposed to 'All right', 'Not well' or 'Not very well' (see Figure 13.1).

There were positive correlations between self-rated ageing successfully and good self-rated health, no reported longstanding illness, and good quality of life. There were no statistically significant associations with age. The main reasons people gave for their self-ratings of successful ageing included their physical and mental functioning, followed by psychological well-being, social relationships and financial circumstances^{1,2}. Also, while over a quarter indicated that they felt defiant about ageing when asked how they thought ageing would affect them, about 40% mentioned worse health and/or functioning, about a fifth thought they would be limited in their lives, and about 10% each mentioned worsening mental health and dependency (see Figure 13.2).

In a further study, Bowling and Iliffe²⁰ constructed and tested alternate biomedical, social, psychological and multifaceted lay-based models of successful ageing in a national population survey of people

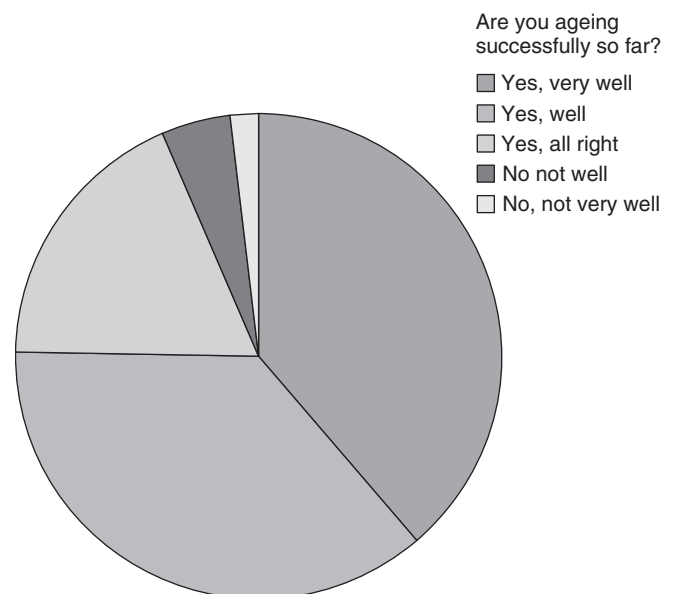


Figure 13.1 Self-rated successful ageing: national population sample aged 50+ in Britain. Data from the *English Longitudinal Study of Ageing* (Steel *et al.*, 2004)

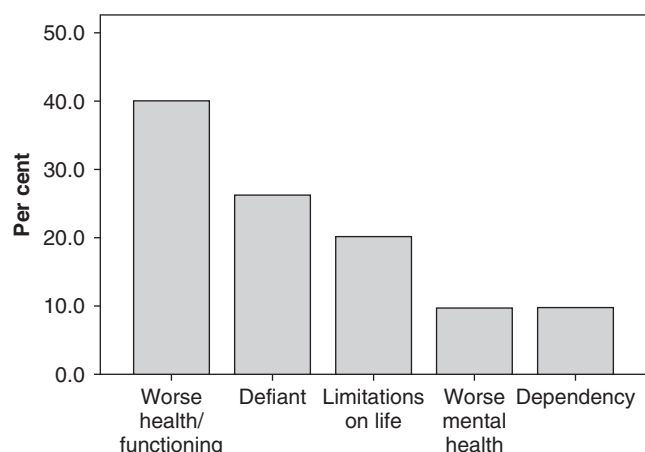


Figure 13.2 How do you think getting older will affect you? (Most common responses shown)

aged 65+ living at home in Britain. Respondents classified as successfully aged with the multifaceted lay model, compared to those classified as not successfully aged, had over five times the odds of rating their quality of life as good rather than not good. The comparable odds ratios from the other, single domain models, while significant, were considerably lower.

Table 13.1 shows the associations between pairs of successful ageing themes mentioned by respondents. While the table shows several instances where mention of one definition was associated with reduced odds of mentioning another, it also indicates the multidimensionality of lay definitions. Respondents who defined successful ageing in terms of health had almost twice the odds, compared to those who did not, of also defining it in terms of finances. Respondents who mentioned social activity had almost twice the odds of mentioning social relationships (and vice versa), possibly reflecting the perceived need for companionship to undertake social activities (e.g. to accompany one on outings). Those mentioning social relations also had over twice the odds of mentioning finances, compared to those who did not. Similarly, respondents who mentioned finances had almost twice the odds of mentioning health and twice

the odds of mentioning social relationships (and vice versa). And respondents who defined successful ageing in terms of neighbourhood factors had almost twice the odds of also mentioning financial circumstances. The importance of these results is the demonstration that successful ageing is not perceived narrowly by lay people, in contrast to most theoretical models. It also illustrates the interaction between domains of life, e.g. social relationships may be needed for people to participate in social activities (to accompany people), and people see having both health and money as important for successful ageing.

CONCLUSION

In conclusion, most authors in this field have made unwarranted conceptual leaps and assumed, often, that they have addressed 'successful' ageing with their chosen outcome indicators, with relatively few attempts at theoretical or conceptual justification. Rowe and Kahn's three-factor biomedical model (including social elements) of successful ageing is the most popular and widely used in biomedical research, even outside the MacArthur studies of successful ageing⁵⁻⁷. In contrast, lay models of successful ageing are more multidimensional, and, in particular, include more psychosocial elements. Also, to be realistic, the concept needs to be broadened, and to be seen on a continuum, rather than categorized dichotomously in terms of successful or unsuccessful. Also, given the inconsistency with which variables are used as either predictor or constituent variables in the study of successful ageing, advances could be made by grounding the term in older people's definitions, and building on multidimensional theoretical approaches.

Thus a definition of successful ageing would include longevity, physical, cognitive, psychological and social health and functioning, including effective coping, living circumstances (finances, neighbourhood) and overall life satisfaction. Precursors of effective coping strategies are likely to be possession of resources such as SOC, as hypothesized by Freund and Baltes (1998)¹². Using this approach, the different models are complementary to each other, and successful ageing is not only about maintaining good health and functioning, but it is also about coping and remaining in control of one's life over the life-course, with the aim of achieving dynamically a status

Table 13.1 Logistic regression: associations (odds ratios; CI, confidence intervals) between successful ageing theme pairs ($n = 854$)^a

Themes (mentioned 1 versus not mentioned 0 = referent) (y):

Themes (mentioned 1 vs. not mentioned 0 = referent) (x):	Health Exp b (95% CI)	Psychological Exp b (95% CI)	Social activity Exp b (95% CI)	Finances Exp b (95% CI)	Social relations Exp b (95% CI)	Neighbourhood Exp b (95% CI)
Health	—	0.713* (0.529–0.960)	0.725** (0.534–0.983)	1.915*** (1.355–2.706)	0.581*** (0.417–0.810)	0.903 (0.551–1.480)
Psychological	0.712** (0.528–0.959)	—	0.643** (0.478–0.866)	0.546*** (0.398–0.748)	0.539*** (0.387–0.751)	0.744 (0.460–1.204)
Social activity	0.725* (0.534–0.983)	0.639** (0.475–0.862)	—	0.703* (0.504–0.981)	1.842*** (1.330–2.551)	0.980 (0.602–1.597)
Finances	1.903*** (0.396–0.745)	0.543*** (0.396–0.745)	0.694* (0.498–0.968)	—	2.001*** (1.417–2.825)	1.981** (1.221–3.215)
Social relations	0.576*** (0.413–0.803)	0.535*** (0.385–0.745)	1.839*** (1.327–2.547)	2.004*** (1.421–2.826)	—	1.000 (0.594–1.684)
Neighbourhood	0.912 (0.555–1.500)	0.755 (0.467–1.221)	0.965 ^{NS} (0.591–1.575)	1.990** (1.231–3.217)	1.008 (0.599–1.697)	—

^aFully adjusted for age, sex and socioeconomic status; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; NS not significant at 0.05 level.

of having successfully aged. Then the question of whether, and the extent to which, successful ageing is achievable can be addressed. Also, clinicians involved in the care of older people need to balance a *dis-ease* with a health and psychosocial perspective of older age, in order to enhance mutual understandings about desired treatment goals.

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Sexuality, Non-Traditional Relationships and Mental Health in Older People

Ian Peate

School of Nursing and Midwifery, Thames Valley University, London, UK

INTRODUCTION

Despite an ageing population, little is known or understood about the sexual behaviours and sexual function of older people in society. Individuals (including the older person) manage their sexuality and sexual identity in a number of ways. Assumptions concerning ageing and intimacy in later life are now being challenged. Specific issues concerning sexuality and ageing will be discussed. In a minority of cases clinicians will be working more and more with older people who are involved in non-traditional relationships – a non-heterosexual context. Issues may arise for clinicians and older people concerning sexual identity. Many of those working with the older person will have had little training or education regarding non-heterosexual relationships and the older person. This chapter will emphasize the need to respect the fact that the expression of sexuality in older age is an important aspect of an individual's being, as well as remembering that for some older people coming to terms with their sexuality may bring with it psychological distress. The chapter addresses the mental health of the older lesbian, gay and bisexual (LGB) person; issues concerning transgender and gender dysphoria will not be addressed here. A brief discussion concerning HIV and the older population has been included.

SEXUALITY AND AGEING

Sexuality according to Ginsberg *et al.*¹ is an activity of daily living that is important for a number of older people. Despite this, Edwards² notes that within health care systems the sexual needs of the older person are often unrecognized and unmet, often as a result of negative attitudes and beliefs towards sexuality, sex and sexual desires. Many believe that these complex concepts can only be likened to youthfulness. Other factors can impinge on the individual's ability to express freely their sexuality, for example, environmental (structure) constraints in long term care facilities may hinder an older person being able to express their sexual needs³. Some common barriers to enjoying sex as a person ages are health problems or lack of a partner as opposed to lack of desire. Little research has been carried out with respect to stereotypical ideas about sex and ageing.

Healthy people are often sexually active people and this has an impact on the quality of an individual's life, therefore to deny an elderly person the option of being sexually active may result in dys-

function and distress. Among older adults there is an internal drive or need for sexual fulfilment⁴.

As people age the frequency in which they engage in sexual activity declines. Nevertheless, a substantial number of men and women engage in vaginal intercourse, fellatio, cunnilingus and masturbation, and some people remain sexually active in their eighties and nineties. The limited data that has been analysed demonstrates that there are some men and women who maintain sexual and intimate relationships and desires throughout their lives⁴.

Illness can seriously impede sexual activity but there is a dearth of literature regarding how illness impacts on the sexual activity of the older person. Altered pathophysiological changes often associated with the ageing process impact on sexual response in men and women, and most of the changes have a negative bearing on the person, both physically and psychologically.

The loss of a partner as a person ages is common (particularly in older women). Problems associated with the sex act may be a precursor to problems related to an underlying illness such as diabetes mellitus, a genitourinary tract infection or cancer⁵. There are a number of age-related changes in the vasculature and smooth muscle tissues involved in the erectile process as well as increased sensitivity to inhibitory signals in the smooth muscle^{6,7}. There are physiological changes that are associated with the menopause (these are complex); for example, a reduction in vaginal lubrication in response to a decrease in oestrogen levels. Attitudinal responses by society to postmenopausal women and their sexuality may also lead to an increase in vulnerability to depression.

Sexual problems for men can include difficulty in achieving or maintaining an erection, lack of interest in sex, climaxing too quickly, anxiety about performance and an inability to climax. For elderly women bothersome problems include lack of interest in sex, difficulty with lubrication, an inability to climax, disliking sex and pain – often felt at the vagina during entry⁴.

If problems associated with sexual activity are not treated or are left undiagnosed this may lead to depression or social withdrawal. There are also a number of medications that can result in sexual dysfunction that patients need to take for an ongoing physical or psychiatric illness. The result of sexual problems arising from the taking of prescribed medications may induce the person to stop taking them in an attempt to reduce the negative side effects related to them.

Bancroft *et al.*⁸ emphasize the effect of relationship factors and mental health (particularly with regard to women) as being more important predictors of sexual well-being than the physiological factors of sexual arousal and response. For a number of women (tentatively, this could also be said for some men) being in a relationship, the quality of that relationship and a partner's sexual problems are more important than their sexual responsiveness. Bancroft *et al.*⁸ considered only heterosexual women in his study; further research is needed to consider the impact of relationships versus sexual responsiveness in the LGB population. Kellett⁹ suggests that counselling may allow a couple who are experiencing sexual problems to express their fears and inhibitions, with the therapist educating the couple about the normal changes that accompany ageing.

ISSUES OF CONSENT AND COGNITIVE IMPAIRMENT

The law demands that both parties engaging in sexual relations must consent; this is equally true for the older person, who may have issues associated with cognitive impairment such as dementia. Sexual abuse is a criminal offence. Free will and capacity are germane to informed consent. It may be difficult to ascertain if a person who is cognitively impaired has the capacity to consent to sexual relationships and as such this renders that person vulnerable. There are several potential ethical and legal issues that may arise as a result of this (Mental Capacity Act, 2005). Assuming that a person with dementia cannot make decisions and consent to intimate relationships or that they are unable to comprehend the consequences of decisions associated with consent, sex is unacceptable.

Dementia leads to a variety of changes in people's lives and one area that receives little attention is in respect to sexual relationships. Dementia in the older person is common, as is drug-induced confusional state; these issues are discussed elsewhere in this text. In drug-induced confusional state, a review of current medication is needed. A feature of dementia is the development of several cognitive deficits that include memory impairment. These cognitive deficits can be so severe that they can cause impairment in social functioning, including the ability to consent freely to engage in sexual activity with another person. The deficits may also predispose the person to inappropriate sexual behaviour.

Dementia can impact on the individual's feelings, desires and needs; sexual behaviour and their ability to express intimacy can change. The clinician should explain to the person and others that these changes are not a reflection on any individual and that it is possible to express intimacy in other ways if their chosen way has changed. People with dementia can experience sudden changes associated with their ability to express their sexuality. A range of behaviours can occur depending on what aspect of the brain is affected; sexual interest may diminish or conversely it may increase; there may also be a change in the level of inhibition.

Usually, sex for many people is a private affair; dementia has the potential to bring many private activities out into the open, revealing many private intimate thoughts, feelings and sexually charged actions; for example, inappropriate touching of self and others, undressing and using sexually loaded language. While these actions may be embarrassing for others, they can also be confusing and distressing for the older person with dementia.

What may appear to be inappropriate sexual behaviour may have a number of diverse causes. The causes can be identified by analysis of antecedents, behaviours and consequences, thus providing the clinician with information that will inform the most appropriate

intervention if needed. Staff may need training in respect to the management of inappropriate sexual behaviours and the most appropriate ways to help the individual, families and other staff.

MENTAL HEALTH OF LESBIAN, GAY AND BISEXUAL PEOPLE

Older LGB people may experience mental health distress for a number of reasons unconnected with their sexuality, as is the case with older heterosexual people. There are, however, a variety of social factors that may have an impact on the lives of the older LGB person and hence their mental health. There are some personal and social characteristics that may further exacerbate mental distress, for example, ethnicity and disability.

Little is known about the mental health of the LGB population in the UK and even less is known about the LGB older population. Evidence that has been collected suggests that anxiety, depression, self-harm and suicidal feelings are more common among the LGB population when compared with the heterosexual population¹⁰. There are also higher rates of drug and alcohol misuse among LGB people. The LGB population has been found to have the highest levels of mental distress. The data cited here refers to the LGB population as a whole in the UK and not specifically the older LGB population; nevertheless, as with all populations, LGB people will age and become older LGB people and some of these findings may well reflect those of the older LGBs. The reasons underpinning these findings are complex and as yet not fully understood. Warner *et al.*¹⁰ note that poor mental health in the LGB population has often been linked to experiences of homophobia, discrimination and bullying. Older people are not immune to the effects of homophobic discrimination and bullying by society generally and by those who provide and plan health care.

HOMOPHOBIA AND HETEROSEXISM

Homophobia could be defined as the unreasonable hatred, prejudice and fear of LGB people. Extreme forms of homophobic behaviour can manifest as bullying and physical attacks. Heterosexism – where a society or community is conditioned to expect everyone to live and behave as heterosexual people do – can have a subtle impact on a person's self-esteem and self-image. There are a number of instances where homophobic and heterosexist behaviours exist in the provision of health care with the outcome being detrimental to the health and well-being of the older LGB person.

Institutional homophobia relies on the promotion of heterosexuality as the norm and when health services are provided where policy provision has neglected to take account of the needs of LGB people. In these instances an individual's sexuality has been seen as inferior to the dominant hegemony – the heterosexual. The health service, legal system and police force all have histories of institutionalized homophobia. There are a number of organizations that work with older LGB people who neglect to take into account the reality that not all service users are heterosexual. Some residential care homes and sheltered housing are often mixed sex and are usually set up in such a way that service provision is directed towards heterosexuals, neglecting or refusing to accept that some of their clientele may be lesbian, gay or bisexual.

Homophobia can have an impact in a number of ways. Being lesbian, gay or bisexual is not in itself a mental health problem; however, coping with the consequences of homophobia can have damaging effects on the health and well-being of an LGB person.

Warner *et al.*¹⁰ have demonstrated a possible correlation between levels of homophobia and mental ill health among LGB people. Levels of anxiety, self-harm and depression among participants in this study were higher than average among the LGB participants. Homophobic experiences include damage to property, physical attack and bullying.

OLDER LESBIAN, GAY AND BISEXUAL PEOPLE

There is often little value in using rigid categories when describing who is old or older as these terms can include a number of different generations. There is the potential when using such descriptions that the person (or people) being described may be disempowered and as such the term should be used with caution and tact.

For the majority of older LGB people, living their life predominantly in the twentieth century may have meant that being open about their sexuality would have resulted in oppression and abuse within the mental health services¹¹ as well as from society. There may be a number of reasons why this occurred; for example, mental health services then reflected the homophobia of the wider society. The Local Government Act (1998) made it illegal for teachers to sanction homosexuality in schools and described gay family relationships as false; this Act was repealed in 2003. Homophobia was also given legitimacy within psychiatry and psychology; theories of mental health pathologised homosexuality. Homosexuality was seen as the cause and effect of a mental illness or even as a mental illness itself. Damaging aversion therapies were often used regularly during the 1960s and 1970s to try to 'cure' homosexuality. Homosexuality was not officially struck off the UK government's list of psychiatric disorders until 1993.

Change is on the horizon and a number of legislative modifications have occurred to combat institutional homophobia in the UK. LGBs are now legally protected from discrimination associated with their sexual orientation from providers of goods and services; this also includes those who provide mental health services. There are some problems that remain. Some people who use mental health services and counselling or psychotherapy services are still being discriminated against with regards to their sexuality, and in some cases this is further exacerbated because of their age. The key factor for such discrimination is associated with lack of awareness among clinicians and due in part to ignorance as opposed to malevolence. A systematic review has been undertaken by the British Association for Counselling and Psychotherapy into the experiences of LGB people who have received counselling or psychotherapy services¹². Gaps in knowledge have been identified as well as revealing negative attitudes among some therapists. The review recommends that these gaps should be addressed in the training and education of therapists.

Caution must always be taken with reviews of mental health services and the needs of the LGB population, as the results may under-represent the actual number of LGB people taking part in or being included in studies or reviews. There are some people who may be reluctant to disclose their sexuality and there may also be some discomfort and embarrassment on the part of the researcher in asking questions concerning sexuality and the older LGB person.

As well as being lesbian, gay or bisexual, other characteristics such as age, ethnicity or disability can complicate or exacerbate an LGB person's experience of mental illness. Attempts in the past to cure some older LGB people may have left these people with feelings of guilt accompanied with emotional damage. There may be a number of older people who have never acknowledged to themselves or others that they are lesbian, gay or bisexual.

Negative societal attitudes towards sexuality in older age can also have detrimental effects on a person's health and well-being. Older people are often seen as unattractive and socially uninteresting. The 'gay scene' is generally geared towards meeting the needs of the younger LGB population. Lack of social opportunities can deny older LGB people the chance to meet other older LGB people; social isolation may ensue. Harmful societal attitudes can impact on communication between the physician and the patient. The outcome may be an unwillingness of patients and physicians to initiate discussion concerning sex.

HIV INFECTION IN OLDER POPULATION

HIV infection in the older population has until recently in the main been ignored. Much of the published data regarding immunologic and clinical responses to highly active antiretroviral treatment (HAART) are associated with younger cohorts. The reasons why older people have for the most part been ignored are varied, and could include the risk of age related co-morbidity associated with clinical trials.

With increased life expectancy and the success of HAART accompanied by an enhanced length of survival as a result of the improvement of the immunodeficiency caused by HIV infection, the number of older people with HIV is likely to continue to increase. As a result of this, clinical trials (research) that are age specific, taking into account the needs of the older person (i.e. considering co-morbidity and potential drug interactions) are required in relation to the impact of HIV on this population, including therapeutic and clinical outcomes.

CONCLUSION

There are a number of older people who are sexually active although little is known about their sexual activities, behaviours and attitudes. Sexual problems are widespread among the older sexually active population; these problems are rarely discussed with clinicians. A number of older people may become sexually inactive because of a variety of sexual problems – these may be physiological in origin or as a result of their sexuality and societal reactions.

For some older people heterosexual and LGB sex may play an important part in their relationships and well-being; there are also some who do not see this aspect of their lives as crucial. There may be some older people who would benefit from the input of clinicians who are willing to broach what is sometimes seen as the embarrassing and taboo subject of sexuality and the older person.

Evidence suggests that being able to express one's sexuality is positively correlated with good physical and mental health. Allowing the older person to express their sexuality will enhance their health and well-being in a number of ways. For this to happen clinicians must encourage the older person to discuss the issues that concern them. However, for this to take place the clinician must first feel comfortable with their sexuality and challenge any stereotypes they may have that concern the older person's sexuality.

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The Care Home Experience

Alisoun Milne

School of Social Policy, Sociology and Social Research, University of Kent, Canterbury, UK

INTRODUCTION

This chapter aims to highlight the key dimensions of the evidence base exploring the experience of living in a care home, with a particular focus on dementia. Despite the extent of recent policy and practice attention paid to care homes in both the UK and the US, surprisingly little is known about residents' lived experience. Research is only now beginning to take account of the perspective of users with dementia and is embarking on the not inconsiderable task of developing tools and methodologies that can meaningfully capture their voices¹. By way of introduction, the broader context within which the care home experience is located is provided before moving onto the chapter's core focus. Although much of the evidence presented is drawn from UK research, key messages are equally applicable to the US and mainland Europe.

Background

In the United Kingdom about 5% of the total population aged over 65 lives in care homes. This is comparable with other European countries, the figure being slightly higher in Scandinavia². In the United States 4.2% of the 65 and over population live in nursing homes³. In terms of absolute numbers, in 2007 420 000 people lived in care homes in the UK while in the US over 1.8 million people lived in nursing homes. It is important to note that US figures do not include 'assisted living facilities' whereas UK figures incorporate care homes that do *not* provide nursing care⁴ as well as those that do.

Care homes' residents tend to be very elderly and frail; multiple physical problems and/or co-morbidity with mental disorders are common⁴. Typically, UK residents are aged over 80 years, are female, have previously lived alone, are on a low income and have multiple disabilities. In a recent UK study of 16 000 residents, over half had dementia, stroke or other neurodegenerative disease, 78% had at least one form of mental impairment, 71% were incontinent and 76% needed help with mobility or were immobile⁵; 27% were immobile, confused *and* incontinent. It is estimated that over two thirds of people living in *all* UK care homes have dementia, most often in the advanced stage, and about a third of all care home

places are registered to provide specialist dementia care⁶. In the US it is estimated that 23–42% of residential community/assisted living residents have moderate or severe dementia. Many residents with dementia experience behavioural problems such as activity disturbances (agitation), aggression and psychosis; reported prevalence of these so-called 'challenging behaviours' can be as high as 90%⁷.

In addition, an estimated 50% of all care home residents have depressive disorders that would warrant intervention⁸. Depression in care home populations is associated with functional impairment (e.g. sensory loss, incontinence, loss of mobility), physical health problems (notably pain, dysphasia and heart disease), and social problems such as loneliness⁹. Due to the complexity of assessing the extent of depression among people with dementia and the limited evidence base, it has been suggested that depression in care home residents is often either under- or misdiagnosed¹⁰. Anxiety symptoms are also relatively common; they are particularly associated with depression and stroke¹¹.

Living with Dementia in a Care Home

Despite the predominance of older people with dementia in care homes, research that draws on the experience of this group of residents has only recently emerged. In part, this reflects the liminal status of people with dementia inside, and outside, the 'care system', as well as the genuine complexity of collecting data from people whose cognitive capacity and communication skills may be limited¹². It is notable that an accumulating body of evidence offers valuable insights into the subjective experience of living with early stage dementia. It is also increasingly accepted that people in the middle to late stages of dementia retain the capacity for emotional expression and many can reliably express preferences¹³. As improving long term care for people with dementia is now a key policy priority in both the UK and US, the continuing marginalization of this pivotal perspective in both the practice and research arenas can no longer be justified¹⁴.

Currently, there are two main sources of evidence about 'the care home experience'. One draws on practice-based work whose core aim is that of improving care. 'Dementia care mapping' (DCM) is the most prominent example of this type of work; its influence also extends into the realms of research and inspection (see below)¹. The second source is drawn from research that has attempted to capture the nature and dimensions of care home life 'from the inside' and/or through the eyes of carers¹⁵. Predominantly this material is

¹The term 'care home' covers any establishment providing accommodation with personal or nursing care. There are broadly two types of care home: homes that provide nursing care (nursing homes) and homes that provide personal care and support (residential homes).

gathered from observational or questionnaire-based studies, which provide valuable insights and include evidence about the experience of the person with dementia; work that focuses specifically on the subjective experience of users is a new addition to the research portfolio¹⁶.

These two areas of activity combine around the concepts of quality of life and quality of care, both pivotal to the experience of living with dementia in a care home. As quality indicators used by the Commission for Social Care Inspection^{ii,iii} (CSCI) move to focus more on 'outcomes of care', taking account of the perspective of the person with dementia becomes increasingly important¹⁷. A brief review of research findings about quality of life in care homes for people with dementia and 'what is important' to residents will be offered before turning to evidence about their lived experiences.

Quality of Life and Quality of Care

Assessing quality of life among care home residents is a difficult task; it is a complex construct, which is variously measured and evaluated. A number of scales do exist, several of which have been specifically developed for people with dementia; these include the Quality of Life in Alzheimer's Disease (QoL-AD)¹⁸ scale, the DEMQOL¹⁹ and the DQoL²⁰. A persistent challenge in evaluating quality of life is that there are often differences between the ratings of staff, carers and residents. This appears to be a consequence of a difference in emphasis: a recent study found that residents' quality of life scores were most affected by the presence of depression and anxiety, whereas staff ratings were associated with dependency and behaviour problems²¹. A full picture of quality of life may thus require a combination of measures, incorporating the observations of all three groups²².

Despite the difficulties associated with measurement, evidence to date suggests that quality of life in care homes is largely determined by the existence of mental health problems and subjective well-being¹¹. Systematic assessment of residents' needs, and consideration of whether or not they have been met, has been suggested as a means of improving quality of life. The Camberwell Assessment of Need for the Elderly has been used towards this end²³.

Limited consensus also exists in relation to the linked concept of quality of care. First – as with quality of life – there are multiple perspectives to be accommodated. Second, the components of 'care' include those elements that are provided within the home as well as those offered by external sources, such as medical care. Third, good quality care depends on a range of micro level (satisfied staff) and macro level (financial stability of the provider) factors and their interaction; this makes its assessment complex and multifaceted. An important contribution to this field has been the development of DCM, an observational approach where items recording residents' activity can be combined to calculate a care index score²⁴ (see Chapter 30 for details on DCM). Given the limitations of all approaches to gathering information about quality of life and quality of care, an approach that accommodates multiple methods is recommended, rather than relying on a single source of evidence²⁵.

As might be expected, evidence about the quality of care in homes is mixed. Some of the variation between studies results

from methodological differences. For example, studies adopting a 'checklist' approach tend to reach more positive conclusions than those using direct observations²⁶. There is more robust evidence in relationship to those issues that impact negatively on user quality of life. These include prescribing patterns and covert administration of medication, physical restraint, electronic tagging and abuse²⁷.

In terms of therapeutic care practice, a recent survey undertaken by the Alzheimer's Society²⁸ of 4084 family carers, and care home workers and managers found that people with dementia are not always afforded dignity and respect. 'Dementia' had become a label that subsumes all other needs and submerges the person's characteristics; this tendency undermines the delivery of individualized care and encourages a task-oriented approach. Lack of activity and stimulation were also highlighted, particularly for people with severe dementia. As the availability of activities and opportunities for occupation is a major determinant of quality of life affecting depression, physical function and behavioural symptoms, this is a primary concern.

A 2007 CSCI¹⁷ inspection of care homes for people with dementia echoes a number of these themes. Although the inspectors found some excellent examples of one-to-one attention and care offered with warmth, understanding and tolerance, impersonal assistance was widely in evidence. The report noted that quality of staff communication with residents – both verbal and non-verbal – had a significant impact on well-being. Positive communication that is warm and friendly results in the person with dementia feeling happy and relaxed. Conversely, negative or neutral communication – interactions that are impersonal or task focused – leave residents feeling distressed and withdrawn. It is thus evident from this and other CSCI inspections that residents with dementia do not always receive person-centred care – care which is delivered in ways that promote independence and which draw on the individual's life course and experiences. It is to the role of experience in extending understanding of the person with dementia's life in a care home that we now turn.

Evaluating the Experiences of the Person with Dementia

Structured observational methods developed specifically for evidencing quality in long term care settings have a sustained history. They provide an opportunity to include the perspective of the person with dementia by collecting data on their experiences in communal areas, how they spend their time, and how they are treated. The most widely used dementia-specific observational tool is DCM. Kitwood, who developed the early prototype of DCM, described it as 'a serious attempt to take the standpoint of the person with dementia, using a combination of empathy and observational skill' (p. 4)²⁹. DCM requires training to employ but even with a standardized training programme the inter-rater reliability of practitioners is not high; those who use DCM for research purposes can achieve good reliability²². A linked example of an observational tool is the Short Observation Framework for Inspection (SOFI). This draws heavily on DCM and involves structured observation of a sample of five residents in a communal area and over an extended lunch period¹⁷. As part of an overall inspection, SOFI adds observational depth and detail.

More recently video and digital recordings have also been used in care settings³⁰. They can provide fine-grained analysis enabling in-depth observation to occur. Video evidence can be particularly valuable when working with people with very advanced dementia whose speech on first listening seems meaningless, but on repeated replay shows clear attempts at communication³¹.

ⁱⁱThe CSCI has responsibility for monitoring standards in care homes. In April 2009, the CSCI was replaced by the Care Quality Commission.

ⁱⁱⁱRegulatory bodies are established in each UK country to apply and monitor care standards: in England, it is the Care Quality Commission; in Wales, the Care Standards Inspectorate; and in Scotland, the Care Commission.

The extent to which selfhood or identity is preserved in people with dementia has been a key focus of observational studies³². Results suggest that although the self is affected by dementia, manifestations of selfhood persist even in late stages of the illness along with the capacity to develop positive relationships³³. Questionnaire-based studies have also begun to address this issue, concluding that aspects of identity, as with selfhood, are retained by people with advanced dementia³⁴. Research also identifies recurrent issues of loss, communication difficulties, frustration and sadness among residents along with lack of meaningful occupation. Minimal levels of well-being are widely noted in many studies of care homes; these are particularly pronounced for people with the greatest dependency needs³⁵.

Very recently attempts to explore the subjective experiences of people with advanced dementia in long term care have been made. A seminal study by Clare *et al.*¹⁶ provides an interpretive phenomenological account of the subjective, psychological experience of living with moderate to severe dementia in a care home. The thematic account highlights four interrelated experiences (see Table 15.1). Daily experience was shaped by the losses resulting from dementia for most residents and was characterized, to a considerable degree, by distressing thoughts and feelings. The psychological impact of 'being in the home' was associated with a sense of uncertainty, lack of control and limited self-determination. These feelings were compounded by multiple experiences of loss – lost abilities, lost memories, and lost identity – which resulted, for some, in feelings of worthlessness. Fear of 'being alone' or 'being lost' was also a dominant experience. However, through their accounts the residents emerged as 'agents actively seeking to cope with their situation' (p. 718). Many found ways to contribute and focused on the positive aspects of home life, including being part of supportive relationships. Such relationships appeared to be pivotal to maintaining a sense of well-being; their absence contributed to feelings of distress and alienation³⁶. Although participants displayed many constructive ways to cope, the effects of changes resulting from dementia, coupled with the context of institutional care, placed severe limitations on their expression of personal agency. Consequently, some residents experienced frustration, anger and boredom, especially around minimal activity and daily occupation³⁷. Lack of freedom and independence was experienced by some residents as 'restrictive' and communal living could give rise to considerable confusion. If we are serious about addressing current deficits in care home provision, understanding the subjective experience of people with dementia is a fundamental dimension of enhancing practice and thereby improving both quality of life for

users and quality of care. The implications of this shift in emphasis are the focus of the final section.

IMPLICATIONS FOR PRACTICE: ENHANCING QUALITY OF LIFE IN CARE HOMES

Much of the evidence reviewed above identifies an overarching need to embed person-centred values into care planning and delivery in care home settings. The pivotal role of developing meaningful relationships and an emphasis on effective communication appear to be the twin routes to enhancing well-being in residents with dementia³⁸. There is a related need to address a number of practical and therapeutic deficits. Extending levels of engagement for people with dementia by offering meaningful activities is a prominent example; supporting the continued expression of personal agency and autonomy is a secondary challenge³⁹. Managing the difficult and often negative emotions that many residents experience is also important; this depends on the establishment of genuine staff–resident relationships and the capacity of staff to respond sensitively and on an individual basis to need. Supporting role identity is another element of good care; this depends on staff engaging with residents' life course and promoting opportunities for residents to have a continued social role. Being aware of the challenges of living a semi-public life in an institutional setting is an additional facet; this includes working with residents to deal with difficult relationships and providing opportunities for privacy¹⁶.

As noted above, evidence suggests that preservation of self and identity is possible even in those with advanced dementia. The maintenance of previous relationships with friends and relatives is key to providing biographical continuity. Moving into a care home tends to disrupt existing relationships, which may impact negatively on users' sense of self, a process compounded by loss of independence⁴⁰. In this context the relevance of care that is truly person centred becomes clear and understanding what matters to an individual, including his or her wishes, is critical. Story-telling and biographical work can help to develop relationships between staff and residents; this not only increases the likelihood of the resident being seen and valued as an individual⁴¹ but also helps to maintain their cultural and ethnic identity.

Recognition of residents' emotional and social needs – in addition to their physical needs – is crucial to achieving person-centred care. Spending time engaging people with dementia 'in conversation' can also provide a powerful counterweight to the often task-oriented exchanges between residents and staff. It has been suggested that relationships are the key to maintaining well-being in people with dementia and that effective communication – the by-product of a good relationship – undergirds good quality dementia care⁴². Some commentators even argue that caring for a person with advanced dementia is *essentially* about finding ways to communicate even when these may be unfamiliar. Meaningful interactions require the development of a set of core skills among staff: attentiveness, active listening, observation of non-verbal signs, and the use of personal objects to support communication⁴³. Staff can also enhance effective communication by ensuring that they face a resident when speaking, have light upon them rather than behind them, using gestures that are consistent with what they are saying, and presenting information simply and slowly⁴⁴. A part of this process is also supporting the 'coping strategies' the user has developed to manage the difficulties he or she encounters in the home.

For many care staff, being able to effect meaningful communication with residents is a crucial component of job satisfaction; lack

Table 15.1 Key themes from the study of Clare *et al.*¹⁶

<i>Nothing's right</i> : isolation, alienation, lack of choice, lack of control, fear, worthlessness
<i>I'll manage</i> : making the best of things, valuing contacts and friendships, finding ways of continuing to be useful, being accepted as you are, having a friend in the home, having links with relatives/family, acknowledgement of getting older
<i>I still am somebody</i> : part of coping, affirming one's sense of identity, managing well despite limitations
<i>It drives me mad</i> : frustration and anger at the situation, confined, wanting more independence, boredom, lack of activity, annoying behaviour of other residents, uncertainty, fear, irritation

of opportunity to build personal attachments is a strong predictor of staff burnout⁴⁵. This evidence suggests that enhancing communication skills – a widely noted practice deficit – needs to be a distinctive focus of dementia care training and that care homes need to find ways to ensure staff have the time and expertise to build up and sustain interactions with residents. It is important to recognize that providing care that takes residents' emotional experiences and wishes seriously, facilitates choice and provides a sense of security and reassurance is both time consuming and intensive⁴⁶.

A number of key characteristics mark out those care homes that successfully promote and sustain good quality care: clear leadership, a positive ethos, and staff training and support to enhance communication skills and promote retention⁴⁷. A recent project – the 'Enriched Opportunities Programme' – offered a multilevel approach to enhancing the quality of care in three care homes for people with dementia: it included a strong emphasis on leadership and dementia expertise, a trained care team with empathy for residents, and a programme of care and activity developed to meet the needs of individuals. It evidenced that by adopting a coherent focused approach that takes full account of the experiences of residents, care practice and the overall culture of care can be significantly improved⁴⁸.

CONCLUSION

People with dementia living in care homes face enormous challenges. In addition to declining cognitive powers, users have to cope with a new and often unpredictable environment. They may also be cared for by people who know very little about them and who are, encouraged by an over-reliance on 'procedures', to focus on their physical safety rather than their emotional well-being. Additionally, frailty, communication difficulties and dependency on others often means that their needs are overlooked and their voices marginalized. Understanding more about the experience of living with dementia in a care home is a critical contribution to improving both quality of life and quality of care. Prioritizing relationships and communication, the establishment of genuine staff–resident attachment, managing distressing emotions, and ensuring that care is individually planned and delivered are key dimensions of practice that place the user experience at its core. Intimate biographical knowledge about the user and their life history, and bolstering the user's abilities, sense of self and identity are key aspects of providing person-centred care. The provision of tailored day activities and recognition of the stresses communal life can cause are also important issues highlighted by research. Excellence in dementia care begins with an understanding of what it is like to live with the illness *throughout* its trajectory⁴⁹. As there is no doubt that residential care is, and will continue to be, one of the dominant types of provision for people with advanced dementia in the developed world, increased emphasis on research that explores the user experience and practice that foregrounds it, is a central component of effective and positive practice in care home settings.

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Ageing: International Statistical Trends and Prospects

Fiona E. Matthews¹ and George M. Savva²

¹*MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK*

²*Department of Public Health and Primary Care, Institute of Public Health, Cambridge, UK*

INTRODUCTION

The term 'ageing' is a generalized complex terminology that can address a number of concepts, including aspects such as the demography of the whole population or trends within specific age groups (such as births or the older population). But the term 'ageing' is also a generic term for the older population and factors associated with it. Within this chapter we aim to investigate some of these factors and show how the population of the world has changed, how historical changes will affect health in the next decades, how our estimates of population change are challenged by diseases and treatments and what can we currently say about the health of the older population.

TRENDS IN POPULATION SIZE

The historic, current and future population demography demonstrates historic and interesting changes. Over the course of the last 50 years and in the next 50 years there has been and will be a fundamental shift in the distribution of the human population. Different areas of the world display different demographic shift patterns; for example the shifts in the United Kingdom and United States show patterns that are different from those seen in China and India¹. Nevertheless, all countries are experiencing population ageing.

Figure 16.1 shows the demographic changes across different regions of the world. China and India have not only had a large change in the distribution of the population, they have also increased dramatically in size. The shift in this distribution means that the proportion of the population that is already considered 'older' varies greatly by country. Current estimates of the proportion of the population aged 60 years and over are shown in Figure 16.2. Although the relative distribution shifts from Europe and North America in 1950 towards Asia by 2050 (Table 16.1) there are large numbers in the older population throughout the whole world.

Despite these differing demographic patterns already 64% of the older population (aged 60 and over) live in developing countries and by 2050 nearly 80% of those aged 60 and above will live in developing countries². This definition, however, includes only Europe, North America, Japan, Australia and New Zealand within the developed countries – a pattern that may not reflect true differences³.

Table 16.1 Percentage distributions of those aged 65 and older by region, 1950–2050

Region	1950	1975	2000	2025	2050
World	100	100	100	100	100
More developed regions	49.0	48.7	40.7	31.5	21.7
Less developed regions	51.0	51.3	59.3	68.5	78.3
Africa	5.5	5.4	6.2	6.8	9.4
Europe	34.4	33.5	25.6	17.8	12.1
Asia	43.9	43.6	51.6	57.9	62.1
North America	10.8	10.8	9.3	8.7	6.4
Latin America and the Caribbean	4.7	6.0	6.7	8.1	9.4
Oceania	0.7	0.7	0.7	0.7	0.6

TRENDS IN FERTILITY

Trends in fertility affect the composition of the older population many years later. While this ensures that surprises are not often encountered in the description of the older population it also means that demographic influences are less immediate at solving the challenges predicted. The decisions made on childbirth both between the two World Wars and after the Second World War are now shaping the composition of the older population. The generation of children to the 'baby boomers' in the 1960s are now reaching middle age and the size of this demographic bubble can be clearly seen in the population pyramids (Figure 16.1). Many European countries have for a number of years been below the reproductive factor (2.1 births per woman²). This rate of replacement of the younger population will again shift the relative balance of the population in terms of young and old. In this case there is a double impact, as the baby boomers reach old age with a lack of grandchildren to replace the status quo of the pyramid. This will create, at least for the next 50 years, an ageing society. The current fertility decisions of the early adults are not suggesting that this imbalance will refocus. In fact the decisions to delay or reduce childbirth across the whole of the developed population (and wider in many cases) mean that the majority of countries are now below the 2.1 factor.

In the less developed regions where infant mortality is still high, despite advances resulting from the Millennium Development Goals (UN Millennium Goal 4), the fertility rate is still relatively high but is reducing dramatically. The developing countries are still experiencing an ageing population, but in a more historically understood way, although many unknowns remain⁴. A recent UN report states that fertility levels are unlikely to rise again to the historic highs and therefore the expression of population ageing is irreversible⁵. However future population size is sensitive to small but sustained deviations from the replacement level⁵.

The patterns of fertility affect not only the absolute level of the future middle-aged and older population but they also have a direct impact on the life of the older population at the individual level. The number of available carers within a population is almost universally linked to the extended family support. As this family structure shifts so will the life of the older person⁶. An international comparative

survey on the older population undertaken in 1996 showed that the proportion of the older population aged 60 and over living in three-generation households was 29–43% in Asian countries compared with 2% for European and North American countries⁷. If this structure is mimicked with the changing demographic then it will impact enormously on policy.

TRENDS IN LIFE EXPECTANCY AND HEALTHY LIFE EXPECTANCY ACROSS THE AGE RANGE

There has been a steady and consistent increase in life expectancy at birth across all continents and in both males and females (Figure 16.3). However, the major issue in the statistical trends in healthy life expectancy is whether with the extension of longer life there is also an extension of healthy life (i.e. the total remaining life that can be expected to be free of disability). Three patterns of

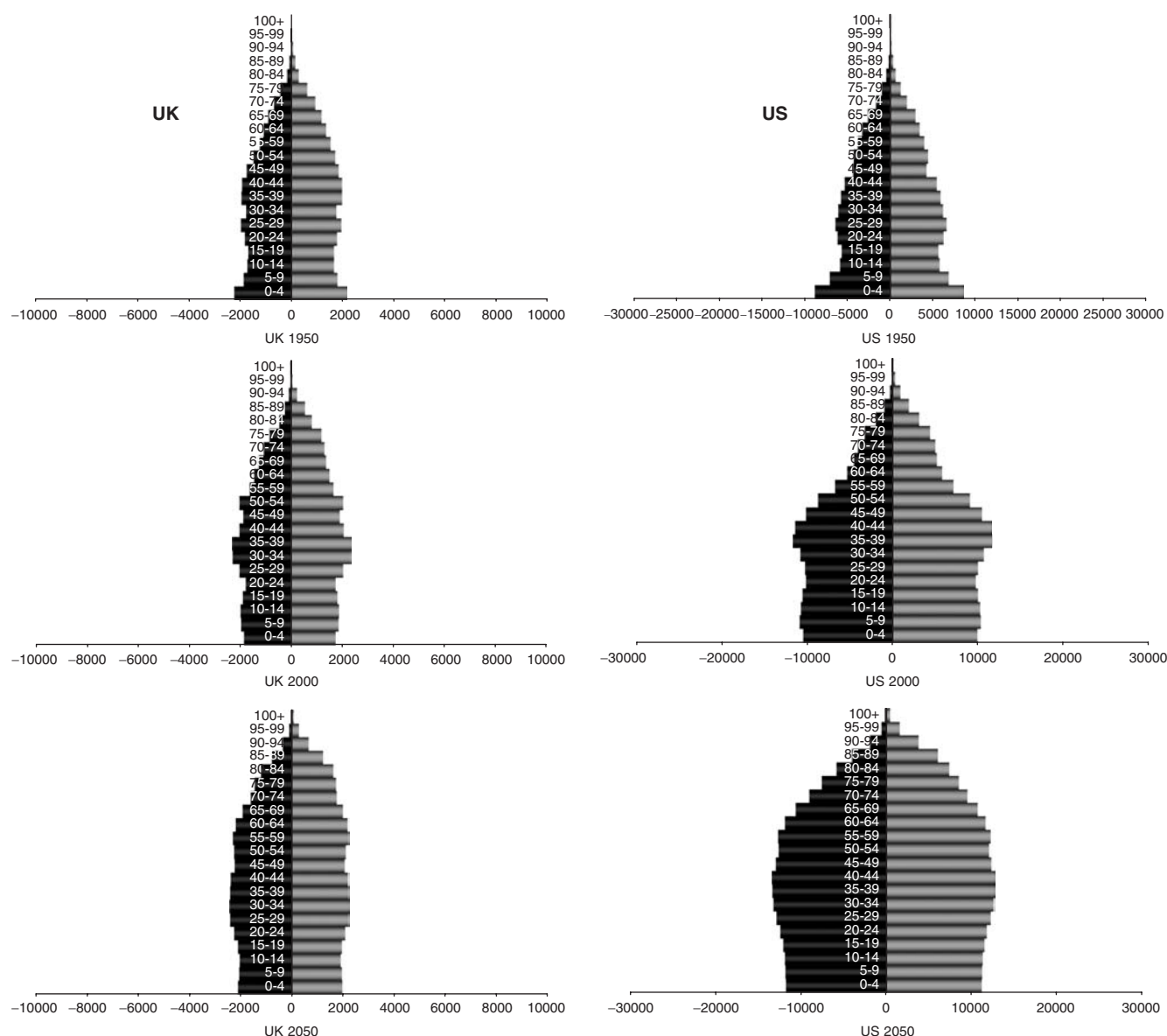


Figure 16.1 Population pyramids and changing distribution. Bars refer to the size of the population (in thousands) of men (left) and women (right) in each age group

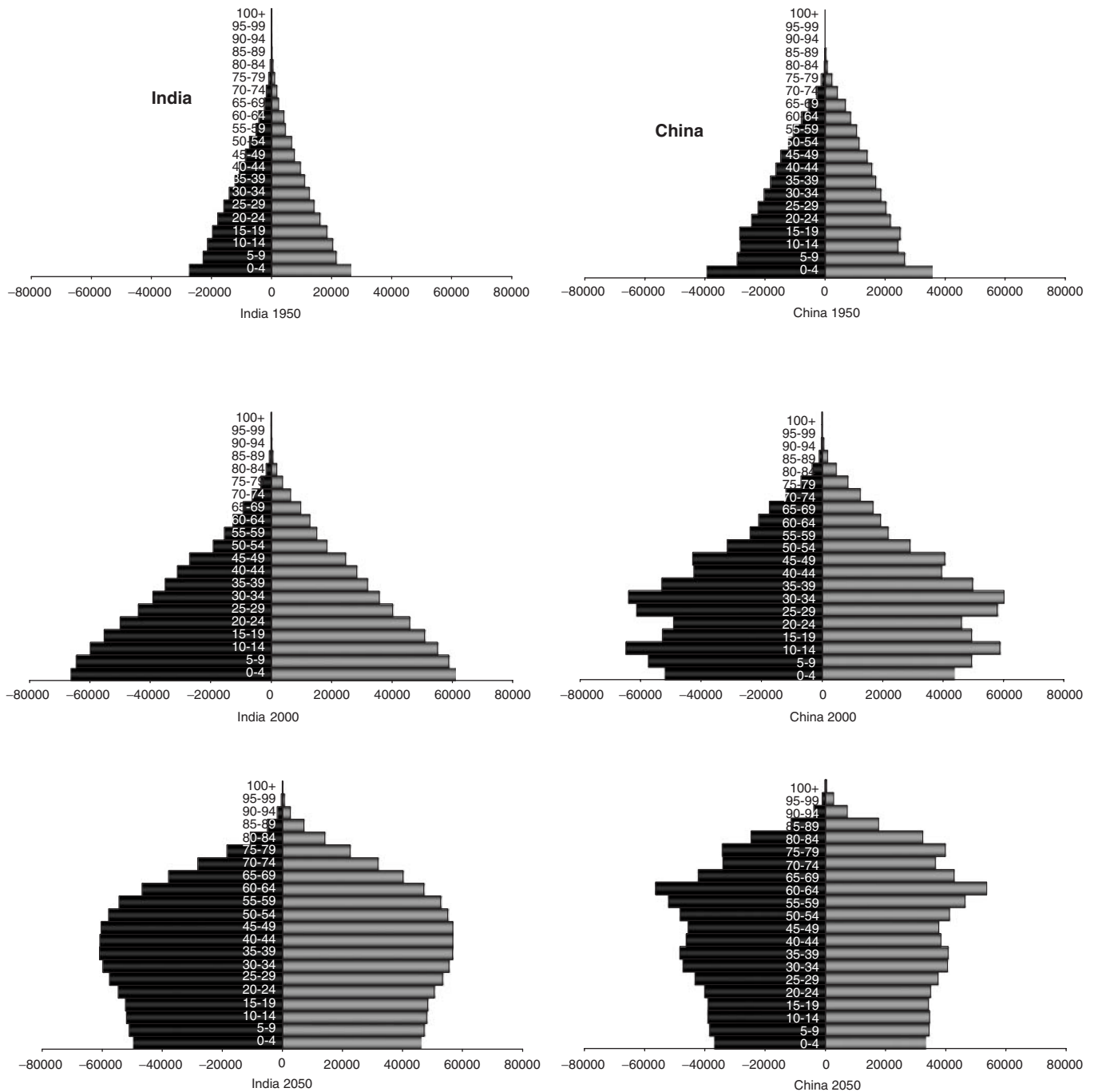


Figure 16.1 (continued)

population change in healthy life expectancy have been proposed, an expansion of morbidity⁸, a compression of morbidity⁹ or dynamic equilibrium¹⁰. Expansion of morbidity would imply longer life expectancy but at the same time longer life expectancy in ill-health, compression of morbidity would imply that the life extension is predominantly from the healthy life and dynamic equilibrium implies that severity may change, but the burden remains constant. Evidence to date suggests that all three scenarios can occur in different populations at different times.

MEASURING THE CHANGING HEALTH STATUS OF THE OLDER POPULATION

Assessing the compression or expansion of morbidity relies on being able to measure the health status of the older population. Complementary insights regarding the changing health of the older population can be gained from several major sources, each with their own merits and drawbacks. In developed countries routinely gathered statistics such as census data and birth and death certification may be used and these provide reliable information on demographic changes. Routine

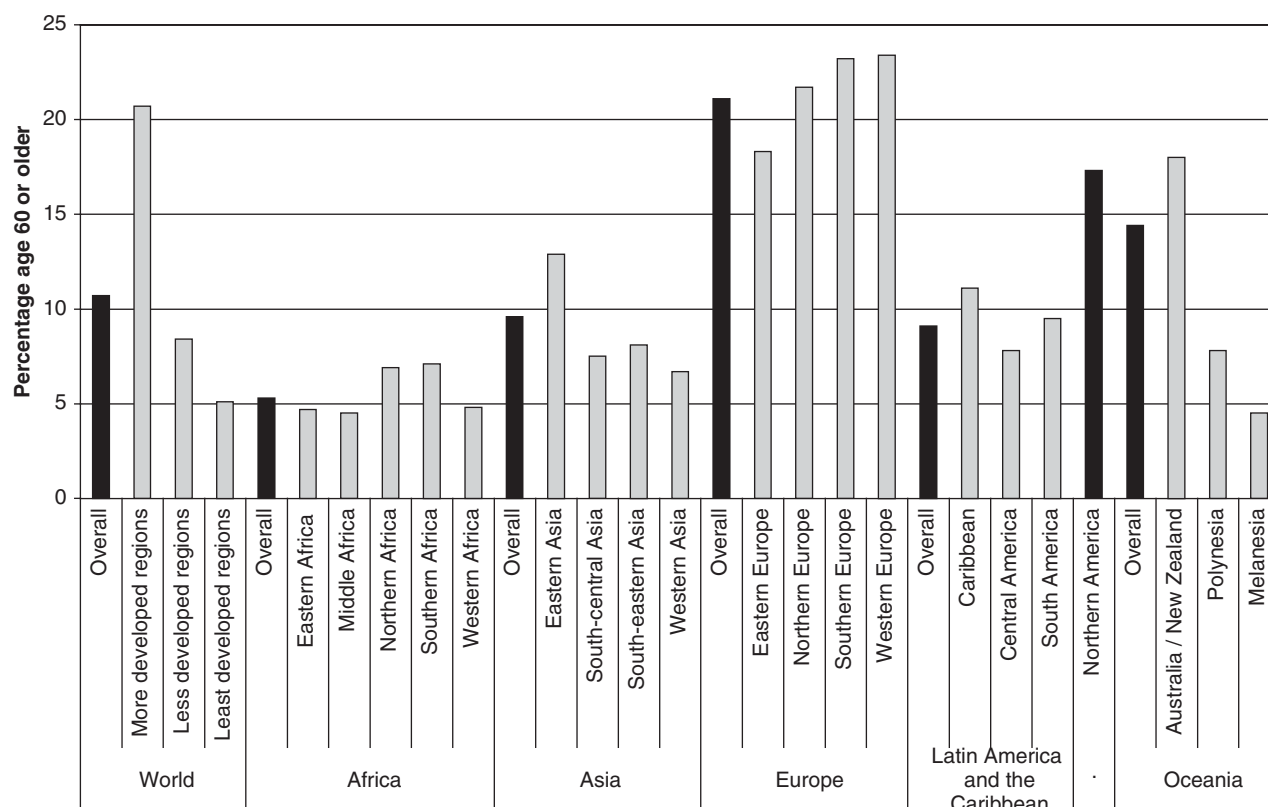


Figure 16.2 Proportion of the older population by country

medical databases, such as hospital admissions data, prescription records or disease registers provide another source. However the reporting of medical conditions to these registers may be biased by various processes. Both the mechanisms by which older people come to the attention of health care providers and reporting practices change with time, particularly in the older population, as a result of changing awareness, attitude and perception of health both by older people and their health care providers. Reporting practices can also vary geographically. Psychiatric conditions in the older population are particularly likely to be under-reported, and death certificates often do not mention major diseases such as dementia despite it being present or a major contributing factor to the death of an older person. Using routine data to record the health and in particular the psychiatric health of the older population is therefore unreliable. Furthermore in many areas of the world such statistics are not collected routinely.

To overcome some of these methodological difficulties, epidemiological studies are conducted. These typically involve recruitment of a cohort who are chosen to be as representative of the population as possible, and these are then subjected to a standardized assessment of their health. Repeating standardized assessments in the same cohort over time leads to a longitudinal study in which changes in the health of the population can be examined. Longitudinal epidemiological studies of health are not without their difficulties. Biases in selection and drop-out are possible and must be examined carefully. Epidemiological studies often have limited applicability outside the populations in which they are conducted, and compared with routine statistics they are limited by their size in terms of detecting

small changes. Studies that rely on self-report may still be influenced by changing understanding or perceptions of health¹¹, or by cross-cultural differences in the interpretation of questions, and so questionnaires must be designed to be as objective as possible.

Projections about the future burden of disease in the older population are generated by combining demographic data on the likely future numbers of older people with epidemiological data regarding disease prevalence and the impact of disease.

TRENDS IN GLOBAL HEALTHY LIFE EXPECTANCY

The international patterns of disability and healthy life expectancy are not consistent with different patterns seen within different populations. Countries have reported both an increase in the prevalence of disability (Sweden¹²), rates stagnating (Australia¹³), or decreasing (United States¹⁴, France¹⁵, Finland¹⁶, Japan¹⁷) and different evolutions reported for subgroups (men and women in Spain¹⁸ and Denmark¹⁹) or for mild rather than severe disability (Netherlands²⁰). Trends in disability rates are not sufficient, however, as changes in the age distribution of the population need to be combined with the changes in the disability rates to see the full population, and hence conflicting results with another study from Australia found evidence of a compression of morbidity²¹. A recent European comparison has shown that there are still large variations across Europe, and that these inequalities may be becoming larger, particularly between Eastern and Western Europe, and that healthy life expectancy may show more variations than life expectancy²².

In the developing world there is currently little evidence to investigate whether there is a compression of morbidity or an

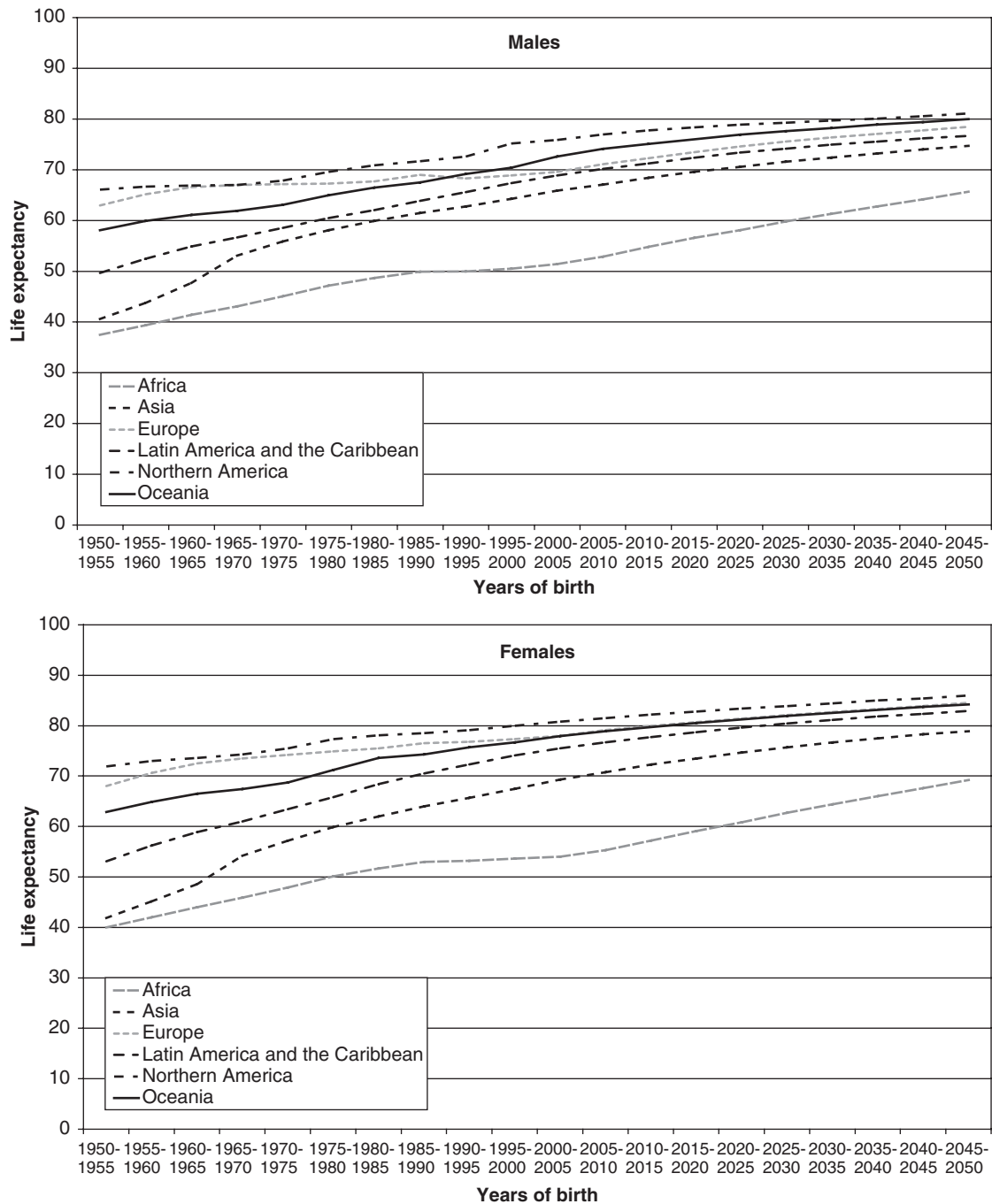


Figure 16.3 Life expectancy at birth across world regions. From Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat¹.

expansion²³. These countries are at the early stages of the chronic disease growth, though it is becoming an increasing problem. The challenge for a healthy older population across the entire world is one of a focus on lifelong health, not just health in mid to late life²⁴. This sort of focus is long term and often overlooked within a resource scarce environment.

It is also possible that these different balances will fluctuate in different populations at different times and may well be modified by intervention strategies and changes to national care policies.

CHANGES IN MARKERS OF HEALTH

As well as varying across cultures, whether the health of the older population is improving or worsening also depends on which measures of health are considered^{25,26}. Most studies of changes of health in the older population focus on changes in the levels of disabilities, since this is one of the major determinants of poor quality of life, the inability to live independently and the need for long-term care. Many such studies have shown improvements between cohorts with time. However, the level of disability of an

individual is determined both by their underlying health conditions leading to functional impairment and by their environment. Changes in levels of disability may therefore be caused by changes in lifelong exposure to risk factors affecting the prevalence of diseases, the changes in the impairments caused by diseases when they occur, and by changes in technology and the environment. Changes in the prevalence of health conditions may reflect both changes in incidence and in survival with that condition.

The evidence regarding age-specific trends in disability in the older population is mixed. Some evidence of an improvement has been seen in the prevalence of mild disability, while the level of more severe disabilities has remained constant or has worsened slightly. In contrast, most comparisons of health conditions in the older population have shown an increase in major disease prevalence and co-morbidity as well as in objective measures of specific functional limitations^{12,27,28}. Consistent improvements in survival with diseases such as heart disease and stroke have not been offset by reductions in their incidence, leading to an increase in prevalence. On the other hand, disability among stroke survivors and those with heart disease has decreased.

Although much of the increase in human life expectancy in the past century has been caused by a reduction in infant mortality, life expectancy of the older population is also increasing. This will lead to changes of the population structure within the older population, particularly in an increase in the numbers of the oldest old compared with the younger old²⁹. The oldest old are an emerging population group in terms of research and information on changes in their health and demographic characteristics are only beginning to become available. The oldest old have high rates of physical and cognitive impairment and are likely to live in institutions³⁰. A recent report highlighted changes in the demographic and socioeconomic characteristics of the oldest old population in England and Wales³¹, revealing an increase in the numbers of the oldest old living alone and as well as an increase in health care resource utilization. More research is needed on the oldest old.

CHANGES IN MENTAL HEALTH

Mental health is increasingly recognized as a significant independent contributor to the burden of disease and as a mediator of aetiological factors for other diseases³², and maintaining healthy brains in later life is now a research priority³³. Mental health issues such as schizophrenia and depression affect the whole population, and in the older population dementia and cognitive decline are of specific importance. Mental health in early and midlife is a strong predictor of mental health in old age.

Little reliable evidence is available regarding trends in the prevalence of psychiatric conditions in the older population. A comparison of two studies with similar methodology carried out 10 years apart showed a significant increase in major depression diagnoses in all sociodemographic groups³⁴.

The effect of changes in age structure of the global population on the number of people with dementia was estimated by a Delphi consensus study, which combined all the available evidence regarding dementia prevalence and future population trends³⁵. The number of people aged over 60 with dementia in Europe and North America is likely to have increased by 50% from 2001 numbers by 2020 and will have doubled or trebled by 2040. The numbers with dementia in East Asia and Africa are expected to increase by four times in this time period. There are projected to be 81.1 million people worldwide

with dementia in 2040 compared with 24.3 million in 2001, with 70% living in the developing world. However these estimates are based on limited information; while reliable estimates for dementia prevalence are available in the developed world, direct estimates are not available in many areas, although cross-cultural studies that have been undertaken suggest that patterns may be different and further information on global dementia epidemiology is urgently being sought.

Changing incidence and survival with dementia and changes to the disability associated with dementia will affect its impact in the ageing population, and these trends will depend on changing prevalence of risk factors as well as interventions and management. The age-specific incidence of dementia and cognitive impairment has been suggested to have decreased slightly, possibly due to the effects of improved health-related lifestyle and education³⁶, while the increase in survival from stroke, might suggest an increasing prevalence³⁷. Social networks and intellectual stimulation are increasingly recognized as being important determinants of health and mental health in the older population. Models estimating the impact that changes in dementia trends and treatments will have on the future disability burden illustrate the uncertainty in predictions and highlight the need for treatments that will alleviate that burden³⁸.

FUTURE PROSPECTS AND DIRECTIONS

International trends in ageing are difficult to predict, though recent publications have attempted to investigate not only the population shift⁵, but also the trends in disability and health³⁸. However it is not just the population shift that requires careful consideration, other factors including changes in food, water, housing, education, early and midlife health and behaviour and the physical and biological environment will all affect our future health prospects³⁹. Trends seen across the world raise a number of concerns for the future of the ageing population, foremost of which are the increase in the burden of disease and dependency. Interdisciplinary research across the whole world and in all populations is required in both the ageing process of an individual and the effects of an ageing population, in order to understand and meet the challenges now and in the years ahead⁴⁰.

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Economics of Ageing and Mental Health

Anders Wimo

*KI Alzheimer's Disease Research Center, Department of Neurobiology, Care Sciences and Society,
Karolinska institutet, Stockholm, Sweden*

INTRODUCTION

The greying of the world and the high prevalence of mental disorders have highlighted the vulnerability of the social and health-care systems. Based on demographic forecasts, almost apocalyptic scenarios have been presented. The number of people 65 years and older will increase from about 500 million people in 2010 to about 1 billion in 2030. The diseases of the elderly and mental disorders are in general chronic, resource demanding, more or less incurable and long lasting (decades). These disorders also involve many sectors of the society; not only the health-care sector but also to a greater extent social services and informal carers, and they cause a substantial loss of well-being and life-years worldwide¹. If we also add a financial crisis in the many public care systems we must consider fundamental issues such as economic burden, cost effectiveness of treatments, priority settings, equity, how to organize, finance and distribute care in any health economics analysis.

Health economics is the application of economic theory to health care². There are, however, several methodological issues in this field, which also link to fundamental health economics questions. Some basics in health economics must also be considered. The main focus in this chapter is on dementia and similar disorders, but the principles are applicable to any mental or chronic disorder and so we have also included examples from other mental conditions.

PERSPECTIVE

A health economics analysis can be seen from different viewpoints such as a societal perspective or specific cost-bearers (e.g. county councils, municipalities, insurance companies)³. A societal perspective is preferable and should include all relevant costs (that is both direct costs within the health sector and indirect costs due to production losses and costs of informal care) and outcomes. Depending on the selected viewpoint, the outcome of the analysis may vary.

RESOURCE UTILIZATION AND COSTING

A key issue in all economics is the cost concept. The opportunity cost, which most economists recommend using in descriptive studies and economical evaluations, is the value of a resource in its best alternative use². Care resources are more or less always scarce and

the use of a resource in one specific way will result in some lost benefit because resources were not allocated to another option⁴.

Ideally, opportunity costs should be based on market prices, which in health care are not always easy to identify. For example, for an informal caregiver, who because of the care-cost demands is not working, the opportunity cost is the value of the forgone work that could have been done.

Costs can be divided into direct medical costs, direct non-medical costs and indirect costs. In a simplified approach, direct costs refer to the value of resources used and indirect costs to resources lost. Direct medical costs refer to resources used in the medical care system, such as costs of hospital care, drugs and visits to clinics. Direct non-medical costs are those outside the medical care system, such as costs for formal community care and transports. Depending on how care is organized, costs of long-term care and home care can be regarded as a medical or non-medical direct cost.

Indirect costs are costs due to production losses (such as sick leave, early pension, impaired productivity) or mortality. Costs of informal care (see below) is a complicated issue in itself^{5,6}, and are often classified as indirect costs, but this is not always obvious.

The costing process usually consists of two phases: first the use of resources is measured in terms of physical units (e.g. days in hospital, hours of home support) during a specified period of time; secondly, this resource utilization is calculated into costs. For economic studies of dementia, we have developed a process called resource utilization in dementia (RUD) (Table 17.1)¹¹. Because the organization of dementia care varies between countries, the process must be adapted to the particular national situation. This process also includes linguistic adaption, because the meaning and the costs of care concepts (such as 'institutional care') may vary between countries even if the basic language is similar, e.g. if English is spoken in the UK and South Africa, it does not necessarily mean that the interpretation of care concepts is the same. In multinational trials, it is recommended that the aggregation of results from different countries is in physical units and not in costs.

TYPES OF STUDIES

Several approaches can be used in health economics analyses (see Table 17.2)⁷. With the cost description (CD) approach, the costs of a single treatment are described without outcomes/effect measures

Table 17.1 Components of a resource utilization in dementia (RUD) plan³⁸

<i>Patient</i>	<i>Caregiver</i>
Accommodation/long-term care (Work status)	Informal care time (for patient) Work status
Respite care	(Respite care)
Hospital care	Hospital care
Outclinic visits	Outclinic visits
Social service	Social service
Home nursing care	Home nursing care
Day care	Day care
Drug use	Drug use

Table 17.2 Different types of health economics studies

CD	Cost description
CA	Cost analysis
CMA	Cost minimization analysis
CEA	Cost effectiveness analysis
CBA	Cost benefit analysis
CUA	Cost utility analysis
CCA	Cost consequence analysis
COI	Cost of illness

and without making any comparisons with alternative treatments. In a cost analysis (CA), the costs of different treatments/therapies are compared, but there are no outcomes/effects included in the analysis. A complete health economics analysis should include both measurements of costs and outcomes and comparisons between different treatment alternatives. This is often expressed as a ratio: the incremental cost-effectiveness ratio (ICER)

$$\Delta C / \Delta E = (C_A - C_B) / ((E_{AT1} - E_{AT0}) - (E_{BT1} - E_{BT0}))$$

where C = costs, E = outcomes/effects, A, B = treatments, $T0, T1$ = time for assessments.

There are, however, other approaches such as net benefit analyses (net monetary benefits and net health benefits)⁷. Irrespective of approach, a willingness-to-pay level (for a specific outcome) is crucial.

In a cost minimization analysis (CMA) there is evidence that the effects/outcomes are similar between the treatment options and thus the analysis is focused on identifying the therapy with the lowest cost. The difference between CA and CMA is that in a CA there is no data about effects/outcomes.

In a cost-effectiveness analysis (CEA), the effect is expressed as a non-monetary quantified unit such as the cost per death or nursing home admission averted. Other outcomes may be functional measures such as activities in daily living (ADL) capacity, severity states of disease and cognition (e.g. scoring on different scales). In a cost benefit analysis (CBA), costs and outcomes are described in the same unit (usually monetary). Early CBA analyses had a simple human capital approach, while the modern theory of CBA is complex and includes willingness-to-pay approaches such as contingent valuation^{8,9}. In a cost utility analysis (CUA), the effect is expressed in terms of utilities, such as quality of life. In CUA, the concept of quality adjusted

life years (QALY) is frequently used (as well as other similar measures such as disability adjusted life years (DALY) and healthy years equivalents (HYE)).

In a cost consequence analysis (CCA), cost and outcomes are analysed and presented separately and there is no direct mathematical connection between these two measures.

Cost of illness (COI) studies are descriptive (such as the costs of illness of dementia in Sweden in SEK 50 billion/year). Two approaches can be used: the prevalence method and the incidence method. With the prevalence approach the costs include for all cases for a specified time period, most often one year, including those already suffering from dementia and for new cases occurring during the period in question^{10,11}. With the incidence approach the costs for new cases during e.g. one year are estimated, here both the annual costs and future (discounted) costs are included. The choice of approach depends on the purpose of the study: if the aim is to illustrate the economic consequences of interventions, the incidence approach is preferable. If the idea is to estimate the economic burden during a defined year the prevalence approach is the best option.

Another issue in COI studies is whether to use a top-down or a bottom-up approach. In top-down analysis, the total costs for a specific resource (e.g. health-care costs) are distributed over different diseases. Such studies often rely on data from national registers or similar. The bottom-up method starts from a defined sub-population (often from a local area) with for example dementia and registers all cost of illness related to the disease, followed by an extrapolation to the total dementia population. The problem here is compensating for co-morbidity and net costs may be difficult to estimate. It is also important to specify the included cost categories (e.g. cost of informal care). COI studies can be expressed as costs per case and year or as total costs in a specific country/region. Examples of COI studies of mental disorders are seen in Table 17.3. The cost figures highlight the great variation in cost estimates and the importance of identifying the included cost categories.

INFORMAL CARE

Family members and friends or others close to people with mental disorders are heavily involved in their care. Their situation is of great interest from two aspects. First, mental disorders have consequences for the carers themselves. In this sense, their situation is often very stressing (it can be described in terms of burden, coping, but also in terms of morbidity and mortality).

Secondly, in their role as informal carers they are producers of unpaid care. This production of care is a very important part of the costs of mental disorders from a societal perspective. Costing of informal care is complicated and controversial. There are two frequently used methods: the replacement cost approach and the opportunity cost approach, both of which have drawbacks when applied to mental disorders. The replacement cost approach means that if informal care has not been provided, professional staff must be hired on a 1:1 ratio (e.g. one hour of informal care corresponds to one hour of professional care).

In our opinion, informal care should be valued by its opportunity cost, which for a person of working age, is a production loss, but regarding leisure time and contributions by retired persons or persons with no position on the labour market, it is more complicated and there is no given answer.

In most cases, the replacement cost approach results in higher costs of informal care than the opportunity cost approach.

Table 17.3 Examples of COI studies of mental disorders

Country/ Region	Disorder	Costs (billion US\$ 2006)	Annual costs per patient (US\$ 2006)	Cost categories included	Source
World	Dementia	326.8	11 138	D, IC	(42)
EU27	Dementia	195.6	26 761	D, IC	(43)
UK	Dementia	34.7	47 847	D, IND, IC	(44)
Sweden	Dementia	7.4	52 095	D, IND, IC	(45)
Europe	Depression	138.5	5 016	D, IND	(46)
Sweden	Depression	4.8	NA	D, IND	(47)
Europe	Psychosis/schizophrenia	46.2	10 011	DC	(48)
UK (London)	Schizophrenia	NA	11 981	DC	(49)
Spain (Santander)	Schizophrenia	NA	2 365	DC	(49)

D = Directs costs; IND = Indirect costs; IC = Costs of informal care

Currency conversions by PPPs (purchase power parities), time transformations by national price index of health

Sources: see^{39–41}.

Table 17.4 Randomized controlled trials with empirical economic data on pharmacological interventions in Alzheimer's disease

Drug	Disorder	Country	Duration	Results (US\$ 2006)	Reference
Donepezil	Alzheimer's disease	Nordic	1 year	1 228 (ns)	(50)
Donepezil	Alzheimer's disease	Canada	6 months	320 (ns)	(51)
		France, Australia			
Donepezil	Alzheimer's disease	UK	60 weeks	−907 (ns)	(52)
Memantine	Alzheimer's disease	USA	6 months	7 946 (p < 0.05)	(53)
Risperidone (r), olanzapine (o) and quetiapine (q)	Alzheimer's disease	USA	9 months	(per month)2002, ITT 193(r), −9(o), −199 (q) Overall p = 0.02 (placebo lower)	(54)

BOOTSTRAPPING

Cost data are often skewed (large variation in resource utilization and costs and lots of zero values), making traditional statistical analyses questionable. To compensate for these problems, bootstrapping is frequently used. By resampling from the original database, a new database is created. After each drawing from the original database to the new database, the drawn case is returned to the original database. There are many ways of bootstrapping but in general the new database has the same number of cases as the original sample. After repeating the resampling process several times (e.g. 100–10 000 times, using statistical software), statistical analyses, such as calculating confidence intervals, can be performed, assuming a better representativeness compared to the original reference population¹². Confidence intervals are often more narrow with bootstrapping than without.

OUTCOME MEASURES

A health economics analysis is incomplete if there is no outcome/effectiveness measure related to the costs (mostly as a cost-effectiveness ratio). In mental disorders or diseases of the elderly, the choice of effectiveness measure is not obvious. The priority discussions may be between different treatments of a particular disease, but also between treatments of different diseases (e.g. schizophrenia and stroke). In the first situation, diagnosis-specific outcomes may be used (e.g. depression scales in depression,

cognition in dementia), but in the latter case, generic outcomes are necessary. Also when diagnosis-specific outcomes are used, there may be interpretation problems – what is the societal value of an incremental cost of X US\$ for a one-point reduction in a depression scale?

Health-related quality of life (HRQoL) is often suggested as the most relevant outcome measure in chronic disorders (such as mental diseases). HRQoL instruments consist of several dimensions (e.g. ADL, social interaction, cognition, perception, pain, anxiety, economic status) and they can be diagnosis-specific or generic¹³. A specific problem in dementia and other mental disorders is that the subjective dimension may be difficult to measure. Thus, proxies (mostly caregivers) are often used¹⁴. Indirect measurement per se, with proxies is, however, not necessarily a problem – the US Panel for cost effectiveness recommended that the general public should value health states¹⁵. However, if the proxy is a family member, the answers may more or less reflect the situation and interests of the proxy and not the patient's viewpoint.

Examples of instruments used in dementia are the dementia quality of life instrument (DQoL)¹⁶ and quality of life – Alzheimer's disease (QoLAD)^{17,18}. The quality of life assessment schedule (QoLAS) is an instrument that has been used in neuropsychiatric disorders^{19–21}. Since these instruments are not preference based^{15,22}, they are less appropriate for cost utility analysis.

Generic HRQoL scales provide opportunities to make comparisons with other diseases. There are also two types of generic scales.

Table 17.5 Economic evaluations with bootstrapping approaches

<i>Intervention</i>	<i>Disorder</i>	<i>Country</i>	<i>Design</i>	<i>Study length</i>	<i>Outcome</i>	<i>Cost difference (US\$ 2006*)</i>	<i>ICER in base option (US\$ 2006)</i>	<i>Sensitivity analysis or similar</i>	<i>References</i>
Case management	Dementia	Netherlands	RCT + bootstrapping	6 months	Successful treatment	\$246*	4 315/unit	95% vs. WTP of 34 000€	(55)
Case management	Dementia	Netherlands	RCT + bootstrapping	3 months	Successful treatment	\$2 247*	Dominance (94% probability)	99% vs. WTP of €2000 per 'successful treatment'	(56)
Psychotherapy of 55+	Depression	Netherlands	RCT + bootstrapping	12 months	Recovery, QALYs	\$798	ICER 366 921/recovery Intervention not cost effective	Bootstrapping: 17% more effective, less expensive. 35% more effective, more expensive, 37% less effective, more expensive. 11% less effective, less expensive	(57)

Table 17.6 Examples of economic evaluations with modelling approaches

<i>Intervention</i>	<i>Disorder</i>	<i>Country</i>	<i>Design</i>	<i>Model length</i>	<i>Outcome</i>	<i>Cost difference (US\$ 2006)</i>	<i>ICER in base option</i>	<i>Sensitivity analysis or similar</i>	<i>Reference</i>
Donepezil	Alzheimer's disease	USA	Markov model	2 years	QALYs	92	Dominance	<0 to 529 566 (all scenarios)	(58)
Rivastigmine	Alzheimer's disease	Canada	Survival model	2 years	QALYs	438	Dominance	NA	(59)
Galantamine	Alzheimer's disease	UK	AHEAD model	10 years	QALYs	−817	14 755	9 861–29 585	(60)
Memantine	Alzheimer's disease	Sweden	Markov model	5 years	QALYs	13 454	Dominance	<0 in all scenarios	(61)

Examples of indexes or profiles are the sickness impact profile²³, the short form 36 (SF-36)²⁴ and shorter versions; SF-20 and SF-12.

Regarding caregivers, burden scales, such as the burden interview²⁵, can in some sense be used as indicators of QoL, but the interplay between patient characteristics, caregiver QoL and burden is complex²⁶.

Other types of generic scales are used to calculate quality adjusted life years (QALY)²⁷. These include the health utilities index (HUI)^{22,28}, the EuroQoL/EQ-5D²⁹ and the index of well-being/quality of well-being scale (QWBS)³⁰.

The QALY concept reflects both quantity of life and quality of life^{22,31} and is expressed as figures between 0 (death) and 1 (perfect health); it is widely used in CUA. The use of QALYs is under debate, particularly regarding the elderly³². Chronic, incurable, progressive disorders may be disfavoured when compared with e.g. surgical treatment such as cataract or hip replacement surgery.

Postponing institutional (long-term) care has sometimes been defined as an advantageous effect of interventions, making itself a potential outcome. However, this approach can be questioned for several reasons. The concept of institution is not homogeneous³³. There are also situations where institutional care is a better alternative than insufficient care 'at home'. If postponing nursing home care is successful, there will also probably be a shift from formal care in an institution to formal home care but, which is more notable, also to an increased period of informal care. The latter shift may cause consequences on the caregiver's private situation, and also from a societal cost perspective.

MODELLING

Dementia and other mental disorders most often last for many years. The economic literature in this field with empirical data from interventions is often based on short periods of time. Such studies are shown in Tables 17.4 and 17.5 (Table 17.5 with bootstrapping approaches). The longest study period in these studies is 60 weeks. Since for practical reasons is difficult to perform interventions studies lasting for several years, there is a great interest in using different approaches of modelling to catch the long-term effects³⁴. In an economic model, results from a short empirical core period are extrapolated to a longer period. Inputs from several sources, e.g. efficacy, costing and progression, are used. Various applications of Markov models³⁵ are frequently used, but several other approaches are at hand. In a review, Cohen and Neumann identified 13 types of models regarding Alzheimer's disease³⁶.

Discounting of costs (and perhaps outcomes) with rates between 3–5% is recommended¹⁵. Examples of different modelling approaches are given in Table 17.6. Notable is that most models tend to indicate cost effectiveness. One reason is that the models are based on a positive efficacy effect of the active treatment and a relation between disease progression and costs. Factors that neutralize are the costs of the treatment itself (e.g. not only the drug but also diagnostics and laboratory tests that follow treatment), effects on mortality and costs of side effects.

Models are controversial: the results are highly dependent on the assumptions. Long-term effects, such as exhaustion of carers and staff, which do not occur in the early stages of a disease, and symptoms which do have not a linear progressive course, such as behavioural and psychological symptoms in dementia (BPSDs)³⁷, are difficult to model. A model is also linked, implicitly or explicitly, to a specific organization of care. Although we regard modelling as an essential part of health economics, many drug authorities and clinical researchers are often sceptical about models; they regard such studies as not being 'empirical'.

PHARMACOECONOMICS AND PROGRAMMES

Even if the literature on health economics is sparse, there is a great deal concerning health economic evaluations of drug treatment. Other clinical interventions (here referred to as 'programmes') such as day care, caregiver support, psychotherapy, case management, housing programmes are common in the clinical reality, but sparse in the health economics literature of dementia and other mental disorders. There are several reasons for this. A drug intervention is rather easy to define and operationalize, while concepts such as 'day care' are more vague. Furthermore, it is difficult to include a sufficient number of study objects in an evaluation of a programme, resulting in poor statistical power. The basic field conditions (e.g. care structure, staff situation) at one study centre may differ considerably from another, making the intervention itself (e.g. day care) difficult to differentiate between different sites. In this sense a pill is much easier to define. The costs of a programme may also be very high if a lot of staff is involved and the economical strength of the sponsors is often weaker than the resources of drug companies.

CONCLUSION

Due to the enormous socioeconomic impact of chronic disorders of the elderly (such as dementia and other mental disorders), it is

obvious that there is a great need to obtain information about 'value for money'. Many clinicians take a position that it is unethical to discuss cost effectiveness of diseases that affect weak patient groups. Our position is the opposite: it is unethical NOT to discuss cost effectiveness of the treatment and management of these disorders. Care for these patients demands great investment and if we have no idea of what we get for the money, there is a great risk for a waste of money and resources. This is indeed unethical.

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The Influence of Social Factors on Mental Health

Donna D. McAlpine¹ and David Mechanic²

¹*School of Public Health, University of Minnesota, Minneapolis, USA*

²*Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, USA*

Social factors have an enormous influence on the life course, affecting development and socialization; the relative influence of family and peers; opportunities for education, work, recreation, social participation and patterns of social integration; and independence as one reaches the later years of life. They also influence the availability of various health providers and health care settings if one seeks medical care. It is not surprising, therefore, that almost every aspect of mental health and well-being is influenced by social factors¹.

Understanding the social context of mental illness requires appreciating how social factors may be causally related to either the first-onset or re-occurrence of mental illness, and, in turn, how individuals' social circumstances are shaped by having a mental health problem early in life. Moreover, at all stages of the life course, social context and social policies help explain variation in response to symptoms, treatment patterns and outcomes.

A life course perspective acknowledges that individuals carry into their later years all their prior experiences that influence health status as they age. Such a perspective also directs attention to cohort and historical differences in life circumstances and the experience of health and illness. With the rapidity of social change, persons living a normal life span are required to modify their expectations and behaviour on many occasions if they are to adapt successfully to shifting social conditions. Transformations in technology, sexuality, fertility, family and work life, household structure and many other aspects of life also make it inevitable that different age cohorts will have diverse life experiences and thus, different experiences of health and illness.

Epidemiological studies indicate that ageing is not associated with greater risk of experiencing a mental disorder. Moreover, among community residents, the lifetime prevalence of disorders such as depression appears to be lower among older persons compared to their younger counterparts². This finding may be due to methodological difficulties inherent in asking persons to recall their first onset of disorder, the omission of elders living in institutional settings from these studies, age differences in willingness to acknowledge feelings, or the fact that persons with mental disorder die earlier than those without such disorders. Given recall and selective reporting problems, the reliability and validity of lifetime estimates of mental illness can be seriously questioned. But the finding may also in part be suggestive of an important cohort difference; younger cohorts may be at greater risk of some mental disorders such as depression². If these findings are supported by further evidence, and these conditions

are not self-limited, we might expect that as younger cohorts age, the prevalence and societal burden of mental illness among older persons may increase.

The discussion that follows focuses more on severe mental illness than on levels of psychological distress or emotional well-being. The distinction between major mental illness and emotional distress is not always clear. The boundaries between what constitutes elevated symptoms of distress and what constitutes clinical disorder are porous and do not always reflect clinical reality. While the risk of experiencing a clinical disorder may not increase with ageing, there is evidence that depressive symptoms or psychological distress do increase in older age³. Mirowsky and Ross suggest the approximation of a U-shaped pattern with high depressed mood in late adolescence and young adulthood, lower levels in the middle years, and highest levels at old age⁴. Many studies deal with symptoms that do not reach the threshold of disorder but such symptoms can still have devastating effects on functioning and quality of life, and are a major source of disability, surpassing in impact many serious chronic diseases⁵.

Overwhelmingly, research indicates that mental illnesses are neither randomly distributed nor solely the result of one's genetic heritage. But, investigating the social causes of mental illness is not inconsistent with the potential causal role of biology or genetics. Severe mental illnesses such as major depression, bipolar conditions and schizophrenia result from complex, but poorly understood, interactions between biological vulnerabilities and psychological and social influences. Adverse social and developmental factors may increase susceptibility to serious mental illness, or may trigger illness among vulnerable persons. There is increasing interest in gene–environment interactions and the role of early abuse and stress interacting with genetic vulnerabilities⁶.

There is a large body of research documenting that social characteristics and position are associated with the prevalence and incidence of mental disorder. Generally, the research indicates being female, unmarried or from a disadvantaged social class increases risk for experiencing mental health problems. Much debate continues on the relative role of social selection and social causation in influencing these patterns. While the impact of these factors among the elderly has been less well studied, it appears that similar patterns characterize later life⁷.

Explanations for the social patterning of mental disorder have explored both social causation and social selection. The search for the

social causes or contributors to these disorders has been dominated by the stress paradigm that largely focuses on depressive symptoms. Childhood abuse, stressful events and chronic strains, poor coping resources, lack of intimate and instrumental relations and low self-efficacy have all been found to be associated with the occurrence of depressive symptoms and to a lesser extent major depression. Experiences very early in life such as death of a parent, and physical or sexual abuse during childhood may be related to onset of depressive disorders well into adulthood⁸. Prenatal and nutritional deficiencies may play a role in neurodevelopmental processes and possibly conditions such as schizophrenia^{9,10}. Research among the elderly supports the significance of the stress process for understanding the occurrence of depressive disorders in later life⁷.

Research has also emphasized the importance of social support, both as a buffer to life stress and its absence directly contributing to the onset of depressive symptoms or disorder. However, social support remains a vague concept, having varying operational definitions ranging from marital status, network size and instrumental support, to the subjective qualities of relationships such as intimacy¹¹. While not conclusive, the research suggests that lack of emotional support is most strongly associated with risk of major depression and most strongly buffers the potential deleterious effects of life stress¹². Contrary to popular impressions, research indicates that individuals are able to maintain supportive relationships as they age; emotional support appears relatively stable across old age, while instrumental support appears to increase¹³. However, as people reach old age, lifetime networks become depleted as friends and intimates die. Support when significantly diminished may increase vulnerability to mental distress.

There is growing attention to the role of religion or spirituality as causally related to health outcomes, including mental disorder^{14,15}. Results from many studies indicate that persons who are more involved in religious activities such as going to church report less psychological distress and lower rates of depressive disorder than those who are not involved in such activities¹⁵. Religion may be particularly important for the elderly and for specific cultural groups such as African Americans¹⁶. The pathways through which religiosity affects mental health remain unclear. One plausible hypothesis is that the emotional support and instrumental assistance that might result from religious involvement contribute directly to better health as well as help one cope with the difficulties of life. Research in this area continues to confront difficult selection bias, in that persons in better health may be more able and inclined toward religious participation and that persons drawn to various religious practices may be different in their personalities, attitudes and behaviours than those with lesser or no participation^{17,18}.

While it remains difficult to control for selection effects when trying to untangle the causal roles of social factors, it seems clear that social causation more powerfully explains social patterns of less severe disorders such as depression and is less significant in explaining psychotic disorders such as schizophrenia¹⁹.

Understanding the importance of social selection requires taking a life course perspective that highlights the importance of social or health experiences for understanding the occurrence and consequences of mental disorder among the elderly. People bring into later life all the experiences related to family, friends, stressful life events and strains, employment and socioeconomic status that they have accumulated over their lives. All of these experiences influence how we are sorted or selected into various circumstances as we age. The early onset of mental disorder is one such experience. Having a severe mental disorder early in life increases the likelihood of remaining unmarried, especially for men, and increases the risk

of divorce and separation among those who do marry²⁰. Thus many people with severe mental illness will enter their later years without the benefits of a partner to provide emotional and instrumental support. Early onset also shapes later opportunities for education, employment and earnings^{21,22}. Even if symptoms remit later in life, it is difficult to overcome these early experiences, and persons with early onset of mental disorder are more likely to find themselves living with significant economic disadvantages in later life.

Selection effects are particularly important for understanding the social correlates of severe and persistent disorders such as schizophrenia. Scant research suggests that social factors cause schizophrenia, although early work in the area found that stress acts as a trigger affecting the occurrence and timing of episodes²³. A significant body of work on 'expressed emotion' indicates how modification of interactions can prevent and/or reduce episodes²⁴. Experiences subsequent to the onset of schizophrenia importantly shape one's life course. The weight of the evidence supports the view that the impairment associated with schizophrenia prevents upward mobility comparable to one's age cohort and loss of social position because of difficulties completing one's education and maintaining employment^{19,25}. Older persons with schizophrenia often carry these deficits they acquired when they were younger.

It is clear that those persons who had their first onset of major mental illness early in life bring into their later years life histories likely to be characterized by significant periods of disorder and disruption. But, they also may bring an array of skills and coping strategies, acquired through dealing with illness over many years, and such adaptive skills may help mitigate the potential negative impact of illness during later life. Research indicates, for example, that having a sense of meaning in life, especially a sense of purpose, buffers the effects of traumatic events early in life on symptoms of depression in old age²⁶.

For the majority of older people who have a mental health disorder, it will be a recurrence or continuation of a condition that first occurred much earlier in life. By some estimates, 95% of all cases of major depression have first onset before age 65². For the majority of persons with depression, age of onset is early in life and seems to be causally related to social factors such as socioeconomic status, exposure to stressful life events and chronic strains, limited coping resources, and deficient social support. Re-occurrence of depression when one is older is commonly associated with similar social factors. In contrast, for the minority of persons who experience first onset of depression in later life, health status may play a larger role. Some research suggests that first-onset of depression in later life is more driven by the experience of health problems than psychosocial circumstances²⁷. Similar findings have been observed for first onset of bipolar disorder in later life²⁸.

Like depression, most persons with psychotic disorders such as schizophrenia have onset early in life. The prevalence and aetiology of late-onset psychoses remain unclear, although there is a growing literature devoted to the topic. It has been suggested that there may be two types of late-onset psychoses: schizophrenia that occurs first after the age of 40, and schizophrenia-like psychotic disorder that first occurs after the age of 60²⁹. Both types of disorders are rare and few social factors seem to be associated with risk. One notable exception is gender; the bulk of research suggests that women are at greater risk for late-onset schizophrenia²⁹, although the reasons for this increased risk are not well understood.

It is also clear that social factors matter a great deal for understanding responses to symptoms of mental illness, treatment patterns and

outcomes. Processes of help-seeking are influenced by broad social beliefs about the nature and what should be treated, characteristics of the individual and the social context in which mental illness occurs, and the organization of services and their physical, social and economic accessibility¹. Members of varying age cohorts have been socialized differently in relation to the recognition of symptoms, appropriate sources of help and social stigma of seeking help from particular types of providers. Selection from the community to varying types of service providers is a two-stage process, which depends on general factors affecting the inclination to seek assistance, and other factors more specific to choice among alternative practitioners. Recent evidence suggests that older persons with a mental disorder are less likely to receive care than their younger counterparts³⁰ and are more likely to seek care in the general medical care sector than in the specialty mental health sector.

Treatment for mental disorders in older age is shaped by other social factors. Women are more likely to receive care than are men³¹. Economic disadvantage is also a substantial barrier to access to health services and prescription medications in settings without adequate health insurance coverage³². While treatment of depression among older persons has increased dramatically in recent years, there remain significant ethnic and socioeconomic status disparities³³.

Differences in patterns of treatment may reflect variation in help seeking behaviours and differences in response to symptoms by health professionals. Older persons with mental disorder are less likely than their younger counterparts with the same disorder to perceive a need for mental health care³⁴. Many may normalize the symptoms of depression as part of normal ageing³⁵ or perceive such symptoms as less important compared to competing physical and social problems³⁶.

Interpreting symptoms as indicative of mental illness is also complicated by common use of drugs to treat physical illnesses during this stage of life. Prescription and non-prescription drug use is high in elderly populations because of the prevalence of physical illnesses and dementia. The inappropriate use of pharmaceuticals among elderly persons is also common and includes physicians over-prescribing to older patients, self-medication and drug interactions³⁷. Drug sensitivity changes with age-related changes in individuals' capacity to absorb and metabolize drugs; therefore dosages effective in young patients may be ineffective or excessively high for older patients. Antipsychotics are commonly used 'off-label' to treat older persons with dementia, but there is current controversy about such treatment practices because they appear to increase risk of mortality³⁸.

Social factors such as socioeconomic status put persons with mental illness at risk for a number of negative outcomes not directly associated with the illness. Inadequate housing or homelessness remain significant problems for persons with mental illnesses and compromise efforts to provide meaningful services, yet we know little about these issues in older populations³⁹.

Ageing brings more positive outcomes for persons with schizophrenia than might be expected based on research focused on younger persons and clinical samples who remain in treatment for long periods. Research indicates that with ageing, the positive symptoms of schizophrenia abate or remain in remission for longer periods, and that for a significant minority of persons complete remission is possible⁴⁰. Longitudinal studies of persons with schizophrenia observe much heterogeneity in its long-term course, with many patients having long remissions, late course improvements and complete remissions^{41,42}. Most make adequate adjustments to living in the community although social isolation and

limited quality of life are common^{1,43}. The impact of family on the course of schizophrenia has received the most research attention, although this research is focused on younger persons. This research suggests that a highly involved critical orientation contributes to relapse²⁴. Other research suggests that maternal warmth and praise is associated with better quality of life outcomes among middle-aged persons with schizophrenia⁴⁴.

Social policies also influence the types of institutions where elderly people receive care. In the 1950s and 1960s, the organization of services in the United States and many Western nations meant that many persons with mental disorders ended up in psychiatric hospitals and nursing homes, and many elderly persons with mental illnesses had spent much of their lives in such institutions. In the United States large scale deinstitutionalization was only possible with the expansion of welfare programmes that provided subsistence and payment for alternative residential care for mentally ill patients in the community.

Current cohorts of elderly persons with major mental illnesses confront a much different landscape of services than their predecessors. Among those seeking help, most will be seen in primary care, not specialty mental health care³⁴. Assessing depression within the constellation of physical concomitants that might be attributed to a variety of other conditions poses diagnostic challenges to the general physician. It is not surprising, therefore, that depression among older persons often goes undiagnosed⁴⁵. This problem may be even more pronounced for African American patients⁴⁶.

There has been much recent effort to integrate mental health services into primary medical care. Large-scale multifaceted interventions bringing mental health care into primary care settings have been found to be effective in reducing symptoms and improving quality of life for persons with depression, while also being cost effective. These interventions are intensive, typically including enhanced screening to improve the identification of cases of depression, patient and provider education, case managers responsible for tracking patient outcomes and adherence to treatment, and the availability of a psychiatrist for consultations. However, even at their best, these interventions show how difficult it is address the needs of the elderly with depression. In the most widely replicated model, IMPACT, for example, only about one quarter of patients in the intervention (compared to less than 10% in usual care) achieved remission at 12 months⁴⁷.

While most of the research on how social factors impact the occurrence of mental illness or the response to symptoms of mental illness is based on community samples, nursing homes remain the social environment where many elderly persons find themselves. In some sense, the traditional nursing home echoes the conditions of the long term psychiatric hospitals that characterized care for the mentally ill in the past. Typically admissions to nursing homes occur when individuals are incapable of caring for themselves, when their physical and psychiatric problems create unmanageable burdens for their caretakers, or when community caretakers are no longer available. Admission is often triggered by such events as a loss of function following trauma, such as hip fractures, confusion and wandering, and incontinence. Traditional nursing homes, like the traditional long-term mental hospital, contribute to an institutional syndrome resulting from vulnerabilities of patients as they respond to decreased social participation, sensory deprivation, loss of efficacy and control over daily life decisions, institutionalization, routinization and the like. There is persuasive evidence that efforts to keep patients involved

and participating in valued activities help for both mental and physical function. Many nursing homes fail to give these social aspects of life adequate attention, and patients spend much of their time in isolation and uninvolved. Moreover, historically, there has been evidence that psychotropic drugs were being over-prescribed in nursing homes to control patients and ease staff workloads. Recent evidence suggests that these practices have been reduced as the result of legislation in the late 1980s in the United States⁴⁸.

Nursing care may be the best treatment context for some patients who are seriously incapacitated and require a broad range of services difficult to provide in the home or in other community settings, but most impaired elderly benefit from settings that are more successful in sustaining self-efficacy and social engagement. Recent developments in the nursing home industry suggest that such settings are possible; for example, the Green House model emphasizes small residential (family-like) housing, privacy, independence and control over activities of daily life as much as clinical status allows⁴⁹. Early results indicate that functioning and quality of life, including emotional well-being, are more positive for individuals in such types of homes compared to traditional nursing home settings⁵⁰.

Demographic shifts mean that the social patterning of mental illness in later life and our responses to it may be very different with future cohorts of older persons than what we see today. The United States and many other nations are facing an ageing population, with the number of older persons with mental illness more prevalent. The capacity for any society to cope with mental illness depends on the organization of kinship groups and households, and the existing social institutions in a society. The growing prevalence of divorce, single-person households, small families, high female participation in the workforce, geographic mobility and other trends make it difficult to put increasing reliance on informal social networks for caretaking. Developing alternative structures that are financially viable and humane constitutes a growing challenge.

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Diagnosis and Assessment

Classification of Dementia and other Cognitive Disorders in ICD-10 and DSM-IV

A. Jablensky and J.E. Cooper

Department of Psychiatry and Behavioural Science, Medical Research Foundation Building, Perth, Australia

The classification of mental disorders in the Tenth Revision of the International Classification of Diseases (ICD-10) includes a revised content that reflects the most important advances in research and clinical practice at the time of its conception. It is presented in different versions for different types of professional users. The differences are, however, in degrees of detail, and the versions are compatible with each other since they are all derived from the same basic document, the 'Clinical Descriptions and Diagnostic Guidelines'¹.

THE USES OF ICD-10

ICD-10 has necessarily retained its historical purpose of facilitating the recording of national and international statistics of morbidity and mortality, but has the added values of also being designed as a uniquely international aide to clinical work, teaching, and research. It achieves these objectives by means of an updated list of diagnostic rubrics, a set of glossary-type definitions of disorders, and additional explicit diagnostic criteria. The latter have been developed in two versions: (a) clinical diagnostic guidelines for routine use, allowing sufficient flexibility and discretion in the application of "clinical judgement" in the hospital ward or the out-patient clinic; and (b) diagnostic criteria for research (ICD-10-DCR) providing stringent decision-making rules to increase the specificity of diagnostic classification and thus ensure a high level of sample homogeneity for the purposes of clinical, biological and other research².

As a result of a great deal of collaboration between the advisers to the World Health Organisation and the several Task Forces that assembled DSM-IV on behalf of the American Psychiatric Association during the last few years of the preparation of both the classifications, there are very few important differences between them. Since the same body of internationally published research experience and literature was available to both sets of experts during the processes of development, those differences that remain are mainly differences of opinion rather than of fact. Some differences reflect the need for ICD-10 to accommodate a much broader base of international experience and opinions than a national classification. In the development of ICD-10, experts from many different cultures and languages were involved from the earliest stages.

As in ICD-9, Chapter V deals with "Mental and Behavioural Disorders", and is intended for the recording of the clinical syndromes

as presented and experienced by the patient. If a specific underlying cause of the disorder is known (or highly probable), additional codes should also be used from other chapters of ICD-10, such as Chapter I; Infectious and parasitic diseases, Chapter II; Neoplasms, or Chapter VI; Diseases of the Nervous System.

DEMENTIA IN ICD-10

In ICD-10, the dementias are embedded in the section on organic and symptomatic mental disorders (codes F00-F09) which contains the following major rubrics:

- Dementia in Alzheimer's disease.
- Vascular dementia.
- Dementia in diseases classified elsewhere.
- Unspecified dementia.
- Organic amnesic syndrome, other than induced by alcohol and drugs.
- Delirium, other than induced by alcohol and drugs.
- Other mental disorders due to brain damage and dysfunction and to physical disease.
- Personality and behavioural disorders due to brain disease, damage and dysfunction
- Unspecified organic or symptomatic mental disorder.

In contrast to ICD-9, the distinction between psychotic and non-psychotic illnesses is of no taxonomic consequence in ICD-10, where disorders of different psychopathological expression are grouped together on the basis of established or presumed common aetiology. In the particular instance of section F0, in which the dementing disorders are included, the underlying classificatory characteristic of "organic" is defined in the sense that "the syndrome so classified can be attributed to an independently diagnosable cerebral or systemic disease or disorder". The subsidiary term "symptomatic" is not used in the titles of individual disorders but it is included in the overall title of the block F00 – F09. This is because it is widely used in many countries to indicate those organic mental disorders in which cerebral involvement is secondary to a systemic extra-cerebral disease or disorder. In other words, 'symptomatic' in this context is a subdivision of the wider term 'organic'.

Another feature of ICD-10, as compared to earlier classifications, is the omission of any reference to age as a defining criterion of the disorders accompanied by a cognitive deficit. The terms “senile” and “presenile” are practically absent in the classification, and there is no provision for identifying any mental disorder as necessarily a result of aging. The classification does, however, allow the recording of an unusually early or late onset of the disorder. In other words, the mental disorders occurring in the elderly are no longer considered to belong in a separate category of morbidity. This is very much in line with research conducted in the past three decades which has demonstrated that the relatively high prevalence of mental morbidity in the elderly in Western cultures is related to a wide range of psychosocial factors (e.g. social isolation, cultural uprooting and institutionalization), as well as to physical co-morbidity, but that the aging process itself does not produce nosologically specific forms of disorders.

If section F0 of ICD-10 is used as a diagnostic decision tree, there is a choice of five entry points at the level of clinical syndrome: (i) dementia; (ii) amnesic syndrome; (iii) delirium; (iv) organic quasi-functional disorder (affective, delusional, hallucinatory or other); and (v) personality or behavioural disorder. Once a disorder is identified at this general syndrome level, the next step is defined by the diagnostic guidelines which lead into more specific diagnostic categories. The diagnostic decision rules for dementia illustrate the point.

The syndrome of dementia is defined in ICD-10 by “evidence of a decline in both memory and thinking, which is of a degree sufficient to impair functioning in daily living”, in a setting of clear consciousness. For a confident diagnosis to be established, such disturbances should have been present for at least 6 months. Deterioration of emotional control, social behaviour and motivation represent significant additional features but the overriding criterion is the presence of memory, learning and reasoning decline. The ICD-10 DCR (research criteria) add anchor points for a grading of the deficits into mild, moderate and severe, separately for memory and intellectual capacity. The overall grading of the severity of dementia is made on the basis of the function which is more severely impaired.

Once the presence of the syndrome of dementia is established, the diagnostic process branches off into the different clinical varieties of dementia typical of Alzheimer’s disease, vascular dementia, and dementia in diseases classified elsewhere (including Pick’s disease, Creutzfeldt-Jakob disease, Huntington’s disease, Parkinson’s disease, HIV disease, and a range of systemic and infectious diseases such as hepatolenticular degeneration, lupus erythematosus, trypanosomiasis, and general paresis). Dementia in Alzheimer’s disease is subdivided into Type 1 (onset after the age of 65) and Type 2 (onset before the age of 65). Although the ICD-10-DCR criteria emphasize the ultimate criterion of the neuropathological examination and the supporting role of brain imaging, they nevertheless allow for a confident clinical diagnosis to be made, if clear evidence of a memory and intellectual performance deterioration has been present for 6 months or more. The ICD-10 criteria for vascular dementia are broader than the corresponding DSM-IV criteria: they include not only multi-infarct (predominantly cortical) vascular dementia, but also the subcortical dementias (Binswanger’s encephalopathy being an example), as well as the mixed cortical and subcortical forms.

As regards the diagnosis of delirium, ICD-10 has abandoned the distinction between acute and subacute deliria; the condition is defined as “a unitary syndrome of variable duration and degree of severity ranging from mild to very grave”, with an upper limit of 6 months’ duration and a subdivision into delirium superimposed on dementia and delirium not superimposed on dementia.

The rubric “other mental disorders due to brain damage and dysfunction and to physical disease” includes disorders with “functional” characteristics (e.g. hallucinosis, catatonia, schizophrenia-like disorder, and mood disorders) which arise in the context of demonstrable organic illness, such as cerebral disease, systemic disorders, and brain dysfunction associated with toxic disorders (other than due to alcohol or drugs). An important, not yet fully validated, addition to this rubric is the “mild cognitive disorder” attributable to physical co-morbidity which is defined as transient but nevertheless involving memory and learning difficulties. However, the requirement that “this diagnosis should be made only in association with a specified physical disorder” is in need of revision, since in a proportion of cases this diagnosis may reflect the early, pre-dementia stage of Alzheimer’s disease.

Finally, personality and behavioural disorders due to brain disease, damage and dysfunction include familiar conditions such as organic personality disorder (the frontal lobe syndrome but also other lesions to circumscribed areas of the brain), postencephalitic syndrome, post-concussional syndrome, and some new entities, e.g. right hemispheric organic affective disorder (altered ability to express and comprehend emotion without true depression).

In conclusion, two features of ICD-10 should be emphasized. First, as already noted, it does not identify the mental disorders in the elderly as a separate or special category of psychiatric morbidity. In addition to the F0 section listing the organic and symptomatic mental disorders, psychiatric disturbances arising in the elderly population can be classified, according to their presentation and course, in any of the other major sections of ICD-10 (except for F8 and F9, which deal with developmental disorders and behavioural and emotional disorders occurring in childhood and adolescence).

Second, although ICD-10 is not explicitly a multiaxial classification, there are two ways in which multi-axial coding can be achieved if required. The simplest way is to use extra codes from the other chapters of ICD-10 in addition to those in Chapter V; any physical disorders present can be recorded by codes from Chapters I to XIX, and codes from the final two chapters can be used to cover other noteworthy aspects of the clinical picture. These are Chapter XX; External Causes of Morbidity and Mortality (the X and Y codes, covering drugs causing adverse effects in therapeutic use, and injuries and poisoning), and Chapter XXI; Factors Influencing Health Status and Contact With Health Services (the Z codes, which include a variety of social, family and life-style factors). Another and more comprehensive option is to use the special Multi-axial System now available, which was developed by means of an international collaborative study organised by WHO Geneva³. This provides three descriptive axes: Axis I – Clinical Diagnosis, Axis II – Disabling, and Axis III – Contextual Factors. These Axes are a convenient re-arrangement of the chapters of ICD-10 listed above, with the addition of a brief set of ratings covering physical disabilities.

DEMENTIA AND OTHER COGNITIVE DISORDERS IN DSM-IV

In DSM-IV (and its revised version DSM-IV TR) dementias and other mental disorders associated with brain disease are grouped into a section entitled “Delirium, dementia, and amnesic and other cognitive disorders”. In contrast to ICD-10 and the earlier DSM-III-R, the term “organic” mental disorders is no longer used in DSM-IV, to avoid the implication that “nonorganic” mental disorders do not

have a biological basis¹⁴. While ICD-10 retains a general description of dementia as a syndrome occurring in Alzheimer's disease, cerebrovascular disease and "other conditions primarily or secondarily affecting the brain", the DSM-IV classification lists dementias as specific disorders which "share a common symptom presentation but are differentiated based on etiology". Specific diagnostic criteria are provided for dementia of the Alzheimer's type, vascular dementia, and dementia due to other medical conditions (HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease and Creutzfeldt-Jakob disease). A separate DSM-IV category, which has no counterpart in ICD-10, is substance-induced persisting dementia, defined as significant cognitive impairment persisting long after the symptoms of substance intoxication or withdrawal have abated. Another difference from ICD-10 involves the category of "dementia due to multiple etiologies", introduced to cover "the common situation in which the dementia has more than one etiology", such as a condition arising as a result of Parkinson's disease with co-occurring long-term substance use. Finally, the DSM-IV section contains residual categories for "dementia not otherwise specified" and "cognitive disorder not otherwise specified", to enable the coding of dementing illnesses or other cognitive dysfunction that do not meet the criteria for any of the specific types, or for which no specific etiology has yet been established.

While the DSM-IV diagnostic criteria and the ICD-10 diagnostic guidelines for delirium essentially agree, there are differences between the two classifications regarding the specific rubrics and their composition. Thus, the ICD-10 heading for the group of delirious disorders is "delirium, not induced by alcohol and other psychoactive substances", with separate coding provisions for delirium not superimposed on dementia, delirium superimposed on dementia, other delirium and delirium unspecified (alcohol or substance use induced delirium is coded in the ICD-10 section "Disorders due to psychoactive substance use"). In DSM-IV, both "delirium due to a general medical condition" and substance-induced delirium are coded within the same section, along with "delirium due to multiple etiologies" and "delirium not otherwise specified".

Another difference between ICD-10 and DSM-IV concerns the placement of psychiatric syndromes and personality or behavioural disorders associated with cerebral disease. The ICD-10 section "Delirium, dementia, and amnesic and other cognitive disorders" provides a fairly detailed classification of "organic" hallucinosis, catatonic disorder, delusional disorder, mood and anxiety disorders, personality disorders and specific syndromes, such as postconcussional and postencephalitic syndrome. Notably, the same section contains the category "mild cognitive disorder" and provides diagnostic guidelines for this rubric, while acknowledging that "the boundaries of this category are still to be firmly established". In DSM-IV, "mild neurocognitive disorder" is an inclusion term under "cognitive disorder not otherwise specified", with diagnostic criteria contained in Appendix B "for further study".

Both ICD-10 and DSM-IV have proved to be essential tools for clinicians, epidemiologists, and – perhaps to a lesser degree – for researchers working in the rapidly evolving areas of the neuroscience and genetics of neurocognitive disorders. In a thoughtful commentary and critique of the two classifications, Reisberg¹³ noted that in several respects the present diagnostic manuals reflect knowledge that is somewhat dated and fail to incorporate recent advances. Thus, the DSM-IV definition of dementia requires "impairment in memory" as a cardinal and necessary criterion, not acknowledging

that diseases such as vascular dementia and frontotemporal dementia are not characterized by prominent memory impairment, at least in their early stages. The DSM-IV definition mentions disturbance in executive functioning but omits the behavioural and emotional changes, as well as the diminishing capacity to carry out activities of daily living. Importantly, the DSM-IV definition proposes that the diagnosis of Alzheimer's type dementia can only be made by exclusion, i.e. once other etiologies for the dementia have been ruled out. This is at variance with the current international consensus (including the American Geriatric Society) that Alzheimer's disease should be amenable to diagnosis by inclusion, rather than exclusion. Another suggested change is the removal, from both DSM and ICD, of the distinction between early onset (before 65 years of age) and late onset (after 65 years) Alzheimer's disease. Further proposals concern introducing in the future classifications staging procedures for dementia; broadening the definition of Pick's disease to include frontotemporal dementia; and revising the description of dementia in Parkinson's disease and Lewy body dementia.

PROSPECTS FOR THE FUTURE

It is only a few years before the next edition of the international classification, ICD-11 is ready for use, and there are at present plenty of issues worthy of debate. Both terminological and conceptual issues related to the current ICD-10 classification of this group of conditions have been raised since its introduction in the early 1990s. Thus, the term "organic", sitting uneasily within the title of the ICD-10 section, has often been singled out for critique as a legacy of a dualist tradition and a schism between brain-based "neurological" diseases and "functional" psychiatric disorders that is no longer tenable^{4,5}. The non-invasive techniques for brain imaging, such as MRI, SPECT and PET-scans, are demonstrating a variety of structural and functional abnormalities in the brains of some (but by no means all) patients with the familiar clinical syndromes, that are also present in substantial proportions of normal subjects. These changes are 'organic' in a general sense of being something physical, but not in the way the term is used in the ICD (that is, to indicate a concurrent and diagnosable physical disorder).

It will probably soon be time to abandon 'organic' as a term to be used in a classification, and to develop new terms and concepts that will make these more subtle differentiations clear. The term "neurocognitive disorders", thought to capture both the concepts of cognitive disturbance and of an altered neural substrate, has been proposed in a recent review of the evidence supporting the grouping of the dementias, amnesic syndromes and deliria into a single classificatory "cluster"⁶. In addition, a critical examination of the very term "dementia" has also found it wanting for three main reasons⁷. First, it is now clear that memory impairment is just one of several cognitive domains that are affected to varying degrees in this group of disorders (other domains include language, attention, executive function, visuospatial ability, speed of information processing and manual dexterity). Secondly, the operational definitions of the diagnostic criteria for dementia in both ICD-10 and DSM-IV are insufficiently specific, leading on occasions to gross discrepancies in the assessment of the prevalence of dementia in population studies^{8,9}. Thirdly, in its categorical usage the term is stigmatizing and has connotations of extreme disability and dependence that tend to arouse severe anxiety in patients and family members. As a possible remedy, terms like "vascular cognitive disorder", or "cognitive disorder in Alzheimer's disease" have been proposed.

Complex problems with far-reaching conceptual implications for the classification of this group of disorders arise out of recent advances in their study with the tools of molecular genetics, proteomics and biomarker research. While conditions such as Alzheimer's disease, Huntington's disease, or Creutzfeldt-Jakob disease have been traditionally regarded as being among the few "true" discrete disease entities within the psychiatric classification, owing to the presence of "hallmark" brain lesions, recent evidence challenges seriously this view¹⁰. Current molecular classifications distinguish between four groups of neurodegenerative diseases: tauopathies (e.g. Alzheimer's disease, Pick's disease, frontotemporal dementia, progressive supranuclear palsy); alpha-synucleinopathies (e.g. Parkinson's disease, dementia with Lewy bodies, multiple system atrophy); neurofilamentopathies (e.g. dementia with neurofilament inclusions); and prion diseases (e.g. Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia). There is, however, increasing evidence of marked individual variability within the groups, as well as extensive overlap across the diseases and syndromes in terms of structure, molecular composition and distribution of brain lesions, raising the question of common aetiological and pathogenetic mechanisms^{11,12}. In the presence of both genetic heterogeneity and clinical pleiotropy, the nosological status of the individual disorders becomes less certain than previously assumed. Generally, two positions have been articulated in the recent literature (Armstrong *et al.* 2005): (i) the benefits of retaining the concept of distinct nosological entities outweighs its limitations; the latter can be constrained by using the existing diagnostic criteria in conjunction with refined molecular and other biomarker analysis; (ii) the traditional disease entities represent points on a continuum of neuropathological change and a clinical spectrum of syndromes rather than diseases.

Whatever form the ICD-11 classification takes, it seems likely that the principle of recording the clinical picture by means of Chapter V and the underlying cerebral or other physical cause by means of other chapters will remain. Research is now providing many, though not entirely consistent, clues about the exact place and the histological and molecular nature of the lesions in the central nervous system that give rise to the clinical syndromes, but the clinical syndromes themselves will not change, and will always need to be reliably recorded.

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Taking a Psychiatric History from Elderly Patients

Sunita Sahu and Monica Crugel

Oxleas NHS Foundation Trust, Memorial Hospital, Shooters Hill, London, UK

INTRODUCTION

When taking a psychiatric history from an elderly person, the general guidance on establishing rapport and taking a medical and psychiatric history apply, but there are also a few particularities. The great heterogeneity of this population in terms of general health and frailty, cognitive abilities and the need for support requires the approach to be adjusted in each case. Clinicians may often be enquiring about someone's life lived before 'their time' and can use this as an opportunity to allow the patient to feel empowered – after all the clinician might know better than the patient what their general and mental health problems are at the moment but only he/she is an expert in their own life history. Sometimes, a little more encouragement and verbal and non-verbal cues of friendliness, respect and openness than with an younger adult patient are needed for establishing a good rapport and obtaining the information. For fear of wasting your time or bringing irrelevant issues into discussion, your elderly patient might not tell you part of the story. Also, pre-conceptions about 'normal' ageing might lead to essential symptoms such as acute or chronic pains, low energy, lack of hope, poor sleep, boredom or lack of social interaction not being mentioned by the patient. Attention to non-verbal cues as well as reassurance that you are interested to hear it all and prompting can help complete the picture.

GETTING READY FOR THE INTERVIEW

Before meeting the patient prepare for the interview. Determine the reason for referral and look at the available medical and psychiatric history and current medication. Ask if the patient will be attending alone or accompanied and if special arrangements will be required in the room, for example if the patient is in a wheelchair.

THE INTERVIEW

After introducing yourself, make sure the patient and their companion are comfortable and check if the patient can hear and understand you. If not, can communication be improved with hearing aids or writing things down and/or involvement of interpreter or the sensory team?. Apart from sensory problems, cognitive deficits (short attention span, memory problems) and dysphasia can affect communication and prevent relevant information being obtained from the patient. In these cases an informant is essential for proper assessment. Adjust the pace of dialogue to the patient's needs: too slow

for a cognitively intact patient can sound condescending, too fast for people who cannot keep up can be disastrous.

If the patient is accompanied, establish who the companion is and what their role will be during the interview. Are they an informant or will they provide support for the patient? Have they requested the assessment?

The first interview with the patient and the psychiatric history obtained in this session is extremely important as future assessments will refer to it. Thus, details on nature and onset of all previous episodes, triggers and prodromes, risk factors, duration of episodes, medical co-morbidities, interventions (medication, hospitalization, sectioning, psychotherapy, home help, etc.) and their effect, pharmacological history including compliance, quality of recovery and level of functioning when recovered, should be recorded whenever possible. Your knowledge in psychopathology should guide the questions into obtaining relevant information.

To start the interview, allow the patient or/and informant to explain their view of the presenting complaint.

Start with general questions such as 'Have you ever had any problems to do with your mental health?' and 'Have you ever seen your GP or a psychiatrist for these?', then explore each concern in turn. A patient with poor insight into his previous psychiatric problems might acknowledge having been under psychiatrists for a long time but not having had a mental health problem. Conversely, many people suffer from sub-clinical symptoms or even disorders of clinical severity but have never been assessed or had any treatment.

HISTORY OF THE PRESENTING COMPLAINT

The context of symptoms' onset is of great relevance in geriatric psychiatry. Social and medical factors can play a greater role than genetics in some psychiatric disorders with late onset and, without addressing these, the patient might not recover fully.

Consideration of recent losses such as retirement, bereavement, change in social and financial circumstances, social isolation, loss of abilities and increase in dependency etc. must inform therapeutic intervention, thus recording them is important.

Medical conditions as well as medications prescribed for these can be associated with psychiatric disorders: stroke¹ and cancer² have a high co-morbidity with depression; organ failure may cause delirium³; respiratory problems are frequently associated with anxiety or panic attacks⁴; some antihypertensives can cause depression⁵; cortisone⁶ and anti-Parkinsonian drugs may cause psychosis; drugs

with anticholinergic effects can cause or accentuate confusion, to enumerate only some.

Conversely, care must be given to falsely perceived onset of symptoms. A classic example is memory problems starting 'suddenly' after the spouse's death; it is often the case that the patient's memory problems had been more longstanding but not apparent due to spouse's interventions and prompting. Careful questioning of relatives and other informants would probably reveal cognitive problems prior to bereavement. Sometimes the perceived onset is in fact an aggravation of pre-existing symptoms or the moment at which their intensity becomes significant.

An answer such as 'I have always had this problem' requires clarification as to why they presented for assessment now.

The present disorder might have started in a different form, for example psychosis or confusion following a long depressive episode pointing towards a diagnosis of psychotic depression; confusion following a serious illness, surgery or stroke suggesting delirium; depression with previous episode(s) of mania suggesting bipolar disorder; dementia starting with depression, anxiety or psychosis; substance abuse starting with anxiety or depression. A sudden onset of psychiatric symptoms can suggest organic aetiology.

After identifying the presenting complaint, brief questioning about any other problem, be it social, medical or psychiatric, will help complete the picture.

PAST PSYCHIATRIC HISTORY

One approach is to start with the personal history and once you have information about the patient's lifeline and major life events start asking about the psychiatric history. On one hand this reassures the patient that you are assessing them in an holistic way and are not only 'fishing' for symptoms and, on the other hand, it gives you a better view of the previous level of functioning and, if applicable, the impact of the psychiatric problem on their lives. Some patients may prefer to go straight to the problem.

It is not unheard of for serious lifelong psychiatric illnesses to be diagnosed in old age and a thorough psychiatric history is essential to achieve this. People suffering from generalized anxiety disorder, phobias or obsessive compulsive disorders, might never have seen a psychiatrist before. Careful questioning about long-lasting symptoms (e.g., 'Have you always been a worrier?' 'Have you always avoided travelling in cars/trains/planes?') can reveal a long history of psychopathology. The mood fluctuations in bipolar disorder sometimes accentuate with age and retrospective diagnosis of a sub-clinical life-long disorder can be made on a thoroughly taken history.

You will need to actively ask about important issues such as mood symptoms, psychotic features, anxiety, sleep and appetite problems, suicidality.

PHARMACOLOGICAL HISTORY

Obtaining an accurate pharmacological history is important as response to previous treatments and their side effects can inform current prescriptions. However, this can be more difficult than with younger adults as elderly patients might not remember the names of drugs they have been taking over the years. Your knowledge of older psychiatric treatments and interventions as well as older indications for certain types of treatments will help put the information into the right context⁷. For example, ECT, lithium, chlorpromazine and haloperidol were the only treatments available for mental illnesses

until the 1950s when imipramine (the first antidepressant) was introduced; although the current use of antipsychotics is mainly for psychosis, low doses of neuroleptics used to be prescribed in the treatment of depression, anxiety and somatic symptoms; ECT, now mainly used for severe depression and catatonia, was frequently used in the treatment of various psychiatric disorders 30–40 years ago; admissions for treatment were more frequent and much longer than nowadays.

Enquiring about the patient's previous compliance with prescribed treatments, as well as the reasons for non-compliance, when this was the case, can reveal important information. Poor compliance can have various causes and most are similar to those in younger adults, for example, the patient is not convinced that trying a treatment would help, is lacking insight into their psychiatric problem, is experiencing side effects or unpleasant effects from the drugs, stops treatment when they feel better, stops after just a few days due to lack of effect etc. In elderly patients, especially those with cognitive deficits, poor compliance can be due to forgetfulness. This is a serious problem in this population with high levels of co-morbidity and chronic conditions and can lead to relapse of physical or mental condition, under- or overdosing, withdrawal syndromes or other adverse drug reactions. There are various ways to address this such as, enhancing the doctor–patient relationship, psychoeducation, technical solutions (e.g. using dosette boxes), intensifying care (e.g. prompting by carer, administration of drugs by a carer, moving to a more supported accommodation) or, at the extreme, stopping some or all medication if none of the options work and there are associated risks⁸.

FAMILY HISTORY

There are understandable differences between taking a family history in a younger adult and an elderly patient. In the elderly, usually the parents of the patient would have died a long time ago, possibly at a younger age than one would expect to now, as a result of which there may not be a history of any problems with an onset in old age, for example dementia. Often the condition from which the parent was suffering may not be known, as the diagnosis may not have been given or may not have been known. Siblings, children, grandchildren and great grandchildren would now be part of the family history. Family interactions can be complex and exploring them can shed light on factors associated with the patient's problems. It will be important to note if the patient is involved in looking after any young children in case child protection issues arise. The converse may also be true if the children or grandchildren are involved in caring for the patient and younger adult protection concerns arise.

Any history of mental disorders in the family must be recorded when available, be it in the patient's parents, children or grandchildren. This would represent third-party information and appropriate confidentiality must be maintained. A history of suicide in a first degree family member represents a risk factor for the patient⁹.

PERSONAL HISTORY

This would usually be of much greater length than that of a younger patient. Information on developmental milestones might not be available or relevant but educational attainment and work history will be important for assessing the impact of the psychiatric problem on their lives or when interpreting test results for dementia. It is also an important indicator of the premorbid level of intellectual functioning. Your patient might want to tell you about their war experiences which

may have left important psychological marks on their lives. Many more significant life events would have taken place such as loss of parents, relatives and friends. Other kinds of losses such as perceived loss of social status due to retirement, loss of earnings and having to live on a meagre pension, are almost always present. They may have to be living at a lower standard than they were accustomed to and poverty is significant among the elderly¹⁰.

Retirement is a stressful life event for some¹¹. Circumstances of retirement may have precipitated depression. Symptoms of dementia interfering with their job may have led to early retirement on medical grounds.

Gross inaccuracies in recalling family history, names and birthdays can be a clue of memory problems.

PAST AND PRESENT SOCIAL SITUATION

This is a broad domain that must be explored in detail when assessing elderly patients. Social and medical care often go hand in hand in helping to improve the patient's quality of life and minimize the risks. For example, a social history revealing a patient living alone, unable to care for himself and under a significant risk to health, might be the single most essential information which will change your short-term treatment plan from prescribing a treatment at home to transferring to hospital or other care facility.

It may be helpful to start with the patient describing a typical day. This should yield rich information about their current circumstances, what they can and cannot manage and what help they are getting from family, friends and neighbours, and voluntary or statutory services. It will also reveal the degree of impairment and the risks to the patient and can point towards other available services which the patient would benefit from, for example day centre, sitting service.

Risks that might need immediate attention can be revealed by asking about the patient's participation in activities of daily living (ADLs). Can they attend to personal hygiene, are they able to do the house chores, use the cooker or the telephone, are they safe on the stairs, are they safe outside the house etc.? (see chapter 34).

Try and obtain information on the finances of your patient and most importantly their ability to manage them. It is necessary to enquire about their current pensions (state or private), benefits and savings, and think about any other benefits they might be entitled to. You can always request social services, working in partnership, to do a full financial assessment. If the patient is unable to manage their finances, arrangements for this to be done by someone else must be made. Family and patient may need to be encouraged to make a lasting power of attorney (LPA) for both property and welfare, a will or an advance decision or at least to start thinking about where they want to live in the future, what kind of care would be acceptable to them etc. Information about the patient's religion, values and beliefs must be recorded as this can play a great role in their life and must be taken into account when planning future care.

A driving history would indicate whether the patient is at risk when driving. If there are issues, the patient or you might need to inform the DVLA.

PERSONALITY

While a thorough personality assessment cannot normally be done in a first interview, keeping a careful eye on personality issues right from the beginning can be very useful. We usually take our personality into old age and a history of significant changes from the

premorbid personality reported by the informant will sometimes be a clue to a diagnosis of frontal lobe dementia. Knowledge of premorbid personality traits can be helpful in identifying personality change caused by a mental illness. It may also suggest coping strategies which manifest as symptoms.

PSYCHOSEXUAL HISTORY

As in younger adults, this is an area that can be relevant to your patients' relationships and mental health as well as compliance with medication so offer to discuss this with them. Specific problems in the elderly include sexual dysfunction, the loss of sexual partner by death or serious illness and sexual urges in people with dementia living in care homes.

ALCOHOL AND DRUGS HISTORY

Incidence of alcohol misuse in elderly is thought to be lower than in younger adults but a failure to identify patient's presenting with alcoholism might contribute to the lower figures¹². With the increase in life expectancy it is predicted the actual number of cases with alcohol-related problems will increase in the following years¹³.

Presentation with a fall, confusion or medical complications may mask an underlying alcohol problem. Hence enquiring about current or past alcohol and drug use must be a routine part of the assessment. This should include the age when first used, development of the problem, quantity and frequency and presence of dependence syndrome for each substance used. If alcohol abuse has started in old age, the circumstances might reveal underlying loss, bereavement or depression.

In this age group physical or psychiatric complications of alcohol abuse (e.g. cirrhosis, peripheral neuropathy, cognitive impairment) might have already developed and can be found in the context of continuing or past alcohol abuse. Also, effects of previously well-tolerated quantities of alcohol may increase due to changed physiology.

Onset of memory problems can interfere with a person's usual pattern of alcohol use, for example, by precipitating withdrawal in someone with alcohol dependency who forgets how to obtain the alcohol or causing acute intoxication or even dependency in someone with no prior history of abuse, but regular use, who repeatedly drinks his usual non-harmful amount to intoxication levels.

Knowledge of the type of alcohol consumed can suggest strategies of changing the alcohol to one of lower strength and then gradually tapering the amount, effectively detoxifying the patient. One can use alcohol assessment screening tools but these need to be age-specific, as many of the more traditional rating scales lack validity. The Short MAST-G is commonly used, but others such as the Drinking Problems Index and Alcohol-Related Problems Survey, are used in more specialized settings.

Physical complications of alcohol misuse are numerous, but commonly affect the stomach (ulceration), liver (alcoholic hepatitis, progressing to cirrhosis), blood (anaemia), nervous system (peripheral neuropathy – lack of sensation in legs) and can lead to instability and falls related to episodes of intoxication. Falls may lead to head injury and subdural hematoma. Alcohol may also alter the way in which medication is metabolized by the body and can accentuate the side effects of drugs such as opiates (commonly found in prescribed painkillers).

Inadvertent benzodiazepine dependence is common in the elderly. Again, this relates to a time when not enough was known about

benzodiazepines and they were prescribed for anxiety or depression and continued for long periods resulting in dependence. A thorough history of use of these drugs would provide useful information about past illness.

FORENSIC HISTORY

In elderly presenting for psychiatric assessment a forensic history is very rarely present. The number of elderly offenders has remained stable over the years; however, the number of elderly in prisons has increased sharply¹⁴.

When taking a psychiatric history in a usual community or hospital setting the interviewer may feel that asking about forensic history can offend the patient and is not relevant. However, it is worth exploring and should not be ignored. There is a risk of offending in people with frontal lobe dementia when this is associated with disinhibition, hoarding or obliviousness to social rules. Also, aggressive behaviour in all types of dementia is frequent, especially towards the carer. In Lewy body dementia, vivid hallucinations, hallucinatory behaviour and cognitive fluctuations can sometimes lead to high risk of harm to others. But even when these lead to serious incidents. Police are rarely involved and charges are often not brought.

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Mental State Examination in the Elderly

Joanne Rodda and Zuzana Walker

Department of Mental Health Sciences, University College London, UK

The Mental State Examination (MSE) provides a snapshot of a patient's symptoms and signs at the time of the interview. The approach to the MSE in older adults is very similar to that in the younger adult population, although there are a number of important considerations. For example, a significant proportion of patients in old age psychiatry services present with cognitive impairment and there are generational differences between older and younger adults. Physical illness can also complicate the MSE; the assessment of mood can be difficult if someone is frail, immobile or in pain, and acute confusion can be mistaken for dementia, psychosis or mania. These and other factors mean that the observable manifestations of mental illness in the elderly often differ from those in younger adults.

APPEARANCE AND BEHAVIOUR

A great deal of information can be gained from simple observation of the patient walking into the room; for example, posture, gait, presence of abnormal movements, level of personal hygiene and appropriateness of attire can immediately direct the clinician towards important areas for further enquiry.

A deterioration in dress presentation may reflect a decline in personal care; clothing can also give clues about disinhibition or dressing dyspraxia. The level of personal hygiene can clearly demonstrate personal neglect although a well-kempt appearance might be maintained by a carer.

The level of general awareness and alertness may be affected by physical illness or drugs, and fluctuations may be associated with delirium^{1,2} or dementia with Lewy bodies^{3,4}. Too little or too much eye contact might suggest low mood or disinhibition although it may be necessary to make allowances for visual impairment. Similarly, hearing or visual impairment may result in the appearance of distractibility and confusion. Irritability and hostility are sometimes said to be more common in mania in older adults. However, objective evidence from the few studies available suggests that the presentation of mania in older adults is similar to that in their younger counterparts^{5,6}.

Over-familiarity or disinhibition is suggestive of mania or frontal lobe syndromes and can be a feature of many types of neurodegenerative disorder. An older person may be more reserved in their interactions with others and so a level of familiarity or inhibition that fits into the realms of social acceptability may still represent a change from normal for that individual. Conversely, a gregarious person may always have been that way; information from relatives or carers is therefore often important to determine whether the current

presentation represents a change from the patient's usual way of interacting.

Psychomotor changes are often prominent in depression in the elderly⁷⁻⁹ although bradykinesia and reduced mobility in Parkinson's disease can be difficult to distinguish from psychomotor retardation or apathy. There are a host of motor signs – e.g. dystonic movements, mannerisms and stereotypies – that may occur as a feature of schizophrenia, mania or organic disorder^{10,11} or as a result of side effects of medication. Hyperorality and stereotyped, utilization or repetitive behaviours are suggestive of pathology involving the frontal lobes, e.g. frontotemporal dementia¹⁰.

SPEECH

In the elderly, speech can be affected by a number of factors unrelated to mental state, including ill-fitting dentures or oral pathology. An increase or decrease in the rate, quantity and/or volume of speech can be associated with mania and depression, respectively. Pressure of speech is characteristic of mania or frontal lobe involvement. In depression, poverty of speech may occur to a degree that the patient appears to be mute or dysphasic, although such a severe impairment in language is more frequently a result of neurodegenerative or cerebrovascular disease than functional illness. Circumstantiality and tangentiality occur in psychosis and mania, but are often related to dementia in the elderly. Similarly, flight of ideas is characteristic of mania but can also occur in frontal lobe syndromes.

Nominal dysphasia is common in the early stages of Alzheimer's disease when it would normally be associated with at least some degree of memory impairment. Conversely, in primary progressive aphasia (PPA) impairments in language precede deficits in other cognitive domains^{12,13}. Language deficits in PPA are predominantly expressive and usually associated with loss of fluency; in semantic dementia there is loss of expressive and receptive vocabulary in the presence of fluent but 'empty' speech^{10,14}. Clearly, it is important to ensure that any apparent receptive dysphasia cannot be accounted for by a hearing impairment and that an apparent expressive dysphasia is not in fact the result of dysarthria. Dysphonia is a disorder of phonation due to inability to produce voice sounds using the vocal organs; this is distinct from dysarthria and can occur in Parkinson's disease, stroke and other organic disorders¹⁵ or as a psychogenic phenomenon¹⁶.

Other abnormalities of speech are suggestive of specific disorders. For example, perseverative speech is almost pathognomonic of organic brain disease, particularly involving the frontal lobes. Verbal

stereotypies, mannerisms, echolalia, paraphasia and neologisms also occur in organic (often frontal) syndromes although may also occur in mania and psychosis.

MOOD

Elderly people may be less likely than younger adults to report sadness or dysphoria. This does not appear to be a cohort effect and has been reported in different generations of older adults¹⁷; whether this will hold true for the current young-old population is not known. The concept of 'depression without sadness' has, however, been criticized by some, who suggest that apathy, withdrawal and loss of vigour can represent a depletion or disengagement syndrome that reflects normal age-related changes¹⁸. A similar picture may also result from physical illness due to chronic pain, fatigue and disability. Likewise, the bradykinesia and bradyphrenia of Parkinson's disease can lead to difficulties in differentiating depressive from physical symptomatology. Apathy, loss of interest and motivation and even abulia may occur in dementia, particularly in subcortical^{19,20} and frontotemporal subtypes²¹, and can overlap with or be misinterpreted as depression^{22,23}. Changes in mood may be also present in the prodromal stages of dementia, before cognitive deficits are apparent²⁴. In established dementia, affective disturbances are common and may present with behavioural changes^{25–27}.

Given the overlap of symptomatology, it is helpful to pay close attention to the presence of biological features of depression, particularly diurnal mood variation, appetite, early morning waking and anhedonia. Cognitive symptoms of guilt, helplessness and worthlessness are also useful pointers towards a depressive disorder.

Emotional lability can be present in affective disorder and psychosis but can also be a feature of organic syndromes, e.g. cerebrovascular disease²⁸, Parkinson's disease²⁹ and other brain pathology³⁰, and may be confused with depression. Euphoria is a feature of mania and frontal lobe dysfunction, and may be present in other organic disorders.

THOUGHT

Thought Form

As in younger patients, psychotic illness in the elderly can be associated with a broad spectrum of abnormalities of thought form, e.g. circumstantiality, flight of ideas, loosening of associations (from tangentiality through to word salad) and, at the other extreme, thought block. However, apparent thought disorder in the elderly may represent confusion or language disorder as a result of delirium or neurodegenerative illness. Careful attention to the overall picture, including the context of the patient's presentation and simple cognitive testing, can help to clarify the situation.

Thought Content

Delusions are fixed beliefs out of keeping with an individual's social, cultural and religious background, which are based on unsound reasoning and are maintained even in the presence of evidence to the contrary. In the elderly, delusions may form part of a psychotic or affective illness but are also common in delirium and dementia. In delirium, delusions are often fleeting and persecutory. In dementia, delusions of theft are common and often relate to misplacement of objects. Well-formed delusional systems are uncommon in dementia

but do occur. Delusional misidentification is also common in organic disorder³¹, e.g. patients with dementia may insist that their spouse or even their own reflection in the mirror is an impostor.

As in young adults, delusions can be sub-classified into several types, e.g. persecutory, grandiose, nihilistic and bizarre delusions, and delusions of jealousy. Autochthonous or primary delusions arise spontaneously and 'out of the blue' while secondary delusions occur as a result of some other experience, e.g. secondary to hallucinations or affective disturbances. Primary delusions in the elderly suggest functional rather than organic disorder. Delusions must be differentiated from overvalued ideas, which are beliefs that may not be unreasonable but are pursued to an unreasonable degree by the patient. Overvalued ideas are often associated with personality disorders.

Obsessions are recurrent and persistent thoughts, images or impulses that the patient tries to but is unable to resist. They may occur in the context of an obsessive disorder but can also be a feature of depression or dementia. Sometimes repeated checking in dementia is related to anxiety and forgetfulness rather than obsessive-compulsive behaviour and can present a diagnostic challenge, particularly in the early stages.

Passivity Phenomena

Thought insertion and withdrawal, thought broadcast and 'made actions' represent a disintegration of boundaries between the self and the outside world and are typical of a functional psychotic disorder rather than dementia or delirium.

PERCEPTION

A hallucination is a perception in the absence of an external stimulus and may occur in any modality (auditory, visual, tactile, olfactory, gustatory, somatic) in the context of psychosis, affective disorder, organic disorder or delirium. Sensory impairment, both visual and auditory, is particularly important in older people and predisposes to hallucinations. Charles Bonnet's syndrome of visual hallucinations in people with visual impairment in the absence of psychiatric or neurological illness is well known. These hallucinations are typically complex, not distressing and are usually associated with a good degree of insight. The most common cause is age-related macular degeneration (see Schadlu *et al.*³² for a recent detailed review). Auditory hallucinations (typically of music) occurring in clear consciousness in people with hearing impairment are also common and have been described as an auditory form of Charles Bonnet syndrome³³. The pathophysiology underlying these experiences may relate to deafferentiation of visual or auditory cortical structures, resulting in hyperexcitability and increased spontaneous activity³⁴. Sensory impairment is also an important maintaining factor for hallucinations occurring in the context of schizophrenia or other disorders.

Auditory hallucinations occur in schizophrenia regardless of the age of onset, although in late-onset psychotic illness visual and olfactory hallucinations are also relatively common³⁵. It is important to ensure that an acute confusional state or other organic cause is excluded before new-onset hallucinations in the elderly are attributed to functional illness. Visual hallucinations, typically of people or animals, are one of the core features of dementia with Lewy bodies and are often associated with some degree of insight⁴.

Illusions are false internal perceptions that result from a combination of imagery and the perception of a real external object. They are common in people with visual impairment as well as in psychotic

or organic disorder and are accentuated by affect and poor attention. Sensory distortions are changes in the perceived quality or intensity of a stimulus (e.g. hyperacusis) and are suggestive of organic disorder or drug intoxication. Perceptual abnormalities must be discriminated from visual agnosia, which is the failure to recognize objects despite normal function of the eye.

COGNITION

General observation throughout the interview will provide information about cognition, e.g. the general level of orientation, the presence of confabulation, repetition of questions or statements and the ability to follow the conversation and to remember facts and names. The presence of hearing impairment, anger, irritability, anxiety, depression and psychosis can lead to an underestimation of cognitive ability and it is important to bear these factors in mind. Conversely, older people with marked cognitive impairment can maintain a façade that is convincing enough to mask their deficits in the absence of collateral history or objective cognitive testing, particularly in the context of a high premorbid level of intellectual ability. Memory is relatively well preserved in the early stages of some dementias and in these cases deficits in other cognitive domains may only become apparent on formal testing. Examples include visuo-spatial impairments in dementia with Lewy bodies⁴ or deficits in sequencing and executive function in frontotemporal dementia¹⁰.

Relatives' accounts of cognitive function can also be inaccurate, e.g. due to expectations of increasing forgetfulness with ageing, the insidious nature of their relative's decline or difficulties in accepting the change in their loved one and its significance. It is therefore important to include at least some form of objective cognitive testing during even the most basic examination of mental state. The Mini Mental State Examination (MMSE)³⁶ is the most widely used cognitive screening tool in clinical practice, although it is weighted towards verbal memory and does not include items to assess executive function. Furthermore, individuals with high premorbid intellectual function may score well within the normal range despite marked cognitive and functional decline from previous levels³⁷.

More detailed brief assessment scales include the Addenbrooke's Cognitive Examination – Revised (ACE-R)³⁸, Modified Mini Mental State Examination (3MS)³⁹ and Cognitive Abilities Screening Instrument (CASI)⁴⁰, although all take longer to complete than the MMSE⁴¹. Supplementing the MMSE with other brief tests like letter fluency (FAS)⁴² and the clock drawing test^{43,44} may be a practical compromise for the initial assessment and to guide the need for more detailed neuropsychological assessment.

INSIGHT

Insight is a fluid and multifaceted phenomenon and has been conceptualized in many ways. The dimensions of insight in psychosis have been summarized as: (i) recognition of the illness, (ii) attribution of the illness to a mental disorder, (iii) awareness of the benefit of treatment, and (iv) awareness of the social consequences of the mental disorder⁴⁵. Insight in dementia is also a complex entity, and both explicit and implicit awareness are worth considering⁴⁶. For example, an individual may deny any problem with their memory but acknowledge that they have performed poorly on a test or need to use memory aids at home to ensure that they remember appointments. It can sometimes be difficult to discriminate between lack of insight and cognitive impairment itself; this is particularly relevant when considering medication compliance.

It has been suggested that some individuals have insight into subtle cognitive deficits before they are apparent on objective testing, and that as these objective cognitive deficits develop, insight progresses in an inverse U-shaped curve so that ultimately there is established dementia with little insight⁴⁷. However, insight in mild cognitive impairment is variable⁴⁸ and the significance of subjective memory complaints in the absence of objective cognitive deficits is as yet uncertain.

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The Physical Examination: A Guide for Old Age Psychiatrists

Stephen Todd, John O'Hare, Bernadette McGuinness and A. Peter Passmore

*Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences,
The Queen's University of Belfast, Belfast, UK*

INTRODUCTION

The medical and psychiatric history obtained from the patient and informant, together with the mental status assessment, provide the majority of the information required in the evaluation of the older person presenting to the old age psychiatrist. However, the physical examination retains a crucial role in the evaluation of the older person for several reasons (Table 22.1).

First, it is an expected component of the consultation by the patient and/or their relative or carer and assists in developing the doctor–patient relationship. Second, a particular physical sign or constellation of signs will increase or decrease the pretest probabilities in the differential diagnosis under consideration following the history. Third, a more rational and focused plan of investigation will be instituted. Fourth, serial examination over time allows the clinician to observe the course of the disease, assess the effectiveness of any treatments commenced, and, if necessary, reconsider the diagnosis in the light of these data. Fifth, on occasions, an adequate history may not be obtainable, for example in delirium. The physical examination therefore assumes greater weight in determining further management until such history becomes available. Finally, co-morbidity is the rule rather than the exception in the older person. Commonly, there will be several aetiologies for a particular presenting complaint. The old age psychiatrist assesses the older person in a variety of settings, including the home, clinic, hospital ward, or institution, and may be the first or only contact that person may have with a clinician. Therefore, the old age psychiatrist should have the skill and ability to perform a brief but thorough physical examination, interpret the findings, plan a logical series of investigations, and determine if referral to a specialist, including other members of the multidisciplinary team, is indicated¹.

Table 22.1 Role of the physical examination in the older person

Expectation by patient and/or relative in consulting a doctor
Provides additional, pertinent information to history obtained
Allows judicious use of investigations and resource
Repeated assessment permits observation of disease course and therapeutic effects
Detection of contributory or important co-morbidity

CONSIDERATIONS

A number of differences between older and younger people are reflected in the pattern and presentation of illness (Table 22.2). First, diseases that commonly occur in older people have taken many years, sometimes decades, to develop. Examples of such chronic 'degenerative' diseases are atherosclerosis, cancer, degenerative joint disease, and neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases.

Second, co-morbidity is common and interacts with normal physiological ageing changes of the body to modify presentation of disease. Impairment of physiological homeostatic mechanisms results in reduced capacity to cope with changes in the body (brought about by disease) or in the environment (such as absence of a carer or admission to hospital). Thus, the older person will be more severely affected by an insult that might be relatively minor to a younger adult. These 'reduced reserves' of older age also lead to slower recovery from an acute insult. For example, hospital length of stay is twice that of younger adults. However, even old, seriously ill individuals can recover if given sufficient time and support.

Third, in older people symptoms of disease often are less specific and uninformative, making the task of establishing the diagnosis/diagnoses more challenging for the clinician. This non-specific mode of presentation often takes the form of a 'giant of geriatrics' syndrome – instability (falls); immobility ('off feet' or 'off legs'); incontinence; intellectual impairment (delirium and dementia). However, a thoughtful approach and careful attention during physical examination will frequently direct the choice of investigations and treatment.

Some practical considerations in the conduct of the physical examination should be kept in mind and will reap considerable reward in the information obtained (Table 22.3). Time and patience are necessary virtues of clinician and patient.

Table 22.2 Differences between older and younger people

Background of chronic disease
Impaired homeostasis/physiological changes of ageing
Less specific presentation of disease

Table 22.3 Practice points when examining the older person

Older people may require longer, and need assistance, to:

- Transfer from chair to standing
- Mobilize into the consulting room
- Transfer from chair to examination couch
- Remove items of clothing
- Replace items of clothing

The examination may also be limited by:

- Fatigue
- Frailty
- Pain
- Breathlessness
- Poor hearing or eyesight and missing aids
- Confusion

The student and doctor in training are encouraged to take the time to follow a standard scheme of examination for each body system and to repeat this scheme again and again not in a thoughtless way but with consideration to each point in the scheme, the finding elicited being examined for its significance in light of the other available data. Such an approach will produce a skilled clinician who can not only perform a rapid and seamless physical examination but also detect pertinent physical signs of relevance to the care of the older person.

GENERAL EXAMINATION

During the Interview

Physical examination commences on first meeting the older person, continues during the interview, and concludes with the 'formal' examination. Observation is thus the key initial tool, later to be supplemented, to a greater or lesser degree, by inspection, palpation, percussion and auscultation. Brief mention is made of the carer. Attention to carer demeanour and their relationship with the patient is important. Mental and physical ill health in the carer may adversely impact on the patient.

The general appearance of the clothes, face and hands, including nails, may be the first clue to self-neglect or neglect or abuse from a carer, depression, or functional decline in completion of basic activities of daily living due to underlying disease(s). Body habitus may suggest malnourishment or cachexia.

The handshake allows closer inspection of hands and nails and will also permit observation of tremor, whether resting or action, wasting of the small muscles, joint swelling or stiffness, or loose jewellery, for example, that will assist in directing enquiry and subsequent examination. Ability to transfer, requirement for an aid or an arm, and gait provide information on functional ability and may suggest dysfunction at various levels of the musculoskeletal and neurological systems which will require more detailed scrutiny.

Observation of the face during the interview may reveal the blank appearance of Parkinson's disease or the lack of expression and poor eye contact of depression. Asymmetry in facial appearance may indicate neurological dysfunction, for example due to stroke or Bell's palsy. Less obvious, perhaps, are symmetrical changes in facial appearance, such as the pallor of anaemia, the fat deposition and telangiectasia of Cushing's syndrome, or the proptosis and lid retraction of an overactive thyroid gland.

Abnormal movements may be noted during the interview. In the head and face, titubation, orofacial dyskinesia, facial tics or

myoclonus, or fasciculation of the tongue all require explanation. Wincing or grimacing indicates uncontrolled pain, which requires evaluation and alleviation. In the limbs, tremor may again be apparent. The position and posture of the limbs may suggest current or previous musculoskeletal or neurological problems.

Speech will be assessed during the interview and might direct further testing to determine if there are one or more problems affecting comprehension, such as loss of hearing or receptive dysphasia; articulation and pronunciation, such as dysarthria, expressive dysphasia and dysphonia; or content, such as confusional states, delusional or psychotic disorders, or depression. Limitation of speech due to pain or dyspnoea indicates serious cardiovascular and/or respiratory compromise or perhaps profound anaemia.

Examination

The general examination continues from and expands on observations made during the interview. A general 'head to toe' inspection of the patient will take closer note of the hands, face, head and neck, nutritional and hydration status, and the presence of abnormal swellings and masses.

A systematic approach to the hands will inform the examiner on the presence of a multitude of systemic disorders. The nails may be pitted in psoriasis or clubbed in a number of respiratory, cardiac, gastrointestinal and other disorders. The pattern and distribution of swelling and deformity of the small joints may suggest the presence of osteoarthritis, rheumatoid arthritis or psoriatic arthropathy. Abnormal pigmentation of the skin may indicate anaemia if pale or chronic liver disease if jaundiced. Atrophy of the small muscles may be a marker of generalized weight loss and ill health or suggest median nerve entrapment at the wrist if isolated to the thenar eminence.

Closer inspection of the eyes may also suggest anaemia or liver disease if there is pallor of the conjunctiva or jaundice of the sclera, respectively. Aphthous ulceration of the mouth is a marker of ill health. The presence of oral thrush can suggest recent antibiotic therapy, deficient oral hygiene or poorly controlled diabetes mellitus. Poorly fitting dentures can cause trauma. The condition of teeth that are present should be noted. Poor dentition can cause pain and reduction in oral intake.

The neck should be inspected for the presence of masses and the thyroid gland palpated before and while the patient swallows a glass of water. This should prompt general consideration of thyroid status and evidence of over- (warm sweaty hands, tachycardia, particularly atrial fibrillation, or tremor) or under- (cold, hoarseness, bradycardia, 'peaches and cream' complexion) activity. The cervical lymph nodes should be palpated. Localized or generalized enlargement will be confirmed by subsequent palpation of axillary and inguinal chains.

The skin should be exposed, with judicious use of a gown or drape, to assess colouration and pigmentation and characterize contusions, rashes, masses or tumours. Skin turgor in older people is less reliable than in younger adults as an indicator of hydration. Dryness of mucous membranes or axillae and sunken eyes are suggestive of dehydration whereas a moist tongue is evidence against dehydration. Further evaluation of hydration follows in the cardiovascular section.

CARDIOVASCULAR SYSTEM

The patient should be positioned at forty-five degrees with neck and chest exposed. While palpating the radial pulse at the wrist, the examiner should note the rate and rhythm. Atrial fibrillation is

the commonest arrhythmia in older people and is a strong risk factor for cerebral infarction. The character of the pulse is better assessed by palpation of the carotid artery. The blood pressure is measured both lying and after standing for two minutes. Falls are common in older patients, particularly in those with dementia. Postural hypotension is indicated by a fall of 20 mmHg or greater on standing for at least one minute.

The face should be inspected briefly with consideration of jaundice or xanthelasma at the eyes and cyanosis of the lips and tongue. In the neck, the right internal jugular vein is inspected for the jugular venous pressure (JVP), noting the vertical height above the sternal notch and the character. The carotid arteries are palpated separately, noting the character.

Inspect the praecordium for scars, deformity, position of the apex beat and pulsations. Palpation for the apex beat should consider the position and character. A laterally displaced apex beat can denote left ventricular dilatation. Tapping, thrusting and heaving beats occur in mitral stenosis, mitral regurgitation and left ventricular hypertrophy, respectively.

Auscultation is done in the area of maximal acoustic advantage for each of the four valves – apex (mitral); lower left sternal edge (tricuspid); second left (pulmonary) and right (aortic) intercostal spaces. The examiner listens separately to each phase of the cardiac cycle. The first and second heart sounds should be identified and considered normal or abnormal in intensity. The presence of added sounds (extra heart sounds or murmurs) is considered, noting location in the cardiac cycle, character and position heard maximally. Added sounds may be accentuated by repositioning the patient – left lateral for mitral stenosis and upright for aortic regurgitation.

With the patient sitting forward, the examiner may inspect and palpate for sacral oedema. The peripheral pulses should be palpated and other evidence of peripheral vascular disease, such as cool dusky skin, loss of hair and prolonged capillary refill, and peripheral oedema sought.

Other signs to consider during later examination are dullness to percussion and reduced breath sounds (pleural effusion), inspiratory crepitations (pulmonary oedema), hepatomegaly (right ventricular failure) and a pulsatile epigastric mass (abdominal aortic aneurysm).

RESPIRATORY SYSTEM

During the general inspection, notice whether the subject is dyspnoeic or using accessory muscles of respiration. In the hands, observe for tar staining, clubbing, anaemia or wasting of small muscles. The respiratory rate should be counted. In the face, unilateral meiosis and ptosis may suggest Horner's syndrome (damage to the sympathetic nervous system). The contents of the sputum pot should be inspected. Listen for the high-pitched inspiratory note of stridor. In the neck, palpate for tracheal position and presence of cervical lymphadenopathy.

Expose the chest completely and place the patient in a seated position. Both front and back of the chest should be examined with the following suggested scheme. First, inspect for scars and deformity and assess the degree and symmetry of expansion on maximal inspiration. Expansion is then assessed by palpation. Next, palpate for tactile vocal fremitus. The position of the apex beat may suggest mediastinal displacement.

Chest percussion compares left side with right side as the examiner progresses down the chest, not forgetting apices and axillae. The percussion note may be dull, for example with pleural effusion or consolidation, or resonant, with pneumothorax or emphysema. Finally,

the chest is auscultated. The character of the breath sounds, whether normal or bronchial, and their intensity is noted. The presence, location and timing of added sounds are then considered. Crepitations or crackles may be pan-inspiratory and in the lower zones in pulmonary oedema or end-inspiratory and with either an upper or lower zone location in pulmonary fibrosis. Wheeze is generally expiratory and polyphonic in chronic obstructive pulmonary disease (COPD). Expiration is prolonged in COPD. Asthma is less prevalent than COPD in older people.

GASTROINTESTINAL SYSTEM

The abdomen should be completely exposed and the patient recumbent with one pillow to support the head. On general inspection, the examiner should have appreciated body habitus. In the hands, evidence of chronic liver disease such as clubbing, white nails, palmar erythema or Dupuytren's contracture may be noted. Bruising, scratch marks and spider naevi may be noted on the torso. Jaundice is best appreciated at the sclera. The mouth should be illuminated and inspected for stomatitis, glossitis and ulceration. Parotid enlargement and, in men, gynaecomastia are also pointers to chronic liver disease.

The abdomen should be inspected for scars, masses, bruising, distension, hernia and prominent veins. The examiner should also bend down to inspect from the side as masses may be visible. Abdominal movement on respiration is then noted.

The patient should be asked to indicate the site of pain, if present. On light palpation of all areas of the abdomen, the examiner should observe for evidence of pain, including wincing, grimacing or guarding. Each region should be deeply palpated in turn for masses if no pain is elicited. Continue to palpate specifically for the presence and location of hepatomegaly and splenomegaly. The kidneys may be bimanually palpable. The groins are palpated for adenopathy and hernia. Percussion of the abdomen starts in the midline and works toward the flank. If dullness is noted the examiner should seek to demonstrate if it shifts on repositioning the patient. Auscultate for the presence of bowel sounds and for bruits over the renal areas. The gastrointestinal examination is completed with digital rectal examination.

NEUROLOGICAL SYSTEM

Neurological examination is an essential component of the evaluation of every older person presenting to the old age psychiatrist. An experienced clinician will complete a thorough screening assessment in a few minutes and conduct a detailed follow-up examination as indicated with only minimum further effort. Neurological examination is crucial for several reasons (Table 22.4).

Observation during interview and general examination of tremor or blank facies will direct the examiner towards other evidence of Parkinsonism, whereas a drooping lip or stiff, immobile limb might suggest stroke and a search for asymmetric upper motor neurone deficits. However, it is recommended that a standard scheme is followed to ensure thorough assessment.

Table 22.4 Importance of neurological examination

Diagnostic criteria specify neurological signs ²⁻⁴
Development of signs can mark disease progression
Recognize side effects of psychiatric medications
Ability to localize pathology by pattern of signs

Cranial Nerves

Assessment of olfaction is generally limited to an enquiry regarding the sense of smell.

The eyes are examined 'from out to in'. Visual acuity, corrected with the person's glasses, is assessed in each eye with a Snellen chart. If the top line cannot be read, acuity should be recorded as the best of finger counting, hand movement, or light appreciation. Knowledge of visual acuity is important in cognitive testing. Visual fields are assessed by confrontation to the examiner's (which are assumed to be normal). The examiner should be seated at least one metre from the patient and on the same level. Each eye is tested in turn and, as a minimum, all four quadrants in each eye should be probed. Any deficit detected must be mapped in detail. The presence of visual inattention is assessed by stimulating both fields simultaneously. Extraocular muscle function is assessed by asking the subject to track a moving object through a horizontal and then a vertical arc from the neutral point. The examiner may place a hand on the patient's forehead to prevent movement. In addition to the direction of reduced or absent movement, the presence of diplopia and direction and speed of nystagmus is noted. The pupils are inspected for size, shape and regularity and compared for equality. The direct reaction of the pupil to light and the consensual reaction of its pair are tested with a bright light shone from the temporal side. Reaction of the pupils to accommodation is tested by asking the patient to change focus from the distance to an object placed close to the face. Cataract may be detected by absence of the red reflex. The corneal reflex is elicited using a strand of cotton wool advanced from the temporal side. On fundoscopy, evidence of retinopathy from diabetes mellitus or hypertension and papilloedema from raised intracranial pressure should be sought.

A scheme of examination of lower cranial nerves is described, although it should be noted that this does not follow each nerve in sequence. Thus, the examiner should remain cognisant of what is being tested. A simple command, followed by demonstration of the desired manoeuvre facilitates compliance with motor examination not only of cranial nerves but also the limbs, to be described below.

Instructions to 'raise your eyebrows', 'close your eyes tightly', 'puff/blow out your cheeks', 'show me your teeth' and 'clench your teeth' assess motor function of the facial and trigeminal nerves. The ability to raise the eyebrow in the presence of ipsilateral lower facial palsy indicates upper motor neurone aetiology. Sensation is tested in the dermatome of each of the three branches of the trigeminal nerve by touching forehead, cheek and jaw on each side. The sensation of taste is not routinely assessed clinically.

Several functions should be assessed once the patient is instructed to 'open your mouth'. While the tongue rests in the floor of the mouth fasciculation may be noted. Movement of the uvula to one side on the command 'say ah' indicates a palsy of the contralateral glossopharyngeal nerve. The gag reflex is tested using an orange stick to press on each side of the oropharynx. Finally, the patient is asked to 'stick out your tongue'. A deviated tongue points to the side of the lesion. Assessment of motor function is completed by asking the patient to 'look to the side' (sternomastoid) and 'shrug your shoulders' (trapezius). Hearing is assessed informally by asking the patient to repeat a phrase whispered into each ear in turn.

Primitive reflexes, such as pouting or palmo-mental, may be present in advanced dementia.

Limbs

Tables 22.5 and 22.6 summarize the scheme of neurological examination of the limbs.

Table 22.5 Neurological examination of the upper limbs

Inspection	
• wasting	
• fasciculation	
Tone	
Power	
• pronator drift	
• shoulder abduction	(C5,6)
• elbow flexion	(C5,6)
• elbow extension	(C6,7)
• wrist & finger extension	(C7)
• wrist flexion & grip	(C8)
Coordination	
• finger-nose	
• rapid alternating movements	
Reflexes	
• biceps	(C5,6)
• supinator	(C5,6)
• triceps	(C6,7)
Sensation	
• pin-prick	
• vibration	
• joint position	
• light touch	

Table 22.6 Neurological examination of the lower limbs

Inspection	
• wasting	
• fasciculation	
Tone	
Power	
• hip flexion	(L2,3)
• knee flexion	(L5,S1)
• knee extension	(L3,4)
• ankle dorsi flexion	(L4,5)
• ankle plantar flexion	(S1,2)
Coordination	
• heel-shin	
• foot tapping	
Reflexes	
• knee	(L3,4)
• ankle	(S1,2)
• plantar	
Sensation	
• pin-prick	
• vibration	
• joint position	
• light touch	
Gait	

Upper limbs (Table 22.5)

Assessment of tone may be affected by voluntary or involuntary movement and is often confounded by the instruction to 'relax' or 'let your arm go floppy'. Asking the patient to tap the foot can help. Reduced tone occurs in the early stage following stroke but usually indicates lower motor neurone pathology. The increased tone of longstanding upper motor neurone lesions eventually releases in a 'clasp-knife' pattern. In Parkinsonian syndromes, tremor superimposed on rigidity leads to a 'cog-wheel' pattern. Extrapyramidal signs may be caused by chronic neuroleptic use.

Pronator drift remains a sensitive marker for weakness. One muscle group innervated from each cranial nerve root should be tested (Table 22.5). It is prudent to assess grip strength and function of the hand and fingers. Power is tested in the position of maximal activity and graded on a standard scale, according to age, build and gender. Stroke predominantly affects flexor muscles.

If the deep tendon reflexes are increased, a positive Hoffmann's reflex (flicking the nail of either the second, third or fourth finger will cause a flexion of the thumb) and finger jerk confirm hyperreflexia. Reinforcement, for example by clenching the teeth, may be required if a reflex appears absent. Coordination is assessed by the finger–nose test – assessing for intention tremor and past-pointing – and rapid, alternating hand movements – which may be slow and clumsy in cerebellar and extrapyramidal disorders.

When testing sensation, the distribution of any abnormality should be determined and may be dermatomal (nerve root or spinal cord lesion), involve a single peripheral nerve territory (for example, carpal tunnel syndrome) or the 'glove' loss of a peripheral neuropathy. Testing for sensation may be unrewarding in subjects with dementia.

Lower limbs (Table 22.6)

Tone is assessed during hip rotation and knee flexion. Clonus, a sustained, rhythmical contraction of muscles under sudden stretch,

is checked at the knee and ankle and is present with increased tone from an upper motor neurone lesion. Each lumbosacral nerve root is tested for motor and sensory function. Loss of posterior column modalities is often found in normal elderly people.

The plantar reflex (Babinski sign) is elicited by drawing the stimulus along the lateral border of the sole of the foot from posterior to anterior and then medially across the ball of the foot. Spreading of the toes and dorsiflexion (extension) of the great toe due to upper motor neurone pathology must be distinguished from a withdrawal response.

In the heel–shin test the patient is instructed to slide the foot smoothly down the shin from the knee to the ankle and repeat. Rapid, alternating movement is tested by the patient tapping the foot on the ground.

Finally, the gait is observed with the patient walking normally, turning and walking back. Walking heel to toe and performing Romberg's test (the patient stands with the feet together and is asked to close their eyes) assesses cerebellar and posterior column function.

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Investigations in Old Age Psychiatry

Sujatha Merve¹ and Robert C. Baldwin²

¹*Chasefarm Hospital, Enfield, UK*

²*Manchester Royal Infirmary, Manchester, UK*

INTRODUCTION

This chapter reviews a range of laboratory and imaging investigations with which an old age psychiatrist should be familiar. Physical illness has been shown to be present in 20–80% of psychiatric patient populations surveyed¹. Physical illness of relevance to the presenting psychiatric symptoms is reportedly in the range 9–46%¹. Concomitant medical disorder was found in up to 63% of psychiatric patients presenting to an emergency department². However, a retrospective study demonstrated that only 0.8–4.0% of abnormal tests were clinically significant¹ (defined as those that contributed to a diagnosis of a medical disorder not identified by history taking and physical examination and which led to a medical consultation or changed further management). Accordingly, some have argued against using routine batteries of tests^{1,2}.

The older adult population may be an exception to this, as the chances of a physical illness presenting primarily with psychiatric symptoms is increased. Examples include delirium (infections, metabolic abnormalities, polypharmacy); dementia (thyroid disease, B₁₂ deficiency); psychosis (substance withdrawal/toxicity, space occupying lesions in the brain); depression (anaemia, thyroid disease, some drugs, malignancy); mania (stroke, drug side effects); anxiety (thyroid disease, cardiac arrhythmia); and perceptual abnormalities (visual defects, migraine, temporal lobe epilepsy, withdrawal from drugs). Further, mental disorder may contribute to the onset of new physical illness or deterioration in an existing one due to factors such as self-neglect or cognitive difficulties.

Investigations should be guided by findings from history taking, mental state examination and relevant physical examination. Unlike in general medicine, the role of laboratory and other investigations is mainly supportive and to rule out an organic aetiology of psychiatric presentations. However, there are several other reasons for conducting physical investigations in the older patient (Table 23.1).

Ancillary investigations can aid diagnosis, especially in the dementias and in delirium. Many older patients have known physical comorbidity that requires further evaluation or are at high risk of common morbidities, which can affect management (ischaemic heart disease, anaemia, etc.). Because of self-neglect, those with dementia and depression may suffer under-nutrition and require investigation for this. Last, some psychiatric procedures and medication require pre- and/or post-testing (Figure 23.1).

Investigations may therefore be classified as primary or 'routine' (most patients receive them), secondary (indicated only in patients with certain clinical characteristics) and mandated (patients meeting certain criteria must have them) (Figure 23.1). The limitations of this approach should be recognized. Some tests (e.g. for neurosyphilis, see below) will show abnormal results very rarely but with important clinical implications. Others (e.g. full blood count or plasma viscosity) will often be slightly abnormal and of uncertain significance. A good deal of skill is required to interpret results in relation to a particular patient.

An example of an investigation of immediate relevance to management is a patient with a history of depression now presenting with what appeared to be a recurrence but also with recent confusion and difficulty in walking. On computerized tomography (CT) brain scan he was found to have a glioma. In another instance a patient with dementia deteriorated with poor appetite and weight loss. Investigations revealed anaemia and a markedly raised C-reactive protein, found on further testing to be due to inflammatory bowel disease. Here investigations helped clarify whether it was dementia or comorbid pathology causing physical deterioration. Sometimes investigations are of uncertain relevance. An example is a patient presenting with late-onset psychosis and who was found to have a sodium of 125 mmol/l due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH; see below) and a raised thyroid stimulating hormone (TSH) level caused by not taking thyroxine for former radio-iodine treated thyrotoxicosis. Optimizing these abnormalities made no obvious difference to her mental state, which improved only after the introduction of an antipsychotic agent. This also illustrates that even when there is an apparently obvious physical cause for an observed mental state, it is often necessary to treat psychiatric comorbidity as well as optimizing the management of physical disorder.

HAEMATOLOGICAL INVESTIGATIONS

The full blood count (FBC) and differential count help detect various conditions, including anaemia (low haemoglobin, low red cell count, micro/macrocytosis), infections (raised white cell count, neutrophilia), allergies or parasitic infections (eosinophilia), blood malignancies (raised cell count, abnormal cells in blood smear) and effects of drugs on particular cell lines (neutropenia or

Table 23.1 Reasons for conducting investigations in old age psychiatry

To rule out causative organic physical illness
To aid in the diagnosis of some psychiatric conditions (e.g. dementia)
To assess secondary physical effects of the presenting psychiatric disorder
To help assess the impact of known medical co-morbidities
To screen for common co-morbidities not obvious at presentation but likely to affect management
To screen prior to the commencement of some medications and procedures
To monitor drug levels in the blood
To monitor potential side effects of prescribed drugs

agranulocytosis with clozapine). The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are non-specific tests that can point to infection, inflammation, anaemia, malignancy, temporal arteritis and autoimmune conditions. The ESR rises with advancing age and so becomes more difficult to interpret.

The incidence of psychiatric symptoms with B₁₂ deficiency has been reported to vary between 4% and 50% depending on the population studied³. A correlation between serum cobalamin level and measures of cognitive function has been noted in some studies, although this has been disputed in those aged over 60⁴. Deficiency of folate may be more likely to cause depressive symptoms and a low B₁₂ has been linked to psychosis⁵. The true nature and reversibility of a B₁₂ deficiency-induced dementia has been debated. In addition,

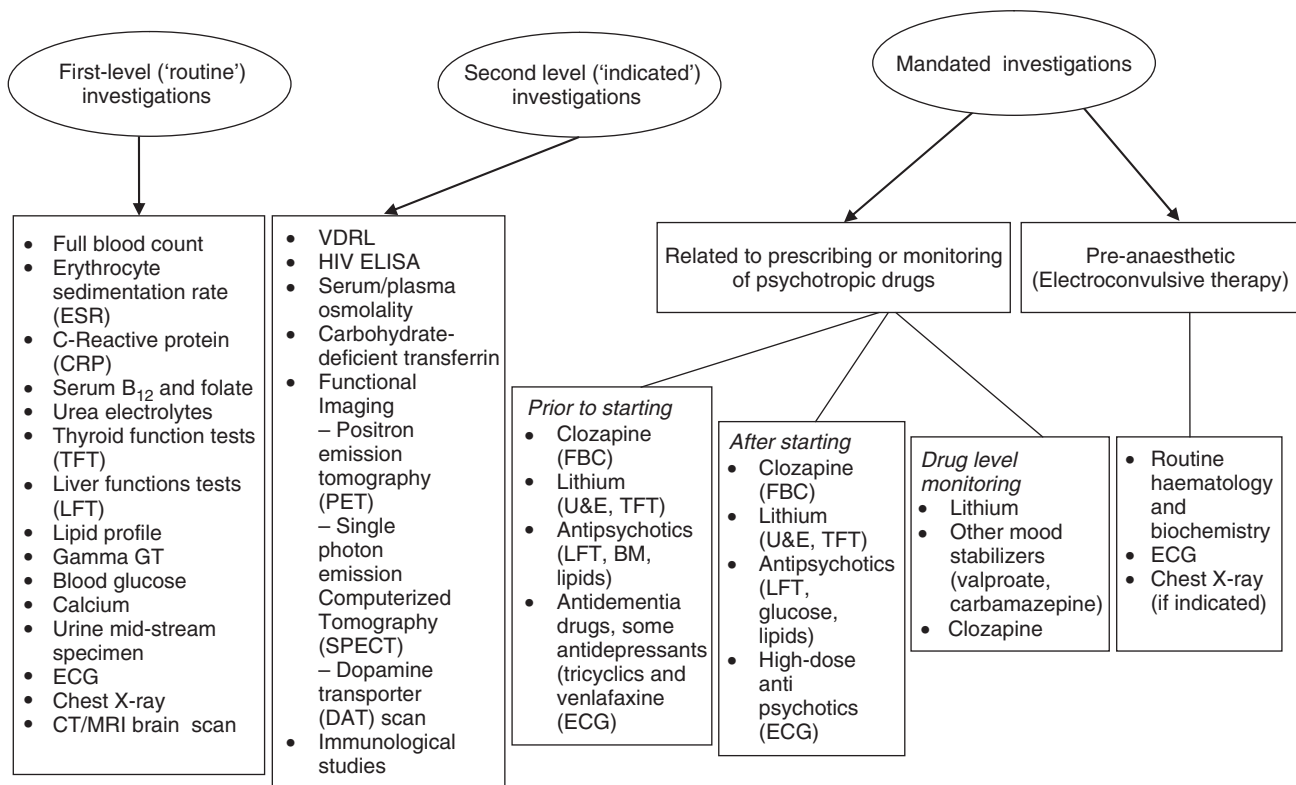
deficiency of folate has been linked to poorer response to antidepressant treatment⁶. Confirmatory tests for the aetiology of vitamin B₁₂ deficiency include gastric parietal cell antibodies, intrinsic factor antibodies and the Schilling test.

BIOCHEMISTRY

Routine biochemistry may detect electrolyte disturbances, dehydration and abnormal organ functioning (kidney, liver). The commonest psychiatric presentation of most of these is delirium. In addition, biochemical investigations are used to monitor the metabolic side effects of antidepressants or antipsychotics (e.g. SIADH and abnormal liver function tests [LFT]) and mood stabilizers (urea and electrolytes and thyroid function with lithium). SIADH is characterized by hyponatraemia (levels below 125 mmol/l are usually symptomatic), low serum osmolality and inappropriately elevated urine osmolality. SIADH can develop early after initiation of drug therapy, especially with selective serotonin re-uptake inhibitors (SSRIs). Increasing age, female gender and medical co-morbidities are risk factors.

Transient asymptomatic rise in LFT is not uncommon during the first few weeks of prescribing psychotropic drugs. Gamma glutamyl transpeptidase (γ GT) is elevated in liver disease, pancreatic disease, obesity and enzyme induction by drugs or alcohol, and 52% of alcohol dependent patients have been reported to have high γ GT⁷. Due to its low specificity, γ GT is not indicated as a screening test for alcohol misuse. More specific is the carbohydrate-deficient transferrin (CDT) enzyme immunoassay.

A random glucose above 11 mmol/l suggests diabetes. Hypoglycaemia can cause delirium and can be seen in depressed diabetic patients who take their medication but neglect to eat.

**Figure 23.1** Types of investigations in old age psychiatry (see text for meaning of abbreviations)

Thyroid function testing (TFT) should be performed because of the well-known association of depression and hypothyroidism, easily overlooked in the elderly, and because 'apathetic hyperthyroidism' can be mistaken for depression. Patients on lithium should undergo TFT every six months. Raised corrected serum calcium can indicate malignancy (metastasis, multiple myeloma and lung cancer) and these patients may present with depressive symptoms. Iron studies including serum ferritin and total iron binding capacity are performed to help diagnose the type of anaemia (iron deficiency, sideroblastic or anaemia of chronic disease).

Because of the risk of the metabolic syndrome, fasting lipid screening is important in patients receiving antipsychotics. Waist measurement is a simple test of risk for this syndrome and there are international guidelines on waist measurement⁸.

MICROBIOLOGY

Mid-stream urine (MSU) assessment is usually carried out to assess patients with confusion. In a sample of 68 patients Gregory *et al.*² reported an overall percentage of significant results in 3.1% of their review of general psychiatry patients. Kolman⁹, though, studied older patients and found positive test results in 21% of patients. Non-contaminated samples are hard to obtain from patients with delirium or dementia.

RADIOLOGY

The patient's age correlates with the frequency of abnormal findings on chest X-ray¹⁰. A review of 746 psychiatric admissions¹¹ identified that the 9% of patients who had a significant X-ray finding also had concomitant physical signs and symptoms. Chest radiology of all patients presenting with psychiatric symptoms is not warranted, and clinical suspicion remains the best yardstick. It should always be performed on patients at risk of conditions like tuberculosis (homeless persons, alcohol/drug misuse and patients with HIV infection) and (ex-) smokers with weight loss.

Chest radiography is usually performed routinely as a pre-anaesthetic screening tool prior to patients receiving ECT (some centres perform it on a mandatory basis on patients aged above 35).

Endoscopy and barium X-ray tests of the gastrointestinal system may be indicated for patients with weight loss and microcytic anaemia. These investigations are sometimes poorly tolerated by psychiatric patients so advances in CT imaging are important. Helical CT scanning of the abdomen with oral contrast, besides being rapid and non-invasive, can identify a range of pathologies of the gut and other structures.

SPECIALIZED BLOOD TESTS

Syphilis

The Venereal Disease Research Laboratory test, commonly known as the VDRL test, is a screening test for syphilis that measures antibodies to the spirochete *Treponema pallidum* in the blood or cerebrospinal fluid (CSF). The newer test analogous to this is the rapid plasma reagin (RPR). *Treponema pallidum* haemagglutination assay and the fluorescent *Treponema* antibody tests (TPHA/FTA ABS) are highly specific for *Treponema* antigens and are used at some centres as confirmatory tests, especially of CSF.

Clinically significant results were found in 0.3% (0–0.6%) of psychiatric patients routinely screened¹. A retrospective study of all inpatients (mean age 74.5) undergoing syphilis screening in a UK hospital¹² revealed that 16 of 423 tests were positive (3.8%). In four of the seven patients who received treatment, syphilis was identified as a likely contributor to the psychiatric presentation. The authors suggested that routine screening of elderly patients was justifiable where an organic aetiology was suspected, especially in dementia. Hilton¹³, though, highlighted the importance of considering local epidemiology, risk factors, neurological/neuropsychiatric features and ethics prior to the routine screening of patients. In the guidance on dementia issued by the National Institute for Health and Clinical Excellence (NICE), routine testing for syphilis is not recommended¹⁴.

Immunology

Psychiatric symptoms may be caused by systemic autoimmune diseases such as systemic lupus erythematosus, scleroderma, sarcoidosis, Sjögren syndrome, primary vasculitides and antiphospholipid syndrome. The range of autoimmune antibodies found in the spectrum of conditions include antinuclear antibody (ANA), anti-DNA (single stranded or double stranded), anti-Ro, anti-La, anti-phospholipid antibodies, anti-smooth muscle, rheumatoid factor (RF), anti-neutrophil cytoplasmic antibodies (ANCA) and antibodies to thyroid peroxidase. Table 23.2 illustrates the more common tests in relation to some immunological conditions. Catatonia and some rare encephalopathies are associated with autoimmunity, e.g. anti-NMDAR antibodies¹⁵.

NEUROIMAGING

Focal neurological signs on physical examination or an acute change in the mental status not completely explained by other causes require

Table 23.2 Autoimmune conditions and relevant investigations

Condition	Psychiatric presentation	Relevant tests
Systemic lupus erythematosus	Psychosis, delirium, depression, global cognitive deficits	Anti-nuclear, anti-double stranded DNA, antiphospholipid, anti-neuronal
Hashimoto's thyroiditis	Dementia, delirium, hallucinations	Thyroid antibodies (antithyroid peroxidase and antithyroglobulin), anti-neuronal antibodies
Sjögren's syndrome	Cognitive dysfunction	Anti-nuclear, rheumatic factor
Polyarteritis nodosa	Delirium, auditory and visual hallucinations, dementia	Raised erythrocyte sedimentation rate (ESR), arterial biopsy
Temporal arteritis and polymyalgia rheumatica	Delirium, depression, hallucinations, cognitive dysfunction	Raised ESR, arterial biopsy

consideration of neuroimaging. Subdural haematoma is easily overlooked in older adults, especially when chronic. Fluctuating confusion, unsteady gait, falls and heavy alcohol use are all clues. Imaging is important if normal pressure hydrocephalus (cognitive impairment, gait disorder, incontinence) is suspected. On magnetic resonance imaging (MRI) the typical 'fluid void' sign may be seen but imaging alone is often not diagnostic.

There are clinical diagnostic rules for assessing which patients with dementia should undergo neuroimaging but they are not precise enough to ensure that patients with potentially reversible lesions are not missed¹⁶. The cost-effectiveness of routine imaging in patients with suspected dementias has been questioned but with the likelihood of more effective treatments emerging in the future the situation may change. Guidelines concerning the indications for neuroimaging are available from the National Institute for Health and Clinical Excellence¹⁴, the Scottish Intercollegiate Guidelines Network¹⁷ and the American Psychiatric Association (APA)¹⁸. NICE recommends MRI scanning as the preferred modality to assist early diagnosis and detect subcortical (vascular) white matter changes. The APA recommends neuroimaging in cases with subacute onset (less than one year), symptom onset before age 65, vascular risk factors suggesting a higher likelihood of cerebrovascular contributory factors or a history or neurological examination findings suggesting a possible focal lesion. The usefulness of neuroimaging in late stage disease has not been established¹⁸.

CT is widely available and may be acceptable for anxious/disturbed patients. In one study¹⁹ of 178 CT scans carried out, only 4 cases of potentially reversible neurological conditions were identified and in no case did this knowledge change treatment. On the other hand 32.8% had evidence of ischaemic white matter disease. As CT is not as sensitive as MRI (see below) in detecting this, when unequivocally reported on CT scanning such ischaemic changes ('leukoaraiosis') support a diagnosis of mixed type dementia.

MRI provides more detail of brain structure and function. As the patient must remain motionless in a tunnel for up to 20 minutes, MRI

is not suitable for anxious or claustrophobic patients nor for those with metallic implants (pacemakers, aneurysm clips). There are few diagnostic signs relevant to psychiatry with MRI. An exception is the pulvinar sign in variant Creutzfeldt–Jakob disease (CJD), which has been found to be highly accurate and may obviate the need for more invasive testing²⁰. More usual is the frequent finding on MRI of white matter hyperintensities, which are commonly interpreted as evidence of small vessel ischaemia but are of uncertain diagnostic significance unless graded as severe.

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) utilize radioactive isotopes to assess brain metabolism (PET) and perfusion (SPECT) and provide information about the functional status of brain tissue. These investigations are discussed in detail elsewhere. Although clinical criteria may be more sensitive than SPECT, the latter is more specific in differentiating different types of dementia²¹ and so is recommended to aid in the differential in cases of doubt¹⁷.

Functional imaging of the dopamine transporter to assess the integrity of the nigrostriatal dopaminergic pathways is the basis of the DAT scan. DAT scanning can be helpful in distinguishing drug-induced Parkinsonism from idiopathic Parkinson's disease and in the diagnosis of Lewy body dementia. In the latter, low striatal DAT occurs whereas DAT activity is normal in Alzheimer's²².

The development of additional imaging tools such as quantitative MRI, functional MRI, investigational PET compounds, and other methods aimed at imaging senile plaques in the brain may help improved diagnosis, early recognition, and more precise assessment of disease progression in the future.

ELECTROCARDIOGRAPHY (ECG)

The main use of ECG in psychiatry is to monitor serious cardiac side effects of psychotropic medication (Table 23.3). It is ordered in at-risk populations, e.g. those with pre-existing cardiac abnormalities or

Table 23.3 Summary of common cardiac effects of psychotropics

<i>ECG parameter</i>	<i>Drug</i>	<i>Effect</i>
Heart rate	Clozapine; drugs with antimuscarinic side effects: TCAs, MAOIs	Sinus tachycardia; clinicians should suspect myocarditis/cardiomyopathy in patients on clozapine if patients have fever or other cardiac symptoms such as persistent tachycardia
Heart rate variability	Clozapine	Reduced variability associated with increased risk of cardiac death
Cardiac conduction	Tricyclic antidepressants	Prolong QRS complex; such changes in a patient with pre-existing conduction defect can cause complete heart block; in toxic doses (overdose) this can prove fatal
	Antipsychotics	Can prolong QTc interval
	Haloperidol in high doses	At-risk patients can develop torsades de pointes and fatal ventricular arrhythmia
	Any intravenous antipsychotic	Some antipsychotics may cause atrial fibrillation, heart block, changes to P and T waves
Cardiac rhythm	Lithium	May affect T waves and rarely cause heart block
	All drugs that have an effect on cardiac conduction	Torsades de pointes, ventricular arrhythmias and sudden cardiac death have all been reported; monitoring mandatory for at-risk population (pre-existing cardiac disease, high-dose antipsychotic use, overdoses especially TCAs and those with metabolic/electrolyte abnormalities)
Cardiac conduction and rhythm	Acetylcholinesterase inhibitors	Can cause bradycardia, atrial arrhythmias; angina, syncope

conduction defects, those on other drugs that have an effect on cardiac conduction (antiarrhythmics), those with or at risk of metabolic abnormalities (anorexia, renal failure) and patients who have taken an overdose. An ECG should be performed prior to the commencement of a tricyclic antidepressant or a cholinesterase inhibitor.

Patients on high-dose antipsychotics are at increased risk of arrhythmias and sudden cardiac death, and hence ECG monitoring in this group of patients is mandatory^{23,24}. Lithium can change the morphology of T waves and in rare instances has been associated with heart block (Table 23.3).

ELECTROENCEPHALOGRAPHY (EEG)

The EEG is no longer widely used in assessment of patients in old age psychiatry and has been largely superseded by structural neuroimaging. However, in some cases the EEG can provide valuable additional information, e.g. in differential diagnosis of rapidly progressive dementia, episodic neurological symptoms and signs, or complex presentations with inconsistencies in the clinical picture and investigations.

The EEG in patients with Alzheimer's dementia may show non-specific abnormalities even in the early stages of the disease. In frontotemporal dementia the EEG remains unremarkable until late in the disorder. Although not routinely recommended, the EEG can be highly specific (although not sensitive) in cases of sporadic CJD¹⁷, in which case a lumbar puncture to assess for the presence of protein 14-3-3 may help with the diagnosis. The role of MRI in CJD has been discussed.

Patients with dementia of Lewy body type show a characteristic early slowing of dominant EEG rhythm and 50% show focal delta wave activity in temporal regions²⁵. The EEG in patients with vascular dementia is more likely to be normal in the early stages.

Abnormality correlates with the amount of damage in the underlying brain structure, often with focal or asymmetrical changes.

EEG findings of pseudo-periodic sharp wave activity (triphasic) are found in 70% of cases of CJD.

Quantitative EEG (qEEG) uses a computerized programme to statistically analyse EEG recordings and may assist in diagnosis. A literature review²⁶ suggests that abnormalities in qEEG tend to increase with the severity of the dementia. Studies have reported a moderate to high accuracy of differentiating EEG recordings in normal ageing populations and patients with dementia.

PSYCHOTROPIC DRUG MONITORING

Therapeutic drug monitoring is primarily used for drugs with a narrow therapeutic index or which show high inter-patient pharmacokinetic variability²⁷. Drug monitoring is mandatory for some drugs that are toxic in higher concentrations such as lithium. Monitoring can also help confirm treatment adherence. Serum monitoring was useful for tricyclic antidepressants where there was known to be a therapeutic window but with the newer antidepressants, where effective doses are close to starting doses, the need has disappeared.

Most drug levels are measured when they reach steady state concentration; this takes four to five drug half-lives²⁸. Also sample collection should be made within 1–2 hours of the recommended time (trough or pre-dose and 12-hour post-dose, as with lithium). Mood stabilizers are one of the most commonly monitored classes of psychotropic drug (Table 23.4), although lithium is the most important because of its narrow therapeutic-to-toxic ratio. Blood levels of valproate and carbamazepine do not necessarily relate to clinical effectiveness.

For clozapine, a number of patient factors have been identified that influence the serum levels. These include the age of the patient,

Table 23.4 Serum monitoring of mood stabilizers

Drug	Investigations prior to prescribing	Side effects	Average daily dosages	Target serum levels
Lithium	Renal function	Polyuria, gastrointestinal upset, tremor, neurological disturbance (toxicity), weight gain, oedema, psoriatic rash	400 mg (slow release)	0.6–0.8 mEq/l
	Electrolytes			
	ECG			
	Thyroid function			
Valproate	Blood glucose (preferably fasting)	Sedation, nausea, unsteadiness, tremor, weight gain	500–1500 mg	65–90 µg/ml (not definitely established)
	Liver enzymes			
	Full blood count			
Carbamazepine	ECG (if history or clinical condition suggests)	Sedation, ataxia, nystagmus, blurred vision, agranulocytosis, hyponatraemia	400–800 mg	4–12 µg/l (levels for epilepsy)
	Liver enzymes			
	Full blood count			
	ECG (if history or clinical condition suggests)			

ethnicity, smoking status and interactions with other drugs. Plasma levels of 350–500 µg/l have been suggested for optimal clinical response. Seizures have been identified to be commoner in patients with levels higher than 1000 µg/l²⁹. Some authors have suggested the prophylactic use of valproate to prevent seizures when the plasma levels are >600 µg/l.

OTHER INVESTIGATIONS

Cerebrospinal Fluid Analysis

Lumbar puncture (LP) is generally performed under the care of physicians or neurologists with the main indications being confirmation of CNS infections (bacterial, tubercular, fungal), inflammatory conditions (vasculitis) or malignancy. With the developments in neuroimaging, many of these conditions can be identified on scans. The role of LP in suspected CJD can be diagnostic and has been discussed.

Sleep Studies

Common sleep complaints include insomnia, excessive daytime sleepiness and parasomnias such as REM sleep behaviour disorder (SBD), as seen in dementia with Lewy bodies. Other conditions that may be misdiagnosed as primary psychiatric illnesses include narcolepsy and sleep apnoea syndrome. The latter is increasingly recognized as a cause of or contributory factor to confusional states.

Primarily the assessment of sleep-related disorders relies on clinical evaluation and sleep charts. Polysomnography is available in specialist centres and involves measurement and observation of different stages/components of sleep along with recordings of EEG, electro-oculogram and electromyogram. Sleep apnoea is diagnosed with simultaneous monitoring of respiratory effort and oxygen saturation overnight and is offered by respiratory medicine departments.

Genetic Studies

Genetic screening and prediction of risk raises many ethical dilemmas. However, old age psychiatrists increasingly see younger patients with dementia for whom genetic considerations apply and they should know when to refer to a colleague specializing in psychiatric genetics.

Ethical issues of confidentiality and information sharing pose a great challenge to clinicians and geneticists. The experience may be emotionally challenging to patients and the results may not be conclusive. Issues of 'the right not to know' and implications for the individual's future employment and discrimination in access to insurance policies need to be considered. Some tests can result in stigmatization and unwarranted anxiety among family members. Genetic testing is predictive for only some conditions.

Alzheimer's disease has been associated with mutations in amyloid precursor protein (APP) and presenilin 1 and 2 genes. Frontotemporal dementia studies have suggested mutations in *tau* protein (in some families involving autosomal dominance) and *α-synuclein* has been recognized in Parkinson's disease. Early onset (<65 years) Alzheimer's disease is associated with gene mutations that are transmitted in an autosomal dominant fashion.

While late onset Alzheimer's disease (>65 years) is generally considered to be idiopathic or sporadic, numerous studies have shown increased risk of developing the disease (odds ratio between 3 and 15) in individuals with APO E4 allele on chromosome 19³⁰.

However, testing for apolipoprotein E4 (*APOE4*) is not recommended for use in the diagnosis of dementia³¹. Commercial kits are available for testing certain genes, for example presenilin 1 (*PSEN1*) on chromosome 14 but careful interpretation is required and should only be undertaken in the context of pre- and post-test counselling¹⁸. In addition, specific genetic testing is available for Huntington's disease and CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy – Notch 3 gene polymorphisms). Lastly, there is current interest in the glucocerebrosidase gene in Lewy body dementia, which may in the future have implications for genetic testing³².

LEGAL CONSIDERATIONS

Always record whether the patient consents to undergoing investigations and if they are unable whether it is in their best interests to undergo them. In English law, in an emergency, the Capacity Act (2005) permits reasonable and proportionate force for necessary testing and the Mental Health Act (2007) allows the Responsible Clinician to make arrangements for testing of detained patients where this is of direct relevance to their mental disorder (this includes withdrawing blood for clozapine monitoring). It does not, however, mandate testing of an unrelated condition, e.g. an endoscopy for incidental anaemia. Colleagues responsible for carrying out the investigation must conduct their own assessment of capacity. For example, an endoscopist must be satisfied that the patient understands the procedure and if this is not clear they will often seek the advice of the psychiatrist who has referred the patient. Colleagues undertaking investigations for the psychiatric team should be forewarned if the patient lacks capacity, both for their own safety and because certain tests will be difficult to perform without collaboration of the patient.

Testing of a patient for the good of others without consent is not permitted. The Human Tissue Act (2004) makes this clear. For example, this includes a member of staff who has been bitten by a patient with dementia and who may wish to know the patient's hepatitis and AIDS status. The Capacity Act (2005) may permit testing if it can be demonstrated that such knowledge is in the patient's interest, e.g. if it might lead to less restrictive nursing. Legal advice would still be needed regarding the disclosure of results to a third party.

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Internet Resources

Dementia guidelines

NICE Dementia Guidelines: www.scie.org.uk/publications/misc/dementia/index.asp; <http://guidance.nice.org.uk/CG42/Guidance/doc/English>

SIGN dementia guidelines: www.sign.ac.uk/pdf/sign86.pdf

American Psychiatric Association: www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007

American Academy of Neurology: www.aan.com/professionals/practice/pdfs/dementia_guideline.pdf

Neurology (journal): www.neurology.org/cgi/content/full/56/9/1143

Legal and Ethical considerations

Mental Capacity Act (2005): www.opsi.gov.uk/acts/acts2005/ukpga_20050009_en_1

Mental Health Act (2007): www.dh.gov.uk/en/Healthcare/Mentalhealth/index.htm

Human Tissue Act (2004): www.dh.gov.uk/en/Publichealth/Scientificdevelopmentgeneticsandbioethics/Tissue/Tissuegeneralinformation/DH_4102169

Bedside Assessment of Cognitive Functioning

Richard Perry

*Department of Neurosciences, Imperial College and Imperial College Healthcare NHS Trust,
Charing Cross Hospital, London, UK*

INTRODUCTION

In the future, clinicians are likely to make ever more use of newer diagnostic techniques such as multimodal MRI imaging, PET imaging and CSF analysis. These ancillary investigations are only helpful in the appropriate clinical context in terms of their ability to discriminate between various diseases and in how their results are interpreted. As always in medicine, this clinical context comes from careful and considered history and examination.

HISTORY TAKING IN COGNITIVE ASSESSMENT

One key aspect of the cognitive history is the necessity of gaining a witness or corroborative account. By their nature, cognitive impairments may include lack of insight and impaired ability to express details of the history as a result of memory, language or other cognitive deficits. It is therefore strongly recommended that a witness history is taken and it is often beneficial to perform this separately from the patient, particularly if personality or behavioural changes are to be exposed.

An in-depth discussion of all aspects of the cognitive history is beyond the scope of this chapter and we have excluded the well-known aspects of past psychiatric history, past medical history, educational and occupational history and social and family history in favour of highlighting some tips specific to cognitive history taking, which although not meant to be foolproof, nevertheless may provide helpful clues to direct the clinician.

Initial Presentation and Impressions

Although not without exception, on the whole, if a spouse, friend or carer is the instigator of the referral, this is more suspicious of an underlying organic brain disorder than patients who self-present. Patients who attend a clinic alone have a much greater chance of having an underlying affective cause of their symptoms than those who are accompanied.

Many patients who are 'brought' to a consultation adopt this role very quickly and defer to their spouse or friend in sitting down and answering questions. A common occurrence is the response to the first greeting or question – when the examiner asks why the patient has come to see them, the patient may immediately turn to their spouse for help or confirmation without actually addressing

the question. Anecdotally this reaction seems to have a fairly high specificity for underlying organic brain disease.

Presenting Complaint

It is important to clarify the first symptom that has been noticed by the patient or carer. Patients presenting with moderate stages of dementia may have a multitude of symptoms that overlap between dementia subtypes and often the first symptom can be instructive regarding diagnosis. For example, memory deficits are invariably the earliest feature of Alzheimer's disease whereas behavioural changes are invariably the initial feature of frontotemporal dementia despite both sets of symptoms being present in both conditions as they progress.

It is often difficult for patients or informants to be accurate about the duration of symptoms which are usually underestimated. A little gentle probing can often extend the history from an initial estimate of six months to several years, thereby narrowing the differential diagnosis. It is useful to ask such questions as 'how were they three years ago – were they the same as 20 years ago?'

Behavioural and Personality Changes

To get a clear history of behavioural or personality change, the interviewing of an informant is critical as lack of insight often accompanies such behavioural changes. Major personality change is usually a result of pathology in the limbic, paralimbic and frontal-striatal systems. They may be seen in space occupying lesions of the frontal lobe and subcortical dementias but the condition where specific personality changes are virtually diagnostic is frontotemporal dementia.

A simple question such as 'have you noticed any changes in X's behaviour or personality?' is usually a helpful opening gambit. A not uncommon response in frontotemporal dementia is that 'they are not the same person that I married'.

Behaviours to probe for include apathy, passivity and lack of initiation. Indeed some patients are often content to let others discuss less than complimentary changes in their behaviour or personality without need to interject or justify themselves in any way. Disinhibited behaviour can be enquired about in terms of whether the patient has done or said anything that causes embarrassment or is inappropriate, especially in public. Rigidity in behaviour may be evidenced by strict and unnecessary time keeping or eating habits such as always eating the same food at the same time of day. Obsessive and compulsive

behaviour should be questioned and the duration of this ascertained to differentiate from longstanding personality traits. Gradual loss of empathy and blunting of emotional repertoires should be sought and a change in food preferences for sweet things or the development of a catchphrase are both behavioural changes that are virtually pathognomonic of frontotemporal dementia.

Autobiographical History

It is useful to go through details of schooling and major life events in early adulthood, primarily to see if the subject has impaired autobiographical memory. An inability to remember where they went to school, when they were married and where, or what their first job was, is concerning for an organic dementia as these memory abilities are not usually affected in psychiatric disorders.

Medications

Elderly populations may have a multitude of medical and psychiatric co-morbidities and hence multiple medications, many of which may affect cognition. Particular medications to note are opiate-based analgesics such as codeine or tramadol, medications with anticholinergic properties such as tricyclic antidepressants, antispasmodics, anti-emetics, anti-parkinsonian medication, bronchodilators, or anti-arrhythmics.

Activities of Daily Living

Ask about performance at work if appropriate, ability to travel to new locations alone, handling of finances and bank accounts, social events, use of household devices including telephones, TVs etc., preparation of meals, organizing of family events such as trips and holidays. A gradual change of responsibilities from patient to spouse or other carer over several years is revealing.

BEDSIDE COGNITIVE ASSESSMENT

Initial Observations

The bedside cognitive assessment starts with observation of the patient. Watch how the patient enters into the consultation room, paying particular attention to their gait and observe how they sit down in a chair.

The gait abnormality of idiopathic Parkinson's disease is easy to recognize if one is watching for it. Slow and shuffling with short steps, narrow base, stooped posture with decreased arm swing. It is surprising how often this is overlooked. If a diagnosis can be made before the patient has sat down, it is very helpful for the rest of the consultation! The gait of cerebrovascular disease is characterized by the sense that the feet are rooted to the ground with a more wide-based gait, again with small steps. The gait of normal pressure hydrocephalus is usually more wide-based than that of cerebrovascular disease and is unsteady with less adherence of the feet to the floor.

Further useful information can be taken from watching the patient sit in a chair – difficulty in orienting to the chair or sitting on the edge or armrest of a chair by mistake suggests significant apraxia. If a patient falls back heavily into a chair, be on the lookout for additional signs of progressive supranuclear palsy.

Throughout a cognitive assessment it is useful to keep the question in mind of whether one is dealing with a predominantly cortical or subcortical picture of impairment. The cardinal features of

a subcortical cognitive impairment are slowing of thought, response and movement with impaired attention. The major cortical deficits to look out for are language impairment (aphasia), visuospatial impairment and praxis and so the finding of one of these deficits suggests cortical involvement (note the rare exceptions of aphasia from basal ganglia lesions). Memory deficits may be present in both cortical and subcortical syndromes.

Another important question to return to during the consultation is whether the patient has an organic or psychiatric origin to their symptoms. Although it is not always possible to be certain, there are certain clues from both the history and examination that may guide the examiner. Symptoms that are fluctuating or specific to either the home or workplace are suspicious for psychiatric symptoms, as are symptoms that are noticed solely by the patient rather than others. In the examination, psychiatric syndromes may often manifest with impaired memory, executive functions and processing speed deficits but the presence of real language deficits, apraxia or visuospatial function is far more concerning for organic brain disease.

Cognitive Rating Scales

The most widely used screening tool for bedside cognitive assessment is the Mini Mental State Examination (MMSE) which typically takes 8–10 minutes to administer and assesses orientation, memory, language and visuospatial function and is scored out of 30 points. As the MMSE is the subject of a separate chapter (see Chapter 27), it will not be described in detail here, but it is worth considering a few of its major advantages and disadvantages.

Advantages:

- ease of administration;
- wide use helps comparison of scores across patients and testing centres;
- suitable for longitudinal assessment;
- quick.

Disadvantages

- does not assess speed of information processing or executive function;
- minimal assessment of memory;
- ceiling effect in mild cognitive impairment and frontotemporal dementia;
- test–retest reliability (intra-rater) of ± 3 ;
- inter-rater reliability suspect on serial 7s and 'world' backwards.

Because of these limitations, which are likely to be inherent in any short screening tool, various adaptations of the MMSE have been devised. The most promising of these is the Addenbrooke's Cognitive Examination (ACE) which includes all of the subtests of the MMSE but is expanded to include more detailed tests that provide scores for each of the five domains of episodic memory, verbal fluency, naming, language and visuospatial function. The latest revised version, the ACE-R, comes on six pages of A4, takes approximately 20 minutes to administer and is scored out of a total of 100. The full ACE-R with administration and scoring guidelines is available on line at <http://pn.bmj.com/supplemental>.

The memory domain includes a seven-item name-and-address test in which the patient is asked to register a name and address (e.g. Simon Williams, 17 Somerfield Road, Croydon, Surrey) across three learning trials and then recall after a 10-minute delay. There are

two tests of verbal fluency. In letter fluency, the patient is asked to produce as many words beginning with 'p' as possible in one minute and in category fluency, as many animals as possible. The naming section is far more sensitive than that on the MMSE and consists of 10 line drawings of low-frequency items.

The authors of the ACE-R have carried out validation studies suggesting two cut-off scores of 88/100 or 82/100 for clinical practice. In the initial publication the upper cut-off score of 88 has a good sensitivity for dementia of 94% and a specificity of 89%¹. This high sensitivity was reproduced in a later study although specificity was considerably lower with many false positives². The specificity of the ACE for dementia is increased at the lower cut-off score of 82 without a major loss of sensitivity.

Proponents of the ACE have examined its potential to differentiate between dementia subtypes. The initial reports used a ratio of the domain scores of verbal fluency + language/orientation + memory (VLOM ratio) to differentiate between Alzheimer's disease and frontotemporal dementia and found that a ratio >3.2 supports Alzheimer's disease whereas a ratio of <2.2 is in favour of frontotemporal dementia¹. Follow-up studies have confirmed the ratio of >3.2 as being reasonably sensitive and specific for AD although the sensitivity of a ratio of <2.2 for frontotemporal dementia is probably too low for clinical utility, especially when such studies do not take into account the pre-test probability of a diagnosis². In clinical practice a diagnosis is not based on the ACE alone but in combination with the history, examination findings and imaging investigations.

A more recent study has attempted to use the ACE in conjunction with episodic memory tests such as the Rey Auditory Verbal Memory Test and the CANTAB Paired Associates Learning to identify MCI cases at greatest risk of conversion to Alzheimer's disease³. There was reasonable evidence that the combination of a broad screening tool of multiple cognitive domains such as the ACE plus two or more episodic memory tasks was effective in terms of both positive and negative predictive value. Indeed it is likely that this combination, which could be performed in a clinical assessment, is almost as effective as a more formal and extended neuropsychological assessment.

In the author's own practice, the subtests that appear to be the most helpful in adding to the MMSE to aid differential diagnosis are the episodic memory task, the verbal fluency task and the naming task. If the ACE were to be improved upon, it would be to further develop the episodic memory task to a word-list learning task with trials of registration and delayed recall. In clinical practice we are often trying to reliably identify which patients have impaired episodic memory that may be the earliest stages of Alzheimer's disease and the current name-and-address task may be too insensitive to fulfil this role, particularly in patients who have been cognitively high performing. Despite this limitation, the ACE is already becoming more widely used and appears to be an easily administered and helpful tool in the memory clinic.

Assessing Different Cognitive Domains

Orientation to time usually includes an assessment of day, month and year. In general, orientation to time is lost before orientation to space and this is particularly true of Alzheimer's disease. Not knowing the date is not specific and indeed many normal subjects are unaware of the date. Usually when testing date with the MMSE a margin of $\pm$ two days is given. It is notable that disorientation to person in the absence of obtundation of conscious level is suspicious of factitious disorder. The catch is with severely and suddenly aphasic patients

who can present to the unwary as confused and even as functional in origin.

Attention can be tested at the bedside with the *serials 7s* or 'world' backwards of the MMSE or ACE.

Memory. The history informs us about autobiographical memory and further assessment can probe for deficits in episodic, working or semantic memory.

Working memory refers to information that is kept 'online' and in constant rehearsal for periods of up to around 30 seconds. It can be disrupted by interference and memories are not actually laid down for later recall. At the bedside this can be tested by forward and backward digit spans: In *forward-digit span*, a series of numbers, usually starting with three (e.g. 492) is read to the subject evenly at one integer every second who then repeats the numbers back. The digit span is taken as the maximum number of digits repeated back until two successive failures at a string length have occurred. The normal range is 6 ± 1 . *Backward-digit span* is performed in the same way except that the subject is asked to repeat the string of numbers backwards (e.g. examiner reads 947, subject repeats 749). The normal range is 5 ± 1 .

Episodic memory refers to memory for events that have been personally experienced. It has two main components: *anterograde memory* (new learning) and *retrograde memory* (memory for past events). The functional neuroanatomy of episodic memory involves the limbic-diencephalic system and its frontal connections and most importantly the hippocampal complex. Patients with disorders of episodic memory will present with forgetfulness for recent events, have difficulty keeping to the plot of novels or even films, may forget messages and rely on lists and may be repetitive.

Assessment of retrograde memory is predominantly from the history including the autobiographical history (see above) and specific questions related to more recent events such as details of holidays over the last year or two, details of family events such as weddings or Christmas and knowledge of recent major news events.

Anterograde memory can be assessed at the bedside and clinicians often use the memory subtests of the MMSE although the seven-item name-and-address task of the ACE is more sensitive. A patient's previous level of performance should be taken into account and even recall of all seven items may be obtained in those high functioning but in the earliest stages of a degenerative disease.

Semantic memory refers to our memory for facts, word meanings and general knowledge. The neural substrate that appears to be important for semantic memory is the cortical area of the anterior/inferior temporal lobe. Deficits can be apparent from the history by 'empty speech' with circumlocutions. Speech content is diminished and words are replaced with generics such as 'things'. Bedside assessment can be with verbal fluency tests, naming of objects or line drawings, tests of verbal knowledge and reading of regular or irregular words. Verbal fluency, as used in the ACE, can test both phonemic fluency (words beginning with 'p', 'd', 'f' etc.) in a minute or with semantic fluency (e.g. animals, tools, fruits etc.). In conditions characterized by semantic memory impairment there tends to be a discrepancy between semantic and phonemic fluency whereas predominant impairment of phonemic fluency is typical of subcortical syndromes such as cerebrovascular disease, parkinsonism, or depression^{4,5}. Tests of semantic knowledge in the verbal domain include questions such as: what colour is grass? where do elephants live? which animal has four legs, a hump and lives in deserts? The ACE language subtests probe for impairment in the reading of irregular words, a difficulty which is often associated with semantic memory impairment. In this context, patients may have difficulty in

reading irregular words such as height or yacht and when asked to read 'mint', 'pint' and then 'rint' may read 'rint' as in 'pint'.

If significant and disproportionate semantic impairment is suspected, further assessment of knowledge about famous people or famous faces can be helpful. Right temporal lobe atrophy and involvement of the fusiform gyrus as seen in the right temporal variant of frontotemporal dementia seems to be particularly associated with face recognition and knowledge impairments⁶. This is one of the only uses the author has found for publications such as *celebrity* magazines!

Language. It is important to differentiate actual language disorders (aphasias) from *dysarthria* which refers to the impairment of the mechanical aspects of sound production. From the history, the examiner will be able to gather important information about spoken language such as its degree of fluency, whether there are any articulatory problems, difficulties with word finding, impairment of intonation, rhythm or musicality (*dysprosodia*), or paraphasic errors. When assessing fluency, the most important issue will be whether the person is able to produce language effortlessly or not, regardless of the actual content. Non-fluent speech is effortful and halting with reduced sentence length, agrammatism and impaired prosody where the normal rhythms and undulations of speech are affected. Phonemic paraphasias may be detected where the sounds within words are incorrect, e.g. incollect rather than incorrect. Where the speech deficits are characterized by slow speech, increased pauses between words and distorted sounds but without phonemic problems, the term apraxia of speech may be used. Fluent speech is characterized by lack of effort and normal articulation but with lack of content and circumlocutions. After listening to speech output a simple assessment of comprehension is valuable using simple instructions in a graded manner. It is helpful to start with one-stage commands such as 'close your eyes' before more complicated commands such as 'lift up your left hand and then stick out your tongue' or 'after touching the desk, touch your left ear with your left hand'.

Repetition is likewise tested in a graded manner starting with simple words such as 'toaster' before more complicated and polysyllabic words such as 'accordion' or 'catastrophe' and then on to short sentences such as 'The orchestra played and the audience applauded' as in the Cambridge ACE. Watch for phonemic paraphasias as described above and whether these are consistent mistakes.

Naming is tested by asking the patient to name particular objects or line drawings. There is a *frequency effect* in which commonly used words are less affected than uncommon words. For example, patients might be able to name high-frequency objects such as 'pen' and 'watch' (MMSE), but may have problems with more low frequency ones such as 'anchor' or 'barrel'.

Reading and its testing at the bedside is influenced by educational factors which need to be taken into account. An in-depth assessment of reading is not frequently required unless the history and general cognitive screen (e.g. 'close your eyes' from the MMSE) identifies specific problems in this area. The Cambridge ACE is a suitable screening tool as it includes regular and non-regular words which can help determine the presence of a surface dyslexia. This form of dyslexia is typical of semantic memory impairment, possibly because these words require semantic knowledge of the word in order to read it, unlike regular words or non-words which can be read without understanding the meaning of the word.

Like reading, writing may not require a detailed assessment unless there are specific symptoms or a fairly circumscribed language deficit is suspected. In these situations, assessment of written spelling and sometimes writing of individual letters is required.

Calculation. A few simple tests of calculation can be extremely useful in a bedside assessment, especially in the situation of progressive aphasia where the clinician wish to differentiate between a perisylvian or frontal opercular syndrome. This cognitive function is highly susceptible to the person's previous arithmetic ability, which will have to be taken into consideration in order to interpret the findings but a few simple examples of mental arithmetic will usually suffice.

Visuospatial function. These can be easily assessed at the bedside by asking patients to copy simple line drawings such as the intersecting pentagons from the MMSE or the cube or clock face from the ACE. If there is disproportionate visuospatial impairment further analysis should include examination for features of *Balint's syndrome*. Although it often presents in a partial or impure state, it classically has several components, the most striking of which is simultanagnosia, which refers to the inability to widen a visual focus and synthesize a wider scene. Often described as a narrowed spotlight of attention, subjects may report only one part of a scene and ignore the wider picture. This can be picked up at the bedside by dot counting (as in the ACE) or in describing visual scenes from magazine photographs. The other features of Balint's syndrome include optic ataxia, which is the inability to accurately reach for objects in the absence of limb ataxia and optic apraxia or sticky fixation which is the inability to move the eyes to a target. The neural substrates of Balint's syndrome are invariably bilateral damage to the parieto-occipital cortex which may result from watershed infarcts or from neurodegenerative conditions such as the posterior cortical atrophy variant of Alzheimer's disease.

Praxis is typically defined as the inability to perform skilled motor movements in the absence of any deficit of power or sensation. Although usually associated with lesions in the left parietal lobe, apraxia may also be seen after lesions to the right parietal lobe, frontal lobes and subcortical structures in the basal ganglia. The description of many subtypes of apraxia such as ideational or ideomotor apraxia has led to considerable confusion due to the inconsistency with which different terms are used by different investigators but in practice such differentiations rarely help in differential diagnosis. The most important aspect of bedside assessment is to demonstrate impaired praxis, which, like visuospatial impairment, is rarely seen in purely psychiatric disorders. This can usually be achieved by asking the patient to copy a series of hand gestures, e.g. 'hitchhiking sign', or by asking them to mimic the use of objects e.g. 'show me how you brush your teeth' or 'show me how you comb your hair'. The presence of impairment in praxis usually suggests organic cortical dysfunction.

Executive function refers to those higher order cognitive capabilities that are called upon to formulate new plans of action and to select, schedule and monitor appropriate sequences of action. A lot of these functions are mediated by the dorsolateral prefrontal cortex and the subserving fronto-subcortical circuit. However, other aspects of the prefrontal cortex are also involved in some of these functions, such as the inferior frontal areas, in abilities that relate to impulse control and inhibition.

Although best tested with formal neuropsychological measures, some assessment is possible at the bedside. Verbal fluency, as described above and assessed in the ACE, is invariably impaired in dysexecutive syndromes, particularly phonemic or letter fluency. Studies show that 15 items in one minute represents a normal performance. Less than 10 items is definitely abnormal. Marked and particular impairment in letter fluency is a hallmark of subcortical disorders. Another bedside task of executive function is cognitive estimates where a subject is asked to make an educated guess to a

question to which they are not expected to know the exact answer. Examples include 'how many people live in London?', 'how fast can a horse run?', or 'how many camels are there in Holland?'. Patients with marked executive impairment tend to give answers that are completely off the mark such as 3000 people living in London. Proverb interpretation, e.g. 'what is the meaning of the phrase 'people in glass houses shouldn't throw stones'?' can be helpful although a patient's age and cultural background may affect their knowledge of such proverbs. A particular aspect of executive function called response inhibition can be tested with the go-no-go test. In this test the examiner asks the subject to place a finger on the desk. The examiner can then tap with their own finger under the desk either once or twice. The subject is instructed to tap once when the examiner taps twice and to tap twice when the examiner taps once. The examiner then begins a series of taps, either once or twice and switches between the two stimuli. Normal subjects pick up the rules to this quickly and can switch without perseverating in their responses.

It is important to remember that executive functions and 'frontal lobe' functions are not synonymous. Executive impairment can manifest from brain injury outside the frontal lobes. A case in point is the cerebellar affective syndrome where cerebellar injuries produce a range of behavioural and neuropsychological deficits very like those seen in frontal lobe syndromes.

The Neurological Examination in Bedside Cognitive Assessment

Specific neurological signs often accompany cognitive and neurobehavioural disorders and although a full discussion of the relevant neurological examination techniques is outside the scope of this chapter, there are some specific systems that should be examined. These should be taken in the context of the observations made of the patient throughout the consultation regarding speed of movement and thought, speech and other motor deficits.

Eye movements. In the context of the bedside cognitive assessment the most important aspects of the eye movements are to look for evidence of cerebellar dysfunction or of supranuclear gaze palsy. Probably the most sensitive measure of dysfunction of the cerebellar system and its connection to the brainstem is the examination of eye movements and nystagmus should be observed for in lateral gaze, upgaze and downgaze. Pursuit movements refer to the smooth tracking of a target from one side to the other and saccadic movements refer to the rapid movement of the eyes from one target to another. All of these eye movements may be affected in cerebellar disease.

Evidence of impairment of supranuclear gaze can be sought by asking the patient to look up to a target and then down while the examiner gently holds the head still. Restriction of upgaze is common with age and is a non-specific marker for extrapyramidal degenerative syndromes. Impairment of downward saccades, particularly slowed downward saccades may support a suspicion of PSP in the right clinical context.

Extrapyramidal signs The cardinal extrapyramidal signs are bradykinesia, rigidity and involuntary movements such as tremor or chorea. Bradykinesia refers to a gradual decrease in speed of movements with repetition and can be elicited in repetitive hand movements or foot tapping. Limb rigidity is suggestive of parkinsonism and axial rigidity, particularly when accompanied by a history of falls and a supranuclear gaze palsy is suggestive of PSP. The tremor of Parkinson's disease is usually, but not always, more prominent at rest and increases with distraction. Lower limb tremor,

particularly unilateral, is very suggestive of Parkinson's disease. Chorea is usually seen as restless flowing involuntary movements, which if mild may just give the impression of a patient being fidgety and should prompt for further exploration of a family history consistent with Huntington's disease and previous psychoactive drug use. Myoclonus refers to intermittent sudden jerks, usually of the limbs and may be stimulus sensitive. Provocation of stimulus sensitive myoclonus may be with a loud clap out of the patient's field of vision. Alternatively upward flicking movements on the underside of fingers of outstretched hands may elicit myoclonic jerks of the same or even contralateral limb. While myoclonus may be present in many neurodegenerative diseases such as Alzheimer's disease, dementia with Lewy bodies and corticobasal degeneration, it is most commonly associated with prion diseases such as Creutzfeldt-Jacob disease, particularly in the presence of a rapidly progressive dementia.

Primitive reflexes. These reflexes are present in newborn babies and tend to disappear with brain maturation. Their re-emergence in adult life suggests disconnection of the fronto-striatal circuits and hence brain pathology. The grasp reflex refers to the involuntary gripping of the examiner's hand when this stimulates the patient's palm. The examiner must tell the patient to let go off the hand. Often attempted withdrawal of the examiner's hand leads to more pronounced grasping. The pout reflex is elicited by putting an orange stick vertically onto the closed lips of the patient and tapping. Other primitive reflexes such as the glabellar tap or palmomental reflex seem to have less discriminatory value.

CONCLUSIONS

As with all aspects of clinical medicine the history is paramount and should be used to guide the clinician to an initial differential diagnosis that can be refined with the examination. While further diagnostic tests are often necessary after bedside assessment, these are most directed and informative if based on a sound clinical assessment.

During this process it is helpful for the clinician to keep in mind a few cardinal questions that can be answered along the way. What were the first presenting symptoms and how long ago did they really start? How is the patient moving and can this help me? Have I got a reliable witness history? Is the presentation psychiatric or organic? Is the pattern cortical or subcortical and what cognitive domains are involved?

By reference back and forth to these questions during the assessment the clinician can interpret the pattern of deficits of a simple cognitive screening tool such as the MMSE or ACE and add refinements to the examination to probe different cognitive functions in more detail. This should lead to a formulation of 'where' the problem lies in terms of the functional neuroanatomy of the brain, which when considered in the light of the onset and progression of the symptoms, can guide towards an accurate differential diagnosis.

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Neuropsychological Assessment

Linda Clare

School of Psychology, Bangor University, Bangor, Gwynedd, UK

Neuropsychological assessment offers a rigorous method of identifying the presence, extent and severity of cognitive impairments. Brief observation and informal interaction can yield valuable information about a patient's condition, but this level of assessment does not usually provide a sufficient foundation for evaluating the degree or extent of cognitive difficulties, and may mean that subtle or mild difficulties are missed. Therefore, a more systematic approach to assessing patients' cognitive functioning is often needed. Neuropsychological assessment achieves this aim through the use of standardized tests.

THE USE OF STANDARDIZED TESTS

Standardized tests assess aspects of current functioning in a systematic way, providing results that can be compared with normative data¹. They are developed with the aim of maximizing reliability and validity; that is, they should provide a consistent measure of the construct of interest. Standardized tests are always administered in the same way, following administration procedures set out in the test manual. Thus, the instructions given to each person taking the test, and all the parameters of the test such as the length of time for which stimuli are presented, are identical. These conditions are exactly the same as those used to obtain data from the reference group or normative sample against which the individual's test scores will be compared, ensuring a valid comparison. Norms typically take into account the effects of age, providing stratified norms for different age groups, and adjustment may be made for other demographic factors that affect test performance, such as level of education. It follows that familiarity with the test procedures is essential in order to administer the test appropriately. Similarly, familiarity with the scientific basis and technical properties of the test, as well as the ability to consider the complex range of factors that may impact on test performance, is necessary for accurate interpretation of test results. For this reason, use of many standardized tests is restricted to those professionals who can demonstrate either by virtue of their professional education or as a result of further training that they are specifically trained in test administration and interpretation.

Neuropsychological assessment of older people combines two traditions of standardized testing: psychometric testing and clinical neuropsychological assessment. These two approaches have been described as *population-based* and *deficit-oriented*, respectively². In practice, the two approaches are typically used alongside one another, with an emphasis on considering patterns of scores across a range of tasks.

Psychometric testing assumes that the ability or factor being tested is normally distributed in the general population, and seeks to establish how the individual's scores relate to those found in a representative sample of that population; for example, whether scores are close to the average for the reference group, or whether they are exceptionally high or low, and thus unusual. The classic example of this would be the measurement of IQ. Standardized tests of this kind typically include items across the range of difficulty, such that there will be some easy items that just about everyone should be able to do and some very challenging items that hardly anyone will be able to answer. Some tests identify different starting and finishing points for different age groups so that a range of items of appropriate levels of difficulty is administered, and some tests have rules specifying that the task should be discontinued in the event of incorrect answers being given on a specified number of items, on the basis that further, more difficult items would not be expected to be answered correctly. Therefore, these tests are suitable for individuals across the ability range and provide a challenging test for even those individuals with the highest levels of ability.

Clinical neuropsychological assessment sets out to determine whether there is evidence of impairment in a particular ability, such that the individual's scores are different to what they would have been if illness or injury had not intervened. This may be determined by comparing performance on abilities thought to be affected by the illness or injury with performance in areas thought to remain intact, or may be inferred from a comparison of the individual's scores with scores obtained by a normative sample, taking into account what would be expected on the basis of the individual's background. In the latter case, normative data will typically have been used to identify a cut-off score, signifying that scores more extreme than this value are unlikely to occur within the normal range. Standardized tests based on this approach rest on the assumption that the normal population will generally perform well and that poor scores are indicative of neurological abnormality.

Scores on standardized tests may be expressed in a number of ways. Most frequently, raw scores are typically converted to either a standard score or percentile rank, allowing comparison across subtests and against norms. The standard scores corresponding to given raw scores on a test are calculated on the basis of normative data collected from a large sample, taking into account the distribution of scores in the sample and the mean level of achievement. Where age is likely to affect performance, the standard scores derived from the raw scores are compared to norms for the relevant age group. The

use of percentile ranks serves a similar purpose, indicating whether a score is in the average range or is very infrequent and therefore unusual. Standard scores provide a consistent scale with a defined mean and standard deviation; for example, in the Wechsler Scale of Adult Intelligence (WAIS-III)³, a scale with a mean of 100 and a standard deviation of 15 is used. Subtest scores are converted to this scale and overall scores are calculated on the same scale. Scores that are two standard deviations above or below the mean are generally considered exceptional, in that they arise very rarely. Scores of 70 (two standard deviations below the mean of 100) or below occur in approximately 5% or fewer of the population. Some tests use a mean of 10 and a standard deviation of 3; in this case, scores of 5 or below occur only in 5% or fewer of the population.

With tests that use population-based norms, the fact that a score is unusual does not in itself indicate that there is an impairment. The observed score may simply reflect the individual's long-standing ability level: the individual may be one of the 5% of the population who score very poorly on the task. Therefore, information about the expected level of performance is needed in order to interpret the results. If the individual's performance is widely discrepant from what would be expected for that individual, this suggests there may be a difficulty or impairment resulting from illness or injury. In practice, expectations about likely performance are usually based on consideration of a number of factors such as the individual's educational and occupational background and level of achievement. For a very high-achieving individual, a score that is in the low average range may reflect a significant decline from previous, superior performance levels. However, in some cases, tests are available that can provide an estimate of expected performance levels. For example, in the English language, the ability to read irregularly-spelled words can be tested with the Wechsler Test of Adult Reading (WTAR)⁴ or the National Adult Reading Test (NART)⁵. Since this is considered a 'crystallized' ability, and fairly resistant to many forms of brain injury as well as the very early signs of dementia, scores on this task can be converted to obtain a predicted score on the WAIS-III³. If comparing this predicted score with the observed score yields a significant discrepancy, with the observed score lower than the predicted score, this is suggestive of a decline in overall intellectual functioning. Similarly, a comparison might be made between the WAIS IQ score and the Wechsler Memory Scale (WMS-III)⁶ score; normative data are available to indicate whether or not a discrepancy in scores is large enough, and unusual enough, to be considered a significant indicator of an impairment in memory relative to what would be expected on the basis of the IQ score.

With deficit-oriented tests, a score that would be unusual in the reference group is generally considered to provide an indication of impairment, given that the poor score cannot be explained by other, contextual factors. The 5th percentile often provides in effect a cut-off for identifying impairment. Scores at or below the 5th percentile in the normal population may be defined as falling into the impaired range. An example of a test using this approach is the Visual Object and Space Perception Battery⁷. For tests using standard scores, as noted above, a score at or below the 5th percentile approximately translates into a score of 70 or below (on the scale with a mean of 100 and standard deviation of 15) or a score of 5 or below (on the scale with a mean of 10 and standard deviation of 3). Some tests use their own classifications, indicating whether a particular score is 'impaired', 'poor', or 'normal'. An example of a test using this approach is the Rivermead Behavioural Memory Test⁸. Some tests reflect tasks that should be achievable by anyone with normal functioning and thus the presence of errors in itself reflects likely

impairments; for example, the Behavioural Inattention Test⁹ identifies scores as impaired if they are below those of the lowest performing normal controls.

Provision of appropriate test norms is not straightforward, and this is especially the case with older age-groups (for a fuller discussion of this issue, see Busch *et al.*²). Where tests were initially developed for younger adults, norms for older people may be unavailable, or may relate to a restricted age range. They may be based on more limited sample sizes than those for younger age groups, or may have drawn upon a non-representative sample containing only those highly motivated to assist with research. Some measures have only one set of norms available, while other frequently used measures offer numerous sets of norms among which the clinician can select those that are most appropriate for the patient and for the questions being addressed in the assessment. Details of many of these can be found in the compendium compiled by Strauss *et al.*¹⁰. Cultural differences may mean that the available norms are not directly appropriate for the individual; for example, an individual who has grown up in a developing country and immigrated to the United Kingdom or United States as an adult will have had different formative and educational experiences from the indigenous population, and thus norms based on a United Kingdom or United States indigenous population may be inappropriate. This in itself does not necessarily preclude the use of the test, but the lack of appropriate norms will place constraints on the interpretation of results. Availability of neuropsychological tests in languages other than English is limited, and use of interpreters during testing is unsatisfactory, especially where these are family members. Translation of tests is a highly skilled and complex task and cultural, as well as linguistic, equivalence must be established. For a fuller discussion of cultural issues in assessment, see the review by Manly¹¹.

Comparison with test norms provides an indication of the degree to which the observed score would be infrequent or unusual in a healthy population of the same age. In some cases, this is sufficient to clarify the presence of an impairment in a particular area. However, as noted above, the situation is not always clear-cut. Furthermore, individual test scores elicited on a given occasion may be affected by a range of factors. Some of these relate to the individual, for example low mood, anxiety about being tested, physical health problems, pain, drug effects or fatigue. Some relate to the testing environment, for example uncomfortable seating, inadequate lighting or high levels of noise. Other factors relate to the tests used, for example the extent to which they require dexterity or mobility, whether stimuli are in large enough print to be easily visible, and so forth. The extent to which the assessor is able to build rapport with the individual, and respond to any emotional reactions to the assessment, may influence motivation and willingness to engage. Therefore, individual scores must be interpreted in the context of the overall situation. The neuropsychologist's observations of the individual during testing, and comments on the testing situation, will form an important part of the picture when drawing conclusions based on the test results.

The neuropsychological assessment provides a profile of the individual's strengths and difficulties. This profile may be used to contribute to problem identification or diagnosis, to inform decisions about treatment or management, or to monitor change over time. In so doing, information from the neuropsychological assessment must be considered alongside information obtained from other sources¹². The pattern of scores on neuropsychological tests is only one part of the picture, and needs to be considered alongside the medical history

and the results of other tests, for example those that can detect possible physical causes of cognitive impairment, such as heart disease, vitamin deficiency or infection. It is also important to consider information about functional ability. Although cognitive status is related to functional ability¹³, performance on cognitive tests does not fully predict functional ability. Therefore a direct assessment of activities of daily living may be advisable. See Little and Doherty¹⁴ and Chapter 34, for a discussion of assessment of functioning, behaviour and daily living skills. An informant perspective is extremely important and should be obtained wherever possible, with the informant interviewed separately in order to obtain a full account. A home visit can provide valuable insights into the person's living situation and social networks.

If results are unclear, they can be seen as providing a baseline, and testing can be repeated after a suitable interval (e.g. one year) to see if there has been any change. However, repeated testing may give rise to practice effects and therefore needs to be undertaken with a degree of caution, and only in those cases where it is really essential. Some tests provide parallel versions of equivalent difficulty which can be used for repeated testing, for example the Rivermead Behavioural Memory Test⁸ and the Test of Everyday Attention¹⁵. The need for repeated assessment is particularly likely to arise in cases where the aim is to differentiate the very early stages of dementia from normal ageing, given the range of factors that can affect test performance on any given occasion. Sometimes the appropriate outcome of a neuropsychological assessment is a decision to re-evaluate after a period of time has elapsed. While there is sometimes pressure to assign a diagnostic category following initial assessment, it is very important for the sake of the individual and family to avoid the risk of a false-positive diagnosis, and in many cases the best approach is to reassess after a period of time has elapsed in order to monitor the presence or absence of change over time, which in itself may be the most significant diagnostic indicator¹.

AIMS AND SCOPE OF NEUROPSYCHOLOGICAL ASSESSMENT

Usually a neuropsychological assessment will be indicated where information about the cognitive profile will assist in answering a specific question or set of questions. Perhaps the most common situation is the need to distinguish between normal ageing, mild cognitive impairment and the early stages of dementia, or to identify whether cognitive difficulties are the result of depression or mental health issues or an indication of early-stage dementia, or to distinguish between different subtypes of dementia or help identify the precise nature of the progressive neurological condition involved (see also Chapters 42 and 62). An assessment might be required in order to identify the presence and nature of cognitive difficulties following a stroke or in the context of other conditions such as Parkinson's disease. In some cases, information from the neuropsychological assessment may be needed to contribute to decisions about ability to continue driving or about the extent to which the individual has capacity to make specific decisions and choices regarding, for example, medical treatment, financial affairs, or where to live.

When conducting neuropsychological assessment with older people, it is important to have a sound knowledge of the profile of cognitive changes arising as a part of normal ageing, including the underlying neuroanatomy, as well as the diagnostic profiles of the range of relevant neurological and psychiatric disorders and their

behavioural presentation in older people, and an understanding of the potential impact on cognition of neurological injury (for a fuller discussion of these issues, see by Potter and Attix¹⁶). Special considerations arise with regard to particular groups of older people, such as those with lifelong intellectual disability or those with long-term mental illness, where the availability of suitable tests may be limited and change may be especially difficult to detect (e.g.¹⁷). It is also necessary to be aware of the way in which neuropsychological factors relate to abilities such as driving or to definitions of capacity (for a fuller discussion, see pp. 175–87 in Zarit and Zarit¹).

While we typically think of cognitive functions as somewhat discrete entities, such as memory, attention or language, in practice these functions are closely interrelated. Changes in one may be mistaken for problems with another; for example an impairment in attention may mean that information is not encoded, giving the appearance of a problem with memory. Furthermore, if the assessment is contributing to a diagnostic process, sampling just one cognitive function will be inadequate; for example, a diagnosis of Alzheimer's disease requires impairment in memory and at least one other cognitive domain. In most cases, it will be necessary to sample a broad range of cognitive functions. Generally it is the pattern of results across domains that is most informative.

The questions that will be asked are first whether there is an overall decline in cognitive functioning; second whether there are impairments in specific domains and processes; and third, if the answer to either of these is affirmative, whether there are any factors other than neurological impairment that could account for the poor performance. Where neurological impairments are identified, this leads to the questions of what the pattern of impairments suggests, what are the implications for the individual's daily life, and for the family where appropriate; and whether intervention is indicated. If there are factors other than neurological impairment that may be affecting performance, such as depression, then these may be treated prior to reassessment. It is also worth noting that some patients may not show any objective impairment, and in such cases it is necessary to consider the reasons for the expressed concern and how best to respond.

In gathering the necessary information, various approaches can be taken. An extensive standard battery of tests can be applied to every individual, or tests can be selected on an individual basis for each new patient. Most commonly, clinicians use a combination of these two methods. A comprehensive selection of tests that covers the essential cognitive functions and is likely to help in answering the most important kinds of questions can be supplemented by the selection of particular tests that are appropriate for the particular questions raised by the individual patient's profile and that make it possible to follow up on particular hypotheses that the clinician may have developed based on the initial test responses. For example, if initial testing suggests an impairment in language, attention or executive function, further tests can be selected to provide a more detailed profile. It is important to tailor the selection of tests to the level of functioning of the individual patient and the aims of the assessment. Thus, an assessment aimed at identifying very subtle difficulties that might constitute the earliest signs of dementia in a 65 year old would require a challenging and extensive set of tasks, while it would be more appropriate to test a patient who showed more obvious signs of impairment, or who was very frail, with a briefer neuropsychological screening battery, perhaps supplemented by one or two brief tasks.

A comprehensive assessment will usually include an evaluation of general intellectual functioning (IQ). The most widely used test for

this purpose is the WAIS-III³. This includes seven tests of verbal ability (e.g. vocabulary, comprehension, digit span) and seven tests of performance ability (e.g. block design, picture arrangement, matrix reasoning). The full test is lengthy to administer but an overall score can be obtained by administering selected sub-tests or by using the Wechsler Abbreviated Scale of Adult Intelligence¹⁸. Alongside this, a test that predicts lifelong optimal level of intellectual functioning, such as the WTAR⁴, is usually administered. As discussed above, a significant discrepancy between predicted and current IQ would indicate a decline in current functioning. Several specific cognitive domains will also be assessed, typically visuo-spatial perception, language, attention, executive function (the capacity for abstract thinking, planning, problem-solving and inhibition), and memory. For a full discussion of these areas and of the tests that can be used to assess them, see books by Lezak *et al.*¹⁹ and Strauss *et al.*¹⁰.

Memory assessment will usually cover both long-term memory, comprising episodic memory (memory for personally experienced events) and semantic memory (memory for factual information) and working memory. It may also cover prospective memory (ability to remember future intentions) and autobiographical memory. As well as these types of memory, assessment should consider the processes that constitute memory and learning: registration and encoding of information, storage of information and recall of information. Memory should be tested in various ways including recognition, immediate recall and delayed recall, and in various modalities including visual and verbal. Where there has been a discrete injury or insult, such as a closed head injury or stroke, it is useful to consider whether memory difficulties relate to information acquired before the injury (retrograde) or since the injury (anterograde). One of the most widely used memory assessments is the WMS-III⁶, which includes 11 subtests providing scores for general memory, working memory, immediate memory, auditory immediate memory, visual immediate memory, auditory delayed memory, auditory reception delayed and visual delayed memory. As with the WAIS-III³, the WMS-III is a lengthy test and in some cases it may be appropriate to use only a selection of subtests. Many other tests are available to assess specific aspects of memory, for example the Rey-Osterrieth Auditory Verbal Learning Test (RAVLT)¹⁰ or California Verbal Learning Test (CVLT-II)²⁰. The Rivermead Behavioural Memory Test⁸ focuses on everyday uses of memory, testing memory through the kinds of activities that require memory skills in daily life.

Visual perception can be assessed with subtests from the Visual Object and Space Perception Battery⁷, with figure drawing using the Rey-Osterrieth Complex Figure Test¹⁰, or with the clock drawing test¹⁰. Language is often assessed through tests of naming such as the Boston Naming Test²¹ or Graded Naming Test²². Attention can be assessed with subtests from the Test of Everyday Attention, and executive function with subtests from the Delis-Kaplan Executive Function System (D-KEFS)²³, which include trail-making and verbal fluency.

As noted above, neuropsychological screening batteries can be employed where patients have obvious impairments or are unable to complete a full assessment. An example of the latter is the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)²⁴. This includes 12 subtests, providing scores in five categories: immediate memory, delayed memory, attention, language and visuo-spatial/constructional ability. The availability of parallel versions of equivalent difficulty is an advantage where repeated testing is indicated. For people with very marked impairments, the

Severe Impairment Battery²⁵ assesses various aspects of cognition using a range of simple tasks.

THE PROCESS OF NEUROPSYCHOLOGICAL ASSESSMENT

The process of conducting a neuropsychological assessment will be influenced by whether the neuropsychologist works as part of a multidisciplinary team or receives referrals as an individual professional. If working as part of a team, information about medical history and factors such as mental state and mood may be available from the psychiatric examination. These areas may therefore require less extensive evaluation as part of the neuropsychological assessment, although some investigation will still usually be made, and standard questionnaires such as the Hospital Anxiety and Depression Scale²⁶ or Geriatric Depression Scale²⁷ (see Chapter 29) may be used. The advantage of teamwork lies in drawing together the results of the neuropsychological assessment with the findings from other aspects of the assessment, including for example functional assessments conducted by an occupational therapist.

In planning a neuropsychological assessment, the first consideration will be to ensure that sufficient time is available. A comprehensive assessment may require several hours' contact with the patient and may need to be conducted over more than one visit. Even a brief assessment using a neuropsychological screening battery may take 1.5–2 hours. The neuropsychologist will require sufficient information to select an appropriate set of tests. It is particularly important for the neuropsychologist to be made aware of any factors that would influence the selection of tests, including illiteracy, sensory impairment, restricted mobility and likelihood of fatigue. It is essential that patients are asked to bring with them reading glasses and hearing aids if they use these. Cultural factors should also be considered. In particular, if English is not the patient's first language, this will place constraints on the assessment. Even if the patient speaks very good English, comparison with norms derived from native speakers is unlikely to be appropriate.

On meeting the patient, the neuropsychologist will be concerned to establish a good rapport and ensure that the patient fully understands the nature and aims of the assessment process. At this stage informal discussion can help to elicit the patient's views about his or her difficulties, about the assessment and about the reasons for attending. If an informant is available, the neuropsychologist will want to talk with him or her individually as well as together with the patient. Patients are often anxious about being tested and worried about giving the wrong answers. It can be helpful to explain to them that the tests are designed to challenge everyone, so there is no expectation that anyone would get all the answers right, and the important thing is just to do the best they can. There is no doubt that patients, especially those in the older age groups, often find the neuropsychological assessment a strange process, but there is no need for it to be aversive if the neuropsychologist is able to develop a good rapport and show sufficient sensitivity. Throughout the assessment the neuropsychologist must be attentive to signs of fatigue and to expressions of frustration or distress. The former can be alleviated by suggesting a short break and offering refreshments, while the latter can be addressed by sequencing tasks so that tests which the patient finds difficult are followed by tasks that can be completed more easily. The neuropsychologist will also carefully observe the patient's reactions and behaviour during the session in order to gain

an impression of the patient's level of motivation and awareness, and identify any factors that may have affected performance.

Following the assessment, the neuropsychologist will calculate the patient's scores on the various tests administered, a process which can be quite time-consuming, and will usually prepare a concise but comprehensive report detailing the results of the assessment²⁸. This will typically contain the following sections: background to the referral and any relevant history, and the reasons for the assessment; outline of the neuropsychologist's observations of the patient's behaviour and responses during testing; details of the tests administered; profile of results for each domain of cognitive functioning assessed; any additional data such as findings from questionnaires assessing mood; summary and recommendations. In the summary and recommendation section, the neuropsychologist will usually comment on the profile of results and what this implies; for example, he or she may comment that the profile is, or is not, consistent with a diagnosis of Alzheimer's disease. This section will also contain any practical recommendations that the neuropsychologist is able to make regarding how to assist or support the patient and family, or improve management of the patient's condition.

The neuropsychologist will generally aim to meet with the patient, and if appropriate the family as well, to provide feedback on the results of the assessment. Feedback should be tailored to the needs and concerns of the patient and family. In the team context this meeting may be jointly arranged with another professional such as the psychiatrist. In some cases it may be necessary to convey unwelcome news such as the diagnosis of dementia. Diagnostic disclosure should be 'patient led' and based on the individual situation²⁹. The process should be conducted sensitively and sufficient time should be allowed to ensure that discussion is not rushed and that the patient and family are able to ask questions. A single meeting may not be adequate and it may be advisable to arrange a follow-up discussion. Emphasis should be placed on linking the patient and family with appropriate support networks and on identifying any possible treatment approaches.

Finally, it is important to emphasize that the scope of the neuropsychological assessment is not restricted to assisting in reaching a diagnosis. Ideally, and perhaps particularly so in the case of older people, the knowledge gained about the patient's strengths and difficulties in cognitive functioning as a result of the neuropsychological assessment will form a basis for offering information and advice about managing the patient's condition or informing the development of a treatment plan³⁰ based on principles of neuropsychological rehabilitation.

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Overview of Rating Scales in Old Age Psychiatry

Kenneth C. M. Wilson, Ben Green and Pat Mottram

Department of Psychiatry, University of Liverpool, UK

SOME OF THE ISSUES

The needs which rating scales are expected to fulfil in the psychiatry of old age differ little from those in other age groups. However there are a few issues, which are worth considering.

The rating of behaviour concerned with the ageing process remains a contentious issue and does not play a significant role in driving the development of rating scales designed for this age group. The main influences have been the problems imposed by the measurement of psychiatric symptoms in the context of co-morbidity and the relatively high prevalence of organic cerebral disease experienced by older people. These two issues have informed the development of numerous rating scales for the assessment of cognition and have led to adaptation and subsequent development from many well-recognised rating scales used for the assessment of functional symptoms in younger people. Both significant physical morbidity and cognitive dysfunction will impact on the design as well as the content of the rating scale. Such rating scales need to be brief, allowing for problems in concentration and fatigue. Data may have to be recruited from sources other than the patient. In addition, it is important to emphasise the influence of age related cultural differences. It is usual for the interviewer to be as much as two generations younger than the interviewee. Such a generation gap will carry with it differing expectations, understandings and experiences.

An interesting example of this is that up to one third of older people say that they do not feel depressive mood when many other symptoms point inevitably to the presence of a depressive syndrome. This is unlike the experience of other age groups. It is tempting to introduce the concept of denial when trying to explain this. However, it is just possible that older people understand the term differently or have, throughout their life described the feeling of depression differently; such as feeling 'empty inside'. If a particular rating scale is weighted so as to emphasise the importance of experiencing depressed mood then it may well not address the experiences of a significant proportion of older people with depressive syndrome.

A well-recognised book, devoted to the compilation of rating scales in old age psychiatry lists well over 200 different rating scales¹. It is well beyond the scope of this brief overview to provide a comprehensive review of each of these instruments. However, as the field of instrumentation expands it is equally important to draw attention to issues relating to the development and selection of these rating scales.

THE DEVELOPMENT OF A RATING SCALE

A number of approaches have been taken in developing rating scales. Good examples are found in scales designed to rate depression; some are developed from 'gold standard' diagnostic criteria. For example, the OARS Depressive scale² is derived from depressive symptoms listed by DSM III diagnosis. Other scales have been developed from already existing rating scales. A good example of this is the Carroll Rating Scale (CRS)³ which was developed from the Hamilton Depression Rating Scale and the Beck Depression Inventory. Being aware of the developmental source of an individual instrument will inform choice in the context of the purpose and population in which the instrument is to be applied. For example, there are significant and important questions relating to the validity of DSM criteria in the diagnosis of depression in people with other disorders such as Parkinson's disease¹¹. This generates the obvious question as to whether rating scales derived from these criteria are suitable for, or have been validated in these specific populations. Likewise, those rating scales that have been developed from other rating scales pose the same questions; have the source rating scales been validated in the target populations? Has there been subsequent validation of the specific rating scale in the relevant population? An obvious example is the use of rating scales for rating depression in patients with dementia. Another lies in the problem of rating depression in people with significant physical illness, where some of the physical illness symptoms, such as appetite loss; may be the same as some of those that are rated as depressive symptoms by the scale.

The same issue relates to rating scales designed to rate cognitive symptoms. The Mini Mental State Examination⁴ is probably one of the most commonly used cognitive assessment instruments. Its original purpose was to differentiate organic from functional disorders and was designed to quantify change in cognitive state. Despite its popularity, the instrument does have its critics as a screening instrument⁵. There are two important issues worth highlighting in relation to its use. Firstly, the instrument does not and should not be used to allocate a diagnosis. When used in the context of an acute medical ward, it is as likely to pick up cognitive deficit in people with acute confusional states as a consequence of physical illness as it is to identify cognitive problems associated with dementias. Secondly, the instrument fails to assess all cognitive domains, in particular, failing to address specific deficits relating to frontal cortex. This problem is reflected in the adaptation of the instrument over many years of use.

A good example of this is the development of the ACE-R¹², which was derived from the Mini Mental State Examination but includes a section addressing frontal lobe assessment.

VALIDITY OF AN INSTRUMENT

Many of the above issues fall within the over-all heading of 'validity'. Proving the validity of an instrument is seminal to its development. The concept addresses a number of issues in which the characteristics of the instrument in terms of its performance are addressed within defined populations. Hence, an instrument may be valid in one setting (or in rating symptoms in one type of population) but may not be valid in another. In testing the validity of an instrument; the degree to which it adequately probes the specific issues that are being rated is tested. Its ability to differentiate between people that are known to be dissimilar is tested, and finally, the instrument is examined in terms of the demonstrating that certain explanatory constructs account to some degree for the performance of the test. From a practical point of view it is critical that the choice of an instrument is informed by evidence of validation in populations similar to those that are intended to be interviewed.

Many rating scales have been developed as potential 'case' finding instruments. Usually a rating scale will generate a numerical 'score', often purported to represent severity of a particular set of signs or symptoms. Common examples include the Geriatric Depression Scale.

The scale is not a diagnostic instrument in that it does not exclude conditions, other than depression, which might affect its performance. However it can be used as a screening instrument in that, using a 'cut-off' score it will identify individuals with a degree of symptom severity that correlates with a depression diagnosis. This is done by examining the sensitivity and specificity of the instrument in relationship to an already established instrument or other clinical criteria. In the case of the full, 30-item Geriatric depression Scale; a cut-off score of 11 has been established⁶. However this is further complicated by subsequent developments of the instrument. There now exist shortened versions of 15, 10 and four items, all of which have different 'cut-offs'. It is self-evident that when choosing an instrument the right 'cut-off' score should be used. Many studies fail to report which version of the instrument is used, making comparisons between studies and study replication very difficult.

RELIABILITY OF THE SCALE

Understanding why the instrument was developed in the first place, the subsequent evolution of the instrument and being aware of the populations in which the instrument has proven validity are critical in informing choice of instrument. The 'Reliability' of the instrument must also be considered. This is a technical term referring to a number of concepts.

Firstly; the internal consistency of an instrument refers to the reproducibility of measurement across different items within the rating scale. The 'test-retest reliability' refers to the likelihood of the instrument producing similar ratings when consecutively conducted on the same patient (assuming the condition being measured has not changed in the intervening period).

Secondly; the inter-rater reliability refers to the likelihood of the instrument producing similar results when delivered by two different interviewers simultaneously. Obviously, the interviewer plays an important role in terms of reliability performance. This issue is generally addressed (particularly in the context of research) through training and standardisation. Unfortunately, this is not common practice in clinical settings. The implications of this can be fairly profound in terms of patient care. Again, taking the example of the Mini Mental State Examination; which is recommended in the rating of change in cognition in the context of prescribing anticholinesterase inhibitors in England and Wales. If the instrument is not used in a standardised way then the generated scores will vary; affecting patient care. However, when used appropriately the reliability is fairly good⁷. Another area of potential concern lies in applying those rating scales employing graded or continuous variables in rating individual items. An example of this is the Nursing Home Behaviour problem Scale¹⁰. This instrument requires a rating of 'never', 'sometimes', 'often', 'usually' and 'always'. Each of these options is associated with a different score. One of the problems facing the rater will lie in the differentiation between these grades. For example, how does one consistently differentiate between 'often' and 'usually'? The answer lies in clear instructions/descriptions and standardisation through training of the raters. A good example of a well-established and reliable instrument of this nature is the BECK Depression Inventory¹³ (not specifically designed for older people), which rates each item 0–3. Each score has a brief but clear description associated with it, facilitating high levels of reliability. This is one of many self-rating scales.

DIFFERENT METHODS OF DELIVERY

Another typical example of a self-rating scale, specifically designed for older people is the SELF-CARE D rating scale⁹. It is derived from the Comprehensive Assessment and Referral Evaluation Schedule (CARE)⁸ and is used to differentiate between people with and without depression in primary care settings. It takes about 15 minutes to complete. The advantages of using self-rating scales have to be balanced by the disadvantages. Experience suggests that the apparent time and resource savings may be offset by the frequent need to help people complete them. Obviously, the patient population must be able to read the questions (if required) and understand the instructions. The BASDEC is a hybrid rating scale, designed to measure depression in institutionalised settings in which patients may be over-heard or embarrassed by answering sensitive questions out loud. Nineteen cards with statements on are presented to the patient and the patient indicates whether each statement is true or false. Each 'True' answer generates a score of '1', 'don't know' generates a score of half a point and 'false' generates a '0' score.

Some scales are specifically designed to capture information about the patient from other sources. The Cornell Scale for Depression in Dementia has been designed to capture information from informants and through observation¹⁴. The Dysfunctional Behaviour ~Rating Scale¹⁵ was designed for carers to make observations relating to older people with cognitive impairment. In particular cases, data may be gleaned from either the patient or the rater; as is the case in the 'Quantification of physical illness in psychiatric research in the elderly'¹⁶.

TYPES OF INSTRUMENTS

Even though some rating scales have been developed as screening or 'case finding' instruments; these should not be confused with diagnostic instruments that have been specifically designed to enable an allocation of a standardised diagnosis. Such instruments are usually derived from diagnostic systems such as the International Classification of Diseases (ICD) or the Diagnostic and Statistical Manual (DSM criteria). These are usually semi-structured interviews in which a psychiatric syndrome is established. Importantly, they will often include 'exclusion criteria' in which specific psycho-syndromes are excluded as part of the process in establishing a diagnosis. For example, the exclusion of cerebro-vascular disease will influence the certainty by which Alzheimer's Disease may be diagnosed.

Rating scales are specifically designed to rate specific variables and can usually be classified by the nature of the variables that they are designed to rate. This overview has already drawn on rating scales designed to measure depression severity, physical illness severity and behavioural problems in people with cognitive disturbance. There are of course, a wide variety of instruments including those designed more specifically for rating aspects of the dementias, quality of life, morale, issues relating to carers and activities of daily living performance. In addition to the Mini Mental State Examination, there are a number of rating scales designed to rate memory and other aspects of cognition. A good example of a practical and innovative instrument is the IQCODE¹⁷, which is used with an informant to quantify cognitive decline over time. These rating scales should not be confused with formal psychometric assessments usually carried out by experienced and trained psychologists.

RATING SCALE SELECTION

In the first instance it is important to establish why and when a rating scale should be used. Staff on acute medical wards often use rating scales for the identification of patients with dementia and may use these to trigger referral for psychiatric assessment. Often enough, the psychiatrist will be referred a patient in an acute or sub-acute confusional state as a consequence of unstable physical illness. This is a classical mistake in that the rating scale is being used as a surrogate diagnostic instrument for dementia as opposed to a screening instrument for cognitive impairment. Inherent to this, is the question 'what is intended to be measured?'. Once the answer to this question has been established then a rating scale developed and designed to measure particular criteria can be selected. The next issue to determine is whether the rating scale is designed to measure the symptoms in populations similar to that in which it the ratings are intended. Determination of this will go some way in establishing the valid use of the rating scale in any particular setting.

The next question worth considering is whether the rating scale is to be used as a screening instrument or to measure change over time. If used as a screening instrument then it is important to determine the appropriate 'cut-off score'. Again this might be specific to a particular population and may need some background literature research. As already mentioned, rating scales can be completed by the individual target patient or carer, by the interviewer or by a third party and by a mixture of agents. The choice will depend on the reasons why a

scale is being used and whether or not the person who is subjected to the interview is able to actively contribute towards the rating.

Other considerations relating to choice include; the length of the procedure. In patients with severe illness or short attention span, long interviews may prove problematic. As already indicated, training is required for some rating scales. This is important in terms of validity, reliability and generalisability of the findings. Research protocols in which rating scales are utilised will often include training and subsequent standardisation and inter-rater reliability sessions over the period of data collection. Lastly, the use of many commonly used rating scales are restricted by copyright.

SUMMARY

This brief overview of the use of rating scales in old age psychiatry has attempted to provide a general background to the development of rating scales, drawing on examples of commonly used rating scales in Old Age Psychiatry. The practical implications of validity and reliability of rating scales have been exemplified in the context of selection of rating scales within this age group. As rating scales develop, health expectations increase and resources become more limited, rating scales may offer an apparent, easy alternative to comprehensive psychiatric assessment. It is important to remember; rating scales are refined and specific and if used inappropriately are likely to cause as much harm as they can good.

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The Mini-Mental State Examination*: A Brief Cognitive Assessment

Marshal Folstein¹, Susan Folstein¹ and Jonathan Folstein²

¹*University of Miami Miller School of Medicine, Nashville, USA*

²*Vanderbilt University, USA*

The Mini-Mental Status Examination (MMSE) is a scored, 10-minute form of the traditional cognitive mental status examination. The items include orientation to place and time; registration and recall; attention and calculation; language function; and praxis. It is 'mini' because it tests cognitive aspects of mental functions, but excludes mood, abnormal mental experiences, and the form of thinking¹.

It has been standardized with normative values for age and education and is used by physicians and other clinical professionals worldwide to estimate and communicate the presence and severity of cognitive impairment^{2,3}. The easily understandable items are useful for helping subjects and caregivers to understand the overall severity of cognitive impairment, as well as particular areas of deficits. For example, caregivers benefit from knowing that the patient can understand a one-stage command: 'put on your socks', but not a three-stage command: 'put on your socks, your shoes, and your pants'.

We highlight several instructions from the manual. First, a single administration given under supervision is adequate for training. Second, subjects should receive an explanation of why they are being tested and how the answers might help in their care or, in the case of research, accomplish the aim of the study. Third, successes should be praised, but errors ignored to avoid inducing emotions that might lower the subject's cognitive capacity. Fourth, fearful subjects can be reassured by early success by beginning with easier items such as naming a pencil and watch. Finally, we recommend that the serial sevens test be given, followed by world-backwards only if the subject refuses to do serial sevens, or refuses to complete one subtraction. The world task is easier than serial sevens and decreases the sensitivity of the test.

A score below 24 detects cognitive impairment in most populations⁴ while a score below 27 suggests the need for an evaluation of individuals with greater than a 10th grade education. The MMSE has significant floor and ceiling effects. Many severely impaired patients score zero and the MMSE does not assess superior cognitive capacity.

The MMSE can be used in any population or cultural group; authorized translations are available from the publisher. The distribution

of scores in some populations is lower than those established in the United States. This mainly is due to lower education. In the cultures studied to date, the scores are comparable when education is taken into account. The relationship between education and MMSE reflects social class, nutrition, intelligence and other exposures that affect cognition. Low education is also a risk for some diseases that affect cognition. The MMSE score is thus a snapshot of the end result or composite of the many factors that have influenced cognition over the life span: social class, nutrition, intelligence, disease, and other exposures that have occurred throughout life. If the effects of disease and education are controlled, the effect of age on the MMSE is small.

RELIABILITY AND VALIDITY

The MMSE has excellent test-retest and inter-rater reliability. The MMSE accurately reflects the results of psychological tests and structural and functional measures of brain pathology. For example, the MMSE correlates significantly with the Wechsler Adult Intelligence Scale and many other neuropsychological measures of memory, attention, executive function and language. MMSE has been shown to decline on average 3.3 points per year in Alzheimer's disease and correlates with the severity of pathology found at autopsy or by structural and functional imaging⁵. The MMSE score improves in response to treatments such as donepezil for Alzheimer's disease⁶.

The score of MMSE is more similar in elderly identical twins than fraternal twins, suggesting a strong genetic component to the score. By these methods, the MMSE is 50% heritable in older adults from several countries, i.e. genetic factors account for about half the variance in scores.

Low MMSE scores occur with dementia, delirium, mental retardation, cortical and subcortical dementia and discrete cognitive disorders such as amnesia, aphasia and executive dysfunction. Hearing-impaired and vision-impaired subjects obtain lower MMSE scores. However, if instructions are written, MMSE can be used with hearing-impaired persons. Vision is required for only two points on MMSE.

Although the MMSE is often low in frontal/subcortical dementia as occurs in Huntington's disease, Parkinson's disease, AIDS

*Disclosure: The Mini-Mental State Examination (MMSE) and all its authorized translations are published by PAR, from which the authors receive royalties. Manuals and forms are available at Mini-Mental.com.

dementia and frontal dementia, MMSE is less sensitive to early frontal/subcortical than to cortical dementia. Because of these limitations, we have recently published a revision of the MMSE (MMSE~2), which includes tests that are more sensitive to subcortical cognitive impairment. Low MMSE scores occur in elderly depressed patients; many depressed patients with cognitive impairment later show cognitive deterioration. The MMSE can be used to track delirium but because the cognitive state in delirium fluctuates, MMSE reliability and sensitivity are difficult to determine. The reliability and validity of the MMSE has not been established for children or for developmental disorders of cognition.

The MMSE score does not provide a diagnosis, pathology or aetiology, which must instead be established from the patient's history, physical examination and laboratory findings. Nor does the MMSE define competency to perform complex social functions, such as giving informed consent or driving an automobile; these functions must be tested directly.

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The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

Nicolas Cherbuin¹ and Anthony Francis Jorm²

¹*Centre for Mental Health Research, Australian National University, Canberra, ACT, Australia*

²*ORYGEN Research Centre, University of Melbourne, Department of Psychiatry, Parkville, Victoria, Australia*

INTRODUCTION

Efficient early detection of cognitive decline and dementia is becoming increasingly important. A large number of screening instruments are available, but they vary greatly in their ease of use, psychometric properties and validity in differing cultural contexts, as well as in the presence of co-morbid conditions. In addition, there is a need for cost-effective screening tests which can be administered to large populations across a variety of mediums (orally, paper and pencil, by mail, by telephone, or by computer).

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a brief questionnaire for the assessment of change in cognition which shows very good psychometric properties, has been validated across multiple cultural contexts, and which can be used in clinical practice as well as in large-scale epidemiological studies.

The IQCODE was developed to assess cognitive decline from a pre-morbid level based on informant reports¹. The parent instrument was composed of 39 interview questions assessing memory function (acquisition and retrieval) and intelligence (verbal and performance). Informants were asked to rate the magnitude of change over the previous 10 years in these domains. After initial evaluation, the number of items was reduced to 26 which correlated well together and were relatively easy to rate. The questionnaire was formatted for self-completion and named IQCODE. In its present form the IQCODE requires each item to be rated on a 5-point scale from 1, 'much improved' to 5, 'much worse'². The questions are framed in the form: 'Compared to 10 years ago, how is this person at...' (e.g. remembering things about family and friends such as occupations, birthdays, addresses, etc.).

A short version of the IQCODE consisting of 16 items has been developed². It was found to correlate highly (0.98) with the full version and to have equivalent validity against clinical diagnosis. Consequently there is little advantage in using the longer version.

Versions of the IQCODE have been developed and validated in other languages (Chinese, Dutch, Finnish, French, Canadian French, German, Italian, Japanese, Korean, Norwegian, Persian, Polish, Portuguese, Spanish, and Thai) and copies are available for download at cmhr.anu.edu.au/ageing/iqcode.

Other variations on the IQCODE have also been produced, including questionnaires based on shorter^{3,4} or more flexible⁵ retrospective time frames, as well as short forms in Spanish⁶, Chinese⁷, Portuguese⁸ and in other languages (which to our knowledge have not been validated).

SCORING

Scoring the IQCODE involves summing the items and dividing by the number of items, thus producing a measure ranging from 1 to 5, however, some investigators have preferred adding up all items. Norms have been developed by Jorm and Jacomb⁹ for five-year age groups from 70 to 85+ years, but in practice individual researchers have generally chosen to use an absolute cut-off ranging from 3.3–3.6 in community samples to 3.4–4.0 in patient samples. A practical strategy to choose a cut-off is to identify studies (e.g. in Table 28.1) with characteristics most similar to the target population and select their cut-offs.

ADMINISTRATION

The IQCODE is a pen and paper test which takes between 10 and 25 minutes to complete, depending on the form chosen (long/short) and is generally perceived as relatively easy to answer. It can be mailed to informants and could potentially be administered by telephone or by computer (although we are not aware of any validation data with these administration media). The IQCODE can also be used as an alternative screening test when individuals are not able to complete another test such as the Mini-Mental State Examination (MMSE). In a survey of 839 community-based older individuals, Khachaturian *et al.*¹⁰ found 74 subjects who were unable to complete the 3 MS but the IQCODE could be completed by an informant. Seventy-one of these were subsequently diagnosed with dementia. In addition, Cherbuin *et al.*¹¹ reviewed the literature to assess the suitability of dementia screening instruments for self- or informant-assessment, particularly in an electronic format (local computer or web-based). They concluded that the IQCODE was one of three most

Table 28.1 Performance of the Mini-Mental State Examination (MMSE), and the long and short versions of the IQCODE as a screening test for dementia⁴⁷⁻⁵¹

<i>Study</i>	<i>Sample</i>	<i>Diagnostic criteria^a</i>	<i>Cutoff</i>	<i>N</i>	<i>Age/Age range</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>ROC curve</i>
MMSE								
Morales <i>et al.</i> (1997) ¹⁴	Urban epidemiological study (Spain)	1	21/22	97	75	0.73	0.78	—
Morales <i>et al.</i> (1997) ¹⁴	Rural epidemiological study (Spain)	1	21/22	160	74	0.83	0.74	—
Callahan <i>et al.</i> (2002) ⁴⁷	Epidemiological study (USA)	1	23/24	344	74	0.95	0.87	0.96
Swearer <i>et al.</i> (2002) ⁵¹	Primary care clinic outpatients and independent retirement community residents (USA)	2	23/24	46	80	0.13	1.00	—
Ferrucci <i>et al.</i> (1998) ⁴⁸	Geriatric clinic patients (Italy)	2	23/24	104	75	0.97	0.55	—
Heun <i>et al.</i> (1998) ⁴⁹	Epidemiological study (Germany)	1, 4	23/24	287	77	0.84	0.99	—
Jorm <i>et al.</i> (1996) ²⁷	Ex-servicemen (half former prisoners of war) (Australia)	1	23/24	144	73	0.45	0.99	0.81
Knafelc <i>et al.</i> (2003) ⁵²	Memory clinic patients (Australia)	1	23/24	323	75	0.84	0.73	0.86
Nasreddine <i>et al.</i> (2005) ⁵⁰	Memory clinic patients (Canada)	2	25/26	183	75	0.78	1.00	—
Isella <i>et al.</i> (2006) ²¹	Cognitively normal volunteers and 45 MCI patients (Spain)	6	28	100	71	0.82	0.73	—
IQCODE (long version)								
Jorm <i>et al.</i> (1991) ¹⁸	Patients seen by a geriatrician (Australia)	3, 4	3.60+	69	80	0.80	0.82	0.87
Jorm <i>et al.</i> (1994) ⁴⁰	Epidemiological study (Australia)	1	3.60+	684	70	0.69	0.80	0.77
Law and Wolfson (1995) ³⁶	Epidemiological study (Canada)	1	3.30+	237	81	0.76	0.96	—
Fuh <i>et al.</i> (1995) ⁷	Non-demented community resident and dementia patients (Taiwan)	1	3.40+	399	69	0.89	0.88	0.91
Morales <i>et al.</i> (1997) ¹⁴	Urban epidemiological study (Spain)	1	3.27+	97	75	0.82	0.90	0.89
Morales <i>et al.</i> (1997) ¹⁴	Rural epidemiological study (Spain)	1	3.31+	160	74	0.83	0.83	0.83
Jorm <i>et al.</i> (1996) ²⁷	Ex-servicemen (half former prisoners of war) (Australia)	3	3.30+	144	73	0.79	0.65	0.77
Mulligan <i>et al.</i> (1996) ³⁷	Geriatric patients (Switzerland)	1	3.60+	76	82	0.76	0.70	0.86
Del-Ser <i>et al.</i> (1997) ³⁸	Neurology clinic outpatients (Spain)	1	3.62+	53	69	0.84	0.73	0.81
Flicker <i>et al.</i> (1997) ⁵³	Memory clinic patients (young, Australia)	1, 5	3.9	299	73	0.74	0.71	—
Flicker <i>et al.</i> (1997) ⁵³	Memory clinic patients (old, Australia)	1, 5	3.9	78	80	0.79	0.78	—
De Jonghe (1997) ¹²	Psychiatric patients (49 with dementia) (Netherlands)	1	3.90+	82	78	0.88	0.79	—
Senanarong <i>et al.</i> (2001) ⁵⁴	Community elderly (Thailand)	2	All	87	52-85	—	—	0.93
Lim <i>et al.</i> (2003) ⁵⁵	Cognitively normal volunteers and 53 dementia patients (Singapore)	2	3.40+	153	—	0.94	0.94	—
Stratford <i>et al.</i> (2003) ⁵⁶	Memory clinic patients (Australia)	4	4.00+	577	73	—	—	0.82
Tang <i>et al.</i> (2003) ¹⁵	Stroke patients (China)	2	3.40+	189	68	0.88	0.75	0.88
Isella <i>et al.</i> (2006) ²¹	Cognitively normal volunteers and 45 MCI patients (Spain)	6	3.45	100	71	0.84	0.75	—
IQCODE (short version)								
Jorm (1994) ²	Epidemiological study (Australia)	1	3.38	684	70+	0.79	0.82	0.85
Jorm <i>et al.</i> (1996) ²⁷	Ex-servicemen (half former prisoners of war) (Australia)	3	3.38+	144	73	0.75	0.68	0.77
Del-Ser <i>et al.</i> (1997) ³⁸	Neurology clinic outpatients (Spain)	1	3.88	53	69	0.79	0.73	0.77
Harwood <i>et al.</i> (1997) ⁵⁷	Medical inpatients (England)	1	3.44	177	65+	1.00	0.86	—
Knafelc <i>et al.</i> (2003)	Memory clinic patients (Australia)	1	3.60+	323	44-93	0.94	0.47	0.82
Narasimhalu <i>et al.</i> (2007) ⁵⁸	Dementia clinic patients and stroke patients (Singapore)	2	3.38+	576	66	0.78	0.86	0.89

^a 1 = DSM-III-R dementia; 2 = DSM-IV dementia; 3 = ICD-9; 4 = ICD-10 dementia; 5 = Clinical diagnosis; 6 = Mild cognitive impairment (Petersen 1996 criteria).

promising tools and they recommended further validation studies for these delivery platforms.

PSYCHOMETRIC CHARACTERISTICS

The IQCODE's reliability and validity have been extensively researched. A number of studies have assessed the internal consistency of the scale using Cronbach's alpha. Alpha was found to range between 0.93 and 0.97 across nine studies^{1,7,9,12–17} which can be regarded as excellent. The stability of scores over short periods was found to be high, with test–retest reliability showing correlations of 0.96 over three days and 0.75 over one year^{9,18}.

Other studies have conducted factor analyses to investigate the factor structure of the IQCODE. They all found a large main factor accounting for 42–73% of the variance which is thought to represent 'cognitive decline', while other factors were generally small with the second factor explaining less than 10% of the variance^{7,9,13,14,17,19}.

VALIDATION AGAINST CLINICAL DIAGNOSIS

Many studies have assessed the validity of the IQCODE against clinical diagnosis. Table 28.1 contrasts measures of sensitivity and specificity of the long and short forms of the IQCODE and the MMSE^{11,20} and shows comparable findings for the two tests, confirming that the IQCODE is a valid screen for dementia. However, moderate correlations between the IQCODE and the MMSE in 15 studies ranging from -0.37 to -0.78 ²⁰ with a sample size weighted average of -0.58 suggest that these two tests, although largely overlapping, each have some unique variance. As a consequence, a number of studies have investigated whether the concurrent administration and scoring of the IQCODE and the MMSE improves dementia detection. They generally reported somewhat increased sensitivity and/or specificity of the combined tests, but cost-benefits of this combination varied depending on the methodology or the type of sample used²⁰. The IQCODE has also been investigated as a predictor of conversion to mild cognitive impairment over three years and was found to be as sensitive as the MMSE for this population (sensitivity 0.82, specificity 0.71 for a cut-off of 3.19)²¹.

In addition, the IQCODE has been shown to be a predictor of incident dementia in stroke patients²² and in non-demented hospital inpatients²³ over 2–3 years follow-up. However, application of the IQCODE to complex clinical populations should be considered carefully, as one study found that the IQCODE and the MMSE were poor at detecting dementia in a sample of first-ever stroke patients²⁴.

VALIDATION AGAINST NEUROPATHOLOGY AND NEUROIMAGING

Diagnoses of dementia based on post-mortem histological examinations have been compared to pre-mortem IQCODE scores in two studies. Using a cut-off of 3.7 and a neuropathological diagnosis of Alzheimer's disease, Thomas *et al.*²⁵ found the IQCODE to have a sensitivity of 73% and a specificity of 75%. While Rockwood *et al.*²⁶, with a cut-off of 3.42 and a diagnosis of Alzheimer's disease, vascular or mixed dementia, reported a sensitivity of 97% and a specificity of 33%. Another six studies found associations between neuroimaging measures and the IQCODE. Jorm *et al.*²⁷ found significant associations between the IQCODE and the width of the third ventricle ($r = 0.29$), and infarcts in the left ($r = 0.35$)

and right ($r = 0.26$) hemispheres in a community sample of older ex-servicemen. Cordoliani-Mackowiak *et al.*²⁸ reported significant correlations between leukoaraiosis ($r = 0.38$) and IQCODE in elderly stroke patients. Henon *et al.*²⁹ found significantly higher mean IQCODE measures in individuals with smaller medial temporal lobe measures. And in a diffusion tensor imaging study of stroke patients, Viswanathan *et al.*³⁰ detected lower diffusion measures in the non-affected hemisphere, which were interpreted as showing decreased cerebral tissue integrity in those whose pre-morbid cognition was below a cut-off of 3.4 on the IQCODE. High scores on the IQCODE have also been associated with greater cerebral atrophy^{31,32}.

BIAS AND LIMITATIONS

One complicating issue associated with many cognitive tests is that they can be open to bias when applied to specific sociodemographic, ethnic, language, gender, clinical or cultural groups. For example, scores on the most widely used dementia screening test, the MMSE, have been shown to be affected by gender, age, education, cultural background, language spoken at home, socioeconomic status, occupation and presence of a mood disorder^{33,34}. The IQCODE has been shown to be minimally influenced by education^{2,7,9,12,35–38} and by proficiency in the language of the country of residence³⁹. However, small associations between the IQCODE and anxiety and depression have been reported^{14,37,38,40}. They may be due to a direct link between mood disorders and cognitive function or to the fact that the informant may have difficulty differentiating between cognitive decline and depression and anxiety.

In addition, the influence of informant characteristics has also been investigated as possible bias. Jorm *et al.*⁴¹ found that measures of informant anxiety, depression and their perception of how caring or controlling the subject was perceived to be were more strongly correlated with IQCODE scores than with the MMSE score. This suggests some contamination of the informant's ratings by the respondent's characteristics but these influences appear to be relatively weak and account for less than 6% of the variance in IQCODE scores. In contrast, the length and type of relationship and the age and education of the informant have not been found to be associated with the IQCODE^{7,42}.

OTHER APPLICATIONS

Although the IQCODE was developed to assess cognitive decline from a premorbid state, it has also been used for other purposes. Priner and colleagues⁴³ assessed the short form of the IQCODE as a screen for the prediction of postoperative delirium following hip or knee surgery and found that those with a score greater than 3.1 had a more than 12-fold increased risk of delirium. In another study, the premorbid cognitive status of stroke patients was assessed retrospectively with the IQCODE and those with a score greater than 4 were found to be at higher risk of developing epileptic seizures⁴⁴ and of dying⁴⁵. Pasquini *et al.* also investigated the risk of institutionalization in stroke patients⁴⁶ and found that those with an IQCODE score greater than 4 at admission had a higher risk of being institutionalized three years later.

Finally, the feasibility of using the IQCODE as a self-report instrument has been investigated by Jensen *et al.*¹⁶ who administered the questionnaire by mail to 2841 individuals (58.9% of target population) initially recruited during general practice visits. They found

that more than 60% reported completing the questionnaire without help and, although responses were not validated against full clinical diagnoses, mean IQCODE scores were higher (3.7 versus 3.3) in patients suspected of having dementia by their GP and the authors commented 'the IQCODE-SR meets the basic requirements of a good measurement'.

CONCLUSION

The IQCODE is a valid screening instrument for dementia and cognitive decline. It is particularly useful in assessing individuals with less proficient language skill, lower education levels or different cultural background or when direct cognitive testing is not possible. Its administration in conjunction with other tests (e.g. MMSE) can improve overall detection rates. Its ease of use and format make it suitable for use in clinical settings as well as in large epidemiological studies.

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Geriatric Depression Scale

Meghan A. Marty, Renee Pepin, Andrea June and Daniel L. Segal

University of Colorado at Colorado Springs, USA

The Geriatric Depression Scale (GDS) is a popular and well-validated screening measure for depression among older adults. It consists of 30 self-report items and is widely used in research and clinical services. This chapter provides an overview of its development, psychometric properties, alternate forms, and use with special populations.

DEVELOPMENT, ADMINISTRATION AND SCORING

The GDS was developed to address the limited applicability of existing depression scales with older adults^{1,2}. One such problem with scales that were developed and validated with younger populations relates to somatic complaints. Though somatic complaints can be a useful indicator of depression in younger samples, it is common for older adults to report somatic problems that can skew the sensitivity and specificity of a screen where older adults are more likely to have false positive depression scores. As such, the GDS does not include many somatic components in the scale and also consists of questions that are appropriate for the ageing population both in content and format. Initially, 100 questions were selected by researchers and clinicians with geriatric experience and administered to both non-depressed and depressed older adults. Of the original 100 items, the 30 items that correlated most highly with the total score were included in the final scale.

The scale was designed so that it could be administered easily in a self-rating format that would not be cumbersome for patients or medical personnel². Most individuals complete the GDS in under 10 minutes. The GDS has a forced-choice response format where individuals are asked to respond *yes* or *no* to each item. However, some patients have problems with the yes/no dichotomy, instead preferring to answer 'sometimes' by either writing it in or by circling the space between the yes and no responses, though neither is a scored answer. It can help if explicit instructions are provided to patients to respond to each item in the way that *best* answers the question. In the initial validation study, the examiner read the items orally and recorded responses for individuals who could not complete the form without assistance. However, later studies found significant differences between mean scores for self-administered and staff-administered modes of presentation, with higher scores reported for self-administered scales^{3,4}. There is no significant difference between scores of a card-based administration and verbal administration of the GDS⁵.

For each of the 30 GDS items, the depressive response garners 1 point for a maximum total of 30 points. Regarding general cut-offs, total scores ranging from 0 to 9 indicate normal mood; scores ranging from 10 to 19 indicate mild depressive symptoms, and scores ranging from 20 to 30 indicate severe depressive symptoms. The measure is free to use and in the public domain. It can be accessed at www.stanford.edu/~yesavage/GDS.html.

PSYCHOMETRIC PROPERTIES

Reliability

The GDS has been shown to be internally consistent and reliable over time. In the original reliability study, split-half and alpha coefficients were both 0.94². Other studies have demonstrated similar findings with diverse populations, showing alpha and split-half coefficients ranging from 0.80 to 0.99^{6–8}. Several studies have examined reliability of scores over time, finding high test–retest correlations between 0.85 and 0.94^{2,7–9}.

Validity

An important psychometric property of a depression screen is its ability to differentiate between depressed and non-depressed individuals (i.e. criterion validity). The sensitivity of the GDS refers to its ability to correctly identify individuals who are depressed whereas the specificity refers to its ability to correctly identify those individuals who are not depressed. Brink *et al.*¹ found an 84% sensitivity rate and a 95% specificity rate for the GDS among community-dwelling older adults. Several other studies have examined the sensitivity and specificity of the GDS with diverse populations, finding acceptable levels above 80%. These have included medical patients, stroke patients, individuals suffering from dementia, nursing home residents, and psychiatric inpatients (for a thorough review, see Stiles and McGarrah¹⁰).

The correlation between the GDS and other screening measures for depression is an indicator of the scale's construct validity. The GDS was initially validated against the Hamilton Rating Scale for Depression¹¹ (HRS-D) and the Zung Self-Rating Depression Scale¹² (SDS), finding high correlations suggesting that the GDS measures similar constructs as the HRS-D and SDS. Other comparisons with the GDS have also been conducted, including the Beck Depression

Inventory¹³ (BDI) and the Center for Epidemiological Studies Depression Scale¹⁴ (CES-D). These comparisons also yielded significant correlations, adding to evidence supporting the construct validity of the GDS^{15–18}. Furthermore, the GDS has non-significant correlations with measures of cognition, adding to the empirical evidence that the GDS measures depression and not another construct^{19–21}.

Dimensionality

Factor studies on the 30 items of the GDS have yielded mixed results. Sheikh *et al.*²² proposed a five-factor solution among community-dwelling older adults. Abraham and colleagues²³ proposed a six-factor solution among nursing home residents. These studies contrast the findings from Parmelee *et al.*⁹ and Salamero and Marcos²⁴, which both found the GDS items to be highly intercorrelated and suggested the scale has only one factor. Based on these results, both advised the GDS should only be interpreted from a single total score.

ALTERNATE FORMS

Brief Forms

Several brief forms of the GDS have been designed for use in settings where time is limited for depression assessment and with frail individuals for whom fatigue and poor concentration are concerns. Sheikh and Yesavage²⁵ developed a 15-item version of the GDS, commonly referred to as the Short Form (GDS-SF), by taking the 15 items from the original scale that had the highest correlation with depressive symptoms in earlier studies. Findings from their validation study suggested both forms were highly correlated ($r = 0.84$) and effectively differentiated depressed from non-depressed individuals. A subsequent study reported cut-off scores for the GDS-15 as *normal* (0–4), *mild* (5–9) and *moderate to severe* (10–15)²⁶. Older adults rated the GDS-15 as an acceptable measure that was not difficult or stressful to complete²⁷.

Evidence for the validity of the GDS-15 is mixed. Some studies suggest the GDS-15 is not a suitable substitute for the full scale GDS in community-dwelling older adults^{26,28} or cognitively impaired individuals²⁹. It does appear effective for screening depression in older adults who are cognitively intact and medically ill²⁹, have affective disorders³⁰, or who are seen in primary care clinics^{27,31}. The GDS-15 was shown to consistently identify depressed individuals in a VA nursing home population³². Chiang and colleagues³³ suggest that the GDS-15 may be less effective as a screening tool, but that it could be most effectively used to detect changes in moderate levels of depression.

Hoyle and colleagues³⁴ developed a five-item GDS for use in a geriatric outpatient population by selecting items from the GDS-15 that had the highest correlation with a clinical diagnosis of depression. Using a score of 2 or greater to indicate possible depression, the GDS-5 had a sensitivity of 97%, specificity of 85%, and alpha coefficient of 0.80. The GDS-5 was found to be as effective as the GDS-15 in an Italian sample of cognitively intact older adults across three settings: a geriatric acute care ward, a geriatric outpatient clinic and a nursing home³⁵. In addition, validity of the GDS-5 has been demonstrated for older sedentary adults.³⁶ Weeks and colleagues³⁷ compared two versions of four-item GDS measures and the GDS-5 to the GDS-15 in a sample of acute care patients. They found the GDS-5 showed the highest sensitivity (97%), but led to a high number of false positives. The researchers re-ordered the GDS-15 items

into a two-tiered instrument, named the GDS-5/15, so that the full GDS-15 would only be administered to individuals who scored a 2 or greater on the initial GDS-5 items³⁷.

Many brief forms of the GDS have been compared to a single-item depression screen. For example, D'Ath *et al.*²⁷ created three versions of the GDS containing 10 items, 4 items, or 1 item ('Do you feel that your life is empty?'). While the 10-item form performed well using either 2/3 or 3/4 cut-off scores, the 4- and 1-item versions had low sensitivity and specificity. Hoyle *et al.*³⁴ found a single-item depression screen ('Do you often feel sad or depressed?') performed significantly worse than the 15- and 5-item GDS, with a sensitivity of 85% and specificity of 65%. Likewise, a comparison of different versions of the GDS in a Dutch population found the diagnostic value of 30-, 15-, 10- and 4-item scales did not differ significantly; however, the 1-item version performed no better than chance³⁸. Almeida and Almeida³⁹ determined the 15- and 10-item scales were good screening instruments for depression in a Brazilian population, but cautioned against using 4- and 1-item forms because of low reliability and failure to show severity of depressive episodes.

Nursing Home Forms

A 12-item GDS was created for use with individuals living in residential care settings, including those with cognitive impairment (GDS-12R)⁴⁰. During administration of the longer GDS in residential care facilities, interviewers found difficulties with a few of the items that appeared irrelevant or ambiguous to residents (e.g. 'Do you prefer staying in rather than going out and doing new things?'). Removal of these items increased internal reliability from 0.76 to 0.81, with no significant difference in internal reliability for those with cognitive impairment. A cut-off score of 4/5 maximized both sensitivity and specificity of the GDS-12R and was suggested for research purposes. A cut-off of 3/4 was suggested for clinical use⁴⁰.

Similarly, Jongenelis *et al.*⁴¹ developed a version of the GDS that would be more user-friendly for nursing home residents. Clinical experts (a psychologist, a physician and a nurse) reviewed and rated the usefulness of the items of the GDS-15, eliminating seven items that were presumed to be offensive or confusing to nursing home residents. The eight-item instrument demonstrated high internal consistency (alpha coefficient of 0.80) with equal sensitivity (96.3%) and greater specificity than the GDS-15 (71.7% versus 63.3%) at a cut-off point of 2/3. They concluded that although the GDS was created for older adults, it was not necessarily designed for frail nursing home residents and alternate versions perform better with this specific population⁴¹.

Collateral Forms

Nitcher *et al.*⁴² created a 30-item Collateral Source Geriatric Depression Scale (CS-GDS) by simply changing the pronouns from *you* to *they* on the original GDS items. Patients with cognitive functioning ranging from normal to moderate dementia and an informant with extensive personal knowledge about the patient completed a self-report version of the GDS-30 and the CS-GDS respectively. Informants reported a higher frequency of symptomatic responses for all symptoms, but both versions were consistent with an independent diagnosis of depression. Correlations between the CS-GDS and the GDS varied by familial relation, ranging from 0.55 for sons to 0.32 for daughters-in-law. A cut-off score of 21 maximized sensitivity and specificity (both at 68%). In addition, the CS-GDS has been shown

to maintain adequate reliability and validity when administered via telephone, using a cut-off score of 19⁴³.

Brown and Schinka⁴⁴ developed a 15-item informant version of the GDS (GDSI-15) for use as an adjunctive measure to self-report versions of the GDS or as an independent measure of depression. Cognitively intact older adults and an informant completed a self-report version of the GDS-30 and the 30-item CS-GDS, respectively. Item characteristics for all 30 items of the CS-GDS were examined; the same items used in the original version of the GDS-15 were found to have the best scale characteristics for the shortened informant version. Consistent with findings from the CS-GDS, informant scores were significantly higher than patient scores and had a 0.55 correlation with the self-report GDS-15. A cut-off score of 5 for the GDSI-15 was found to be optimal⁴⁴.

USE WITH SPECIAL POPULATIONS

Long-Term Care

The GDS has been shown to be a reliable and valid instrument for identifying depressed nursing home residents^{8,45,46}. Abraham *et al.*²³ demonstrated that the factor structure of the GDS represents six common facets of depression in nursing home residents: life dissatisfaction, dysphoria, hopelessness/decreased self-attitude, rumination/anxiety, social withdrawal/decreased motivation, and decreased cognition.

Compared to a visual analogue scale, which required participants to mark their level of depression on a line, the GDS was better able to predict ratings of depression by a psychologist, particularly with residents with better cognitive functioning⁴⁷. These researchers slightly modified four items of the GDS to be tailored to nursing home residents. Heiser⁴⁸ found the GDS was better at detecting depression in nursing home residents than the Minimum Data Set.

Targeting the concern of nursing home residents being too frail to complete a multiple item scale, Jongenelis *et al.*⁴⁹ evaluated the diagnostic accuracy of the GDS (30-, 15-, 12-, 10-, 5-, 4- and 1-item versions) among nursing home residents. Scales with greater than or equal to four items were useful for screening depression, but scales with lower numbers of items had less specificity. That is, scales with 4 items were able to detect major depression, but 10 items were necessary to effectively detect milder depression.

In a similar study, researchers⁵⁰ examined various versions of the GDS (30-, 15- and 8-item) and compared them to the Montgomery Asberg Depression Rating Scale (MADRS)⁵¹. Using the same data set utilized in the study by Jongenelis *et al.*⁴¹ mentioned previously, not surprisingly, the authors found a similar pattern of results from the various forms of the GDS. They found the GDS was preferable to the MADRS due to the ease of administration; however, the MADRS, a longer instrument, was superior to all GDS versions in detecting depression in nursing home residents.

Cognitive Impairment

Several studies suggest that the accuracy of the GDS decreases as the level of cognitive impairment increases^{29,47,52–54}. The majority of these authors (with the exception of Burke *et al.*⁵²) suggest that the GDS can be used with older adults with mild to moderate cognitive impairment. A more preferable type of screen may involve the reporting of a collateral source such as the Cornell Scale for Depression in Dementia⁵⁴ (CSDD) or the informant versions of the GDS.

Some authors^{54,55} propose shifting the cut-off score (between 4 and 6) when using the GDS with a cognitively impaired individual.

Primary Care

A large study⁵⁶ of older adult primary care patients found the GDS to be reliable and valid in this population. A systematic review⁵⁷ of nine studies of the GDS in primary care settings found high sensitivity (ranging from 79% to 100%) and adequate specificity (ranging from 67% to 80%). Bijl *et al.*³¹ examined the cut-off score of 5 in primary care patients and reported adequate sensitivity (79%) and specificity (67%). These positive results suggest that use of the GDS provides reliable and accurate depression screening in primary care settings⁵⁸.

Oldest-Old Individuals

De Craen *et al.*⁵⁹ examined the sensitivity and specificity of the GDS-15 in adults aged 85 years and older. Results indicated a low cut-off point (2/3) had high sensitivity (100%) and adequate specificity (68%). Findings from another study with adults aged 85 and older demonstrated that the GDS was able to detect increases in depressive symptoms after negative life events such as the loss of a spouse⁶⁰. This suggests that the GDS is an appropriate measure to use for assessing longitudinal changes in older adults. A comparison between the GDS-15 and the General Health Questionnaire-12⁶¹ (GHQ-12) in Chinese old-old adults found the GDS-15 had higher reliability and higher sensitivity⁶².

Ethnic Groups

The GDS has been evaluated in several different ethnic groups both within and outside of the US, with mixed results. It has shown to be a satisfactory screening tool in Chinese⁶³, Portuguese⁶⁴, Iranian⁶⁵ and Japanese American older adults⁶⁶. Results from a study comparing Korean and American older adults indicated the GDS-SF had good reliability with both groups, but the underlying factor structure differed⁶⁷. Costa and colleagues⁶⁸ found that reliability was good for the GDS, but it did not perform better than the GHQ-12⁶¹ and neither was an ideal screening tool for Brazilian older adults even with adjustment of cut-off scores.

SUMMARY

Use of the GDS for the screening and detection of depression among older adults is widespread. As with any psychological measure, test performance of the GDS varies depending upon population characteristics (e.g. individuals with different levels of cognitive functioning). Brief forms of the GDS, as well as versions designed for specific populations (e.g. residents in nursing homes), detect depressive symptoms as well as, if not better than, the original GDS. Further research is needed to explore the factor structure of the GDS. The GDS remains a popular and well-validated screening tool for diverse older adult clinical and research settings.

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Dementia Care Mapping

Dawn Brooker

*University of Worcester Association for Dementia Studies, Institute of Health and Society,
University of Worcester, Worcester, UK*

INTRODUCTION

Dementia Care Mapping (DCM)^{1,2} is an observational tool that has been used in formal dementia care settings such as hospital wards, care homes and day care facilities since 1991. Its main uses are:

- at an individual clinical level to elucidate situations where an individual is displaying distress behaviours or to improve well-being;
- as an instrument of practice development for shifting the culture of care to one that is person-centred rather than task focused;
- as a tool in research to assess quality of care and quality of life.

DCM is grounded in the theoretical perspective of a person-centred approach to dementia care. Person-centred care values all people regardless of age and health status, is individualized, emphasizes the perspective of the person with dementia and stresses the importance of relationships³. DCM originated from the pioneering work of the late Professor Tom Kitwood in person-centred approaches to dementia care. In his final book⁴ Kitwood described DCM as: 'a serious attempt to take the standpoint of the person with dementia, using a combination of empathy and observational skill' (p. 4).

THE DEVELOPMENT OF DCM

Tom Kitwood and his PhD student Kathy Bredin developed the original tool through ethological observations of many hours in nursing homes, hospital facilities, and day care facilities in the United Kingdom¹. It was designed primarily as a tool to develop person-centred care practice over time with data being fed back to care teams who could then use it to improve their practice. The original development work is not available in the public domain⁵.

DCM has been through a number of changes since its inception. From 1991 to 1997, the first publically available version, DCM 6th edition, was used. This was revised based on feedback from practitioners in the UK resulting in the 7th edition being launched in 1997. The unexpected death of Tom Kitwood in 1998 created a need to have more formalized structures around DCM. The role of strategic lead for DCM was created at the University of Bradford in 2001 which the author fulfilled until 2009. The formal network of DCM trainers and the DCM International Implementation Group had their inaugural meetings in 2001 and 2002 respectively. DCM underwent a further major revision 2002–2004 drawing on the international per-

spectives. In 2005 DCM 8 was launched. The revised tool (DCM 8) was validated against DCM 7th edition⁶.

The DCM tool is only available through undertaking a registered courses delivered by licensed trainers using standardized training methods. Those undertaking the basic DCM training course (3–4 days duration) do not need any formal qualification although the complexity of the method requires reasonable numeracy and literacy skills. DCM is not aligned to a particular discipline. There are a number of different levels of training that have developed over the years to equip users of DCM at a variety of different levels.

DCM training has been available in the UK since 1991. The worldwide spread of DCM has been remarkable. Tom Kitwood taught the first DCM course outside the United Kingdom in the United States in 1998. In the same year, the materials were translated into German and training commenced there. Australia ran its first course in 2001. The Danish translation and the first course in Denmark took place in 2002. Training has been available in Switzerland with support from Germany since 2002. The materials were translated into Japanese and the first basic course took place in Japan in 2003. Translation into Korean occurred a couple of years later. Spanish and Catalan translations were completed in 2009. At the time of going into press the translations into Flemish, Dutch and Italian are being done. Strategic partnerships exist between the University of Bradford and organizations in all these countries to ensure that training in DCM adheres to international quality standards. At time of going into press there are approximately 8000 people trained at basic level worldwide.

The DCM International Implementation Group is an association of all those countries where DCM training is offered or who are preparing to offer training. Its purpose is to consider the training, care practice and research associated with DCM drawing on expertise from around the world and ensuring a common set of quality standards.

DCM has grown in popularity over the years. Many practitioners have used DCM in many different situations and continue to do so. This may be because DCM appears to provide a vehicle for those wishing to systematically move dementia care from primarily a custodial and task-focused model into one that focuses on the well-being of people living with dementia. There are very few other tools that purport to do this or that have been shown to be effective in this endeavour. Whether it has had a sustained impact on practice is difficult to assess. The investment of time and effort in undertaking training and sustaining mapping cycles can be a barrier in practice.

There has been no survey of how many care providers actually use DCM in practice. A survey undertaken some years ago indicated that around 50% of people undertaking the training actually used mapping in practice although many more reported a beneficial impact on their own practice of undertaking the training⁷.

THE DCM TOOL

During a DCM evaluation, an observer (mapper) tracks five people with dementia (participants) continuously over a representative time period. Observation takes place in communal areas of care facilities. Guidelines are provided during training about how to observe in a way that does not increase the ill-being of people with dementia. After each 5-minute period (a time frame) two types of codes are used to record what has happened to each individual. The behavioural category code (BCC) describes one of 23 different domains of participant behaviour that has occurred.

Based on behavioural indicators, a judgement is also made of the relative state of affect and engagement experienced by the person with dementia. This is called a mood/engagement value (ME value) and is rated on a scale ranging from -5 (extreme negative state) to +5 (extreme positive state). ME values are averaged over the mapping period to arrive at a well- and ill-being score (WIB score). This provides an index of relative well-being for a particular time period for an individual or a group. Being in a state of well-being is defined as experiencing a preponderance of positive over negative experiences and feelings over a period of time. Therefore, for a person with dementia, experiencing relative well-being would relate to experiencing more of the indicators of well-being over a period of time than the indicators of ill-being.

Personal detractors (PDs) and personal enhancers (PEs) are recorded whenever they occur. PDs are staff behaviours that have the potential to undermine the personhood of those with dementia. These are described and coded according to type and severity. PEs are staff behaviours that are thought to enhance personhood. These are described and coded according to type and the degree to which it is thought they enhance personhood.

From published papers on DCM⁸ there is consistency of what is reported in DCM data. In long-term care facilities, behaviour codes indicating social interaction, passive watching, and eating and drinking appear as the most frequent codes almost without exception. Codes for walking and sleeping appear as the next most frequently cited. In facilities with lower well-being scores, withdrawn and repetitive behaviours are frequently seen. In facilities with higher well-being scores, creative activity, physical exercise and general leisure activities occur more frequently. Generally, a greater diversity of behaviour and higher well-being scores are reported in day-care facilities. These scores both increase generally during periods of therapeutic activity. Higher levels of personal detractors occur in those facilities with the lowest well-being scores.

LENGTH OF OBSERVATION PERIOD

Most of the published studies here have mapped continuously for 6 hours, although those using DCM for practice-development purposes mapped for longer⁹⁻¹². It also is evident from practice that useful insights can be gained from mapping for just a couple of hours¹³. Mapping an individual at a particular time of day may throw light on the causes and triggers of distress behaviours. Length of maps will depend, in part, on the reason for mapping. Sometimes mapping

is spread over a couple of days. This can have the advantage of sampling a greater amount of variety of staffing situations but some of the continuity may be lost at an individual participant level. For research purposes, a statistically significant correlation between the hour prior to lunch and a 6-hour map on all their key indicators at the group level has been described¹⁴. It is likely that there would be more variation for individual level data.

Maps above 4 hours' duration have been reported to correlate well with longer maps but that those below 4 hours do not⁶. When comparing maps over time it is important to try to map for the same time period to ensure that the same opportunities are available for activity on both occasions. Mapping over a meal time will increase levels of activity for example. So if on the first occasion of mapping, only one meal time is observed it is important to ensure only one meal time is observed on the second occasion.

WHAT DCM EVALUATES

The DCM tool provides in-depth detail about the following:

- variations in individual and group care facility levels of well-being and ill-being;
- how people with dementia spend their time and how this is linked to relative well- and ill-being; and
- staff behaviour that promotes personhood and staff behaviours that undermine personhood.

DCM tells us about the quality of care as it impacts on the quality of life of those living in dementia care settings. Within Kitwood's writing was the assumption that, for people with dementia, well-being is a direct result of the quality of relationships they enjoy with those around them. The interdependency of the quality of the care environment to the relative quality of life experienced by people with dementia is central to person-centred care practice. In placing DCM in the taxonomy of measures of quality of life and quality of care, DCM attempts to measure elements of both. In its BCCs and WIBs, DCM measures relative well-being, affect, engagement and occupation, which are important elements of quality of life. Through PDs and PEs, DCM records the quality of care practice as it promotes or undermines the personhood of those being mapped.

In terms of concurrent validity with other measures there is some evidence that DCM is related to indicators of quality of care^{9,15} and with proxy quality-of-life measures^{14,16}. With persons with more advanced dementia it is difficult to ascertain whether there is a correlation between DCM scores and direct quality-of-life interviews. One study¹⁶ did not find a correlation on a subsample with participants with mild cognitive impairment. In a multi-method study¹⁷ it was noted that during interviews, people with dementia rated their quality of life as better than their DCM scores would suggest.

DCM measures something similar to proxy measures and other observation measures. It is somewhat different from other quality-of-life and quality-of-care measures in that it attempts to measure elements of both. In training to use DCM, mappers are explicitly taught to increase their empathy for the viewpoint of the person with dementia and to use this during their coding decisions.

RELIABILITY OF DCM

In research papers it appears that a reasonable agreement between trained mappers can be achieved. Nineteen studies reported inter-rater

coding agreements ranging from 0.7 to 1.0, most reporting concordance coefficients of 0.8⁸. Mappers in routine practice are likely not to spend time ensuring that their inter-rater reliability is adequate. When many different mappers are engaged in mapping at different points in time, drifts in coding can have a significant impact on results¹⁸ unless systematic checking is in place to prevent this. There are various ways in which reliability can be achieved in routine mapping¹⁹.

Only one paper has reported on test–retest reliability on the same individuals a week apart¹⁴. There was satisfactory correlation between +3 and +5 ME values, overall WIB score and type of BCC. To date DCM data has only been published on DCM 7 data.

POPULATIONS THAT DCM IS USED WITH

DCM is used primarily with people with dementia living in long-term care settings. This covers a wide range of cognitive ability and dependence. There is evidence to suggest that level of dependency is correlated with DCM scores, specifically that low WIB scores are associated with high dependency levels^{9,16,18}. However, this is not always the case^{20,21}. The correlations between low WIB scores and high dependency may of course be related to a third factor of poorer quality of psychosocial care for people with dementia who have high dependency needs. In two studies where DCM was used in a systematic way to improve practice over time, the relationship between dependency and WIB scores disappeared as care quality improved^{9,10}. DCM helps to focus care staff to consider the needs of those whose well-being is lowest, who are usually those with the greatest levels of dependency. Accordingly, DCM can help staff to refocus and adapt their care practices to better meet the needs of more dependent clients.

The evidence that dependency level skews DCM results is strong enough to suggest that a measure of dependency should be routinely taken alongside DCM evaluations so that the results can be scrutinized for this relationship.

Although DCM was originally developed in formal care services for people living with dementia, over the years it has also been used in services for people with learning disabilities²² on general elderly care wards²³ and with people with Huntington's disease²⁴.

USING DCM TO IMPROVE THE QUALITY OF CARE

DCM lends itself well to improving well-being and quality of life for people with dementia at an individual care-plan level. The analysis of individual maps provides a lot of information about how to optimize an individual's well-being over the day. Small things that engender joy or distress, that are easy to miss as part of general care, become very clear in the process of mapping. This can be built upon to ensure that people have the opportunity to experience well-being more often.

At a group level, for example in the management of a hospital ward or nursing home, DCM can be used to improve the organization of care towards one that is person-centred rather than task-focused. An analysis of key events over the day – such as meal times or activity sessions or handovers – often reveals where changes can be made that will improve levels of well-being of the whole group of service users.

At a management level within care organizations, DCM data can help in decisions around skill mix, training needs and staff development. DCM sheds light on those skills that engender well-being. It can be useful in tailoring training and staff development programmes

around specific examples from the lived experience within an organization.

An advantage of DCM is that it can be used over time to monitor change at all these levels, thus evaluating whether the changes have had an impact. DCM data can be analysed to monitor change over time at an individual resident level and at an organizational level. DCM data can be utilized to good effect in fulfilling a number of reporting requirements for commissioners and inspections.

USING DCM TO CHANGE THE CULTURE OF CARE

In 2001, an international 'think tank' of DCM practitioners came together to review their collective experience on DCM²⁵. Their conclusions from practice were that DCM, used within an organizational framework that supported person-centred care, could improve levels of well-being, increase the diversity of occupation, and decrease the incidence of personal detractions. The published developmental evaluations although limited in number supports this assertion both for larger scale quality-assurance initiatives^{9,10} and more in-depth developments in single establishments^{12,26}. A recent Australian cluster-randomized control trial of DCM demonstrated that DCM improved levels of agitation and that the number of falls decreased in care homes that used DCM²⁷.

Using DCM to achieve culture change is not an easy or trivial process. It does not provide a quick fix solution. This fact needs to be engaged with by both staff and management teams prior to deciding to use DCM. DCM is unlikely to have a positive impact unless staff have the necessary knowledge and skills base to use the information it generates. Also, as DCM works through helping staff teams reflect on their practice to bring about quality improvements, mechanisms such as supervision, mentoring, governance and quality assurance groups need to be established at an organizational level for DCM to work effectively over a sustained period of time.

Bringing DCM into an organization as a driver for person-centred care practice is a major undertaking. It requires clear strategic and operational planning if there is to be a maximum return on investment. Many organizations spend over a year planning and ensuring they are prepared before embarking on their first DCM evaluation. The British Standards Institute have developed a Publically Accessible Specification²⁸ to provide health and social care organizations with comprehensive guidance to assist them in this process.

USING DCM IN RESEARCH

The University of Bradford maintains a DCM bibliographic database that contains all known publications on DCM (<http://www.bradford.ac.uk/acad/health/dcm>). It is updated by the Bradford Dementia Group with annual bibliographic searches on Medline, Cinahl, and Psycinfo using the terms 'DCM' and 'dementia care mapping' as well as personal correspondence from practitioners and researchers.

A review of the published literature on DCM⁸ revealed a number of papers of variable quality dating back to 1995 that have used DCM in a research context. These were categorized into the following types:

1. Cross-sectional surveys: Ten papers reported DCM results across a number of different facilities, and the results either compared or pooled. An additional three papers used DCM to investigate the relationship between participants' characteristics and well-being and activity.

2. Evaluations of interventions: In a further ten papers DCM was used to evaluate the impact of various interventions including a number of non-pharmacological therapeutic interventions and a double-blind, placebo-controlled, neuroleptic discontinuation study²⁹.
3. Practice development evaluations: Six papers investigated the ability of DCM to develop practice over time by means of repeated evaluations.
4. Multi-method evaluations: Three articles reported using DCM as part of a multi-method evaluation of a single facility or service.

DCM was not designed to be a research tool. Careful consideration should be given in deciding whether DCM is fit for purpose given the specific topic under investigation. In terms of cross-sectional surveys, there are tools that may be more suited to this task that do not have the attendant time-consuming problems and specialist training associated with DCM.

DCM seems to be suited to smaller scale within-subjects or group comparison intervention evaluations, given that it appears to demonstrate discrimination on a variety of interventions. In multi-method qualitative designs, DCM appears to enrich the data derived from proxy and service-user interviews and focus groups. DCM provides an opportunity to represent a reflection on what could be the viewpoint of service users who are unable to participate fully in interviews.

What is clear is that BCCs do not measure real-time estimates of different types of behaviour¹⁸. Because of the rules of coding in DCM, it will underestimate the occurrence of socially passive and withdrawn behaviour compared with data collected with continuous time sampling. Researchers interested in looking at withdrawn and passive behaviour might be better advised to use another tool. It is worthy of note, however, that despite this, three studies^{21,30,31} found DCM discriminated between groups on social withdrawal in their evaluations. There are a number of modifications to DCM that might prove useful when using DCM in research³².

CONCLUSIONS

DCM has a long history and it has changed over time. It has been taken up by practitioners in many countries who wish to improve the quality of care for people with dementia. It can be used on an individual client level or to improve group care. It requires specialist training to use and it takes careful planning to ensure that it is used to good effect. It has been utilized as a research tool for a variety of purposes.

DCM's advantages are that it is standardized, quality controlled, international, responsive to change, multidisciplinary and has an increasing research base. Its disadvantages are that it is resource heavy in terms of its training and administration. DCM holds a unique position in relation to quality of life in dementia care, being both an evaluative instrument and a vehicle for practice development in person-centred dementia care.

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Staging Dementia

Barry Reisberg¹, Imran A. Jamil¹, Sharjeel Khan¹, Isabel Monteiro¹, Carol Torossian¹, Steven Ferris¹,
Marwan Sabbagh², Serge Gauthier³, Stefanie Auer⁴, Melanie B. Shulman¹, Alan Kluger¹,
Emile Franssen¹ and Jerzy Wegiel⁵

¹*Aging and Dementia Clinical Research Center, New York University Langone Medical Center,
Center of Excellence on Brain Aging, New York, NY, USA*

²*Cleo Ruberts Center, Banner-Sun Health Research Institute, Sun City, AZ, USA*

³*McGill Center for Studies in Aging, Douglas Hospital, Montreal, Quebec, Canada*

⁴*MAS Alzheimerhilfe, Bad Ischl, Austria*

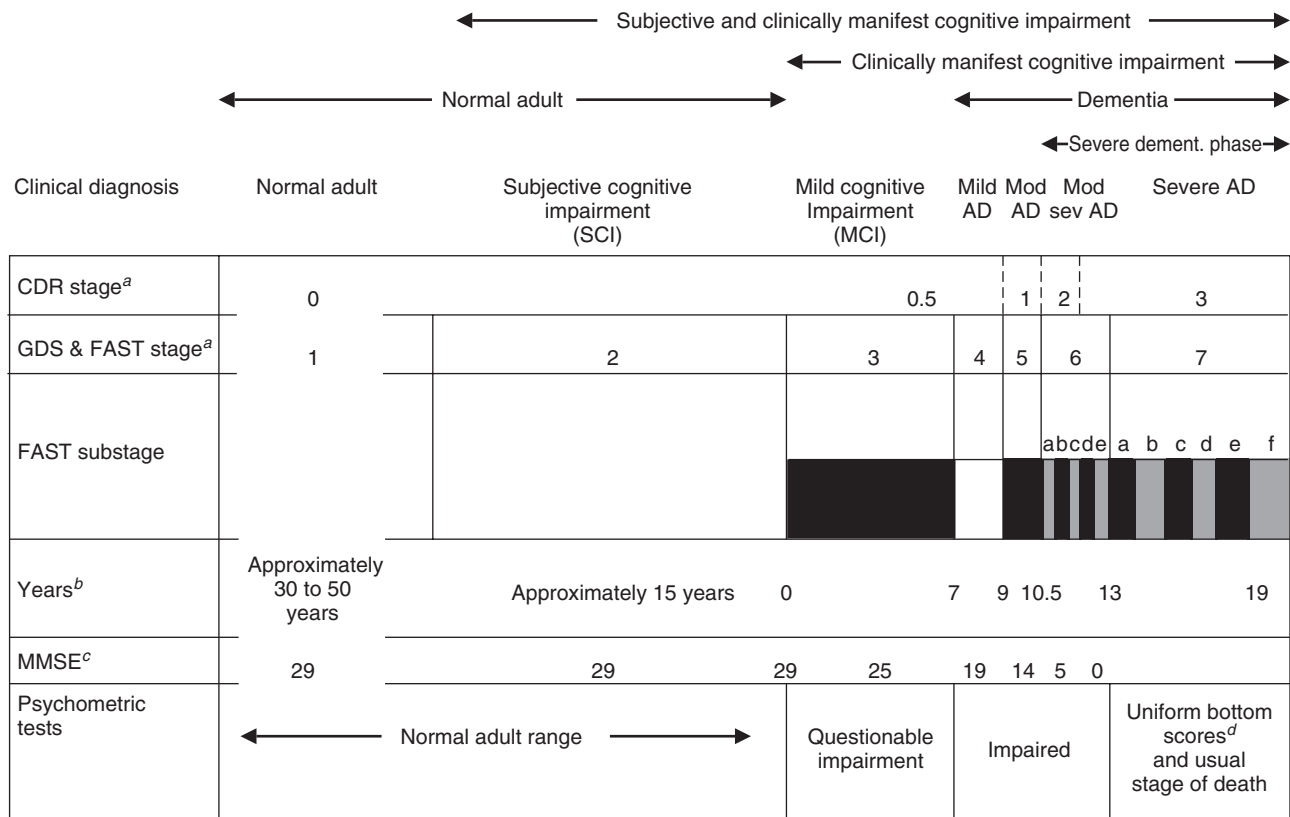
⁵*New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York, USA*

INTRODUCTION AND OVERVIEW OF DEMENTIA STAGING

Dementia is a progressive pathological process extending over a period of many years. Clinicians and scientists have long endeavoured to describe the nature of dementia progression. Such descriptions have generally been encompassed within two broad categories: global staging and more specific staging, sometimes referred to as axial or multi-axial staging. A comparison of the major current dementia staging systems with the most widely used mental status assessment in Alzheimer's disease, the major cause of dementia, is shown in Figure 31.1.

This Figure illustrates some of the major potential advantages of staging. These advantages include: (i) staging can identify premorbid, but potentially manifest conditions which may be associated with the evolution of subsequent dementia, such as subjective cognitive impairment, a condition which is not differentiated with mental status or psychometric tests; (ii) staging can be very useful in identifying subtle predementia states, such as mild cognitive impairment (MCI), wherein mental status assessments and psychometric tests, while frequently altered, are generally within the normal range and, consequently, are not reliable markers^{17–19}; and (iii) staging can track the latter 50% of the potential time course of dementias such as Alzheimer's disease (AD), when mental status assessments are virtually invariably at bottom (zero) scores²⁰. Furthermore, apart from their utility in portions of dementia where mental status and psychometric assessments are out of range, or insensitive, there are clear data indicating that staging procedures can more accurately and sensitively identify the course of dementia in the portion of the condition which is conventionally charted with mental status assessments. This latter evidence comes from longitudinal investigation of the course of AD⁹, pharmacological treatment investigation of AD^{21–23}, and study of independent psychometric assessments of AD²⁴. For example, longitudinal study has demonstrated that the Functional Assessment Staging procedure (FAST)⁵ and the Global

Deterioration Scale (GDS)³ accounted for more than twice the variance in the course of AD over a five-year mean interval, compared to the Mini-Mental State Examination (MMSE)^{7,9}. When employed together, the GDS and the FAST staging procedures explained nearly three times the variance in the temporal course of AD compared to the MMSE (i.e. change in measure versus change in time), with the MMSE encompassing only 10% of temporal change variance and the GDS and FAST together encompassing 28% of the temporal change variance⁹. In pharmacological studies, staging procedures have frequently demonstrated sensitivity to effects of the interventions in pivotal studies where mental status assessment has not shown a significant effect. This superiority in the demonstration of pharmacological treatment efficacy for staging procedures over mental status assessment has been seen for both classes of currently approved pharmacotherapeutic agents; that is, for *N*-methyl-D-aspartate (NMDA) receptor antagonist treatment decreasing glutamate-induced excitotoxicity, and for cholinesterase inhibitor treatment enhancing cholinergic brain functioning. For example, a pivotal, multicentre trial associated with worldwide approvals of memantine treatment for AD found a robust statistically significant effect of the memantine, NMDA receptor antagonist treatment with the FAST staging procedure, but no significant effect was observed with the MMSE evaluation²¹. Similarly, in a pivotal study associated with worldwide approval of the cholinesterase inhibitor, rivastigmine, it was found that low dose treatment (1–4 mg/day) was associated with significant improvement on the GDS staging procedure, but not on the MMSE assessment²². Additionally, study of predominantly institutionalized persons with more advanced AD in the latter portion of the MMSE range (i.e. with MMSE scores of 10 or below), with specially designed psychometric procedures for advanced AD patients, have clearly shown that the FAST staging procedures can robustly track progressive change in these more advanced AD patients, in conjunction with special psychometric procedures, whereas the MMSE does not sensitively change in this more severe range²⁴. Another potential advantage of staging procedures in comparison with mental status



^a Stage range comparisons shown between the CDR and GDS/FAST stages are based upon published functioning and self-care descriptors.

^b Numerical values represent time in years.

For GDS and FAST stage 1, the temporal values are subsequent to the onset of adult life.

For GDS and FAST stage 2, the temporal value is prior to onset of mild cognitive impairment symptoms.

For GDS and FAST stage 3 and above, the values are subsequent to the onset of mild cognitive impairment symptoms.

In all cases, the temporal values refer to the evolution of Alzheimer's disease pathology.

All temporal estimates are based upon the GDS and FAST scales and were initially published based upon clinical observations in Reisberg, *Geriatrics* 1986; **41**(4): 30–46⁸. These estimates have been supported by subsequent clinical and pathological cross-sectional and longitudinal investigations (e.g. Reisberg *et al.*, *Int Psychogeriatr* 1996; **8**: 291–311⁹; Bobinski *et al.*, *Dementia* 1995; **6**: 205–10¹⁰; Bobinski *et al.*, *J Neuropathol Exp Neurol* 1997; **56**: 414–20¹¹; Kluger *et al.*, *J Geriatr Psychiatry Neurol* 1999; **12**: 168–79¹²; Pritchard *et al.*, *Neurobiol Aging*, 2006; **27**: 471–81¹³; Reisberg and Gauthier, *Int Psychogeriatr* 2008; **20**: 1–16¹⁴; Wegiel *et al.*, *Acta Neuropathol* 2008; **116**: 391–407¹⁵; Reisberg *et al.*, *Alzheimers Dement* 2010; **6**(1): 11–24¹⁶).

The spacing in the figure is approximately proportional to the temporal duration of the respective stages and substages, with the exception of GDS and FAST stage 1, for which the broken lines signify an abbreviated temporal duration spacing for this normal adult condition which lasts approximately 30 to 50 years.

^c MMSE scores are approximate mean values from prior published studies.

^d For typical adult psychometric tests.

Figure 31.1 Typical time course of normal brain ageing; mild cognitive impairment associated with Alzheimer's disease and the dementia of Alzheimer's disease. AD, Alzheimer's disease; CDR, Clinical Dementia Rating^{1,2}; GDS, Global Deterioration Scale^{3,4}; FAST, Functional Assessment Staging^{5,6}; MMSE, Mini-Mental State Examination⁷; Mod AD, moderate Alzheimer's disease; Mod sev AD, moderately severe Alzheimer's disease. Copyright © 2007, 2009 Barry Reisberg, MD. All rights reserved

or psychometric assessment of AD and other dementias, is in identifying the management concomitants of severity assessments^{25,26}. Staging procedures have also been successfully applied postmortem to retrospectively assess the diagnoses (i.e. AD or other non-AD dementia) of a diverse assortment of dementia-related cases available for 'brain banking', but on which no antemortem clinical data were available²⁷. Similarly, postmortem retrospective staging procedures have been successful in establishing remarkably robust clinicopathological correlations in longitudinally studied AD cohorts^{10,11,15,20}.

GLOBAL STAGING

Efforts to globally stage progressive dementia can be traced back at least to the early nineteenth century when the English psychiatrist, James Prichard, described four stages in the progression of dementia: '(1) impairment of recent memory, (2) loss of reason, (3) incomprehension, (4) loss of instinctive action'^{28,29}. More recently, the American Psychiatric Association's³⁰ Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III) recognized three broad stages in its definition of primary degenerative dementia³⁰. Subsequently, in 1982, two more detailed global descriptions of the progression of dementia were published. One of these, the Clinical Dementia Rating (CDR) scale¹, describes five broad stages from normality to severe dementia. The other, the Global Deterioration Scale (GDS)³, identifies seven clinically recognizable stages from normality to most severe dementia of the Alzheimer type. A recently published abridged version of the GDS is shown in Table 31.1³¹.

Complete versions of the CDR and the GDS scales can be found in the literature (e.g. for the original CDR, references^{1,32} and for the CDR 'current version', reference²; for the GDS, reference³, and for the tabular format of the GDS, reference⁴). These two global staging instruments, the GDS and the CDR, are generally compatible except that the GDS is more detailed and specific and identifies two stages which the CDR staging does not.

One of these stages identified by the GDS staging procedure but not by the CDR is a stage in which subjective complaints of cognitive deficit occur in the absence of clinically identifiable symptoms

(GDS stage 2). These subjective complaints are now recognized as occurring very commonly in older persons (e.g.^{33–35}). Although this stage of subjective complaints continues to be identified only by the GDS staging system, studies have indicated that persons with these complaints are at increased risk for subsequent overt dementia (e.g.^{12,16,36–38}). A distinct diagnostic terminology, namely, 'subjective cognitive impairment' (SCI), has recently been suggested for otherwise healthy older persons with these symptoms who are free of overtly manifest symptoms of mild cognitive impairment (MCI) or dementia^{14,39}. A recent study, which is apparently the first to systematically examine the prognosis of GDS stage 2, SCI persons, in comparison with persons with no cognitive impairment (NCI, GDS stage 1), from the perspective of the subsequent development of MCI or dementia, has indicated the true morbidity associated with this SCI condition. Over a mean seven-year follow-up, the risk of subsequent decline to MCI or dementia was 4.5-times greater in persons with SCI (GDS stage 2) than in persons who are free of these subjective complaints, after controlling for differences in age and other demographic variables, as well as follow-up time¹⁶. Physiological differences between otherwise healthy older persons with these subjective complaints of cognitive impairment and similarly aged persons without these symptoms (i.e. between GDS stage 2 and GDS stage 1 subjects) have now been reported for brain metabolism and cortisol levels^{40,41}. Longitudinal studies are also presently confirming^{13,14} a previously estimated 15-year duration⁸ for this GDS stage 2 condition, identifying subjective impairment only, in the evolution of brain ageing and AD pathology.

The GDS staging measure and associated assessments from the GDS staging system also identify a stage, GDS stage 3, for which the terminology mild cognitive impairment (MCI) was originally coined in 1988⁴². This GDS stage 3 is described, in part, as a stage in which: (i) the 'earliest clear-cut deficits' become manifest; (ii) 'objective evidence of memory deficit is obtained only with an intensive interview', and (iii) there is 'decreased performance in demanding employment and social settings'. Many of the early observations with respect to the nature of MCI were made using this GDS stage 3 definition (see¹⁷ for a review), and the GDS 3 definition of MCI remains compatible

Table 31.1 Abridged global deterioration scale

Stage 1: NCI. No subjective memory deficit (no cognitive impairment); no problems with activities of daily living.
Stage 2: SCI. Subjective cognitive impairment (subjective memory and/or other cognitive complaints): observations, sometimes accompanied by complaints, of being forgetful, such as of difficulties with recall of names, and/or of misplacing objects.
Stage 3: MCI. Earliest subtle deficits (mild cognitive impairment): difficulties often noted at work; may have become lost; may have misplaced a valuable object.
Stage 4: Mild dementia. Clear deficits on clinical examination (moderate cognitive impairment): decreased knowledge of personal and/or current events; often difficulties with finances or shopping or meal preparation or travel.
Stage 5: Moderate dementia. Can no longer survive independently in the community without some assistance (moderately severe cognitive impairment): difficulty with recall of some important personal details (e.g. address, names of one or more important schools attended); may require cueing for activities for daily living.
Stage 6: Moderately severe dementia. Largely unable to verbalize recent events in their life (severe cognitive impairment): may forget name of spouse; incontinence develops as this stage progresses; requires increasing assistance with activities for daily living such as dressing and showering. Increased behavioural problems (e.g. agitation) or other personality problems are common.
Stage 7: Severe dementia. Few intelligible words or no verbal abilities (very severe cognitive impairment): the ability to walk is lost as this stage evolves. Later, basic capacities such as the ability to sit up independently, to smile, and to move and/or to hold up the head independently are progressively lost.

with the current international consensus definition of MCI, published by Winblad *et al.* in 2004¹⁹. The CDR staging methodology identifies a CDR 0.5 stage originally termed 'questionable dementia', which is somewhat broader in scope than the MCI entity, and which encompasses some of early (mild) dementia, as well as the MCI clinical timeframe.

At the other end of the pathological spectrum, the CDR does not identify any stage beyond that in which dementia patients 'require much help with personal care' and are 'often incontinent'. In contrast, the GDS identifies a final seventh GDS stage in which patients are already incontinent and over the course of which language and motor capacities are progressively lost. Importantly, the CDR does not stage or substage the latter portion of the dementia of AD, representing nine or more years of potential life and continuing decline for these patients (see Figure 31.1). This absence of attention to the nature of severe dementia clinical changes in the CDR staging methodology may add to the neglect of persons with more advanced dementia and, in particular, the dementia of Alzheimer's disease. In marked contrast with the CDR, the GDS identifies two stages (GDS stages 6 and 7), corresponding to the CDR 3 stage range. Additionally, the other elements of the GDS staging system, described below, chart this latter portion of the dementia of AD in detail. For example, the FAST scale (described below) identifies eight substages corresponding to the CDR stage 3, 'severe dementia' range.

In addition to the range differences discussed above and differing staging numbers, the CDR scale and the GDS staging scale also have different procedures for scoring. The original CDR versions used a 'sum of boxes' procedure, with means of the sum of boxes in six CDR assessment categories, i.e. (1) Memory, (2) Orientation, (3) Judgement and Problem Solving, (4) Community Affairs, (5) Home and Hobbies, and (6) Personal Care. However, current scoring procedures for the CDR are much more complex and more weighted towards the memory category. The GDS staging procedure simply requires the choice of the most appropriate global stage, based upon cognition and functioning. GDS staging descriptors acknowledge common emotional concomitants of the stages; however these are not employed in the stage selection. The comparisons shown in Figure 31.1 between the CDR and the GDS/FAST staging categories and other assessment procedures are based upon the CDR functioning and self-care descriptions.

In summary, with respect to range, the GDS staging and associated measures from the GDS Staging System, are much more detailed at both ends of the pathological spectrum of brain ageing and progressive dementia than the CDR staging. As discussed, the GDS staging identifies an SCI stage prior to the development of mild cognitive impairment, which the CDR staging does not refer to. Also, the GDS staging procedures are more rigorous in the definition of MCI and the separation of MCI from early dementia. In the severe end of the dementia spectrum, the GDS staging and the associated GDS Staging System, described in greater detail in the next section, are much more detailed than the CDR.

Staging procedures have been shown to be valid and reliable methods for assessing the magnitude of pathology in AD and related dementing conditions. This validity and reliability is illustrated in this brief review for the GDS, the most detailed and explicit staging procedure.

The validity of the GDS has been demonstrated in several ways. Cross-sectional studies have confirmed the consistency of the ordinal sequence and the optimal weighting of the hierarchically sequenced items embodied in the GDS stages in ageing and progressive Alzheimer's disease (AD)⁴²⁻⁴⁵. Thus, the specific impairments

characteristic of each stage almost always follow the impairments described for the previous stage. Also, the grouping of impairment characteristics within stages appears to be optimal.

For example, naturalistic study has supported the identification of staging phenomena, largely identical to the GDS stages, by independent layperson observers. In this study⁴⁴, a 30-item questionnaire derived from the GDS was completed by a relative or caregiver for each of 115 patients with varying degrees of dementia. Principal components analysis was used to combine the items into a single composite scale that more reliably represents distances between the 30 clinical manifestations along the continuum of cognitive decline. In the study it was found that 'the scale scores for the clinical manifestations were observed to cluster into relatively discrete groups, suggesting naturally occurring stages or phases. Objective cluster analysis methods further confirmed the presence of distinct transitions along the cognitive decline continuum.' It was concluded that the 'utility of empirically derived scale values in staging the course of primary degenerative dementia is suggested.'

The relationship between the GDS stages and mental status assessments, other dementia assessments, scores on cognitive tests and other objective tests and *in vivo* assessments of brain change in ageing and progressive dementia have been studied in considerable detail^{3,42}. These studies have indicated significant correlations between all of these measures of dementia severity and the GDS stages. However, the strongest relationships have been observed between comprehensive dementia assessments such as the Mini-Mental State Examination (MMSE)⁷ and the progression of dementia on the GDS⁴². The GDS also correlates well with independent physical markers of AD progression such as changes in neurological reflexes⁴⁶. Thus the construct validity of the GDS has been well substantiated.

At least six separate studies have examined the reliability of the GDS⁴⁷⁻⁵². Reliability coefficients have ranged from 0.82 to 0.97 in these studies using disparate procedures in diverse settings. These studies have indicated that the GDS is at least as reliable as any other instruments upon which clinicians rely, such as the MMSE. In a reliability study in a nursing home setting⁵¹, the GDS was found to be somewhat more reliable than the MMSE. Importantly, GDS staging has also been shown to be a reliable procedure when assessed using a telephone format⁵².

Global staging scales such as the GDS have certain important advantages in dementia assessment. First and foremost, these scales are strongly anchored to the clinical symptoms, behaviour and functional changes in progressive degenerative dementia, and particularly those of Alzheimer's disease. Consequently, they discourage misdiagnosis. Unlike many mental status and other dementia test instruments, global stages are relatively stable over time and relatively resistant to practice effects. Equally importantly, global staging instruments are minimally influenced by educational background and socioeconomic status, whereas mental status and similar assessments are strongly influenced by such factors. Also, as previously noted, global staging, and in particular the GDS, covers the entire range of pathology in central nervous system (CNS) ageing and progressive dementia, whereas, for example, mental status assessments and most psychometric tests entirely fail to distinguish GDS stages 1 and 2 (i.e. NCI and SCI). Occasionally, patients may display GDS stage 3 symptomatology (MCI) and still score a perfect 30 on the MMSE. Uncommonly, dementia patients may display GDS stage 4 symptomatology (mild dementia), and still score a perfect 30 on the MMSE. Much more commonly, patients may display the clear-cut dementia symptomatology characteristic of GDS stage 4 and achieve

MMSE scores which are near perfect or within the so-called 'normal' range. At the other end of the pathological spectrum, most patients at GDS stage 6 (moderately severe dementia) achieve only bottom scores on traditional psychometric tests. Over the entire course of the GDS 7 (severe dementia) stage, most patients attain only zero (bottom) scores on the MMSE. The GDS, however, describes a final seventh stage, over the course of which patients may survive for many years.

AXIAL AND MULTI-AXIAL STAGING

The observation that the progression of dementia pathology is accompanied by progressive changes in more specifically defined processes, termed 'axes' has resulted in efforts to stage dementia in terms of those processes. Generally, axial staging has attempted to exploit progressive changes in cognition or functioning, although attempts have also been made to hierarchically stage progressive mood and behavioural changes, progressive motoric changes and progressive neurological changes, as well as other observable concomitants of dementia. These efforts can be traced back more than 40 years to the work of de Ajuriaguerra and associates^{53–55}; Swiss investigators who were strongly influenced by Piaget's investigations of the stages of normal infant and childhood development. More recently, Cole and co-workers in Canada employed this approach in their Hierarchic Dementia Scale^{56–58}. A similar approach was pursued, apparently independently, by Gottfries and associates in Sweden⁵⁹.

The CDR staging has a 'sum of boxes' approach which employs a hierarchical, multi-axial-like procedure⁶⁰, or, more recently, a modified, multi-axial-like procedure². Based upon the seven-stage GDS, Reisberg and associates also described axial and multi-axial concomitants of progressive dementia^{61,62} in a measure termed the Brief Cognitive Rating Scale (BCRS). Each of the BCRS axes has been enumerated to be optimally concordant with the corresponding GDS stages. Ultimately, the functional component of these BCRS axes resulted in the most detailed hierarchical staging of progressive dementia proposed to date, a 16-stage and substage measure of progressive functional change. This latter assessment is termed Functional Assessment Staging or FAST⁵ (Table 31.2).

Like the BCRS axes, the FAST has been enumerated to be optimally concordant, in dementia of the Alzheimer type, with the corresponding GDS stages, discussed above. The FAST can be used as an independent staging measure of the magnitude of dementia pathology, or as part of the GDS Staging System⁴⁵. Advantages of the FAST staging procedure include the following: (i) the FAST is capable of describing the entire course of brain-ageing associated, cognition-based functional changes and subsequent dementia of the Alzheimer type, ordinarily (i.e. hierarchically), in unprecedented detail; (ii) the scale can assist in differentiating dementia of the Alzheimer type from other dementia processes^{8,65,66}; (iii) the scale can assist in identifying premature and potentially remediable functional changes in AD patients (e.g. premature loss of ambulation due, for example, to the side effects of medication)^{8,65,66}; (iv) the scale permits the retrospective as well as prospective examination of the temporal course of AD^{10,11}; and (v) the scale is the only current measure which permits the detailed staging of severe AD^{20,23,24,43}. A strong relationship between this FAST procedure and comprehensive cognitive assessments such as the MMSE has long been noted^{64,67}. However, because the MMSE and other cognitive modalities bottom out prior to the final five to eight FAST substages, complete concurrent validation and examination of the FAST had to

await the development of cognitive measures useful in most severe dementia. Such measures were developed towards the end of the twentieth century and do, in fact, evidence strong relationships with the final FAST stages²⁴. Subsequent work showed approximately equally strong relationships between this latter portion of the FAST and ostensibly cognition-independent neurological reflex changes⁴⁶, as well as hippocampal neuropathological changes in volume¹⁰, cell number¹¹ and the percentage of remaining hippocampal neurons with neurofibrillary changes¹¹, with the advance of AD as per the FAST stages and substages (reviewed in²⁰). Also, the second layer of the entorhinal cortex is believed to be a very early site of AD pathology. In this layer, a very robust relationship, across the FAST severity spectrum from FAST stage 3 to 7f, with the decrement in neuronal numbers has recently been reported ($r = 0.9$)¹⁵. The correlations between the advance of AD as measured with the FAST in the latter portion of the course of AD, generally after the MMSE bottom (zero) point, and cognitive, neurological reflex and neuropathological hippocampal measures are generally approximately 0.8–0.9. These diverse relationships are comparable to the correlation between the FAST and the MMSE in the MMSE-sensitive portion of the FAST staging assessment. Because of these properties and others, the FAST has proven to be of widespread utility. For example, in the United States, the FAST staging procedure has been utilized as the Medicare mandated 'gold standard' for hospice admission for more than a decade⁶⁸. Importantly, because of the sensitivity of the FAST staging procedure to the course of AD, not only over the final seventh stage when the MMSE is zero, but also over the course of FAST stage 6, when patients still score on measures such as the MMSE, the FAST measure has shown a significant effect on the course of AD in a pivotal multicentre drug trial, associated with worldwide approvals for memantine as the first medication for advanced AD, whereas the MMSE was not sensitive to change in this study²¹. At the present time, the FAST has been used as an efficacy and/or severity assessment in all pivotal trials associated with United States and European Union approvals of medications for advanced AD (for a review, see²³).

Apart from the utility of the FAST staging, other elements of the multi-axial BCRS staging procedures have also proven useful in AD assessment. On the BCRS, Axis I assesses concentration; Axis II, recent memory; Axis III, remote memory; Axis IV, orientation; and Axis V, functioning. Axis V of the BCRS was developed and expanded in the process of the creation of the FAST staging procedure. All of these elements of the BCRS, including the FAST, have been utilized as part of the syncretic NYU CIBIC-Plus assessment measure⁶⁹. As part of the NYU CIBIC-Plus, these measures have been used as primary outcome measures in pivotal trials associated with regulatory body (e.g. FDA) approvals of two of the three medications currently approved and marketed for the treatment of AD in the United States (i.e. rivastigmine and memantine) (for a review, see²³). At the other end of the brain-ageing and AD continuum, the BCRS Axes I to V have been found to add significantly to the GDS global assessment in predicting the risk of decline and the time to decline to MCI or dementia in ostensibly normal subjects with NCI or SCI (GDS stages 1 and 2)¹⁶.

SUMMARY

Behaviourally based brain-ageing and progressive dementia staging procedures can be useful and, frequently, superior to other assessment modalities in identifying potential treatments for AD and related

Table 31.2 Functional Assessment Staging (FAST) and time course of functional loss in normal brain ageing and Alzheimer's disease

FAST stage	Clinical characteristics	Clinical diagnosis	Estimated duration in AD ^a	Mean MMSE ^b
1	No decrement	Normal adult		29–30
2	Subjective deficit in word finding or recalling location of objects	Subjective cognitive impairment	15 years	29
3	Deficits noted in demanding employment settings	Mild cognitive impairment	7 years	24–27
4	Requires assistance in complex tasks, e.g. handling finances, planning dinner party	Mild AD	2 years	19–20
5	Requires assistance in choosing proper attire	Moderate AD	18 months	15
6a	Requires assistance in dressing	Moderately severe AD	5 months	9
b	Requires assistance in bathing properly		5 months	8
c	Requires assistance with mechanics of toileting (such as flushing, wiping)		5 months	5
d	Urinary incontinence		4 months	3
e	Faecal incontinence		10 months	1
7a	Speech ability limited to about a half-dozen words	Severe AD	12 months	0
b	Intelligible vocabulary limited to a single word		18 months	0
c	Ambulatory ability lost		12 months	0
d	Ability to sit up lost		12 months	0
e	Ability to smile lost		18 months	0
f	Ability to hold up or move head independently lost		12 months or longer	

Adapted from Reisberg, 1986⁸. Copyright © 1984 by Barry Reisberg, MD.

^aIn subjects without other complicating illnesses who survive and progress to the subsequent deterioration stage^{9–16}.

^bMMSE = Mini-Mental State Examination score (Folstein *et al.*, 1975⁷). Estimates based in part on published data summarized in Reisberg *et al.*, 1989⁶³ and in Reisberg *et al.*, 1992⁶⁴. It should be noted that the educational level of the subjects in these studies is high (mean ~15.5 years $\pm$ 3 years, of formal education). The influence of these educational levels on the mean MMSE scores should be given consideration.

dementias^{70–72}, as well as in assessing the course and the management needs of the dementia patient, and also in the diagnosis and differential diagnosis of dementing disorders. In providing an overview of the course of dementias such as AD, from the initial to final clinical symptoms, staging is uniquely useful. Staging is also singularly useful in assessment at various specific points in the evolution of dementing processes. Very importantly, staging can uniquely relate to management needs and the general management import of dementing processes.

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The Clinical Dementia Rating

Rawan Tarawneh, B. Joy Snider, Mary Coats and John C. Morris

Washington University in St. Louis, St. Louis, MO, USA

INTRODUCTION

The Clinical Dementia Rating (CDR) is an instrument used to assess the presence and severity of dementia of the Alzheimer type (DAT); it may be applicable to other dementias as well. The CDR was developed at Washington University School of Medicine in 1982 and revised in 1993 to improve the distinction between different severity levels.

Determination of the CDR is based on separate semi-structured interviews with the patient and an appropriate informant, such as spouse or adult child, to provide information regarding the patient's current level of cognitive function and daily activity in comparison with previously attained abilities.

DEVELOPMENT OF THE CDR

Measuring dementia severity is useful for research as well as for clinical decision making. Accurate staging of dementia is particularly important in clinical trials, both to select appropriate participants with similar levels of disease severity and to monitor disease progression¹. The importance of a standardized approach to dementia staging in clinical trials is highlighted by the US Food and Drug Administration's Guidelines for the Clinical Evaluation of Anti-Dementia Drugs: 'the stage and severity of the dementia affecting each subject participating in a clinical trial must be assessed and recorded systematically in a manner that will be readily understood by other workers in the field'².

Prior to the introduction of the CDR, most attempts at the clinical staging of dementia were based on psychometric tests and behavioural rating scales. Some early instruments included the Dementia Scale (DS) of Blessed, the Global Deterioration Scale (GDS), the 29-item Blessed Information and Memory Scale (BIMC), and the Short Blessed Test, an abbreviated 6-item version of the BIMC.

The CDR is a 'global' scale that assesses impairment in cognitive ability, including the impact of cognitive changes on everyday functioning; it was designed to be performed independently of psychometric test results. The CDR assesses intra-individual change from the individual's prior cognitive and functional ability. Psychometric testing typically compares individual performance to reference group norms. By comparing functional and cognitive changes to the premorbid (predementia) level of function for that individual, the CDR minimizes effects of confounding factors such as age, educa-

tional level and ethnicity (i.e. the individual serves as his or her own control).

The CDR has been validated in several neuropathological studies of Alzheimer's disease³. It has demonstrated strong correlations with other behavioural and functional tests, as well as strong inter-rater correlations, attesting to its validity and reliability. While it may not be suitable for every situation, the CDR has become internationally recognized as a highly reliable diagnostic and severity-ranking scale for dementia, has been cited in over 1000 references (<http://apps.isiknowledge.com>) and translated into 60 different languages and dialects (<http://alzheimer.wustl.edu/cdr/PDFs/translation/>). Although primarily developed to assess DAT, the addition of language and behaviour domains in the Uniform Data Set version of the CDR (UDS) has allowed its use in the evaluation of other causes of dementia⁴.

Online training in the use of the CDR is available at <http://alzheimer.wustl.edu/cdr/Application/Step1.htm> or by writing to the authors.

OVERVIEW OF THE CDR

The CDR is performed in two components: a semi-structured interview with a collateral source that provides information on the individual's premorbid level of function and any changes that have occurred, and an interview with the individual that includes some objective testing. It is determined by rating cognitive, behavioural and functional changes resulting from cognitive loss in each of six categories: Memory, Orientation, Judgement and problem solving, Community affairs, Home and hobbies, and Personal care (Table 32.1). Each category is scored independently on a 5-point scale of impairment (0 = no impairment, 0.5 = questionable or very mild, 1 = mild, 2 = moderate and 3 = severe impairment); one category, Personal care, does not have a 0.5 impairment level. The CDR scoring table includes descriptive 'anchors' that guide the rater in determining individual domain ratings based on both collateral source report and patient performance. The clinician uses his or her judgement to determine each rating, scoring each as independently as possible. With CDR training, clinicians can successfully distinguish between physical and cognitive causes of functional impairment and assign a CDR that accurately reflects dementia severity even in the presence of impaired physical performance⁶.

The global CDR is determined by applying a scoring algorithm (www.biosat.wustl.edu/~adrc/cdrpgm/index.html), where global

Table 32.1 The clinical dementia rating scale

	<i>None 0</i>	<i>Questionable 0.5</i>	<i>Mild 1</i>	<i>Moderate 2</i>	<i>Severe 3</i>
Memory	No memory loss or slight Inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; 'benign' forgetfulness	Moderate memory loss: more marked for recent events; defect interferes with everyday activity	Severe memory loss, only highly learned material retrained: new material rapidly lost	Severe memory loss only fragments remain
Orientation	Fully oriented	Fully oriented but with slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgement and problem solving	Solves everyday problems and handles business and financial affairs well; judgement good in relation to past performance	Slight impairment in solving problems, similarities and differences	Moderate difficulty in handling problems, similarities and differences; social judgement usually maintained	Severely impaired in handling problems, similarities and differences; social judgement usually impaired	Unable to make judgements or solve problems
Community affairs	Independent function as usual in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	No pretence of independent function home; appears well enough to be taken to functions outside the family home	Appears too ill to be taken to functions outside the family home
Home and hobbies	Life at home, hobbies and intellectual interests well maintained	Life at home, hobbies and intellectual interests slightly impaired	Mild but definite impairment of functions at home; more difficult chores, and complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in the home
Personal care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene and keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

Source: Morris, J.C. (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, **43**, 2412–4.

CDR 0 = no dementia and CDR = 0.5, 1, 2 and 3 for very mild, mild, moderate and severe dementia. The CDR-sum of boxes (CDR-SB) is obtained by summing the scores in the individual categories, so CDR-SB ranges from 0 to 18 ('best' to 'worst' performance)⁷. The CDR-SB offers some advantages: it does not require an algorithm to calculate and can be treated as interval data in statistical analysis whereas the global CDR represents ordinal data. More importantly, the CDR-SB offers a wider range of values

and increased precision for tracking changes across time. For example, mild DAT (global CDR 1) spans CDR-SB scores from 3.5 to 10, whereas moderate DAT (global CDR 2) spans 8–15.

CHARACTERISTICS

The CDR has two important properties of a global staging measure: hierarchy and concordance⁸. Hierarchy means that dementia severity

is proportional to the CDR score (e.g. global CDR 3 is more severe than global CDR 2). The CDR captures different disease patterns and can identify subgroups of patients through concordance, another important property. In individuals with DAT, most of the six domains are expected to be reasonably concordant with the memory score (e.g. in global CDR 0.5 most domains would have scores of either 0.5 or 0 or 1). Discordance between different cognitive domains (e.g. a mix of 0, 2 and 3s) is suggestive of a non-Alzheimer's cause of dementia.

The CDR has demonstrated excellent 'face validity' in that it assesses the influence of cognitive loss on the ability to conduct everyday activities. It provides a standardized and meaningful way to describe clinically relevant changes to patients and their families⁸.

The CDR has demonstrated its validity in multiple longitudinal studies with neuropathological confirmation of Alzheimer's disease; both the CDR and CDR-SB have been shown to correlate with the densities of neurofibrillary tangles and senile plaques, particularly in the neocortex³. Since the inception and revision of the CDR, the diagnosis of dementia has evolved, with increasing interest in and recognition of milder stages of dementia. The CDR has demonstrated a high degree of sensitivity (91%) in distinguishing individuals with even the mildest stages of dementia from normal individuals in longitudinal studies with neuropathological confirmation of Alzheimer's disease⁹.

When administered in a standardized fashion, the CDR has excellent reliability. Inter-rater reliability of the CDR in several single and multicentre clinical trials including both physicians and non-physicians is 80% or greater for overall CDR, and $\geq 80\%$ for almost all of the individual boxes^{10,11}.

The stability of the CDR over time was investigated in a 30-year longitudinal study of 1768 patients 63–83 years of age and with CDRs 0, 0.5 or 1 at Washington University¹³. Over time, the participant sample became older, more highly educated, more ethnically diverse, more likely to be female and more likely to have non-Alzheimer's disease dementias. There was a high turnover in the individual clinicians. Despite these changes, the psychometric test scores of individuals with similar CDR ratings did not change significantly over the 30-year period.

DIAGNOSIS AND DETECTION OF EARLY STAGES OF DEMENTIA

In its original form, CDR 0.5 denoted a heterogeneous group with questionable dementia. However, there is a growing body of evidence that many in the CDR 0.5 group are very similar to those with mild DAT in cognitive, behavioural, psychometric performance, longitudinal progression, as well as in neuroimaging and CSF biomarker characteristics.

By relying on intra-individual cognitive decline rather than inter-individual comparison of psychometric performances with arbitrary cut-points for impairment, CDR 0.5 allows the identification of individuals with cognitive impairment that may be too mild to fulfil criteria for mild cognitive impairment. Longitudinal studies have consistently demonstrated that the CDR 0.5 designation, when impairment is believed clinically to be caused by DAT, is followed by progressive cognitive and functional decline over time and by the histopathological changes of Alzheimer's disease at autopsy even when the CDR 0.5 diagnosis is 'pre-mild cognitive impairment'⁹.

CDR 0.5 is now considered to characterize 'very mild' rather than 'questionable' dementia. We attempt to diagnose the aetiology of

dementia even when the degree of impairment is very mild (CDR 0.5).

ADAPTATIONS OF THE CDR

The CDR has been adapted to other clinical settings such as nursing homes and chronic care facilities (CDR-CC). A more abbreviated form of the CDR has been included into the Diagnostic and Statistical Manual for the identification of dementia.

The CDR interview can take 45–60 minutes and may be impractical for some clinical and research settings. A software system for administration and automatic scoring of the CDR using a hand-held device platform was recently developed. The platform includes specific algorithms for each scoring domain and the global CDR. The platform increases ease of data collection and management and is transferable to other platforms, allowing its use in both research and clinical settings. The Palm-based CDR has excellent validity, reliability and high correlation with the traditional CDR and is accurate for distinguishing CDR 0 and 0.5, which is probably the most challenging distinction in practice¹⁴.

A brief informant questionnaire, referred to as 'AD8', has been developed in another attempt to avoid the time limitations of the CDR. The AD8 scores responses to eight questions. It offers a practical screening tool for the presence of dementia, with high sensitivity, specificity and face validity. However, in contrast to the CDR, it cannot be used as a staging tool for dementia¹⁵.

POTENTIAL LIMITATIONS OF THE CDR

The CDR is not without limitations, including reliance on clinical judgement and the availability of an observant collateral source, and the length of time required for administration. Although the semi-structured interview format is flexible and can be adapted to different cultures and socioeconomic groups, social, cultural and educational factors may influence some domains of the scale. Therefore, additional validation studies will be needed to establish the validity and reliability of the CDR in ethnic subpopulations¹⁶.

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GMS-HAS-AGECAT Package and the Global Mental Health Assessment Tool (GMHAT): Epidemiology and Closing the Treatment Gap

John R. M. Copeland

Division of Psychiatry, University of Liverpool, UK

For epidemiological and other studies of mental illness and morbidity in older age it is important to ensure as far as possible that the differences in the levels of cases of illness found between geographical areas and between studies at different points in time are not due to methodological differences and, in particular, the way the diagnoses themselves are made. To overcome this problem, standardized interviews were introduced. The GMS-HAS-AGECAT Package consists of a series of interviews designed to be given to a person for assessing the dementias and depression, with optional sections for minor mental illness. The Geriatric Mental State (GMS) was derived originally from the Present State Examination and the Mental Status Schedule (see the GMS Resource Centre at www.liv.ac.uk/gms). Substantial modifications and additions were incorporated to make it more applicable to older populations and to increase emphasis on organic states. The Package now provides, in addition to the GMS, which is an interview with the subject, the History and Aetiology Schedule (HAS) for an informant, which allows the assessment of onset and course of illness, past history, family history and certain risk factors for dementia, depression and other mental illness.

Standardization of diagnosis is achieved by the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) computer-assisted differential diagnosis based on an extensive decision tree method. The system aggregates the data into scores and allots each subject to levels of 'diagnostic confidence' on each of eight diagnostic syndrome clusters: organic, schizophrenia/paranoid, mania, depression (psychotic and neurotic type) (levels 0–5), obsessional, hypochondriacal, phobic and anxiety neurosis (levels 0–4). Level 3 and above are what would usually be recognized by psychiatrists as cases of illness. The computer then compares these levels with one another to derive a final diagnosis and flags cases where the decision has been difficult. The validity of the AGECAT diagnosis has been assessed against psychiatrists' diagnoses on the same patients. The range of kappa values for the agreement between AGECAT and psychiatrists' diagnoses for organic states is 0.80–0.88 and for depressive states 0.76–0.80. Outcome studies are now providing additional validation. After three years of follow-up, over 83% of AGECAT cases of organic disorder identified in the community study were either dead or still dementing. One third of

depressed cases were also depressed three years later. Postmortem studies have provided some validation of the dementia diagnosis¹.

In the second stage AGECAT uses the data from the HAS to take the diagnosis to a further stage, dividing organic states into acute or chronic, and the latter into the different types of dementia using a standardized form of the Hachinski Ischaemia Score. It also identifies bereavements and flags co-existent immobility, pain, lifelong intellectual function and physical illness.

The GMS can be used by trained lay workers and provides a diagnosis by AGECAT. When used in epidemiological studies it is possible to derive prevalence figures for the full range of psychiatric morbidity using a one-stage design. The measures are therefore economical as well as reliable and valid. The Package does not rely on special psychological tests as these are not applicable across cultures or socioeconomic groups or with populations of varying literacy. The interviews have also been transferred for presentation on laptop computer, which improves accuracy and communication, avoids delays and costs in inputting data, and provides rapid access to results and easy quality control of interviewing techniques.

These measures have been used in a number of projects, including the Medical Research Council (UK) ALPHA study of the incidence of the dementias (Liverpool, UK) and the multicentre MRC Cognitive Function and Ageing Study of six centres in the UK, the EURODEP EC-funded Concerted Action across nine European centres, the ongoing ASIADEP studies in five Asian centres, and the 10/66 Dementia Research Group (www.alz.co.uk), a collective of dementia researchers from the developing world examining the validity of dementia diagnosis in 27 centres in Latin America, Africa, India and South Asia, China and Southeast Asia, as well as forming part of the minimum dataset required by the EURODEM (EC Concerted Action on Epidemiology and Prevention of Dementia). The GMS has been translated and used in 40 different languages. The HAS has been shortened and modified to provide for the criteria of Lewy body dementia, and other recognized dementia classifications².

Of particular interest has been the question of how accurately the GMS Package diagnosed dementia among those persons with little or no education, an environment for which it was not initially developed. Findings now suggest that the GMS does tend to over-identify

organic disorder in low education groups free of dementia. However, overall the GMS appears to have performed well, and with some minor modifications when used in conjunction with the Community Screening Instrument for Dementia (CSI-D) has made an important contribution to one-stage dementia diagnosis for use in the developing world. Ongoing studies have continued to address these issues³.

A recent development has been aimed at developing a clinical tool for areas of the world where there are no or very few psychiatrists or psychiatrically trained nurses. The Global Mental Health Assessment Tool (GMHAT⁴; see www.gmhat.org) has been developed in two versions. The first is for use as a diagnostic tool in primary care for the identification and treatment of mental illness in both young adult and older populations. Taking only 15 minutes on average and only requiring brief training in its use at high school educational level, it can be employed much as a blood test or an X-ray but much more cheaply and quickly. The second or full version, for secondary care where there is no psychiatrist, is designed to be given by a psychiatric nurse trained briefly in the method. The extensive computerized diagnostic algorithms based on the AGE-CAT system have been much extended to include mental illnesses encountered in younger age groups as well as those in older people (All-AGE-CAT) and more extended treatment options. Preliminary trials have begun in the UK, the Netherlands, Ireland, India and Africa. Closing the

treatment gap particularly in low and middle income countries is now of growing concern. Achieving a reliable diagnosis and instituting treatment is the vital rate-limiting step on the road to recovery and return to work. In many parts of the world older people need to continue to work to support themselves and their families, especially in countries ravaged by HIV AIDS.

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Assessing Life Skills

Colin Depp, Veronica Cardenas, Ashley Cain and Thomas L. Patterson

Department of Psychiatry, University of California – San Diego, USA

INTRODUCTION

Particularly among older adults with mental illnesses, functional impairments play a critical role in clinical decisions, whether in determining a patient's ability to maintain residence in the community or gauging how well interventions aid patients in fulfilling life roles. The goal of mental health interventions is to restore functioning as much as possible, ideally to the individual's premorbid level of functioning, and so it follows that the measurement of functional abilities is of paramount clinical importance. By virtually any measure, the functional impact of psychiatric illness is immense and typically lifelong. Among people with schizophrenia, about two-thirds are unable to perform social roles and fewer than one-third are ever employed¹. According to the World Health Organization (WHO), depression is among the commonest causes of days of disability, among all diseases, in the developed world². Dementia due to Alzheimer's disease, which is now the sixth-leading cause of death, is also a leading cause of nursing-home placement in older adults³. In addition to the personal losses associated with functional impairment, disability associated with late-life mental illness imposes substantial monetary costs on society, such as wages lost by sufferers and their caregivers, the expense of services that compensate for functional deficits and other supportive costs.

Historically, much of the focus in psychiatry has been on quantifying and treating the symptoms of mental illness, with relatively less methodological rigour on the conceptualization and measurement of everyday functioning and skills for daily life. However, recent years have seen a rapid increase in the sophistication of approaches to measure the capacity to perform activities of daily living and in the quantification of 'real-world' outcomes that patients and providers care about. In this chapter, we will review the domains of interest and approaches to assessing daily living skills in older people with psychiatric disorders, provide a model linking the factors that contribute to functional disability and review the measurement modalities and the instruments available to measure functional outcomes in geriatric psychiatric patients.

CONSIDERATIONS IN MEASURING FUNCTIONING

Functional abilities encompass a number of life domains and there is no definitive subset of abilities under the umbrella of functional status nor a 'gold standard' defining functional independence or dependence. As a result, dozens of measures of functioning exist that cover

different life domains, with varying theoretical bases and psychometric properties. Recent initiatives, such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)⁴ (sponsored by the National Institute of Mental Health) have attempted to rectify the heterogeneity of functional measurement approaches by validating and recommending a core set of functional assessments. Other NIH initiatives, such as the Patient Reported Outcomes Measurement Information System (PROMIS)⁵, are also underway to provide a standard 'toolbox' with which researchers and clinicians can select standardized population-normed instruments to measure functioning with self-report measures.

While the process of identifying a 'core' set of functional measures is ongoing, several important dimensions must be considered in any approach. The conceptualization of functional impairments generally separates what an individual *can* do (capacity) from what an individual *does* do (actual performance). Functional capacity refers to the ability of an individual to perform a task under optimal conditions and that performance can be measured with the observational or performance-based approaches described in the latter portion of this chapter. Actual performance may be discrepant from functional capacity, as real-world performance is affected by motivation, opportunities and environmental barriers.

In addition to the distinction between capacity and actual performance, the functional consequences of an illness can be judged in a number of ways. Functional status can be assessed relative to age-adjusted norms, premorbid ability or a criterion devised by an external entity (e.g. some government agency standard). The normative basis for assessing functioning is important when interpreting scores from instruments that are generic (e.g. the Medical Outcomes Study – Short Form) and meant to be applicable to the broad population. Alternatively, functioning measures can be disease-specific, such as those focusing on severe mental illnesses (e.g. the Independent Living Skills Survey). Although these latter measures may not provide an estimate of functioning relative to healthy older adults, the items may have a lower 'floor' and thus can guide rehabilitation targets in functionally impaired people.

Another way in which functioning can be classified, typically in population-based studies, are preference-weighted approaches. These approaches use population data on preferences for states of health to create indices of disability adjusted life years (DALYs) or quality adjusted life years (QALYs), which can be compared across illnesses or treatments. For example, the Quality of Well-Being Scale uses a preference-weighted approach. Previous use of this instrument

estimates that the ‘well years’ lost to schizophrenia among middle-aged and older adults are slightly more than that experienced by ambulatory individuals with AIDS⁶.

Yet another distinction in assessing functioning involves the source of the information. Not surprisingly, ratings of functioning provided by patients, their family members and their clinicians often show inconsistencies – for example, patients with depression may overestimate their impairment, while patients with diminished insight due to dementia may believe they are fully capable when they are not. Family and clinician judgements of functioning may depend upon the degree to which they are familiar with the individual’s functioning in the community. Some indicators of functioning, such as employment status or medication adherence, may be dependent on contextual factors such as availability of social support. Furthermore, daily living skills must be assumed to fluctuate within the individual, based both on the context and on the course of the psychiatric illness and its treatment, such that any point-in-time assessment of functioning may be biased by state-level factors (e.g. mood state, fatigue).

Taking all these considerations together, it is clear that attaining reliable and accurate representations of an individual’s level of functioning presents a challenge for clinicians and researchers. The best approach typically utilizes multiple measures of functioning (e.g. performance-based, subjective ratings) in different contexts (e.g. at home and in the clinic).

WHAT ARE THE SKILLS OF DAILY LIVING?

There is no single definition of daily life skills, but the primary functional categories include activities of daily living, social role functioning, decision-making capacity and recovery. The activities of daily living (ADLs) were defined in the 1960s and a decade later they were differentiated from instrumental activities of daily living (IADLs). ADLs include toileting, dressing, transferring and other activities basic to maintaining residence in the community. IADLs are more cognitively complex and involve fine motor movements, including managing medications, using the telephone, arranging transportation, managing money and preparing meals. In the general population, impairment in ADLs and IADLs increases with age, although the overall prevalence of ADL impairment in older people seems to have declined over the past several decades⁷. Change in ADLs often corresponds to change in disease status and not infrequently triggers placement in a care facility. Typically, ADLs and IADLs are rated by an observer or clinician, but self-perceived impairment in functional tasks is also frequently evaluated. Measures of perceived ability to complete functional tasks are embedded in subjective questionnaires (e.g. ‘Are you impaired in your ability to walk one mile?’) as well as whether a disease impacts functioning (e.g. ‘Has your mental health interfered with your social activities?’). Finally, a number of approaches to the measurement of general physical function are used to assess physical fitness in older adults (e.g. grip strength, sit to stand tests), but because these are not specifically tied to daily life skills, we will not describe them here. Interested readers are referred to an excellent review on these physical functioning instruments⁸.

Social functioning is another key domain in functional assessment. Actual performance can be measured in regard to an individual’s roles in the workplace, in close relationships and in leisure activities. In geriatric populations, particularly after retirement, social roles may be less culturally prescribed than among younger adults, which makes determining the extent of social impairment more challenging. Particularly in schizophrenia as opposed to mood disorders or

dementia, social skills may be measured in standardized role-play tasks. These simulate conversations in which the participant’s performance is graded. The use of performance-based measures of social functioning is generally restricted to research.

Another context of functional status that clinicians are frequently asked to evaluate in older adults with mental health problems is decision-making capacity, particularly with regard to medical or other major life decisions. The assessment of capacity to make decisions should be specific to the context. For example, it cannot be assumed that impairment in the handling of personal finances signifies impairment in the making of medical decisions, such as the refusal of treatment. Assessing decisional capacity typically includes four components: understanding, appreciation, reasoning and expressing a choice. Understanding describes the extent to which the individual comprehends what is at stake, i.e. probable outcomes, risks and benefits. Appreciation measures how well the individual can relate the decision to his or her own situation, while reasoning measures the quality of the mental process by which the individual arrives at that decision. Finally, expressing a choice concerns whether the individual is capable and/or willing to express a decision. Research in older patients with schizophrenia or bipolar disorder using standardized measures of decisional capacity has indicated that cognitive impairments are the single greatest predictor of impairment in decisional capacity, over and above psychotic or affective symptoms. However, the manner in which the information is conveyed to the patient, particularly whether it is repeated, appears to make a significant difference in whether capacity is achieved. It cannot be assumed that the presence of a psychiatric disorder translates to a lack of capacity.

Finally, recent years have seen an emergence of a more patient-centred concept of functioning that is termed ‘recovery’. The precise definition of this term is debated, but a consensus panel formed by the US Substance Abuse and Mental Health Services Administration (SAMHSA) provided the following: ‘Mental Health recovery is a journey of healing and transformation enabling a person with a mental health problem to live a meaningful life in a community of his or her choice while striving to achieve his or her full potential’⁹. Although recovery shares a focus with the above domains on functional outcomes, greater emphasis is placed on the patient’s sense of self-efficacy and meaning. The measurement of recovery is thus more idiographic than that of the domains just described. How the construction of recovery changes, if at all, across the lifespan of people with mental illnesses has received little research.

WHAT ARE THE INFLUENCES ON DAILY LIVING SKILLS?

Many factors influence functioning and daily living skills, including illness, cultural issues, environmental contexts and age-related changes. In this section, we review the impact of these factors and provide an integrative model that combines them.

Emerging evidence in a variety of psychiatric disorders suggests that cognitive impairments are the greatest contributors to diminished functional status^{10,11}. On average, the relative influence of cognitive impairments on functioning probably increases over the course of a long-term illness. This is in part due to declines in the acuity of psychopathological symptoms for people with early-onset mental illnesses¹² and also because cognitive impairments beyond those associated with normal ageing may cross thresholds to create functional impairment. A number of studies have examined the relative

impact of cognition on functioning in older patients with mental illness and the general conclusion is that cognitive impairments supersede psychopathologic symptoms in their associations with functional deficits of older adults with schizophrenia, bipolar disorder and depression¹³. Among cognitive abilities, impairment in executive functioning, which includes planning, task switching and other higher order mental abilities, appears to be most influential on functional status. Recent research has suggested that even among older patients with depression or bipolar disorder, both cognitive impairments and functional problems appear to persist between mood episodes.

However, concurrent symptoms do appear to produce disability, particularly in subjective functioning. In addition to cognitive impairments, among older patients with schizophrenia, negative symptoms appear to be more closely associated with functional impairment than are positive symptoms. In mixed-age patients with bipolar disorder, depressive symptoms appear to be more disabling on average than manic symptoms, in part because they are, on average, more frequent and intractable. Another general trend among older adults with severe mental illnesses is that earlier age of onset is associated with greater functional impairment, likely because functional problems have had a longer time to accrue and because patients have a comparatively shorter time in which to establish life roles free of illness. Medical co-morbidities and substance abuse also appear to produce added functional impairment.

Another strong determinant of functional status and one frequently overlooked in assessment, is the patient's environment. The concept of person–environment fit¹⁴ posits that functioning is a product of individual abilities and environmental supports. In this model, the physical and social environment may support or detract from autonomous function. For example, the elimination of high curbs can enable individuals in wheelchairs to function at a level similar to those who are not wheelchair-bound. By contrast, chaotic or novel environments may overwhelm cognitive resources and exacerbate functional deficits in vulnerable older people. Some recently developed interventions for schizophrenia¹⁵ and for dementia¹⁶ emphasize environmental supports to compensate for cognitive deficits and maintain functioning.

Finally, sociocultural influences affect functioning in geriatric patients with psychiatric disorders. Culturally based expectations regarding functioning and mental illness can influence the kinds of daily tasks an older adult can accomplish. For example, older immigrants may have a language barrier or lack the means to acquire resources needed to improve functioning. Moreover, culturally diverse older adults may be accustomed to carrying out daily activities following a different set of steps or using different means from those of the dominant culture. For example, a person may not know how to refill medication by way of telephone as is often done in the United States. The person may also come from a culture with clearly defined gender roles that impede the learning of such tasks as cooking, cleaning or driving a vehicle. Culturally held beliefs about the elderly can also influence daily functioning. For example, family members may feel obligated to do things for ageing relatives to ease their burden, ensure their safety, or to express culturally appropriate reverence. This sense of duty may intensify when a psychiatric illness is involved.

INTEGRATING THE CONTRIBUTORS TO FUNCTIONAL DISABILITY: A MODEL

A number of disablement models have been developed over the past three decades. Most recently, the WHO developed what it termed a revised working disability model. This model clarified certain constructs and operationalized functioning across three levels^{17–20}: the body; the person as a whole; and the person in social contexts. While this model is useful, it lacks specificity and fails to consider a host of other factors which may influence functional capacity, such as cognitive deficits, earlier age of onset of illness, the environment in which a person lives and co-morbidities such as substance abuse.

The following conceptual model of functional capacity (see Figure 34.1), which incorporates many of the issues mentioned above, elaborates on the WHO model. Hypothetical paths between concepts are indicated by arrows. An important feature of this model is the role of mediation – i.e. causal links are implied between illness features and disability. Among older adults with

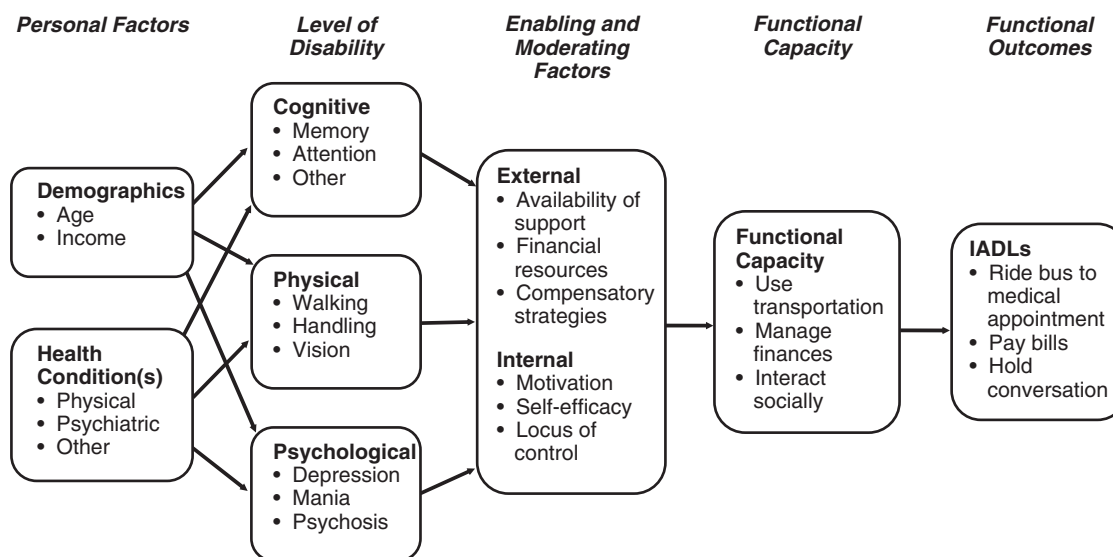


Figure 34.1 Model of functional capacity

schizophrenia, recent evidence shows that the pathway between cognitive abilities and functioning may be mediated by functional capacity. Bowie *et al.*¹⁰ examined the relationships between functional capacity data, scores on the UCSD Performance-Based Skills Assessment (UPSA), case-manager ratings of real-world functioning (covering interpersonal skills, work skills and community activities), neuropsychological test scores and symptom levels, and they constructed a path model showing that neuropsychological performance predicted functional capacity, which in turn predicted all three domains of real-world functioning. Psychiatric symptoms, specifically depression, predicted interpersonal and work skills, while negative symptoms affected interpersonal skills independently of other predictors. However, while real-world adaptive life skills were predicted by neuropsychological performance, symptoms and functional capacity, neuropsychological performance contributed little to the prediction of real-world performance after accounting for functional capacity. This study illustrates how specific paths

in our proposed model can be validated with data and the model provides a heuristic by which to organize assessment data in gauging individual functioning.

DESCRIPTIONS OF SPECIFIC MEASURES OF FUNCTIONING

As described in the introduction, many measures of functioning exist with different psychometric properties, formats and content. In considering which measure to use, it is important to recognize that all have limitations in terms of completeness, ceiling and floor effects, sensitivity to change and applicability across multiple patient groups (e.g. inpatients vs. outpatients). Measures for assessing functioning fall into four broad categories: self-reports, informant reports, clinician ratings and observational measures. Below and in Table 34.1 we have selected from among the best validated of these measures and describe the instruments in detail.

Table 34.1 An overview of specific functional instruments

<i>Measure</i>	<i>Time to administer</i>	<i>Domains assessed</i>	<i>Type of administration</i>	<i>Validity, relationship to real-world outcomes</i>
UPSA	30 minutes	Functional capacity: household chores, communication, finance, transportation and planning recreational activities	Performance-based	Predictive of one's ability to live independently in the community
UPSA-Brief	10–15 minutes	Functional capacity: finances and communication	Performance-based	Highly correlated with full UPSA
SSPA	20 minutes	Social skills	Performance-based	Excellent inter-rater reliability, good test–retest reliability; scores correlate with health-related QWB and observed performance on activities of daily living
MMAA	15 minutes	Medication management ability	Performance-based	Significantly related to prescription refill records, performance-based measures of everyday functioning and self-reported quality of life
ILSS-SR	20–30 minutes	Functional living skills (see text for full list)	Self-report	Marginal to good internal consistency, stability and inter-rater reliability; good ability to predict employability
GAF	5–15 minutes	Functional impairment secondary to mental illness	Clinician-rated	Good reliability and a valid measure of psychiatric disturbance in severely mentally ill
SF-36	5–10 minutes	Mental and physical health-related quality of life	Self-report	Good internal reliability and construct validity
QWB-SA	15 minutes	Quality adjusted life years	Self-report	Results comparable to interviewer-administered version
SAFE		Health-related quality of life Adaptive functioning; social-interpersonal, instrumental and life skills functioning	Observational	Good convergent, discriminant and predictive validity
MOSES		Levels of functioning in self-care, levels of organization, depressed and anxious mood, irritability and behavioural withdrawal	Observational	Satisfactory validity against other established measures (Zung depression, Robertson short mental status, Kingston dementia, PAMIE scales)

SELF-REPORT

Generic Measures

SF-36

The Medical Outcomes Study (MOS) 36-item short-form Health Survey (SF-36) is a self-report measure that covers eight different domains: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. These eight subscales are combined to produce two summary scores: the physical and the mental composite score²¹. An even shorter 12-item (SF-12) scale has been developed that can be completed in one or two minutes²².

QWB

The Quality of Well-Being (QWB) is a preference-based questionnaire that measures health-related quality of life. The original version was administered by an interviewer, but a self-administered version (QWB-SA) was subsequently developed to avoid some of the difficulties associated with interviewer administration. The QWB-SA consists of five sections totalling 56 items that assess acute or chronic symptoms, self-care, mobility, physical functioning and performance of everyday activities. Participants are asked to think about the past three days and indicate if they experienced the symptom or problem on the previous day, two days ago, three days ago, or some combination thereof. The QWB-SA takes approximately 15 minutes to complete²³.

Disease-Specific Measures

ILSS

The Independent Living Skills Survey (ILSS) tests basic functioning in patients with severe and persistent mental illness. There are two versions: informant-rated (ILSS-I) and self-report (ILSS-SR). The ILSS-I consists of 103 items that assess 12 areas of basic community living skills. The ILSS-SR has 70 items that cover 10 different domains: personal hygiene, appearance and care of clothing, care of personal possessions and living space, food preparation, care of personal health and safety, money management, transportation, leisure and recreational activities, job seeking and job maintenance. Participants are asked to indicate by a 'yes' or 'no' response whether they had performed a specific task in the past month. The ILSS-SR takes approximately 20 to 30 minutes to complete²⁴.

INFORMANT RATINGS

ADL

Some patients, such as in Alzheimer's disease, may not be able to complete a self-report measure. In such cases, an informant provides information on life skills. Typically, the informant is a spouse, an adult child, or a caregiver who spends at least two days a week in direct contact with the patient. The Katz activities of daily living (ADL) index is one of the more widely used informant-rated measures. Caregivers rate the patient's level of dependence on others in six different areas: bathing, dressing, toileting, transferring, continence and feeding. A zero score indicates complete independence,

while a three is complete dependence. Slightly more sensitive than the Katz is the Barthel index, which uses 10 different categories. In addition to the six categories used in the Katz, the Barthel index divides toileting into bladder and bowel control and adds walking, stair climbing and grooming. Higher scores are assigned to those with higher levels of independent functioning, for a possible total of 100 points²⁶.

IADL

The Instrumental Activities of Daily Living Scale (IADL) covers the more complex instrumental activities that are needed to live independently. The IADL evaluates ability to use a telephone, shop, prepare food, keep house, do laundry, use transportation, take medication and manage finances. Typically, women are scored on all eight domains, while for men, food preparation, housekeeping and laundering are sometimes excluded²⁷.

RIL

Another example of an informant-completed measure is the Record of Independent Living (RIL). The informant rates the patient on the categories of activities, communication and behaviour. Ratings for activities range from 0 (no change when compared to previous competence) to 4 (patient no longer performs this activity) with allowances for 'don't know' or 'not applicable.' Similarly, ratings for communication range from 0 (no difficulty) to 4 (no longer performs this function). The behaviour section consists of a checklist on which the informant indicates whether specific problem behaviours were present before the illness and whether they are currently present²⁸.

CLINICIAN-RATED

GAF

The Global Assessment of Functioning (GAF) describes a person's overall psychological, social and occupational functioning. It is used as Axis V in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition and consists of 10 'ranges of function' that total 10 points each, for an overall possible score of 100. A perfect score indicates superior functioning, while a score of less than 10 indicates 'persistent danger of severely hurting self or others, or inability to maintain minimal personal hygiene, or serious suicidal act with clear expectation of death'. The GAF co-mingles functional impairment and psychiatric symptoms and so it is not a 'pure' measure of functioning as is the ILSS²⁵.

OBSERVATION

SAFE

The Social Adaptive Functioning Evaluation (SAFE) was developed for a geriatric psychiatric inpatient population to evaluate social-interpersonal, instrumental and life-skills functioning. This 17-item scale is scored using observation, caregiver contact and interaction with the subject. These items assess self-care, social competence and adjustment and miscellaneous skills such as impulse control and cooperativeness. Items are rated on a 5-point scale with higher scores reflecting greater impairment. This scale is useful because the patient can be rated regardless of their cooperation or responses²⁹.

MOSES

The Multidimensional Observation Scale of Elderly Subjects (MOSES) is an observation-based measure that can be completed by nurses or staff at residential facilities. It consists of 40 items that measure five different areas of functioning related to life in a residential facility: self-care, levels of organization, depressed and anxious mood, irritability and behavioural withdrawal. There is also a briefer 24-item version^{30–32}.

PERFORMANCE-BASED MEASURES

UPSA

The UCSD Performance-Based Skills Assessment (UPSA) uses role-play tasks to examine five areas of everyday functioning including household chores, communication, finance, transportation and planning recreational activities. Patients are asked to plan a trip to the beach, write a cheque, read a bus route map, complete a shopping list and call a doctor to reschedule an appointment. It typically takes about 30 minutes to administer and includes several props such as grocery items, maps and a telephone. The UPSA has shown excellent reliability as well as strong convergent validity and good criterion validity with real-world outcome measures³³. Also available is the UPSA-Brief, which includes only the communication and finances sections of the original UPSA. The UPSA-Brief and UPSA show high levels of convergence in predicting real-world functional outcomes.

MMAA

The Medication Management Ability Assessment (MMAA) also uses role-playing tasks, specifically focused on assessing a patient's ability to manage a moderately complex prescription medication regimen similar to one an older adult might typically encounter. The interviewer shows the patient four standard prescription pill bottles with mock labels and filled with differently coloured dried beans. The labels read: Parlenol: Take 2 tablets twice a day with food; BRB: Take 1 tablet 3 times per day; Cyclomeovan: Take 2 tablets three times a day on an empty stomach (i.e. at least 1 hour before or 2 hours after a meal); and Linophen: Take 2 tablets 4 times a day. The interviewer then removes the bottles and an hour later the interviewer asks the participant to 'walk' verbally through his or her day, handing the interviewer the appropriate type and number of pills at the appropriate times. Scores are based on the total number of correct responses for a possible total of 25 points. The number of pills over and under the prescribed amount is also scored. The MMAA has excellent test-retest reliability and good construct validity, with scores significantly correlated with two other performance-based measures of functionality³⁴.

SSPA

The Social Skills Performance Assessment (SSPA) is designed to measure everyday social skills. This performance-based measure consists of two role-playing tasks, each lasting three minutes. In the first task, the interviewer plays a new neighbour and the participant's goal is to initiate an acquaintance with the new neighbour in a 'friendly and informative manner'. In the second task, the participant plays a tenant who must contact his or her landlord (played by

the interviewer) to discuss a leak that needs to be repaired immediately. Each scenario is scored from 1 (low) to 5 (high) on various factors including: interest/disinterest, fluency, clarity, focus, affect, grooming, social appropriateness, overall conversation, negotiation ability, submission/persistence and overall argument. The entire measure takes about 20 minutes to administer³⁵.

SUMMARY

We have described a general approach to assessing life skills in older people with psychiatric disorders, an integrative model linking the determinants of functioning with each other and specific instruments that cover multiple modalities. The best approach to measuring functioning integrates multiple assessments modalities in different contexts and uses both subjective and objective data obtained from the patient, family or other proxy informants and direct observation. The use of instruments validated in geriatric populations, such as the ones we have described, will increase the reliability and interpretability of assessment. As the focus of psychiatric care shifts from symptoms to broader functional outcomes and recovery, expanding the evidence base for functional assessments will become all the more important.

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Quality of Life Measures in Old Age

Juanita Hoe, Martin Orrell and Gill Livingston

Department of Mental Health Sciences, University College London, UK

INTRODUCTION

The maintenance of physical and cognitive functioning and the avoidance of disease are associated with well-being and quality of life (QoL) in old age, as poor health can lead to loss of control, autonomy and independence^{1,2}. Traditionally, outcomes of treatment have been evaluated in terms of mortality or symptoms, but a more important outcome measure may be the patient's perspective, as symptoms may improve in one area while overall quality of life decreases because of the negative effects of treatment³. The emergence of QoL as a fundamental measure for evaluating and monitoring health outcomes in old age is attributed to the ethical and economic concerns associated with the ageing population and the concomitant increase in chronic illness and disability. Birren and Dieckmann⁴ identify three main areas of concern associated with this increase: (i) the impact on health service resources and the potential financial burden anticipated; (ii) the intrusive use of medical technologies; and (iii) the QoL for people in institutions. In chronic illness, people can suffer from both the disability and the treatment⁵. Moreover, treatment can often result in limited gains in terms of survival, or absence of cure, which changes the balance as to acceptable side effects. Aggressive interventions may have therapeutic benefits that are overshadowed by the negative effects, thus leading to reduced QoL overall. Any detrimental impact on QoL needs to be weighed against the advantages offered through treatment⁶. It is the individual's perception that predicts whether they seek help, accept treatment or regard themselves to be well and recovered, and therefore, should be part of any outcome measures⁷. Thus, subjective health measures can be used to help provide a fuller picture of the individual's health state.

THE MEANING OF QoL

The term quality of life is used frequently in everyday life, with most people assuming they know what it means without considering how to define or measure it. In terms of health, QoL has become a popular, broadly used expression that is frequently taken for granted without the meaning being clear. There is debate about the true definition and meaning of QoL, particularly whether ratings should be objective or subjective, what criteria should be used and what is actually being measured, 'the quality of an individual's life, state of life, or the meaning of life in general'⁸. QoL is argued to be less related to basic needs than to individual expectations and experiences of life, which include individual perceptions of well-being,

happiness, goodness and satisfaction with various aspects of their lives and environment^{9–11}. What is apparent is that QoL is a multi-dimensional concept 'just as is life itself'¹². A wide range of domains is suggested for inclusion as QoL indicators, including physical and mental health, intellectual and emotional function, social and role function, activities of daily living, economic aspects, and job and life satisfaction^{13–15}. The expression QoL may also overlap with the terms 'health status' and 'functional status', and have been considered interchangeable¹⁶. Perceptions of well-being may, however, be influenced by psychological factors unrelated to health or function¹⁷.

DEFINITIONS AND CONCEPTUALIZATIONS OF QoL

There are several meanings of the term QoL, which remains a vague, elusive concept for which there is no single widely accepted definition. The definitions provided are broad and varied; indeed, there may be as many QoL definitions as there are people¹⁸. QoL is viewed as 'a concept which incorporates all aspects of an individual's existence'¹⁹ and as 'an abstraction which integrates and summarizes all those features of our lives that we find more or less desirable and satisfying'²⁰. The inclusion of the terms life satisfaction, morale and happiness are debated but may be considered to be transient states which should be distinguished from QoL as they differ in their degree of subjectivity²¹. Alternatively, life satisfaction, self-esteem and physical health are argued to be key dimensions of QoL²². Lawton²³ defines QoL as 'the multidimensional evaluation, by both intrapersonal and social-normative criteria, of the person–environment system of an individual in time past, current and anticipated' and hypothesizes four dimensions of QoL: behavioural competence, perceived QoL, objective environment, and psychological well-being. Each sector is intrinsic and considered core to the concept of QoL and also interlinked. Fundamentally, QoL is perceived as being continuous and dynamic in nature and may be evaluated negatively or positively depending on the individual's own internal perceptions and response to their environment.

HEALTH-RELATED QoL

Within the context of health, QoL is defined as a reflection of patients' perception and response to their health status and to other non-medical aspects that have an impact on patients' lives, and within health-related quality of life (HRQoL) this includes physical,

psychological and social perspectives^{24,25}. This definition is in keeping with that given by the World Health Organization Quality of Life Group (WHOQOL), as ‘the individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns’²⁶. This broad description encompasses the complex nature of the person’s physical, psychological and social well-being in relation to their environment. The recognition of cultural factors is particularly important when considering the QoL of the ageing population and especially those people with dementia. Memory impairment is not regarded as so important in all cultures²⁷. Similarly, functional disability may seem less important in cultural contexts where independence and autonomy in activities of daily living are a less central part of the older person’s role²⁸. Older people are frequently marginalized as society holds a negative view of their QoL, and health and social research tends to focus on decline and disability²⁹. There are, however, both positive and negative elements that impact on an older person’s QoL, and Hughes³⁰ identifies the key domains that should be evaluated when measuring older people’s QoL. These include physical environment, social environment, socioeconomic, cultural and health status, personality and personal autonomy factors.

MEASURING QoL IN HEALTH

Lerner³¹ argues that ‘health is more than just a biomedical phenomenon; it involves a social human-being functioning in a social environment with social roles they need to fulfil’. The use of QoL as an outcome measure focuses the impact of the patient’s condition and treatment on their emotional and physical functioning and lifestyle³. Hence, health-related QoL has become important in measuring the impact of chronic disease¹⁶. This is of particular significance as patients with the same clinical symptoms often differ in their evaluation of what the illness means to their life. The term ‘disability paradox’ is used to describe how patients with significant health and functional problems frequently have high QoL scores despite their health status³². QoL measures can be used to evaluate human and financial costs-benefits of interventions and care provided through assessing change in physical, functional, mental and social health³³.

Calman³⁴ suggests that people perceive QoL in relationship to their past experiences, current lifestyle, hopes and ambitions for the future. QoL measures the gap between the individual’s present experience and their expectations for the future. QoL can therefore be improved by narrowing this gap, either by improving experience or lowering expectations³⁴. Importantly, the model recognizes the highly individual nature of QoL and the influence of culture and past experience³⁵. Carr *et al.*³⁶ further propose a model of the relation between expectations and experience and identify three areas of difficulty in measuring QoL: people have different expectations; people are at different stages of their illness when QoL is measured; and expectations may change over time. By providing health education, information and increasing awareness of risks, patients are helped to adapt to their disability through changing their health expectations. The impact of the disability on their QoL may thus be reduced³⁶.

SUBJECTIVE AND OBJECTIVE DIMENSIONS OF QoL

Testa and Simonson³³ recommend that measures of QoL should cover the objective and subjective components important to the relevant patient group that may be affected positively or negatively

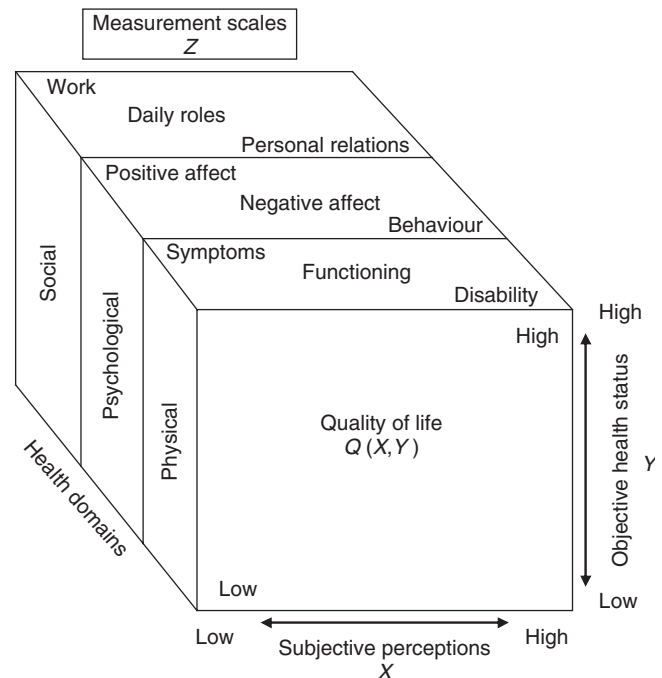


Figure 35.1 Conceptual scheme of the domains and variables involved in a QoL assessment

Source: Reproduced with permission from Testa & Simonson (1996), *New England Journal of Medicine*, 334: 834–840. Copyright ©1996 Massachusetts Medical Society. All rights reserved.

by interventions. Objective factors are primarily needs based and incorporate basic needs that determine people’s well-being in society, such as environment and material resources, including levels of income, crime, pollution, transport, housing type, access to amenities and employment^{2,37}. Subjective factors include life satisfaction and psychological well-being, morale, individual fulfilment, happiness and self-esteem, and are expressed in terms of satisfaction, values and perceptions of individual life circumstances¹. While health status is defined through the objective components, QoL is determined through subjective perception and expectations (Figure 35.1)³³. The subjective perceptions thus translate that objective assessment into the actual QoL experienced³³. Nevertheless, Bowling³ cautions that subjective measures are not designed to be used as substitutes for traditional measures of clinical endpoints but to complement existing measures and provide a fuller picture of health state.

Variation among QoL scales is often due to the different emphasis placed on objective and subjective dimensions, which domains are covered and the question format rather than differences in how QoL is defined³³. The overall satisfaction an individual has with life is argued to be the most important domain of QoL^{2,38}. This means the importance of the individual’s personal sense of satisfaction with various areas of life is recognized; these include physical comfort, emotional well-being and interpersonal connections³⁸.

VALIDITY AND RELIABILITY

QoL scales should be able to demonstrate validity but this is complicated as there is no measure of criterion validity: no scale can provide a full picture of people’s life quality or be relevant to all

individuals^{33,39,40}. Content validity includes evaluation in terms of the applicability of the questionnaire and its comprehensiveness, as well as its clarity, simplicity and likelihood of bias⁴¹. Scales should also have predictive validity, sensitivity and be responsive to change in QoL, particularly for clinically important changes^{3,33,42,43}. This ensures the areas relevant to the patient's QoL are measured and that scales are responsive to the different stages of the disease and interventions or treatment given. Orley *et al.*⁴⁴ argue that QoL is influenced by a broad range of facets and is therefore unlikely to alter markedly from day to day. Fallowfield⁴⁵ recommends that QoL measures should discriminate between patient groups and identify those patients experiencing good QoL and those who are not. In addition, QoL measures used in clinical practice must be appropriate and acceptable for their intended use and the results meaningful and amenable to clinical interpretation⁴³.

GENERIC VERSUS DISEASE-SPECIFIC MEASURES OF QoL

Generic as opposed to disease-specific instruments offer broader measures of health status and are useful for making comparisons with other conditions, while disease-specific instruments are used for assessing disease-related attributes when greater sensitivity to specific aspects of the clinical condition is required^{3,33}. Generic measures include single indicators, health profiles and utility measures. Health profiles attempt to measure all aspects of health-related QoL potentially affected by a condition or its treatment. Thus generic instruments tend to be lengthy to ensure sensitivity and adequate psychometric properties³. They can be applied irrespective of the underlying condition but may be unresponsive to changes in specific conditions. Disease-specific instruments aim to have greater discrimination between severity levels of a particular disease and thus have increased sensitivity to clinical outcomes⁴⁴. They are more concise and should be able to reflect clinically significant change in health status or disease severity. Therefore in order to detect significant clinical changes, generic measures may need to be supplemented with disease-specific measures¹⁶, particularly for evaluating therapeutic interventions within clinical trials³³. The use of disease-specific measures may, however, be limited as their narrow focus may not assess the impact of disease or interventions upon wider aspects of life, which could disadvantage arguments for additional resources^{24,46}.

Essentially the use of both generic and disease-specific measures is recommended to ensure assessment of both disease-specific and wider aspects of life and to detect positive or negative impacts of interventions^{3,16,24}.

METHODS OF QoL MEASUREMENT

Self-Assessment Scales

The use of visual analogue scales is a common method for measuring subjective experiences such as QoL⁴⁷. They are, however, time consuming to complete and may not be relevant to the experience being considered⁴⁵. Self-reports are obtained using standardized measures that have response formats with closed questions in a categorical dichotomous format (e.g. yes/no) or sequences of categorized responses (e.g. strongly agree, agree, disagree, strongly disagree). Standardized measures have fixed questions and a range of answers; Carr and Higginson³² caution that these may not measure patients' QoL unless scores are weighted for the individual patient.

Individual weightings are important for obtaining a true assessment of QoL and being responsive to change. Scores may be calculated for each domain separately or combined to provide a composite or index score of overall life satisfaction. The disadvantage of scales that are calculated to produce an overall score is that the total may result from several combinations of responses, thus leading to a loss of information about the individual components of the scale⁴⁸. Muldoon *et al.*¹⁷ and Lawton⁴⁹ both argue that the use of a composite score fails to recognize QoL measures as being multidimensional and that it is illogical to aggregate scores that combine appraisals of objective measures of behaviour, function and subjective well-being; and there is a need to evaluate individual domains separately within research and clinical practice^{12,30,49}. Alternatively, Gill and Feinstein²⁵ advocate the use of a global rating through aggregating the scores of individual QoL domains as this explains QoL more comprehensively, and they encourage more explicit criteria or weighting of the different components that construct QoL. Furthermore global ratings have been considered more acceptable for use in clinical trials as change in QoL could be more easily distinguished.

Direct Observation

Where self-ratings of QoL are difficult to elicit, such as in dementia, observational ratings may be of more benefit^{50–52}. Observational methods are undertaken either through direct observation of the person with dementia, which records the frequency at which certain behaviours present, or by applying attribute ratings of observed affect states over time. Direct observation is time consuming and costly but, it has been argued, provides the most objective method of rating QoL in dementia as the subjective component is removed^{49,53}. Observation requires a degree of interpretation by the rater and training to reduce any influence on the behaviour observed. In addition, multiple observations of the same individual are needed to achieve a consistent result and cannot be limited to the 'working day' of the observer⁵⁴. Observational tools have, however, been devised that can be used to reliably measure health-related QoL and well-being in people with dementia^{55,56}, with Dementia Care Mapping⁵⁶ being increasingly used to assess the well-being of people with dementia in care settings. Well-being scores were found to be closely associated with QoL⁵⁷.

Proxy Ratings

Proxy ratings involve a judgement of the person's QoL being made by another person to whom they are known and may be provided by a paid or family caregiver. Proxy reports may be the only source of information available, particularly for those people with the most severe levels of cognitive impairment⁵⁸. Proxy ratings have been shown to be a reliable and valid indicator of patient QoL^{59,60}. Nevertheless, proxies impose their own judgement, and in dementia these are thought to be influenced by feelings of caregiver burden and depression as well as by how the person with dementia is feeling^{59,61}. Moreover, QoL is consistently rated lower by caregivers than by patients with mild to moderate dementia^{62–66}. While proxy ratings may be considered necessary where cognitive impairment exists, the inclusion of the individual's own rating of QoL is the preferred method for assessment, as QoL ultimately reflects the experience of the person with the disease^{67,68}.

Utility Assessments (Cost-Effectiveness)

Utility measures of QoL originate from economic and decision theory and are devised to reflect the health status and value of that health status to a patient¹⁶, to assess cost-effectiveness in health care. When applying utility measures, values are placed on different health states, and the preference of a particular health outcome is determined through calculating a single summary score³. A common utility measure is quality adjusted life years (QALY), which are used as indicators of health gain for health service resource allocation. QALYs integrate two concepts, life expectancy and life quality, that offer a mathematical outcome for rationing the allocation of health service resources⁸. Although offering a utilitarian argument for determining the greatest health gain for the greatest number, QALYs are criticized as being ageist and for focusing on cure rather than care and their use marginalizes the most disabled, elderly and chronically ill⁴⁸. Older people have a shorter life expectancy in comparison to younger people. A further criticism of using QALYs is that the 'disability paradox', where QoL scores do not appear commensurate with the patient's health status, prevents direct comparisons of different patient groups for allocating resources⁴³. There are, however, other measures of cost-effectiveness that consider the cost per unit of health gain and do not involve years. Cost-utility ratios are being calculated in some trials in dementia using utility scores computed from the EQ-5D and societal weights. The National Institute for

Health and Clinical Excellence (NICE) now uses cost-effectiveness in consideration of all interventions in the UK⁶⁹.

MEASURING QoL IN OLDER AGE

Early studies identify retirement, bereavement, loneliness and isolation as important influences on older people's lives⁷⁰, whereas, more recent studies found that older people define good QoL as family, social contacts, health, mobility/ability, material circumstances, activities, happiness, youthfulness and living environment⁷¹. Hyde *et al.*⁷² argue that the improved health and financial status of older people means the lives of older people have changed over recent decades, with increased healthy life expectancy and access to personal incomes, such as private pensions, share dividends and rent. The QoL of people entering old age who are younger, healthier and wealthier will differ from those much older people who are more likely to experience chronic and degenerative ill health or require palliative care. Not all older people can be assumed to suffer poor QoL and while health status is an essential component of QoL, it cannot be used as a proxy for QoL in older age⁷². Individual perceptions are therefore essential in assessing health-related QoL in people of all age groups. Magaziner⁷³ reported that a fifth of older adults living in the community and half of those living in institutions are reluctant or unable to be interviewed. In contrast, Livingston *et al.*⁷⁴ administered the Index of Health-Related Quality of Life (IHQL)⁷⁵

Table 35.1 Generic quality of life instruments for use with older people

<i>QoL measure</i>	<i>Target population</i>	<i>Respondent</i>	<i>Item no.</i>	<i>Domains</i>	<i>Single score</i>	<i>Time taken</i>
EQ-5D EuroQoL Group ⁹⁶	General	Self-report	5	Mobility Self-care Usual activities Pain/discomfort Anxiety/depression	Yes	5 mins
SF-12 Ware <i>et al.</i> ⁷⁸	General	Self-report	12–36	Physical functioning Role – physical Bodily pain General health Vitality Social functioning Role – emotional Mental health Health transition	Yes	10 mins
HSQ – 12 item Radosevich and Pruitt ⁷⁷	General	Self-report	12–39	Physical functioning Role – physical Bodily pain Health perception Energy/fatigue Social functioning Role – mental Mental health	Yes	10 mins
CASP-19 Hyde <i>et al.</i> ⁷²	Early old age	Self-report	19	Control Autonomy Self-realization Pleasure	No	Not specified

Table 35.2 Dementia-specific quality of life instruments

<i>QoL measure</i>	<i>Target population</i>	<i>Respondent</i>	<i>Item. no.</i>	<i>Domains</i>	<i>Single score</i>	<i>Time taken</i>
ADRQL Rabins <i>et al.</i> ⁸⁸	Mild/moderate and severe dementia	Caregiver – proxy Formal and informal	47	Social interaction Awareness of self Feeling and mood Enjoyment of activities Response to surroundings	Yes	Not specified
DQOL Brod <i>et al.</i> ⁵¹	Mild/moderate dementia MMSE ≥ 12	Self-report	29	Self-esteem Positive affect Negative affect Feeling of belonging Sense of aesthetics	No	15–20 mins
QOL-AD Logsdon <i>et al.</i> ⁶¹	Mild/moderate dementia Severe dementia MMSE ≥ 3	Self-report+ Caregiver – proxy	13	Physical health Mental health Personal relationships Finances Overall life quality	Yes	10 mins
C-BS Ready <i>et al.</i> ¹⁰⁰	MCI Mild/moderate dementia MMSE ≥ 9	Self-report Caregiver – proxy	19	Negative affectivity Positive affectivity Self-esteem Physical complaints Satisfactions	Yes	15 mins
DEMQOL Smith <i>et al.</i> ⁹⁹	Mild/moderate dementia MMSE ≥ 10	Self-report	28	Health Well-being Cognitive functioning Social relationships Self-concept	Yes	Not specified

to a community sample of 782 older people aged 65 years and older. Their study found that three quarters of the respondents were able to complete the IHQL and the other measures used; interestingly, this included those people with dementia. Those experiencing somatic symptoms or subjective memory impairment were less likely to complete the questionnaires. They found that the scale was not valid in older people. Pettit *et al.*⁷⁶ administered the 12-item Health Status Questionnaire (HSQ-12)⁷⁷ or the 12-item Short Form Health Survey (SF-12)⁷⁸ to a community sample of 1085 older people over 65 years of age. They found that both Health-Related QoL measures were acceptable and valid for use within this population. Completion rates were lower in those people with dementia and the SF-12 was found not to distinguish between people with and without dementia. It is clear, therefore, that most older people and those experiencing dementia are able to complete instruments assessing their own QoL.

MEASURING QoL IN MENTAL ILLNESS

Orley *et al.*⁴⁴ discuss the use of QoL measures in psychiatric patients and consider how QoL ratings may be affected by the impact of the disorder through disturbed affect or thinking and through institutionalization. While psychiatric symptoms such as depression may affect a person's QoL, they do not distort it or make their perceptions invalid. In addition, while institutionalization may mean psychiatric patients perceive a good QoL due to lowered expectations, their assessments are still valid. Proxy ratings for patients with cognitive

impairment may be useful for planning and evaluating care, but they should not be taken as a measure of perceived QoL⁴⁴.

MEASURING QoL IN DEMENTIA

The nature of dementia, which affects cognition and communication, means assessing QoL in dementia offers a unique challenge. The progression of dementia is non-linear; dementia has multiple causes and outcomes and is a complex disorder when compared with other health states⁴⁶. Difficulties are routinely assumed in people with dementia providing subjective assessments of their QoL or care, owing to limitations with comprehension and reliability⁷⁹. Providing an answer does not mean that the question is necessarily understood, and QoL may also be perceived differently as the disease progresses⁸⁰. However, it is logical to assume that people with dementia will have likes and dislikes⁵⁵. Even in the most severe dementia it is possible to display preferences and aversions through emotional expression. Lawton⁴⁹ reasons that although subjective measures demand a degree of cognitive skill, people with dementia can provide reliable assessments of their mood and QoL. The patient's subjective ratings of QoL are suggested as the gold standard for measuring QoL.

Several studies have now shown that QoL can be reliably measured in people with mild, moderate and severe dementia using self-rating QoL scales^{51,61,81,82}. However, there are differences in QoL ratings as given by caregiver proxies and those given by the person with dementia^{62,83–86}. Clinicians should be aware that proxy ratings do

not necessarily replicate the QoL views of the person with dementia, and should not be substituted for self-ratings.

Few studies have employed QoL as an outcome measure for interventions in dementia and at present the evidence is not consistent, possibly due to the variety of measures used. Studies have indicated both an increase and a decrease in QoL as dementia advances^{65,87,88}. Some studies that have identified cognition and dementia severity as a predictor of QoL in dementia^{59,89} were based on caregiver proxy ratings of the person, although more recent studies found caregiver proxy ratings of QoL were strongly associated with depression, disability, and neuropsychiatric symptoms of the person with dementia^{64,83,84,90,91}. Depressive symptoms have most consistently been identified as a predictor of lower QoL in dementia^{59,62–64,66,81–84}. A review of recent studies of QoL in dementia found that depression was most strongly associated with lower QoL in dementia, but found no consistent association between lower QoL and sociodemographic factors or a decline in cognition and functional ability⁹².



By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

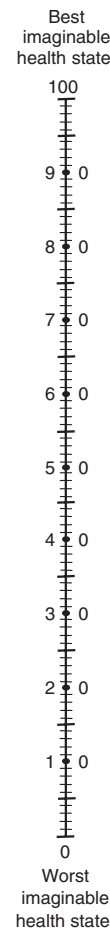


Figure 35.2 (continued)

CHOOSING A QoL MEASURE

There are a broad range of QoL scales that may be used for people with psychiatric disorder^{3,93} and for older people^{42,94}. The evidence for the validity, reliability and acceptability of generic QoL scales with older people is mixed, although their use is encouraged within research and clinical practice to promote evidence-based health care^{1,42,74,94,95}. Table 35.1 gives some examples of generic scales^{72,77,78,96} that have been used in studies involving older people with mental health needs^{76,97,98}. Haywood *et al.*'s^{42,94} review of QoL measures in old age found the SF-36 showed the best reliability and recommended its use where a comprehensive assessment of health is required in older people. Alternatively, the EQ-5D⁹⁶ (Figure 35.2) is recommended where a briefer assessment is needed and significant changes in health are anticipated^{42,94}.

Table 35.2 gives examples of disease-specific QoL scales in dementia^{51,61,88,99,100}. Each of the disease-specific QoL scales has been included in previous literature reviews examining the validity and reliability of QoL scales in dementia and their use is supported^{68,80,101–105}. The QOL-AD⁶¹ (Figure 35.3) is the preferred measure of choice, as it is brief and has demonstrated sensitivity to psychosocial interventions¹⁰¹. However, none of the reviews conclusively identifies a QoL scale for use with people with dementia, and Schölzel-Dorenbos *et al.*¹⁰² state that no QoL scale can be used across all stages of dementia.

Figure 35.2 EuroQol (EQ-5D) UK English version
Source: Reproduced from the EQ-5D User Guide, Version 1, November 2007 by permission of the EuroQol Foundation

ID Number	Assessment Number	Interview Date
Instructions: Interviewer administer according to standard instructions. Circle your responses.		
1. Physical health	Poor	Fair Good Excellent
2. Energy	Poor	Fair Good Excellent
3. Mood	Poor	Fair Good Excellent
4. Living situation	Poor	Fair Good Excellent
5. Memory	Poor	Fair Good Excellent
6. Family	Poor	Fair Good Excellent
7. Marriage	Poor	Fair Good Excellent
8. Friends	Poor	Fair Good Excellent
9. Self as a whole	Poor	Fair Good Excellent
10. Ability to do chores around the house	Poor	Fair Good Excellent
11. Ability to do things for fun	Poor	Fair Good Excellent
12. Money	Poor	Fair Good Excellent
13. Life as a whole	Poor	Fair Good Excellent
Total		
Comments:		

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Logsdon@u.washington.edu

Figure 35.3 Quality of life in Alzheimer's disease (QOL-AD) (participant version)

Source: Reproduced from Logsdon *et al.* (2002), *Psychosom. Med.* Appendix 1, with permission

Overall, QoL measures should be brief, easy to use, valid and reliable, sensitive to change and useful for both clinical and research settings. In dementia these should where possible include both patient and proxy ratings. It is also possible to generate QALYs from the scores of some QoL scales such as the SF-12, EQ-5D and DEMQOL, to provide an economic evaluation.

CONCLUSION

Within health, HRQoL provides a global measure of well-being in patients and is an appropriate outcome measure for the assessment of disease impact and interventions provided to older people. Moreover, in chronic and disabling disorders where symptomatic and functional recovery is unrealistic, improving quality of life is a particularly worthwhile outcome. QoL is now an established outcome measure for older people and should be routinely included within studies evaluating the effectiveness of care and treatment. Further evidence is needed to show how interventions influence QoL provided to older people with mental health needs. The research undertaken in recent years has established the validity and reliability of a number of QoL measures for use with older people, particularly within dementia. Where possible the individual's perceptions should be sought in preference to the views of others, and this may offer a challenge to health professionals working with older people experiencing increasing physical and mental frailty.

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Degenerative and Related Disorders

Delirium

Barbara Kamholz

Department of Psychiatry, Duke University, USA

INTRODUCTION

Delirium is prevalent, dangerous and costly. It is caused by medical or surgical problems and medication burdens that are beyond the physiological tolerance of the patient. Delirium costs between \$38 and \$152 bn per year¹. In ICUs, episodes of delirium average 39% higher ICU costs and 31% higher hospital costs². Long considered a reversible epiphenomenon of hospital care, delirium is an independent risk factor for death and dementia³ and it contributes heavily to lengths of stay, in-hospital complications, and new institutionalization. Deliriums that are more severe or persistent have even more dire outcomes²: 22–76% of hospitalized inpatients with delirium die⁴. Delirium occurs in 15–60% of nursing home patients, 14–56% of inpatients and up to 60–80% of ICU patients⁵. Yet delirium can be prevented or mitigated in health care settings that understand it, diagnose it and implement interdisciplinary programmes across the health care spectrum to address it, and there is considerable economic potential in doing so. Progress in the field has been seriously hampered by difficulties with diagnosis; up to 95% of cases are missed⁶.

PRESENTATIONS, PHENOMENOLOGY AND IDENTIFICATION OF DELIRIUM

Delirium is misdiagnosed in all settings, including emergency rooms, hospitals, and long term and palliative care settings. The clinical presentation of delirium remains a 'black box'; as of this time we have no explanations for the variations in behavioural, affective, sensory and motor signs of delirium. These signs can change within seconds or hours, and most likely reflect the complex underlying pathophysiology. The DSM IV-TR diagnostic criteria are shown in Table 36.1⁷.

Many rating scales have been developed to assist with the diagnosis, the most widely used including the CAM⁸ and CAM-ICU⁹. Inattention and the broad fluctuations of symptoms are characteristics not found in other psychiatric illnesses. At the same time, they are the most difficult to measure and identify. Attention is a complex phenomenon that involves distractibility, vigilance and concentration, and is our most basic interface with the environment. Unless patients are grossly agitated and irrational, the clinical expression of inattention can be very subtle. It is easily mistaken for the withdrawal and lack of environmental engagement found in depression. Fluctuations, unless they are marked, are often written off as fatigue, uncooperativeness, withdrawal, differing responses to different health

practitioners, or reactions to procedures. Given changeovers of physicians and nurses in busy hospitals, such indefinite characteristics go largely unrecognized unless staff nursing notes are carefully mined for evidence of these subtle changes. Nurses are the first to recognize early symptoms of delirium, although they do not reliably diagnose it as such, and are a rich source of descriptive information that can greatly assist with diagnosis¹⁰.

Broadly accepted subcategories include 'active', 'mixed', and 'quiet' delirium. These subcategories may have implications for prognosis or pathophysiology. Significant investigation of these subtypes has been done, although these have not yet provided clear implications for causality, prognosis or intervention. Active delirium is defined as a state marked by agitation, physically aggressive and often violent activity, hyperattentiveness (the inability to suppress responses to the environment or to internal states) and emotional lability. In this condition, deficits in focused attention and fluctuations of presentation are easily identified. Quiet delirium is defined as a state marked by withdrawal, lack of involvement in or communication with the environment, bland or flat affect, and a depressed level of consciousness short of frank stupor. These symptoms reflect an inability to attend appropriately and in sequential fashion to the demands of the environment. Mixed deliriums are considered to be a combination of the two. The prevalence of these subtypes is variably reported but averages 25% for quiet delirium, 45% for mixed delirium, and 30% for active delirium. All subtypes of delirium can present with motor symptoms (dysarthria, difficulty swallowing, gait disturbances), affective symptoms (dysphoria, lability, anxiety), sensory difficulties that are associated with incorrect cerebral processing of sensory data (clinically expressed as difficulties with hearing, appreciation of pain), and illusory phenomena, aphasia (partial or global) and impaired cognitive function (dysexecutive function, disorientation, nonsensical speech). Any of these symptoms may fluctuate, even within seconds. The appreciation and reporting of pain by the delirious patient is particularly problematic, as untreated pain can worsen delirium, yet overtreatment with narcotic agents can have the same result. Psychotic-like symptoms such as disorganized speech and visual hallucinations may also be associated, although the hallucinations in delirium are more illusory than hallucinatory. They commonly involve nonsensical images such as 'clowns on bicycles' or 'tires in the ceiling'. The differentiation of delirium from prominent psychotic illnesses, including schizophrenia, schizoaffective disorder and bipolar disorder, can be problematic. Pre-existing psychiatric diagnoses are a principal cause of poor identification of

Table 36.1 DSM-IV-TR diagnostic criteria for delirium

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- A. Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
 - B. A change in cognition (e.g. memory deficit, disorientation, language disturbance) or
 - C. Development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.
 - D. Disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
 - E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.
-

delirium, as the patients' symptoms are often attributed to them¹¹. In these cases, reliance on clues from the patient's clinical history is critical. Quietly delirious patients are frequently misidentified as depressed. Farrell and Ganzini¹² found that 42% of patients referred to psychiatry consultation services for depression were actually delirious. However, an additional finding was that 60% of patients with delirium have symptoms of dysphoria, and 52% have passive or active thoughts of suicide. Acutely 'suicidal' patients suffering with prolonged hospitalizations and multiple medical problems are prototypically confusing. In such cases, the burden of risk and need for immediate medical intervention rest with delirium rather than depression.

A further consideration is that symptoms of delirium present along a spectrum. Evidence for the existence of subsyndromal delirium has been presented by Levkoff *et al.*, among others¹³. Marcantonio *et al.* found that patients with subsyndromal delirium had worse outcomes than patients with diagnosable mild delirium¹⁴.

The recognition of delirium remains one of the most prominent problems in the field. The term 'recognition' includes not just diagnosis of the medical condition of delirium, but also the recognition that it is a severe illness that cannot be assumed to resolve on its own with few sequelae. Recent appreciation of this has led to skyrocketing numbers of publications in the field in recent years¹⁵.

THE ETIOLOGY OF DELIRIUM

Population at Risk

A multitude of risk factors have been identified in treatment studies of delirium, often with little overlap. However, most would agree that age, cognitive impairment, medication and medical burden define the characteristics of the population at highest risk². Efforts to advance the field by seeking universal 'causes' of delirium have therefore been very frustrating. It is easiest to conceptualize the aetiology of delirium from the perspective of the syndrome of frailty. Frailty has many definitions, but on a physiological level its most commonly accepted conceptualization is sarcopaenia, or progressive deterioration of skeletal muscle¹⁶. It is usually found in patients who are older, cognitively impaired and medically ill, and in fact the majority of patients who develop delirium are frail. Some investigators provide a broader view of the components of frailty by including socioeconomic stressors, psychiatric disorders, medication and

home environment as well as medical vulnerabilities, which reference the broad network of resources that frail geriatric patients require to avoid catastrophic illness¹⁷. The increased vulnerability of frail patients to the catastrophic decline represented by delirium is related to their limited physiological reserve. With ageing, there is diminution of redundant systems such as neurons and neuronal circuits in the brain and excess metabolic capacity in the liver and kidney. Patients with the least reserve are more susceptible to any stressor, however small, than healthier individuals, in a striking resemblance to chemical equations far from equilibrium. The implication is that the patient's underlying vulnerability and disequibrated status (as opposed to any specific 'last minute' precipitating causes), are the most important predictors of delirium in an individual person. It is then easy to conclude that the prominent precipitating causes of delirium are the most common complications, including iatrogenic ones, found in hospitalized patients. A short list includes hyponatraemia, acute blood loss, pain, acute renal failure, fractures, acute infections (urinary tract or pulmonary), the use of longer term indwelling bladder catheters, dehydration, decubiti, malnutrition and the use of psychotropic medications².

Pathophysiology of Delirium

Historically, multiple interacting theories have been proposed to explain the pathophysiology of delirium. Any given delirium may have an unknown number of associated clinical conditions (baseline and precipitating factors), and they do not necessarily occur in the same combinations. It is only when the patient has recovered that there is any clinical certainty that the basic physiological process(es) have been fully addressed. However, many deliriums do not fully resolve. It is also not necessarily the case that two patients who appear to have equal degrees of baseline and precipitating stressors will both become delirious. This lack of reproducibility has wreaked havoc with our investigations of pathophysiology. We are left with broad-based geriatric clinical intervention methods that are helpful but quite non-specific, and this may account for some of our difficulty in making progress in the field.

At a cellular or molecular level, the most compelling evidence indicates that excess dopamine and/or insufficient acetylcholine in the brain could best explain the cascade of metabolic and behavioural complications of delirium. Each has complex and interactive impacts on cellular function within the CNS¹⁸. Impairments in neuronal membrane function appear to underlie much of the pathophysiology of delirium. Neuroimaging has recently been incorporated to evaluate structural and functional processes in the brain during delirium, although the findings are diverse enough that consistent trends have so far been elusive. Yokota and colleagues, using xenon enhanced CT, found that patients with delirium experienced a 42% reduction in overall cerebral blood flow compared to baseline; after recovery from delirium, the findings normalized¹⁹. Such findings may explain the multisystem deficits observed, which include cognitive, affective, sensory and motor function. There is not enough evidence at this time to determine whether structural correlates precede or follow delirium.

Major areas of exploration

Inflammation Inflammatory processes such as urinary tract infection, osteomyelitis and pneumonia, are highly associated with delirium. With ageing there is an elevated inflammatory profile²⁰. Activated glial cells transmit peripheral inflammatory cytokine

responses to the CNS. This is associated with decreased synaptic plasticity, a necessity for the modulation of behaviour, learning and cognition²⁰. Inflammatory states as well as hypoxia and hypoglycaemia are associated with impaired mitochondrial function; this might support a hypothesis that disturbed function of endothelial cells could alter the blood–brain barrier. Release of the inflammatory cytokines TNF- α and interleukin-1 generates adhesion molecules that disrupt cerebral vasculature, further impacting the integrity of the blood–brain barrier²⁰.

Extracellular glutamate in normal brain is quickly metabolized. However, in the presence of impaired mitochondrial function, hypoglycaemia hypoxia, and glucose, excess extracellular glutamate results in increases in cellular influx of Ca^{++} . This in turn leads to stimulation of NMDA receptors, which are excitotoxic². Intracellular Ca^{++} appears to be the main trigger of a series of reactions, including mitochondrial injury and activation of catabolic enzymes that lead to cellular dysfunction and potentially death. During states of cerebral ischaemia, further cellular risk is posed by efflux of dopamine. Use of barbiturates, isoflurane and etomidate, common agents associated with anaesthesia, may mitigate these responses^{2,21}. Few, if any, studies have linked the risk of delirium to the use of anaesthetic agents.

The acetylcholine hypothesis Another principal theory involves decreases in the availability to brain cells of adequate amounts of acetylcholine (ACH). ACH is a fundamentally important neurotransmitter in areas serving attention and memory. Among multiple reports, surgical ICU patients with delirium had higher serum anticholinergic levels. A dose-related relationship was identified by Flacker *et al.*²², who also identified higher levels of endogenous anticholinergic substances. A number of studies, although not all, have associated anticholinergic medications with delirium.

Impact of excessive dopamine Another important hypothesis relates to increased extracellular dopamine. The influx of calcium into cells that occurs during hypoxic conditions in brain stimulates the activity of tyrosine hydroxylase. This results in increased production of dopamine, with resulting disruption of ATP production. Decreases in the production of ATP and the increase in toxic metabolites of dopamine then inhibit catechol *O*-methyltransferase, the main extracellular deactivator of dopamine. These processes collectively result in increased dopamine levels in brain, up to a factor of 500 $\times$ during episodes of striatal ischaemia⁵. Further, dopaminergic neurons themselves are known to be highly susceptible to oxidative stress, which may result in massive releases of dopamine into the extracellular space⁵. Agents that increase available dopamine in the brain, such as stimulants, have also been associated with delirium. D2 blockers such as haloperidol are widely known to improve behaviour in patients with delirium, and possibly the syndrome itself.

Other neurotransmitters The kinetics of neurotransmitters other than acetylcholine and dopamine are also highly sensitive to conditions of hypoxia and hypoglycaemia, as above. Disorders of release, synthesis and degradation of gamma-aminobutyric acid (GABA), serotonin (either in excess or insufficiency), as well as norepinephrine and glutamate, have been linked in various work to delirium⁵. Cerebral oxidative metabolism, as well as cardiovascular and respiratory reserves that support it, decrease with ageing².

Glycemic control Decreased availability of inhibitory neurotransmitters, deposition of neutrophils and mitochondrial damage are associated with poor glycaemic control. Improved glucose control with insulin (specifically) improves the CNS outcomes of critically ill patients²¹.

Molecular genetics Efforts to link the presence of the *APOE4* variant of this gene, which has been well established in association with Alzheimer's disease, have resulted in mixed findings². It has been associated with increased duration of delirium in ICUs. Polymorphisms in *DRD3* and the dopamine transporter *SLC6A3* are the most commonly polymorphisms associated with delirium tremens²⁰.

THE IMPACT OF FOCUSED INTERVENTION TRIALS ON RECOGNITION AND MANAGEMENT

A number of intervention programmes have been employed to address the severe long-term outcomes of delirium, which include death, dementia, increased lengths of stay, decreased function, rehospitalization and new institutional placement. These programmes have been studied in hospitalized patients; there are no published trials among outpatients. A number of these trials have found that they are not helpful for the primary outcome of a decrease in incidence^{23,24}. Other studies have demonstrated decreases in severity and duration of symptoms of delirium in hospital, both of which have been significantly associated with worsened outcomes. Unfortunately the impact of these interventions on longer term outcomes has been mixed and overall disappointing²⁵. In some cases this may be due to the limited time the patient is exposed to the intervention, e.g. when hospitalized as part of a pre-established protocol¹⁴. In light of this, most studies conclude that prevention of delirium is the primary clinical goal. In a prominent study published in 1999²⁶, a complex intervention that involved a significant amount of volunteer work as well as a very high level of nursing care was shown to significantly reduce length of stay, number of episodes and, finally, the incidence of delirium. This may have been due to the highly refined identification of risk factors in this population; Inouye distinguished baseline risk factors for delirium from risk factors for triggering of a new episode. Going forward, this two-phased risk assessment method has helped reshape our conceptualization of treatments for delirium by focusing on modifiable, new onset, precipitating risk factors. This innovation has improved our ability to intervene effectively in cases of delirium.

Marcantonio performed a highly organized and comprehensive geriatric medicine programme that also demonstrated a decreased incidence of delirium in post-hip fracture patients¹⁴. The work of both Inouye and Marcantonio, that has primarily focused on providing basic, but comprehensive care, has demonstrated that the interventions needed in delirium are most often not arcane or difficult to employ, and are largely inexpensive. These interventions highlight an effective level of geriatric care that could be attained in any institution.

DEMENTIA AND DELIRIUM

Delirium is often confused with dementia. A critical part of the diagnosis of delirium involves identifying that the mental status presented

by a patient is not the patient's baseline level of cognition and that a relatively rapid change has taken place. Delirium is an acute, catastrophic response to an inciting medical event. The evolution of dementia is significantly more gradual in most cases. Where there is doubt, it is safest to address the clinical situation as a delirium so that any precipitating causes are addressed as soon as possible. The differentiation of these two clinical problems is complex because the precipitating cause(s) of the delirium may not easily be temporally connected with the onset of the syndrome of delirium itself. Patients with delirium superimposed on dementia had more than twice the risk of mortality at 12 months than patients with delirium alone, dementia alone or patients with neither²⁷. Assisted living facility residents classically have high rates of dementia and the relative risk of discharge of such patients back to institutional settings after an episode of delirium was 9.1¹. There may be priming of the immune system as well. Patients with dementia are increasingly understood to have chronic inflammatory processes within the CNS. Acute systemic inflammatory processes that precipitate delirium may have been 'primed' by the underlying inflammatory process²⁰.

TREATMENT APPROACHES TO DELIRIUM

Priorities of treatment include addressing acute medical contributors to the syndrome as well as stabilizing patient behaviour sufficient to enable the treatment of underlying medical causes. The primary task of clinicians is to identify and address modifiable conditions. In this way the impact of relatively unmodifiable conditions (such as stroke, myocardial infarction end stage renal function etc.) can be minimized. Our effectiveness at treating delirium depends on the extent to which we can provide skilled and sophisticated nursing care that allows time for the multiple interventions required by elderly patients. Avoidance of iatrogenesis that can prolong the delirium is an essential part of this effort. Factors contributing to increased risks of delirium in hospital include the increased pace of health care settings, rapid and increasingly unstable discharges and remarkably limited amounts of time spent with patients. Housestaff may have as little as 3.5 minutes per day per patient⁴. Skilled nursing care alone could provide many of the most effective strategies for minimizing delirium, including mobilization, improvement of cognitive stimulation and minimization of the need for restraints. Up to 50% of cases of delirium can be prevented⁴.

Pharmacological Approaches to Behavioural Stabilization

The use of restraints can worsen delirium, as can the overuse of certain medications. Use of benzodiazepines, while standard for obligate alcohol detoxification regimens and for sedation in ICUs, has nonetheless been found in most studies to carry a high risk of inducing or significantly worsening delirium². There are few double-blinded, placebo-controlled, randomized trials of neuroleptics for behavioural management in delirium. Of all these agents, haloperidol remains the most studied. Haloperidol can be effective in low dosages, starting with 0.25 mg po or IM bid, and increasing to the 2–3 mg per day range only in severe cases. Risperidone in doses ranging from 0.5 to 4.0 mg daily and olanzapine in doses of 2.5–11.6 mg daily have been efficacious for the behavioural treatment of delirium with fewer extrapyramidal effects than haloperidol². In addition, case reports or case series regarding quetiapine, aripiprazole and ziprasidone have been published with no

randomized, double-blinded, placebo-controlled studies yet reported. There are very few such medication trials in the field.

Environmental Management for Behavioural Stabilization

Patients with delirium are unable to manage their environment, make appropriate decisions or care for their basic needs, and they cannot problem solve. Therefore, the environment has to adapt to them. Most studies agree that decreasing the complexity of the environment by limiting rotation of personnel caring for the patient, minimizing room changes, providing rest and quiet at night time, feeding the patient, providing a calming 'interpreter' such as a 'sitter' or family member to reorient and guide the patient, limiting distractions (loud conversation, beepers, overhead speakers, televisions, crowded areas), providing hearing aids and glasses, and providing clear-cut and step-by-step instructions are critical. Mobilizing the patient will minimize recovery time, and also may have modulatory impacts on recovering muscle after a critical illness²⁸. Patients must be kept safe by limiting dangerous objects in their reach, avoiding falls and using assistive devices to limit the possibility of their pulling at lines or touching wounds. Complex protocols exist for the design of the treating environments that are beyond the scope of this chapter¹⁴.

Treating the Causes

Acute medical conditions

The basic principle of treatment of delirium is to aggressively seek and treat the reversible causes of delirium and to mitigate those that have little room for modulation. Emphasis should be placed on illnesses that result in poor cerebral oxygen availability or that are associated with significant metabolic impairments. Elimination of infectious or inflammatory sources, addressing orthopaedic injuries and removal of offending medications are also essential (see below). Given that most cases of delirium occur in the most vulnerable patients, correcting the most common metabolic and infectious factors, such as serum bun, creatinine, sodium and calcium, and treatment of urinary tract infections and pneumonia are remarkably effective interventions. Identification of metabolic trends by graphing laboratory values can be very helpful to determine original causes as well as indicators of further decline or recovery. Head imaging is not helpful in the absence of focal findings²⁹.

Removal of offending medications

Removing offending medications, including opiates, anticholinergics, benzodiazepines and dopaminergics, is extremely important. Medications that alter the dopamine/acetylcholine balance within the CNS are a primary focus. A significant number of deliriogenic medications are found in commonly used medications, including digoxin, penicillin, amantadine, quinolone antibiotics, furosemide, nifedipine and warfarin. Further treatment of this topic is beyond the scope of this publication².

Pharmacological Approaches

Historically, medications have been used to address behavioural problems, but recent evidence indicates that there may be some gains in disease modification.

Neuroleptics

Recent work (see 'Pathophysiology of Delirium', above) suggests that the use of dopamine blockade is useful for disease modification. Agents that block dopamine have the potential to inhibit many neurotoxic events that occur in the presence of delirium, especially during conditions of hypoxia. Recent studies have focused on the usefulness of prophylactic antipsychotic use to diminish the incidence, severity or persistence of delirium. Kalisvaart was able to demonstrate decreased severity and persistence of delirium, although not incidence, among postoperative hip fracture patients by providing perioperative haloperidol use at 1.5 mg/day preoperatively and 3 days postoperatively. This was the first major study to demonstrate that pharmacological approaches could be used for disease modification³⁰. In another randomized, placebo-controlled, double-blinded study of cardiac surgery patients, the incidence of delirium was quite significantly decreased when compared with placebo, even with a single dose of risperidone at 1 mg postoperatively³¹. The use of neuroleptics as preventative or mitigating agents in delirium is not widespread at this time.

Cholinesterase inhibitors

The use of cholinesterase inhibitors has been trialled in delirium. In a randomized, placebo-controlled, double-blinded study by Liptzin *et al.*, the use was not found to have a significant impact on the incidence of delirium among young, relatively healthy patients undergoing elective hip fracture³². In a small retrospective study, a population of dementia patients chronically maintained on rivastigmine had significantly less incidence of delirium than a comparable, non-chronically medicated group³³.

Dexmedetomidine

The use of psychopharmacological agents to treat agitation in the ICU has been largely limited to propofol, which is an alcohol that is associated with hypotension and hyperlipidaemia, or to midazolam, which can suppress ventilatory effort and cause hypotension. Both have GABAergic effects that can worsen delirium. Fentanyl, an opiate IV for pain control and sedation, is also frequently utilized, either alone or in combination with propofol or midazolam, with attendant risks of dopaminergic/anticholinergic impacts. Dexmedetomidine, a very selective alpha-2 adrenergic agonist, has analgesic, sympatholytic, sedative and anxiolytic properties. It has increasingly been trialled as an alternative to the older protocols. In a randomized controlled trial of dexmedetomidine versus lorazepam in the ICU setting, while not significant, there was a dramatic difference in post-ICU mortality at 28 days and one year³⁴.

Delirium is a critical illness that occurs primarily in elderly and frail individuals. Modulation of this very significant problem, however, is increasingly within our reach.

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The Nosology of Dementia

Kenneth Rockwood

Division of Geriatric Medicine, Dalhousie University, Halifax, NS, Canada

INTRODUCTION

Nosology is the classification of disease. How the syndrome of dementia has been classified has changed over the years. Recognizing that textbooks are commonly consulted because readers want pragmatic answers to questions, and that understanding nuances first requires understanding the basic facts, this chapter will begin with the current classification of dementia. A second section will provide some historical context. The third section will suggest some areas that remain to be understood or at least, settled on. The focus will be on understanding the basis for the definition of the syndrome of dementia, which historically has been rooted in the diagnosis of Alzheimer's disease. Separate chapters for many of the other dementing disorders will deal with these in separate detail; here we focus on diagnostic criteria for Alzheimer's disease, and how these have influenced the way in which dementia is understood.

CURRENT NOSOLOGY OF DEMENTIA

At present, three references – DSM-IV-TR¹, ICD-10² and the NINCDS-ADRDA³ criteria – provide authoritative approaches to the nosology of dementia. Each is rooted in the formulation codified in an influential textbook by Lishman⁴, which proposed that dementia was a global cognitive impairment (memory plus other cognitive features) that was sufficiently severe to interfere with social or occupational function. The newly developed 10/66 criteria, discussed below, have drawn attention to difficulties in the operationalization of the idea that the cognitive impairment must be severe enough to interfere with function, and it may be that their approach will become increasingly influential⁵. Similarly, although largely technically infeasible in the low- and middle-income countries being studied by the 10/66 group, another influential proposal suggests that clinical features beyond demonstrable memory impairment count for little, compared with biomarkers⁶. How these newer trends will play out is not clear.

As a syndrome, dementia must be differentiated from other syndromes in which cognition is (or can be) impaired, including delirium, depression and age-associated cognitive decline. This last is variably conceptualized. Each of the syndromes in which cognition is impaired, but which the cognitive impairment does not meet criteria for dementia, forms part of what has been referred to as 'cognitive impairment, no dementia' (CIND). The prevalence of the heterogeneous group of disorders that is CIND is estimated to be about twice that of the prevalence of dementia⁷.

DSM-IV-TR

The Text Revision of the Fourth Edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV-TR) was published in 2000¹. As with DSM-IV, it gives a general (syndromic) definition of dementia, but the actual dementia diagnostic codes are presented by subtype, based on presumed aetiology. These include Alzheimer's disease, vascular dementia, and separate categories for dementia due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt–Jakob disease, other general medical conditions, substance-induced persisting dementia, dementia of multiple aetiologies, delirium and dementia not otherwise specified.

Within the classification of other general medical conditions are listed a variety of other problems. Some, such as structural brain lesions, including subdural haematomas, and brain tumours, are not infrequently encountered, as are dementia due to multiple sclerosis or to systemic lupus erythematosus. Others are less common, such as dementia due to endocrine disorders (e.g. hypothyroidism or hyperparathyroidism) and CNS infection (neurosyphilis, cryptococcus). Still others are often obscure disorders, such as Kuf's disease and adrenoleukodystrophy.

Note, too, that dementia due to Lewy bodies can be classified in DSM-IV-TR as due to 'other general medical conditions' (or as Parkinson's disease dementia; DSM-IV-TR is in this way up to date in noting controversy over whether Lewy body dementia and Parkinson's disease dementia are aspects of the same disorder, or usefully separable)^{8–10}. Frontotemporal dementia, a broader classification than the not unproblematic Pick's disease, can also be recorded under dementia to other general medical conditions.

Although dementia is diagnosed by aetiology, the syndromic aspects said to be 'essential' are repeated for each type. In the criteria for 'Dementia of the Alzheimer's Type' (Table 37.1) these are items A, B, C and E. Item D is adapted to be more disease-specific for each separate dementia classification. Note that DSM-IV-TR maintains the development of DSM-IV in that memory impairment is not further delineated, whereas in DSM-III-R, impairment had to be demonstrated in both so-called short- and long-term memory.

ICD-10

Chapter V of the 10th revision of the International Classification of Diseases (ICD-10) is the World Health Organization's codification of

Table 37.1 DSM-IV-TR diagnostic criteria for dementia of the Alzheimer's type

-
- A. The development of multiple cognitive deficits manifested by both (1) memory impairment (impaired ability to learn new information or to recall previously learned information) (2) one (or more) of the following cognitive disturbances:
- (a) aphasia (language disturbance)
 - (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
 - (c) agnosia (failure to recognize or identify objects despite intact sensory function)
 - (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
- B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
- C. The course is characterized by gradual onset and continuing cognitive decline.
- D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
- (1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
 - (2) systemic conditions that are known to cause dementia (e.g. hypothyroidism, vitamin B or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
 - (3) substance-induced conditions
- E. The deficits do not occur exclusively during the course of a delirium.
- F. The disturbance is not better accounted for by another Axis I disorder (e.g. Major Depressive Episode, Schizophrenia).
- Additional coding, based on presence or absence of a clinically significant behavioral disturbance:
- 294.10 Without Behavioral Disturbance: if the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.
- 294.11 With Behavioral Disturbance: if the cognitive disturbance is accompanied by a clinically significant behavioral disturbance. (e.g. wandering, agitation)
- Specification of subtype:
- With Early Onset: if onset is at age 65 years or below
- With Late Onset: if onset is after age 65 years
-

Source: DSM-IV-TR: Text Revision of the fourth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association.

diagnoses in relation to 'mental and behavioural disorders'. Dementia is included as a so-called 'organic' mental disorder (Table 37.2). The ICD-10 manual states that 'Dementia (F00-F03) is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation' (Table 37.2). Its emphasis on impaired behaviour is noteworthy, although in practice this might not be operationalized as distinct from the impaired 'social functioning' seen with DSM. Like DSM-IV-TR, the ICD-10 classifies dementia into an early onset, before age 65 years, and a late onset, after age 65 years. ICD-10 suggests that the early-onset form should have a more rapid onset and progression than the late-onset form. In general, however, in both DSM-IV and ICD-10, the validity of subgroups of dementia has often been found lacking, at least as employed in routine clinical use¹¹.

The differences in how dementia is operationalized are not inconsequential. Even the minor differences between standard criteria can importantly influence prevalence rates^{12,13}, especially at very late ages¹⁴. In general, ICD-10 has been reported to be less sensitive than earlier versions of the DSM criteria, although that is not always the case^{15,16}.

NINCDS-ADRDA

Even though the diagnostic classification proposed in this 1984 report focuses on Alzheimer's disease, the consensus diagnostic criteria proposed by the National Institute of Neurological and Communicative

Table 37.2 ICD-10 criteria for dementia. Definition of dementia in the ICD-10 (adapted)

-
- G1 There is evidence of each of the following:
- (1) A decline in memory (at least) sufficient to interfere with everyday activities, though not so severe as to be incompatible with independent living
 - (2) A decline in other cognitive abilities characterized by deterioration in judgement and thinking, such as planning and organizing, and in the general processing of information (at least) sufficient to cause impaired performance in daily living, but not to a degree that makes the individual dependent on others
- G2 Awareness of the environment (i.e. absence of clouding of consciousness)
- G3 There is a decline in emotional control or motivation, or a change in social behaviour manifest as at least one of emotional lability, irritability, apathy or coarsening of social behaviour
- G4 The symptoms in criterion G1 should have been present for at least 6 months
-

Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) has served for many years as the standard for a diagnosis of Alzheimer's disease, and its definition of dementia was also normative³. It still heavily influences how research on dementia is conducted, especially as it makes up the usual inclusion criteria for drug trials on Alzheimer's disease (Table 37.3). The original criteria have been adapted somewhat – dementia can be diagnosed with the aid of cognitive screening instruments other than

Table 37.3 NINCDS/ADRDA criteria for Alzheimer's disease

Criteria for clinical diagnosis of Probable AD include:
Dementia established by clinical exam and documented by MMSE or Blessed Dementia scale, confirmed by further neuropsychological tests.
Deficits in two or more areas of cognition.
Progressive worsening of memory and other cognitive functions.
No disturbance of consciousness.
Onset between the ages of 40 and 90.
Absence of systemic diseases or other brain diseases that could explain the cognitive changes.
The diagnosis of Probable AD is supported by:
Progressive deterioration of specific cognitive functions such as language, motor skills, and perception (aphasia, apraxia, agnosia, respectively).
Impaired activities of daily living.
Positive family history, particularly if documented neuropathologically.
Lab results: Normal lumbar puncture, EEG, and evidence of cerebral atrophy on CT or MRI.
Clinical features consistent with diagnosis of Probable AD, after exclusion of other causes of dementia:
Plateaus in clinical course.
Associated symptoms: depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss.
Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased motor tone, myoclonus, or gait disorder.
Seizures in advanced disease.
CT normal for age.
Features that make the diagnosis of Probable AD unlikely or uncertain:
Sudden apoplectic onset.
Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness.
Seizures or gait disturbances at the onset or very early in the course of the illness.
Clinical diagnosis of Possible AD.
May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course.
May be made in the presence of a second systematic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia.
Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

the Mini Mental State Examination (MMSE)¹⁷ or Blessed Dementia Rating Scales¹⁸, and neuropsychological confirmation is not always required. But the key points of a probable cause being the case for a clinical diagnosis, neuropathology providing the definition reference, and the diagnosis being only possible when other disorders are present operate still, even though each is far from an indubitable proposition¹⁹. Over the years, many proposals have been made for how Alzheimer's disease might be subtyped other than by age at onset. For example, rapidity of progression, focality of onset, presence of additional features such as early extrapyramidal signs each has had adherents, but none has made their way into standard criteria¹⁹.

SOME HISTORICAL CONTEXT FOR THE CURRENT CLASSIFICATION

Dementia as a clinical syndrome has for a long time been distinguished from changes that are often seen as people age – especially problems with memory. Even in the last 30 years, however, there have been major changes in how dementia is conceptualized, and to a large extent these are reflected in ICD-10 and DSM-IV-TR. In the early years of the modern era, much effort was put into making clear that dementia was distinct from normal ageing. Even so, ICD-10 still has a conceptually ancient hold-over in the diagnostic

code (Code R54) of 'senility without mention of psychoses', found in a chapter entitled 'The development of more clinically meaningful outcome measures and laboratory findings, not elsewhere classified'. This code can still appear in certain administrative tabulations, and has the advantage of also being in ICD-9, so that under those circumstances it can allow for the evaluation of trends. Still, the 'senility' diagnosis generally represents an outmoded, obsolete and offensive understanding of dementia – as somehow 'normal' ageing – that has no place in modern care.

Early in the modern era – roughly from the late 1950s, and especially following a series of articles in the mid-to-late 1960s by Martin Roth and colleagues^{20–24}, a lot of work was put into distinguishing between the neurodegenerative and vascular causes of dementia. They sought to repudiate the view that 'senility' was due to 'hardening of the arteries' and made the case that the changes in cognitive performance in elderly people was a result of plaques and tangles – Alzheimer's disease – or stroke – 'multi-infarct dementia'. While this was true, we have come to understand that the wall between the two is porous – that vascular risk factors are also a risk for Alzheimer's disease, and that the two commonly occur – even in the original series of cases from Newcastle²⁵ – and can act synergistically (although this last point is disputed)^{26–29}.

The early descriptions were correct in emphasizing how dementia affected the personality of an individual, through the undoing

of what later would be called executive function. For example, a 1971 description of the clinical symptomatology of dementia warned against putting too much emphasis on 'impaired memory and orientation' as an 'undue emphasis on these features may ... obfuscate the richness of the clinical symptomatology. ... an early and frequent complaint is that the patient is "not himself", meaning that the patient and his companions have noted the onset of illness in terms of changes in function that are quite specific to that particular person, whether described in terms of alteration of drive, mood, enthusiasm, capacity to give and receive affection, creativity or other features'³⁰. As later – and comparatively recent – calls for an appreciation of the importance of executive function in dementia have made clear^{31,32}, these descriptions were largely lost soon thereafter. Instead, the view that Alzheimer's disease was predominantly a disorder of memory, that temporal and parietal involvement was early, that frontal lobe involvement was late, and that the standardization offered by psychometric testing would trump the subjectivity of clinical judgement each contributed to the systematic lack of attention to 'what makes a patient him[her]self'.

Another point seen in earlier iterations of dementia criteria that is less commonly emphasized now is that a diagnosis of dementia should only be made in patients in whom consciousness was 'clear'. This was meant to be another way of saying that consciousness should not be clouded, which in DSM-III was seen as a major distinguishing feature of delirium. (In DSM-IV-TR, delirium is again conceptualized as a disorder of consciousness; the only reference that it be clear, however, is the description of 'reduced clarity of awareness of the environment'.) With the recognition of the importance of alterations in levels of consciousness as a hallmark of Lewy body dementia, however¹⁰, this particular requirement has been dropped. Instead, the criteria make reference to the cognitive disorder not being better accounted for by delirium.

FUTURE CHALLENGES IN DEMENTIA NOSOLOGY

The exciting pace of development in the study of dementia means that the field has to look anew at received wisdom. A large number of developments are likely to impact on what will be controversial about the nosology of dementia when the next edition of this textbook appears. Here, a few are sketched out in the barest detail. Even so, they give some hint as to why this most staid of topics is likely to have interest for some time yet.

'Alzheimerization' of Dementia Criteria

Current dementia criteria are, as we have seen, largely modelled on the dementia characteristically seen in Alzheimer's disease. This is a problem for dementias in which memory impairment is not the chief early manifestation. The two most commonly occurring examples are frontotemporal dementia and vascular dementia, especially the so-called 'subcortical' variant³³. In either, affective and behavioural disturbances can predominate early. The consequences of this problem are many. In the case of vascular dementia, Hachinski has long drawn attention to the opportunities missed in dementia prevention³⁴ and in understanding the impact of vascular disease on brain function by underestimating its burden in the wait for memory to become impaired. In consequence, he has proposed the concept of vascular cognitive impairment³⁵. Over time, this has had great influence³⁶, but has yet to be reflected in the standard criteria, including in the NINDS-AIREN criteria for vascular dementia³⁷.

The presentation (and evaluation) of impaired judgement in someone whose memory is reasonably intact can be problematic, especially where social conduct violates legal norms (e.g. theft, sexual impropriety). In some cases, it is clear that a reliable clinical diagnosis of dementia can be made due to other characteristic features in the patient's cognitive profile and how that impacts on function, even if memory is relatively intact. Even so, depending on the literalness of local prosecutors, the understanding that the criteria in real life often are only approximate can be a tricky business. (In such cases, where it is necessary to show that the criteria need not always be applied strictly, I have found it useful to cite Aristotle – who hedged that in biology rules apply 'always or for the most part'³⁸. If that seems a bit obscure, it is always possible to resort to the usual disclaimer for hair loss products: 'Your results may vary'.)

Notwithstanding the incompleteness of the criteria, there are other circumstances of late-onset aberrant behaviour, coupled with some evidence of executive dysfunction, in which only the passage of time and progression of the illness to include other dementia features makes the diagnosis clear.

Cognitive Disturbances with Many Causes

Dementia occurs largely in older people who are more likely to have things wrong with them. In consequence, in clinical practice it is common to encounter patients with many things wrong that might contribute to cognitive impairment. For this reason, dementia diagnostic criteria need to give particular attention to how such problems are to be conceptualized and identified. This is relevant in three situations. 'Mixed dementia' refers to co-existing illnesses and especially to the combination of infarction (or, more controversially, ischaemia) with Alzheimer's disease. As noted, given that vascular risk factors are also risks for Alzheimer's disease, not unexpectedly the two often conclude and can be the most common form of dementia encountered^{26–29,39}. In the ICD-10, NINCDS-ADRDA and NINDS-AIREN criteria, the result is a 'possible' diagnosis – e.g. 'possible Alzheimer's disease, with vascular component'. By contrast, DSM-IV-TR allows for 'Dementia due to multiple etiologies'. (From a coding standpoint, multiple codes are allowed – i.e. each of the codes for the given causes is recorded.)

A similar situation occurs when delirium complicates dementia. Again, this is a common situation, as each is a risk for the other⁴⁰. In addition, delirium which does not resolve is a risk for dementia, and results in an indeterminate period (of between 3–6 months) when features of both may be present⁴¹. The multiple coding approach and the use of codes for delirium-complicating dementia seen in DSM-IV are considered a good way to handle the common co-occurrence of these syndromes, resulting in a proposal that ICD-11 should follow the lead of the DSM^{40,42}. The parallel is also seen when depression complicates dementia⁴³.

Lessons from the 10/66 Experience

The 10/66 Dementia Research group is a collective of dementia researchers worldwide, who are carrying out population-based studies of dementia^{44–46}. The title refers to the fact that two-thirds of people with dementia live in low- and middle-income countries and that 10% (or less) of population research is conducted there. An early and important finding of the 10/66 was how poorly standard dementia criteria applied in many parts of the world. In consequence, the 10/66 group developed its own. These criteria differ from the

standard criteria chiefly in how they operationalized the impact of cognitive impairment on function (relying less on informant reports of decline) and in the use of detailed procedures for operationalization, which were cross-culturally validated. These criteria yielded results that were both more consistent across sites and strikingly higher than those using DSM-IV dementia criteria (e.g. 10/66 criteria suggested prevalence of 5.6–11.7% by country, compared with 0.4–6.4%)⁵. These last results raised the question of whether the criteria were too sensitive, and thereby not specific enough, or whether 10/66 ‘pathologizes’ mild decline that can be accommodated within many cultures in which less cognitive demand is placed on elders. These questions remain to be resolved.

Alzheimer’s Disease without Dementia

At a different spectrum from those who look to diagnose dementia in low- and middle-income countries are groups who are aiming to develop preventive treatment for dementia, or at least ones which could be implemented as early in the disease course as possible⁶. For such groups, the interest is on how to couple the earliest manifestations of dementia with biological markers of the disease. Drawing on a body of work about very early⁴⁷ and prodromal Alzheimer’s disease, and on the apparent promise of biomarkers, a consortium has proposed that biomarkers, coupled with a memory complaint, should form the basis for a diagnosis of Alzheimer’s disease. The clear intent is to provide a test base of people who are at high risk for the development of ‘full-blown’ Alzheimer’s disease, and to see if new interventions might prevent that outcome. How such a proposal will affect more widespread diagnosis of dementia is uncertain. Whether ‘prevented Alzheimer’s disease’ will look like ‘no (or mild) cognitive impairment’ is also uncertain, but the parallel case might exist now for successfully treated Alzheimer’s disease (below).

Executive Dysfunction

As noted, it had been the case that, central to a clinical diagnosis of dementia, was the loss of aspects of an individual’s character which made them essentially themselves. This notion largely was lost for a period, before being rediscovered, under the guise of executive function. While the emphasis on executive function is welcome, it is not at all clear that the usual remedy (to employ measures of ‘frontal lobe tests’) addresses the clinical phenomenon sufficiently well. A cultural bias is at work in rejecting the characterization of an individual’s complaints – what makes dementia a problem for them – as too subjective an evaluation process, and instead substituting finger-tapping or clock-drawing tasks as preferable alternatives. Future criteria will need to examine how they view the notion of subjectivity or objectivity. In this, they might be helped by consultation with philosophers who understand the distinctions that are at play here.

Successful Treatment of Dementia

Even though no current treatment cures Alzheimer’s disease, many people can be treated successfully, to the extent of having important overall improvement on global clinical measures⁴⁸. Evaluations of the notes from patient interviews in which clinicians rated patients as showing overall improvement have shown that typically in such cases some symptoms improve, most are stabilized and some worsen^{49,50}. In short, successful treatment can result not in cure, but in a new state. This state has yet to be operationalized in any terms that could

inform criteria. Even so, it offers a way to retrieve some of the lesson taught by Wells (i.e. the warning that too much emphasis on easily testable cognitive elements might obscure the richness of the clinical symptomology). The approach to this problem that I have used with colleagues is known as goal attainment scaling⁵¹, about which independent reviews suggest it has promise, but needs additional work, chiefly replication and some standardization^{52,53}. Whether the results of partially treated (or partially prevented) Alzheimer’s disease will be stable enough and common enough to warrant special categorization is a development to be evaluated with some interest.

SUMMARY

The nosology of the dementia syndrome is likely to continue to evolve, reflecting developments in how and where dementia is studied. Important challenges to our understanding of dementia reflect continuing development of our knowledge of these dread illnesses.

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Epidemiology of Dementia

Mary Ganguli

University of Pittsburgh School of Medicine and Graduate School of Public Health, WPIC, Pittsburgh, PA, USA

Epidemiology has traditionally been the study of the distribution and determinants of disease in the population. Its principles and approaches are also used to study normal variation, for example changes related to normal ageing in the population at large. Epidemiology helps clinicians by acquainting us with the proportions of given populations that are affected by the conditions we diagnose and treat; the frequency with which different conditions, changes and outcomes occur; and the factors that raise and lower the probability of these conditions occurring. Importantly, epidemiology also completes the clinical picture of disease, demonstrating that patients who seek our services for a given condition are not typical of all individuals in the community with that condition. For example, individuals with dementia who present to a psychiatric clinic may have different characteristics (insight, symptoms, severity, duration, support) than those who are seen in neurological or general practice settings, or who do not seek clinical services at all. As of this writing, efforts are under way to revise the current clinical diagnostic criteria for dementia and its subtypes, including Alzheimer's disease, in the World Health Organization's International Classification of Disease¹ and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders². More than in previous editions, attention is being paid to epidemiological data that bear on diagnosis: for example, the heterogeneity of dementia and cognitive impairment, and the predictive validity of various diagnostic criteria in population settings.

BASIC DEFINITIONS

Prevalence is a cross-sectional snapshot of the disease burden of the population. It is the proportion of individuals in a defined population who have the disease or condition at a given time (point prevalence) or defined period (period prevalence), regardless of how long these individuals have had the condition.

Incidence is the rate at which new disease occurs in the population. It is the proportion of individuals previously free of disease who develop the disease during a defined period (e.g. one year, or 1 000 person-years), within a defined population.

Overall prevalence and incidence estimates (e.g. for everyone aged 65 years and older) are less useful than age-specific estimates, that is, within defined age groups, such as those aged 65–74, 75–84 and 85+ years.

Prevalence is the product of incidence rate and duration of survival with disease. Thus, high prevalence can be the result of high incidence, long duration, or both. Two groups can have the same dementia incidence, with prevalence being higher in the group in which people with dementia live longer.

GLOBAL AGEING, DEMOGRAPHIC TRANSITION, DEVELOPED VS. DEVELOPING COUNTRIES

The world's population is ageing, as improving living standards have increased life expectancy across the globe. The most affluent countries have the longest average life expectancy, and the greatest proportions of older adults. However, population ageing is occurring faster in the low- and middle-income ('developing') countries than in the wealthier ('developed') countries. It is determined by both birth rates and death rates. Populations with high fertility tend to have low proportions of older people, and vice versa. The 'demographic transition' is the process in which, over time, a high-fertility-high-mortality population becomes a low-fertility-low-mortality population, and its average age increases. As people live longer, the public health concern becomes whether their years of extended life are characterized by relative health and independence or by ill-health, disability and dependence on others. Thus, we measure not only overall life expectancy but healthy life expectancy and disability rates.

In affluent countries, disability rates appear to be decreasing as the population ages. In low- and middle-income countries, it seems likely that disability rates will climb as people live longer with chronic disease. The least affluent countries are the least prepared to deal with the challenges of population ageing, given the rapidity with which the demographic transition is occurring in their societies. However, one factor in their favour is the elderly support ratio, which is the number of elderly people for every 100 younger adults in a given population, with younger individuals assumed to be directly or indirectly supporting older ones. This ratio is increasing rapidly in the affluent countries, with greater numbers of older individuals needing support from a shrinking number of younger persons. In the less affluent countries, this ratio is expected to change quite slowly³.

Dementia is a major cause of functional disability, dependence and mortality in the elderly. It therefore reduces both overall life expectancy and active (disability-free) life expectancy, although the extent to which it does so might vary across populations. Dementia is also responsible for increasing use and cost of health services,

particularly long-term-institutional care, in countries where such institutions are available and culturally acceptable. The cost to a given society of caring for its members with dementia depends on its age structure, the numbers and proportions of affected individuals, their length of survival and degree of dependency, the availability of appropriate goods and services, and who bears the costs of these items. These direct costs, as well as indirect costs (e.g. loss of income by the patient and family caregiver) will vary according to the affluence and age structure of a given society.

SYNDROMAL DEFINITION OF DEMENTIA: DSM, ICD, EVOLVING CRITERIA; 'CASENESS'

At the time of this writing, the most widely employed diagnostic criteria for dementia at the syndrome level are those of the Tenth Revision of the International Classification of Diseases (ICD-10)¹ and the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)². Over the years, studies in different countries have used different versions of these criteria. Variations in definitions and criteria can potentially raise and lower estimates of prevalence and incidence across studies and populations. One study demonstrated that the proportion of individuals classified as having dementia varied from 3% using the ICD-10 criteria to 29% using the DSM-III criteria, within the same population⁴.

According to current definitions, dementia is a syndrome of acquired, chronic cognitive impairment, occurring in clear consciousness, sufficient to interfere with social and occupational functioning, and characterized by impairment in at least two cognitive domains. For the past few decades, the definition has further required that memory be one of the impaired domains², but this requirement may not persist in future revisions of diagnostic criteria. For example, it may be possible that an individual with significant impairments in executive and language functioning can be diagnosed as having dementia, even without memory impairment.

Further, there is currently no standard diagnostic entity reflecting a minor level of cognitive decline that is not accompanied by functional impairment, thus falling short of the threshold for being called dementia. This situation too may change as knowledge evolves and preclinical detection of dementing illnesses becomes a possibility. Besides the functional dimension of the diagnosis, the standard neuropsychological criteria for dementia typically require test performance in two cognitive domains to be at least two standard deviations below the mean for the individual's peer group, as defined by age, education, linguistic/ethnic group and sometimes gender. However, appropriate norms are not always available. Thus, the issue of 'caseness', or what makes an individual a true case, has yet to be universally defined, and will become harder as the demand increases for earlier detection of the dementia syndrome.

DEMENTIA SUBTYPES AND THE ROLE OF CO-MORBIDITY

Alzheimer's disease (AD) is a primary neurodegenerative disease which appears to be the single most common cause of the dementia syndrome in older adults, in most populations which have been studied worldwide. The next single most frequent cause of dementia is cerebrovascular disease; either cortical infarcts or white matter disease, or both, can lead to significant cognitive impairment and decline. Diagnostic criteria for vascular dementia and cognitive

impairment have varied as to whether the mere presence of cerebrovascular disease with dementia is sufficient, or whether evidence from neuroimaging is also required, for the diagnosis^{2,5}. However, mixed Alzheimer's and vascular pathology is more common than pure vascular disease or pure degenerative disease, as borne out by the few community studies that have been able to conduct autopsies⁶. Although prominent in specialty clinical settings, dementias related to other primary brain disorders such as frontotemporal lobar degeneration, Lewy body disease and Parkinson's disease appear relatively infrequent in the community at large; population-based estimates are scarce. Opinion is moving towards accepting co-morbidity and multiple causes in a given individual with dementia, rather than selecting one subtype over another in the presence of mixed aetiology.

PREVALENCE AND INCIDENCE OF THE DEMENTIAS

The overall prevalence of dementia, based on many studies in affluent countries worldwide, is in the range of 5–10% of individuals aged 65 years and older. One meta-analysis showed a doubling of dementia prevalence with every 5-year increase in age; for AD the doubling occurred with every 4.5 years and for vascular dementia every 5.3 years⁷. Population studies typically do not employ neuroimaging or neuropathology for diagnosis, but rather use operationalized standard clinical diagnostic criteria. In these studies, AD appears to account for two-thirds to three-quarters of observed cases. Previous reports of vascular dementia being more prevalent than degenerative dementia in some Asian populations may have been the result of varying diagnostic criteria. However, prevalence has not been established for the newer, broader entity called vascular cognitive impairment (VCI) which encompasses all levels of cognitive decline from mild deficits to dementia. The prevalence of dementia of Parkinson's disease has been estimated at about 0.5% of the population aged 65 years and older⁸.

Although incidence rates vary, one meta-analysis showed rates of AD ranging from 0.33% per year for those aged 65–74 to 8.68% for those aged 95+ years⁹. Evidence is inconclusive as to whether incidence continues to increase after age 90. In a study including MRI scans for the diagnosis, the age-adjusted incidence rate for AD was 19.2, and for vascular dementia 14.6, per 1000 person-years¹⁰. While many studies have shown higher dementia prevalence among women, many incidence studies have not shown a gender difference. If incidence is indeed the same in men and women, gender difference in prevalence may be due to longer survival in women. There are few population-based data on early-onset dementias.

Based on a handful of studies from Asia, Africa, Central and South America, and Eastern Europe, prevalence in low- and middle-income countries is much lower than in the affluent countries. It is, however, increasing as their populations age, and seems to be divided between Alzheimer's and vascular subtypes as in the rest of the world¹¹. The prevalence difference is not solely a function of life expectancy. Opinion is divided as to how much of the discrepancy is due to misclassification, given the difficulties in measurement discussed earlier, and how much reflects true differences in disease occurrence. However, all studies report an exponential increase in both prevalence and incidence with age. With the rapid population ageing of the less affluent countries, among which India and China have very large populations, even a lower proportion affected by dementia will reflect a larger number of individual cases in these countries than in the wealthier countries¹².

NORMAL VS. ABNORMAL COGNITIVE AGEING

To differentiate early dementia from the cognitive changes of normal ageing can be challenging in clinical practice, and is no easier at the population level. The majority of older adults experience some slowing of information processing as part of normal ageing. Memory, visuospatial ability and executive functioning/reasoning also are likely to decline with normal ageing. In contrast, verbal/language abilities tend to remain more stable.

Terms such as age-associated memory impairment and age-related cognitive decline have been used to characterize the cognitive changes of normal ageing. Terms including mild cognitive impairment (MCI)¹³ and cognitive impairment, no dementia (CIND)¹⁴ are used to describe states intermediate between normal cognitive ageing and dementia, where individuals experience or exhibit cognitive deficits greater than expected for age, without fulfilling diagnostic criteria for dementia. The prevalence of this variably defined intermediate state in the elderly population is entirely dependent on the definition, and has been shown to vary from 3 to 20% as a function of the criteria employed¹⁵. The key element is mild cognitive decline with little or no functional change. This state frequently but not inevitably progresses to dementia. The rate of progression to dementia is reported as 12–15% per year in patients actively seeking care for memory problems in specialized settings like memory disorders clinics. The rate is lower in the community at large, when MCI is systematically detected by standardized assessment. In fact, MCI in the community appears to be an unstable and heterogeneous state with many individuals remaining stable or even reverting to normal over time. This discrepancy is inadequately understood, but suggests that it is premature to assume that MCI uniformly represents preclinical dementia. Outside specialty clinical settings, other conditions (e.g. anticholinergic medication effects, depression, heart failure) may contribute substantially to the observed impairments. It is likely that the criteria will undergo further refinement to enhance their predictive validity, possibly by including reliable biomarkers of underlying disease.

It must be firmly recognized that no test of cognitive function is entirely free of the effects of culture and education. Individuals of greater age and lesser education will typically perform worse on most neuropsychological tests than younger and better-educated persons. If not carefully accounted for, these factors can lead to misclassification error in epidemiological studies, potentially inflating prevalence estimates of cognitive impairment and dementia in populations with low literacy and education.

CROSS-CULTURAL ISSUES IN DIAGNOSIS AND EPIDEMIOLOGY

With some caveats, the process and functional consequences of brain ageing are assumed to be fairly similar in all populations, while their personal and social impact may not be the same across societies and cultures. Thus, the clinical thresholds may be different, or the same underlying disease biology may cross the clinical threshold to different extents in different populations. This variation can give rise to varying estimates of prevalence and incidence. Such estimates are also influenced by variation in life expectancy, the presence of co-morbid medical conditions, and local norms and expectations. In many cultures, cognitive impairment is considered an inevitable consequence of ageing, and expectations of the elderly are tailored accordingly. It may be the norm for younger family members to

assume most of the older adult's previous responsibilities other than basic self-care. Consider the examples of two older men with AD, one living in a large extended-family setting on a farm, and the other living alone in an urban apartment. Compared to the latter, the former may have to suffer a greater degree of cognitive impairment, and reach a more advanced stage of dementia, before he experiences interference with his own social and occupational functioning or the family reports a problem, resulting in a later diagnosis of dementia. Meanwhile, the second man's environment requires him to independently use household appliances, and manage his own meals, finances and transportation; a lesser degree of cognitive impairment would interfere with his daily functioning and lead to an earlier diagnosis of dementia. Measurements and diagnostic criteria developed in one setting or country may therefore not be entirely appropriate in another; cross-cultural validation is of critical importance as disease concepts and criteria are translated and applied internationally.

RISK AND PROTECTIVE FACTORS AND THE MEANING OF 'RISK'

Going beyond measures of disease distribution (prevalence and incidence), epidemiology also plays a major role in identifying disease determinants (risk and protective factors). As the term 'risk' is most commonly used in epidemiology, it refers to the probability of developing future disease. Thus, ideally, inferences about risk factors should be drawn from prospective studies and not cross-sectional or retrospective studies. Within any population, there are individuals who currently have disease, while the remainder are currently free of disease. A true risk factor is one associated with a significantly higher probability of future disease developing in currently disease-free individuals. The subgroup possessing this risk factor has a higher incidence rate of the disease than the subgroup without that risk factor. Similarly, protective factors are those associated with a lower probability and incidence rate of future disease. It is extremely important to recognize that an identified risk factor may not be the direct cause of the disease. It may be within the causal pathway, or might play a mediating or moderating role between a causal factor and the disease, or may be a surrogate for a causal factor. Further, a risk factor is not necessarily modifiable or preventable. Note that while some studies have singled out risk and protective factors for Alzheimer's disease, many have examined all dementias together, and, other than their genetics, little is known of risk factors for early-onset dementias.

For overall late-onset dementia, which is mostly Alzheimer's or vascular, the strongest known risk factor is greater *age*, as demonstrated by incidence rates increasing with age. Based on similar incidence rates in men and women, at least up until age 90, female *gender* may not be a true risk factor as previously supposed. Several studies have indicated that *lesser education* increases the risk of dementia; the underlying mechanism is not known. Possibilities include education being a reflection of, or a promoter of, greater cognitive 'reserve' capacity that allows the brain to resist or compensate longer for the increasing pathology within it. Alternatively, education could be a surrogate for lifelong socioeconomic status and its consequences, including nutrition and health care; or a confounding variable in the diagnosis of dementia based on cognitive test performance.

A positive *family history of dementia* in a first-degree relative increases the risk of dementia, suggesting a hereditary component. The genetics of AD have been studied the most extensively. While many genes have been reported to play a role in AD, there is, thus far,

conclusive evidence for only three deterministic genes and one susceptibility gene. Mutations of the *APP* (amyloid precursor protein) gene on chromosome 21, *PS-1* (presenilin 1) gene on chromosome 14, and the *PS-2* (presenilin 2) gene on chromosome 1 are all associated with early-onset familial AD. Relevant to the *APP* gene, *Down syndrome*, caused by trisomy of chromosome 21, is a well-established risk factor for AD. The one susceptibility gene consistently associated with sporadic cases and late-onset cases is the polymorphic *APOE* (apolipoprotein E) gene, on chromosome 19, also associated with cholesterol elevation. The *E*4* allele of this gene is associated with higher risk and/or earlier onset of Alzheimer's disease in a dose-related fashion, with homozygosity conferring higher risk than heterozygosity. In epidemiological studies, the *APOE*4* genotype is associated with a two- to three-fold elevation of probability of AD. The exceptions are African populations, where the *APOE*4* allele is of high frequency but appears not to increase AD risk, and African American populations, where risk elevation is present but lower. This paradox has been attributed to competing risk of vascular disease. Unlike the mutations, the *APOE*4* genotype only increases susceptibility and does not guarantee that the disease will occur. A comprehensive review of the genetics of AD and other dementias is beyond the scope of this chapter.

There is growing evidence that a host of *cardiovascular risk factors*, including but not limited to *hypertension*, *hypercholesterolaemia*, *diabetes mellitus* and *obesity*, all increase the risk of not only overall dementia and vascular dementia but also of AD. One explanation is that these factors operate primarily by causing cerebrovascular disease, which interacts with degenerative pathology, leading to earlier onset of the dementia syndrome. Another is that they directly influence neurodegeneration, for example by influencing the metabolism or accumulation of amyloid protein in the brain. From the epidemiological perspective, the most striking finding from long-term prospective studies is that dementia risk is elevated by hypertension, elevated serum cholesterol and obesity that are present in middle age, but in not old age. In fact, the onset of dementia in later life is preceded by a period of low blood pressure and cholesterol. These findings suggest, first, that the brain pathology that causes dementia develops over many decades and, second, that it is not only the presence or absence of a given factor but the timing and duration of exposure to the factor that influence the risk of dementia.

Other reported risk factors from the epidemiological literature are based on less consistent evidence. They include, for example, history of *head trauma* with loss of consciousness, possibly acting synergistically with the *APOE*4* genotype, *thyroid* abnormalities, and exposure to certain general *anaesthetic agents*.

Potential protective factors include the rare *APOE*2* genotype, intake of diets rich in *antioxidants*, exposure to the lipid-lowering drugs HMG Co-A reductase inhibitors ('statins'), exposure to non-steroidal anti-inflammatory drugs (*NSAIDs*), exposure to *oestrogen* supplements, *physical exercise* and *cognitive exercise*. It is difficult to draw firm conclusions about many of these factors because, although they show negative associations in observational studies, intervention studies using them have not revealed benefits in preventing or delaying the onset of dementia. Some observational data suggest that oestrogen supplements taken for several years, starting at menopause, may reduce incidence of Alzheimer's disease at least a decade later. However, clinical trials of oestrogen supplements taken

in later life have not shown a protective effect against dementia and in fact suggested an increased risk. As noted earlier, the timing and duration of exposure to risk and protective factors may be critical.

Two examples will be discussed to further illustrate the complexity of putative risk relationships.

Cigarette smoking has been shown in cross-sectional as well as some prospective epidemiological studies of older adults to be associated with a lower probability of Alzheimer's dementia. Short-term trials of transdermal nicotine patches have been inconclusive.

It is certainly plausible that the nicotine use can have cholinergic effects that promote cognitive performance. However, it is also likely that the apparent protective effect is an artefact reflecting survival bias. Smokers who survive into old age without succumbing to heart and lung disease or cancer might be an unusually hardy group with enhanced capacity to resist many diseases including AD; those who died before they could develop dementia cannot participate in these studies.

Depression: in case-control studies, individuals with AD are more likely than healthy controls to have had previous histories of major depression. Older adults with major depression have cognitive deficits which resolve only partially when the depression remits. Major depression in younger adults has been found to be associated with atrophy of the hippocampal cortex, which has been attributed to prolonged hypercortisolaemia caused by depression¹⁶. The hippocampus and medial temporal lobe are the areas typically affected by AD pathology. An autopsy study of patients with AD showed that those who had suffered major depression earlier in life had greater density of degenerative pathology in their hippocampi than those with no previous history of depression¹⁷. However, one prospective population study was able to divide elderly participants without dementia into one subgroup which developed dementia over the next several years and another subgroup that remained dementia free. Depressive symptoms at the beginning of the study did not predict rate of cognitive decline in either group; subsequent cognitive decline was primarily explained by the incipient dementia¹⁸. A potential unifying hypotheses is that depression earlier in life may increase the brain's vulnerability to dementia, while late-onset depression may be merely an early manifestation of the dementing disorder.

BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Although cognitive impairment is the clinical hallmark of the dementias, Alzheimer's original case report was based on a woman who was brought for care primarily because of her behavioural and psychological disturbances¹⁹. These are still the symptoms that frequently bring patients with dementia into the mental health care system, but they have not been the focus of much epidemiological work. At least two major population-based studies have shown that the majority of patients with dementia have one or more neuropsychiatric symptoms which add considerably to personal distress and caregiver strain. Irritability and depressed mood are somewhat more common in earlier

and milder stages of disease, while wandering, apathy and delusions are more common in more advanced disease^{20,21}.

STUDY METHODS

For a comprehensive review, readers are directed to any standard epidemiology textbook. A few critical points follow. Different inferences should be drawn from different types of studies: for example, observational vs. experimental; cross-sectional vs. longitudinal; clinical case-control vs. population based. The source of the study sample, its size, and its potential for bias should be taken into account when interpreting the results and generalizing beyond that sample. Statistical significance indicates that the result is unlikely to have occurred by chance, but does not mean that the effect was large in size or that it was clinically significant. Screening tools should be selected after consideration of both sensitivity and specificity, which are usually enhanced at the expense of each other. The same tool, with no change in sensitivity or specificity, can have different predictive value in different populations, depending in part on how prevalent the disease of interest is in a given population.

Brain imaging and other biomarker-based approaches to diagnosis are gaining ground in clinical research as well as clinical practice, especially in the more affluent countries. To a lesser extent, epidemiological studies are incorporating these methods to determine their utility and validity for diagnosis at the population level, and to examine the distribution of these markers in individuals outside the specialty clinical setting. Very few epidemiological studies include *autopsy* data. They have shown the remarkable heterogeneity of neuropathology among individuals with dementia in the community, and also the extent of pathology that exists in relatively old individuals who were cognitively intact until the time of death⁶.

FUTURE DIRECTIONS

Future research in the epidemiology of dementia faces both opportunities and challenges. The distribution of dementia and milder forms of cognitive impairment must be understood in a variety of populations, some of which have never been studied. As new tests and biomarkers are developed in specialized research settings, their validity must be ascertained in the community before they are recommended for widespread clinical use. Such research will contribute substantially to improved diagnosis and even preclinical detection of disease. Future studies will also focus on normal ageing, establishing norms for a wide range of populations to help distinguish healthy from pathological ageing. Longer-term population studies must track dementia incidence rates over time, to determine whether or not successive generations are following the same trends as life expectancy increases. They must also examine potential relationships of incidence to the different lifetime exposures in different generations. There is a growing call for 'life-course epidemiology'; that is, studies that start following cohorts of people when they are young or middle aged²². These studies will minimize survival bias and allow risk and protective factors to be studied early enough, and for long enough, to shed light on their long-term relationship with the dementias of later life. Such data will provide greatly improved information regarding potentially modifiable risk factors, and provide the basis for strategies to prevent dementia, or at least reduce its incidence, in future generations.

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An Introduction to the Medical Research Council Cognitive Function and Ageing Studies (CFAS) I and II

Fiona E. Matthews¹ and Carol Brayne²

¹*MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK*

²*University of Cambridge, Department Public Health and Primary Care, Cambridge, UK*

INTRODUCTION

The rise in numbers of older people and the changing proportion of old to young people has been predicted for some time. It has become clear that the potential impact of this ageing phenomenon would have a major impact on population health profiles. Its potential impact on social and economic aspects of the more affluent countries highlights ageing as a sufficiently important issue in resource allocation. Discussion between the UK Department of Health, UK Medical Research Council (MRC), and experts from the scientific and medical communities late last century resulted in the decision that brain changes, most particularly cognitive decline, dementia and their relation to disability were key topics requiring investigation at the population level. This prompted a decision to invest in research into this area and a working group was convened, which included those with epidemiological and biostatistical expertise relevant to such investigation. Out of this working group a successful bid for the study now known as the MRC Cognitive Function and Ageing Study (CFAS) emerged¹.

STUDY DESIGN

The study is a six-centre multidisciplinary multiphased longitudinal design. There are five identical sites and one with a different sampling and interview structure. This centre (Liverpool, also known as the ALPHA study, see Figure 39.1) was already funded at the time of the discussions noted above and thus started earlier than the other five centres². The other five centres (Cambridgeshire, Gwynedd, Newcastle, Nottingham and Oxford) were able to follow a standardized design and are referred to as the five identical sites. Their basic structure was a two-phase design with a screening interview followed by an assessment interview shortly afterwards, with a repeat at two years. The fieldwork began in 1991 to 1993 (centre dependent)³ (see Figure 39.2 for flow diagram). Additional features are more fully described on the website (www.cfas.ac.uk).

In 2008 additional funding from the MRC enabled the introduction of a new cohort in three of the original CFAS centres (Cambridgeshire, Newcastle and Nottingham). Further funding from the Economic & Social Research Council (ESRC) in 2009 will enable a new cohort to be recruited to the Gwynedd centre (plus a new centre in Neath, Port Talbot) which focuses more on the social aspects of ageing.

THE AIMS OF THE STUDY

The aims of the study (see Box 39.1) have evolved over its existence and cover a wide range including descriptive epidemiology, neuropathology, policy, molecular epidemiology and ethics. The principal neuropathological aim was to determine the contribution of different underlying pathologies to the rates of dementia and the geographical variation in these rates, and to the burden of disability.

Box 39.1 CFAS core aims

CFAS I core aims:

The main descriptive epidemiological aims include:

- the estimation of the prevalence and incidence of cognitive decline and dementia, and geographical variation in those rates;
- the determination of the natural history of dementia, in particular the rate of progression of cognitive decline including the distribution of the interval between the identification of cognitive impairment and death;
- the identification of factors associated with differing rates of cognitive decline and with the risk of dementia.

Additional aims included:

- to determine the prevalence and severity of pathological lesions in the brain of an unselected cohort of older people with and without cognitive impairment;
- to determine the frequency of specific pathological diagnoses in people with cognitive impairment;
- to correlate severity of specific pathologies with patterns of cognition, function and behaviour in life independently of clinical and pathological diagnostic categories. CFAS II core aims include:
 - to update profiles of cognitive and physical function, physical and mental health and disability of people aged 65 or over in four of the original CFAS centres: Cambridgeshire, Gwynedd, Newcastle and Nottingham;
 - to estimate the cohort change in prevalence and incidence of cognitive impairment and dementia;
 - to investigate whether the measures that characterize the intermediate stage (mild cognitive impairment) best within the original CFAS are stable across generations;
 - to quantify medication, health, social service use, social support, residential characteristics and care states, including formal and informal care, of people with dementia, frailty or physical disability across the three sites;
 - to assess the contribution of different diseases, particularly dementia, to any change in the burden of disability over time, specifically whether diseases have become more or less disabling and estimate the effect of prevention vs. treatment;

- to compare the size of relationship of known genetic factors with frailty, including cognitive impairment, with those found in the earlier cohort;
- to provide a foundation for other collaborative studies that investigates biomarkers and further investigation of early markers, including imaging, for risk of cognitive decline.

The DNA resource was incorporated in a later phase of CFAS I. In CFAS II saliva is collected at baseline. The main molecular epidemiological aim has been to support genetics studies that have sought genes associated with dementia, Alzheimer's disease, mixed and vascular dementia, cognitive impairment and decline. A later aim of the study was to explore the ethical and legal aspects of brain donation within a population-based sample given changing perception surrounding organ donation. The study also aimed to act as a core resource and provide a framework to support specific sub-studies in lone or joint centres. The Resource Implication Study⁴⁻¹⁰ used this framework to achieve the core policy aim (see above).

METHODOLOGY

Because the main study is focused on cognition and dementia it has collected the necessary dimensions of physical and mental health to arrive at a study diagnosis of dementia. It now has four major themes: (i) dementia (covering all aspects including cognition); (ii) depression; (iii) disability and healthy life expectancy; and (iv) health policy and health. In addition it has particular strengths in that it is one of

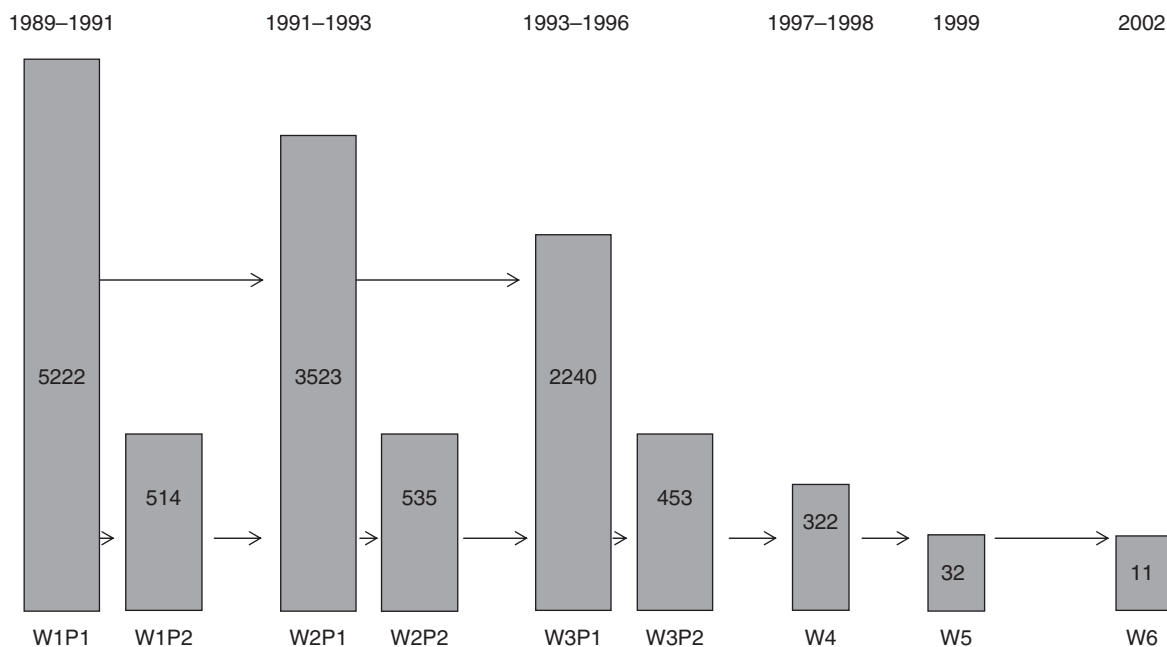


Figure 39.1 MRC Alpha Study: Liverpool centre design number of interviews

Source: Morris, J.C. (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, **43**, 2412-4

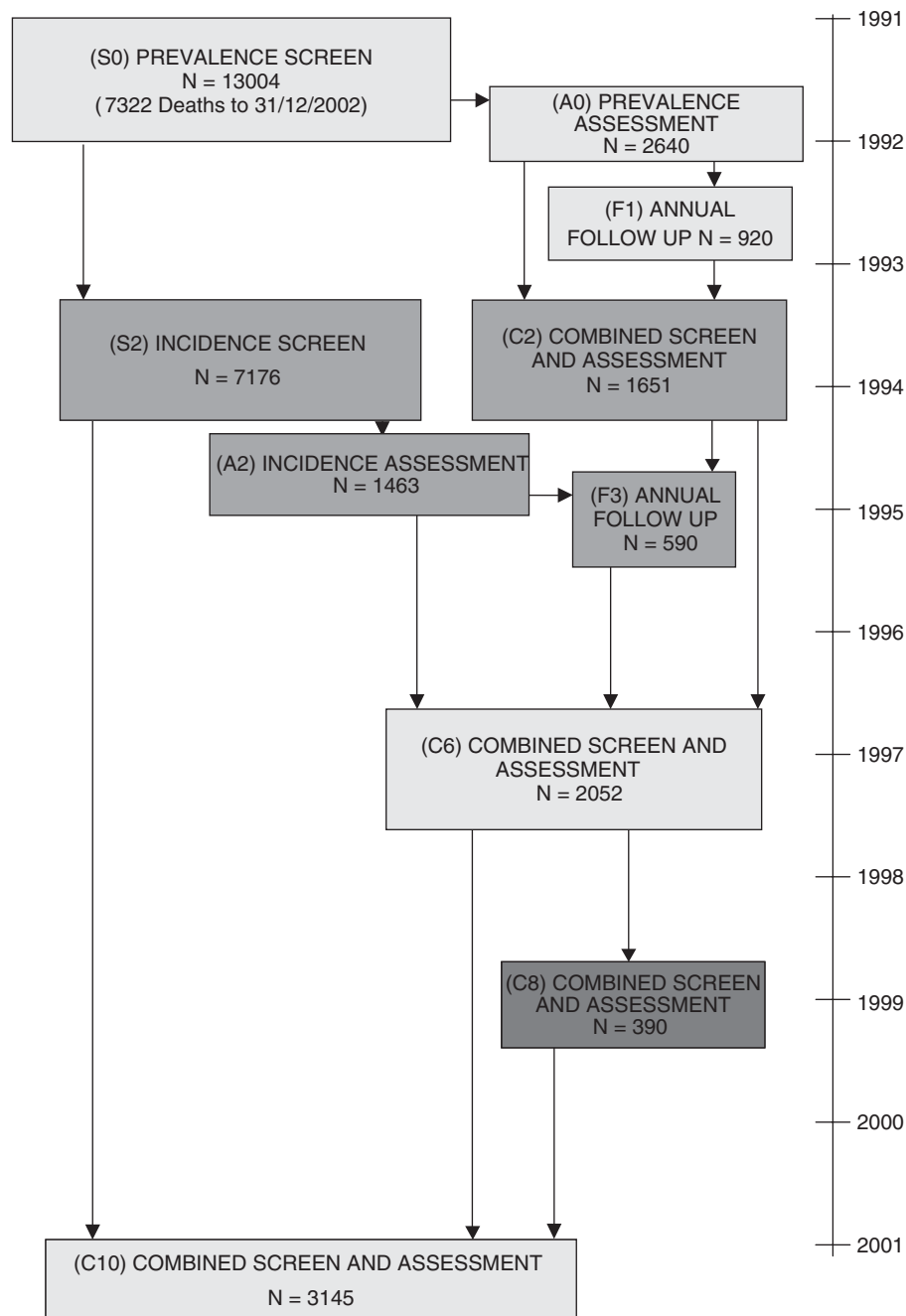


Figure 39.2 CFAS I identical centres study design

the very few truly population-based programmes with a brain donation programme – individuals in the study have indicated whether they wish to contribute to brain research through the donation of their brain after death (declaration of intention to donate).

Study Population

The first aim of the study was to estimate age-specific rates of prevalence of cognitive impairment and dementia among those aged 65

and over. The population is thus all those aged 65 years and over on the index date for centre (1990, 1991), living within a specified geographical location. Background information on the demographics of the populations sampled was collected from the Office of Population Censuses and Surveys (OPCS) 1990–91 census, now Office for National Statistics (ONS), to relate to regional and national data. Family Health Services Authority (FHSA) lists were used as the sampling frame. The frame would be incomplete if eligible members of the population were not registered with a GP. However, individuals

in long-stay hospitals remain registered with their GP two years after institutionalization so sampling from FHSA lists ensured their inclusion. Each centre looked into the practices of long-stay hospitals in their area to confirm this. The FHSA list of individuals was used for sampling on a geographical basis. Each centre defined this area, and the study population was drawn from all those who were resident within it. Problems of inaccuracy, patients who died or moved away but were still on the FHSA list, were resolved by asking GP surgeries to check the lists. On this basis, a sample of sufficient size to yield 2500 interviews of individuals aged 65 years and over, stratified by age (equal numbers aged 65–74 and 75 plus) was chosen from the FHSA lists for each selected area (in Liverpool this was 5000 interviews stratified by sex and five-year age band). The population is flagged at ONS for mortality and the database is updated continuously. The follow-up has been determined by funding and the design of associated bolt-on studies.

The main follow-up waves for the identical sites are captured in the audit trail shown in Figure 39.2, which shows the numbers for the main screen, assessment, one-year follow-up and two-year rescreen, new selection for assessment and further one-year follow-up, six-year follow-up of the assessed (with venepuncture), eight-year follow-up of those with intentions to donate, and 10-year follow-up of the total sample. In addition to this the main associated studies are the Resource Implications Study (four centres – Cambridgeshire, Newcastle, Nottingham, Oxford), which followed those who provided care to the physically and cognitively frail at baseline^{4–10}, the ESRC-funded Healthy Ageing Project, which interviewed in detail those who were not selected into the Resource Implications Study in Nottingham and Cambridgeshire^{11–16}, the Network Study conducted in Gwynedd and Liverpool to examine individuals' social networks, an embedded case-control study at two-year incidence stage (Cambridgeshire), and the ongoing brain donation programme in all centres. This programme, in combination with the bloods taken at year 6, form the major components of the biological resource of the study.

CFAS II will also have the same sampling frame and study size (at each centre). CFAS II is longitudinal at outset with two complete sweeps of the data planned. Each phase is two years apart.

Interview Method

All interviews were conducted in the respondent's place of residence, using portable computers with customized software. If the interviewer felt that the respondent was frail and tiring, or becoming agitated, the short 'priority mode' set of questions could be invoked manually. Permission was also sought to access GP and hospital notes.

Content

CFAS I screening interview contains questions on residence, marital status, education and occupation, living circumstances, contact with friends and family, health and social care contact, self-reported physical health, instrumental activities of daily living and activities of daily living, cognitive measures (Mini Mental State Examination (MMSE) with augmentation) and medication. The assessment interview is mainly the Geriatric Mental State Examination (GMS) adapted for CFAS^{17–19}. This is a structured psychiatric interview, which collects sufficient information for algorithmic 'diagnosis' in

the major psychiatric disorders of old age (dementia, depression, anxiety and psychosis). This has been validated against clinical diagnosis and the instrument has been widely used in Europe and now forms part of the 10/66 international instrument. This interview has been augmented with questions from the CAMDEX (Cambridge Examination for Mental Disorders of the Elderly) including CAMCOG²⁰, the longer neuropsychological assessment. The relative or carer interview is mainly the History and Aetiology Schedule, the informant interview that accompanies the GMS. The combined screen and assessment interview merges the two interviews but compresses some aspects of data collection. Complete versions of all the interviews including the interview questions and responses are available on the website. CFAS II interview contains all the previous screening and assessment interview information plus additional questions on diet, social activity and objective measures of hearing and physical activity. The neuropathological assessment follows the standardized protocol of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)²¹, with the exception that the neuropathologist is blind to the interview data. This covers in a semiquantitative form the main areas required for the assessment of neurodegenerative and cerebrovascular disorders. The forms are available on the website. The main genetic analyses have been on ApoE and ACE. CFAS II has saliva collection at the outset for genetic comparisons. Data collection in Liverpool was broadly similar to the other five sites except that the screening interview consisted of the GMS plus some of the screening interview questions listed above.

Selected Study Findings

The study has reported on prevalence, incidence (see Figure 39.3) and risk factors of dementia (Table 39.1), and lack of variation in these across the five identical sites^{22–24}.

It has provided profiles of cognition for MMSE, extended MMSE and CAMCOG, weighted back to the population^{25,26}. It has reported on risk for incident dementia including ApoE and ACE (Table 39.2)^{27–29}.

It has examined the relationship of cognition to mortality³⁰. In addition, the study has reported on a variety of impairments to healthy life in old age and their population burden^{31–42} and on a variety of neuropathological markers related to dementia and old age (see Table 39.3)^{43–54}.

Recent publications have also included the investigation of behavioural (BSPD) symptoms of dementia and on stability and population applicability of mild cognitive impairment^{55–59}. The Resource Implications Study has provided data for examination of carer burden and the costs of care for the physically and cognitively frail^{6,10}. The data have been used for projection forward for these vulnerable groups and also for the costs of long-term care⁶⁰. Liverpool has published on the prevalence of dementia, depression and neurosis, together with incidence of dementia and schizophrenia^{2,61–66}.

CFAS I AND II AS A RESOURCE

The study is multisite and multidisciplinary. The population is truly representative with high response rates at each stage over diverse sites. Where there is no heterogeneity across sites the study is sufficiently large to provide indicative values for national estimates. The broad scope of measures has allowed the study to contribute to ageing research across a wide range of topics. There are repeat

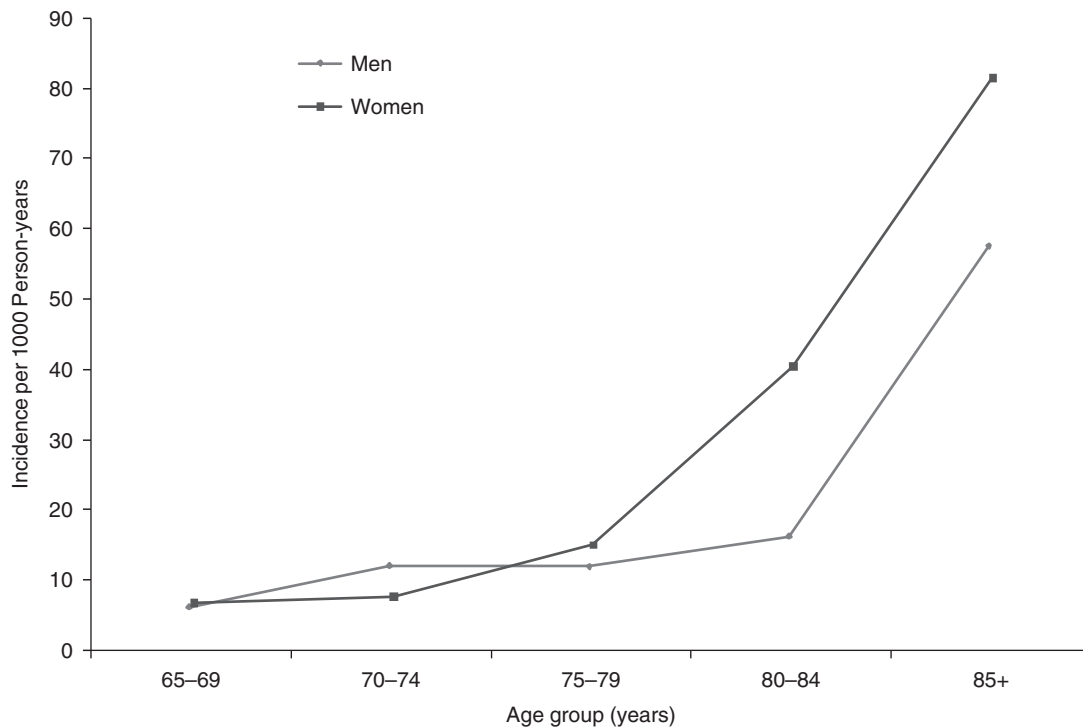


Figure 39.3 Incidence of dementia by sex (five identical centres)
Source: adapted from Matthews⁷¹

Table 39.1 Risk factors for incident dementia (socio-demographic)

	OR*	(95% CI)
Age (90+ years vs. 65+ years)	25.6	(11.6–56.9)
Sex (women vs. men)	1.6	(1.1–2.4)
Education (<9 vs. 10+)	1.9	(1.3–2.2)
Self-reported health (poor vs. good)	3.9	(2.2–6.4)
Stroke (yes vs. no)	2.1	(1.1–4.2)
Parkinson's disease (Yes vs. No)	3.5	(1.3–9.3)
General anaesthesia (Yes vs. No)	0.6	(0.4–0.9)

*Adjusted for all other factors in the table.

Source: Morris, J.C. (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, **43**, 2412–4

measures on cognition and function, which allows examination of trajectories. There are only two other population-based studies with brain donation in Europe⁶⁷. The study weighted the sample towards the over 75 age group at baseline, which has provided more robust data for the oldest old. As in all epidemiological research in older populations it would be desirable to have higher response and lower dropout between waves, but analysis can adjust for loss between interviews^{68–70}. Blood taking and clinical assessment (including imaging) at baseline was not possible because of funding constraints, but venepuncture was included at year 6. The risk measures are self-report, using the available validated measures of the era. The study actively encourages collaboration, and there are established mechanisms for approaching us via the themes mentioned above. Information is available on the website and also through contact with theme leads.

Table 39.2 Incidence of dementia and ApoE genotype

	Comparison using non-demented controls			
	Adjusted*		Adjusted* and weighted**	
	OR	95% CI	OR	95% CI
<i>Allele</i>				
ε2	0.6	0.3–0.9	0.3	0.1–0.6
ε3	1.0		1.0	
ε4	2.2	1.6–3.0	2.9	1.7–4.9
<i>Genotype</i>				
ε2/ε2	0.5	0.0–5.7	0.3	0.1–1.7
ε2/ε3	0.6	0.3–1.1	0.2	0.1–0.7
ε2/ε4	0.6	0.2–2.3	0.2	0.0–1.3
ε3/ε3	1.0		1.0	
ε3/ε4	2.3	1.5–3.6	3.6	1.8–7.3
ε4/ε4	5.0	1.9–13.0	7.9	1.6–39.2

*For age group, sex, education and social class.

**For study design and dropout.

Source: reproduced from Keage²⁹

The study website, www.cfes.ac.uk, configures information under themes, documentation, publications and data. There is also a list of study contacts.

CONCLUSION

The methods and results of the Medical Research Council Cognitive Function and Ageing Studies (MRC CFAS) I and II are described

Table 39.3 Neuropathological factors associated with dementia

Neuropathological findings	Age-adjusted analysis		<i>p</i>	Multivariable analysis			
	OR	(95% CI)		OR	(95% CI)	PAR %	(95% CI)
Age at death							
<80 years	1.0			1.0			
80–89 years	3.2	(1.8–5.5)		2.5	(1.1–5.8)	8	(0–16)
≥ 90 years	5.2	(2.9–9.4)	<.001	3.4	(1.4–8.3)	10	(3–16)
Brain weight for sex							
Low	5.7	(3.2–10)		4.1	(1.9–9.2)	12	(5–19)
Average	2.0	(1.2–34)		2.1	(1.0–4.2)	5	(0–11)
High	1.0		<.001	1.0			
Neuritic plaques in neocortex							
None	1.0						
Mild	1.2	(0.7–2.2)	}	1.0			
Moderate	2.9	(1.7–5.0)					
Severe	18.5	(7.3–47)		9.7	(2.1–43)	8	(3–14)
NFT in neocortex							
None	1.0			1.0			
Mild	1.3	(0.8–2.1)		1.0	(0.5–1.80)	}	
Moderate	8.9	(4.0–20)		7.1	(2.3–22)		
Severe	∞		<.001				(5–19)
Congophilic angiopathy							
None	1.0			1.0			
Mild	1.9	(1.1–3.3)		1.8	(0.8–3.8)	2	(0–6)
Moderate	4.0	(2.2–7.4)	}	2.9	(1.2–6.8)	5	(1–10)
Severe	∞						
Lewy bodies							
No	1.0			1.0			
Yes	3.2	(1.5–6.9)	0.003	3.5	(1.3–9.3)	3	(1–7)
Overall vascular pathology							
None	1.0			1.0			
Infarcts/haemorrhage	1.0	(0.3–3.8)		2.4	(0.4–12)		
SVD/WML/lacunes	2.5	(1.4–4.4)		3.7	(1.5–9.6)	12	(3–19)
Both	2.9	(1.6–5.5)	0.003	4.8	(1.9–12)	9	(3–15)
Hippocampal atrophy							
None	1.0			1.0			
Mild	2.2	(1.3–3.9)		1.8	(0.9–3.7)	2	(0–6)
Moderate	6.9	(3.7–13)	}	3.4	(1.5–7.5)	8	(2–15)
Severe	11.1	(2.5–50)					

Source: adapted from MRC CFAS Neuropathology Group⁵⁴

above, as well as the design and aims of these two studies (started in October 2008). CFAS I and CFAS II are population-based studies of individuals aged 65 and above living in England and Wales. CFAS I has produced a range of results and a selection are shown within the chapter. The study data are part of a facilitated managed resource for collaborations, details of which have been described.

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The Lundby Study

Mats Bogren, Cecilia Mattisson and Per Nettelbladt

Department of Clinical Sciences, Psychiatry, Lund University Hospital, Sweden

From the Lundby Study, reports on dementias in the elderly for the period 1947–72 have been published. In the EURODERM comparative prevalence studies^{1,2}, the Lundby prevalence rates of senile dementia of the Alzheimer type (SDAT) in the age intervals 60–69, 70–79 and 80–89 were 0.3%, 2.5% and 10.9%, respectively, and for vascular dementia 0.8%, 3.5% and 6.3%.

In another study^{3,4}, the cumulative lifetime probability of contracting SDAT was reported to be 25.5% in men and 31.9% in women. For severely impaired cases, the figures were 15.5% and 22.2%, respectively. For vascular dementia the figures were 29.8% in men and 25.1% in women, for severe cases 16.6% and 15.2%, respectively. Background factors to SDAT and vascular dementia have also been studied^{5,6}. The last follow-up in 1997 covering the period 1972–97 has now enabled us to compare the population's first incidence of dementia and other organic brain disorders over the two time periods 1947–72 and 1972–97⁷.

The Lundby study is a longitudinal investigation of mental disorders in a total population. It originally included all people living in a rural area in 1947 or 1957^{8,9}. This population has been investigated in 1947, 1957, 1972 and 1997^{8–11} and at each point information has been obtained about the development of the mental and physical health for all individuals alive at the previous investigation providing an opportunity to observe changes of mental disorders in the population over 50 years.

At the inception, the study population lived in two parishes outside the university town Lund in the southern part of Sweden. In 1947 the Lundby area was rural with 2550 inhabitants, aged 0–92 years. In 1957 1013 newcomers were included (one-third born since 1947; and two-thirds immigrated). In all follow-ups, those subjects who had moved out of the area were also investigated. Information was also collected about those who were deceased since the previous follow-up. The present findings apply to the total cohort ($n = 3563$, male 1823, female 1740).

By 1972 gradual urbanization had changed the Lundby area from a farming district into a suburban area⁴, which was even more obvious in 1997. Moreover, in 1972, many subjects had moved away from the Lundby area; of the 2827 still alive in 1972, 1424 remained, while 1403 had moved; in 1997, 602 of the 1797 survivors remained, while 1195 had moved.

At the follow-ups the aim has been to obtain as much information as possible about all episodes of mental and somatic disorders in

all individuals in the population. Data was gathered from several sources: interviews, case registers, case notes, autopsy reports and key informants^{11–14}.

Thanks to the many data sources the diagnostic attrition 1947–72 was only 1%; although it was 6% between 1972–97. However, in those over 50 years old in 1972 the attrition 1972–97 was 2% in males and 3% in females.

Psychiatrists have conducted all interviews and evaluations of data. The diagnostic principles have been kept similar and were based on consensus^{9–11}. The diagnoses were aimed at getting 'a rough picture of the relative distribution of the main types of mental illness in the population'⁹.

Neurotic and psychotic disorders were disorders without evidence of organic aetiopathology. Neurotic, as opposed to psychotic, indicated preserved insight. Organic brain disorders included states with global cognitive dysfunction or gross personality or behavioural disturbance, with obvious organic causation.

Only one diagnosis per episode of disorder was recorded with organic brain disorders ranking higher than psychotic disorders, which in turn takes precedence over neurotic disorders. Furthermore, every episode of disorder was rated along with the degree of dysfunction caused by it (minimal, mild, medium, severe or very severe) according to the criteria defined by Leighton *et al.*¹⁵. A mild degree of impairment corresponds to a Global Assessment of Functioning (GAF) score of 70–61; medium corresponds to 60–51, and severe to 50–31. Episodes with medium, severe or very severe impairment¹⁶ were chosen to indicate caseness. For all episodes, onset and termination were assessed as closely as possible using all sources of information.

Incidence rates for organic brain disorders in the periods 1947–72 and 1972–97 were obtained as the number of first occurrences of the outcome divided by the total number of person-years under risk for the outcome in individuals who had previously been free from the outcome. Individuals contributed with risk-years until contracting the outcome, dying, dropping out of the study or the end of the study period.

When age- and sex-specific incidences of organic brain disorders in 1947–72 and 1972–97 were compared, the rates had decreased consistently from the first to the last period in all age intervals but 40–49 (Table 40.1). Both male and female age-standardized first-incidence rates decreased significantly from the first to the last period.

In both periods the age-standardized incidence rate of organic brain disorders was higher in males than females. The difference was significant in 1947–72, but not in 1972–97.

When the impairment threshold to indicate caseness was changed from medium to severe, the age-standardized first incidence per 1000 years at risk of organic brain disorders declined from 3.4 to 2.0 in males and from 2.9 to 2.0 in females from 1947–72 to 1972–97. There were no cases of organic brain disorder with impairment level under medium.

In the period 1947–72 dementia constituted 80% and milder organic brain disorders 20% of the category organic brain disorders. In the period 1972–97 the corresponding figures were fairly similar at 83% and 17%, respectively.

When organic brain disorder was divided into dementia and other organic brain disorders not reaching the dementia threshold, one

could still, for both groups, see a decrease of the age-standardized first incidences from the first to the second 25-year investigation period. In males the age-standardized first incidence of dementia fell from 5.1 to 2.1 per 1000 years at risk and in females from 4.0 to 2.1. The age-standardized first incidence of organic brain disorders not reaching the dementia threshold fell from 1.2 to 0.6 in males. Among females there was only a marginal decrease from 0.5 to 0.3.

The age interval responsible for the reduction of the age-standardized first incidence of dementia was above all the 70–99 interval, while the age intervals concerned regarding the reduction of milder organic brain disorders were those under 70. In males aged 70–99 the first incidence of dementia decreased from 28.4 to 10.9 per 1000 years at risk. In females the first incidence decreased from 23.4 to 12.6.

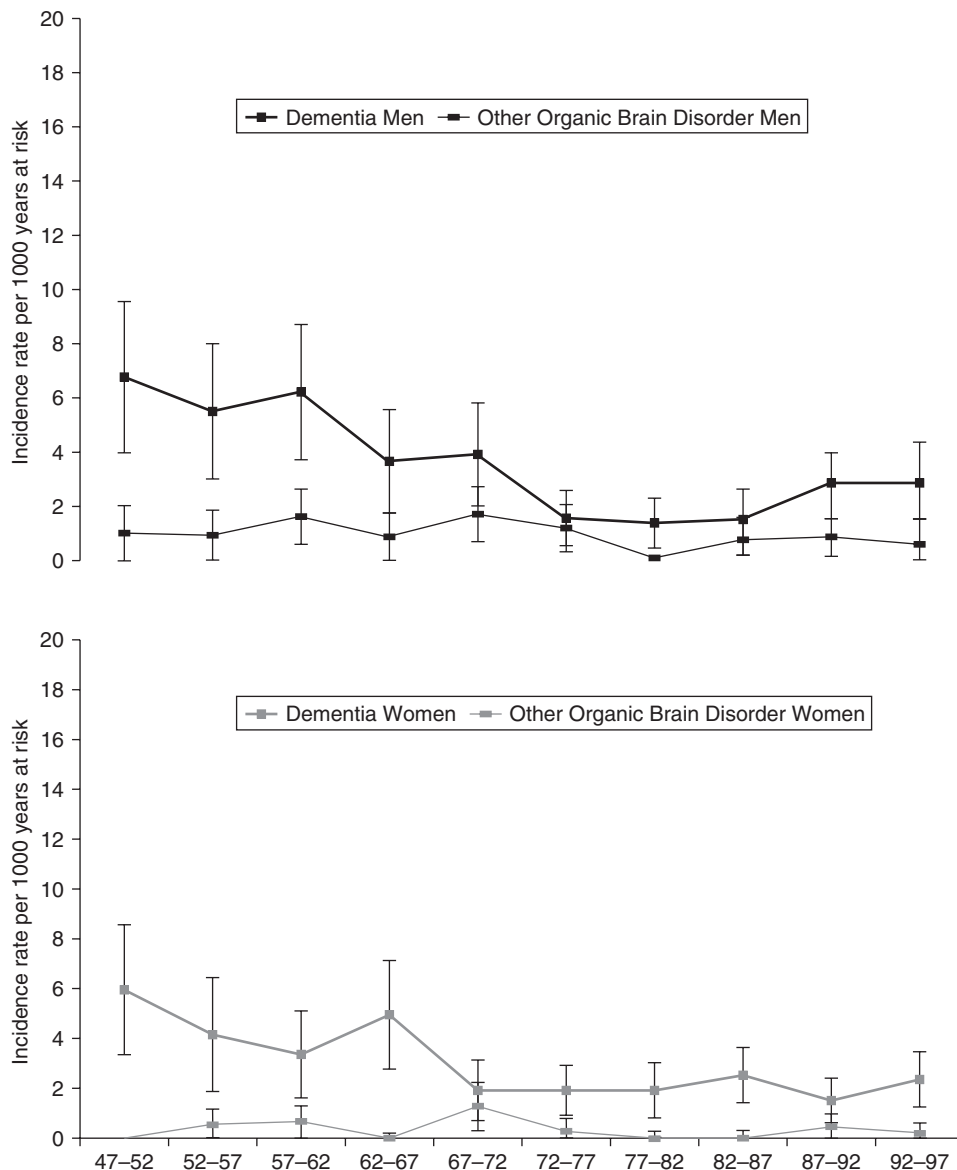


Figure 40.1 Age-standardized first-incidence of dementia and other organic brain disorders of medium + (GAF 60-1) impairment by five-year periods 1947–97

Source: Reproduced with permission from Australian & New Zealand Journal of Psychiatry, 2007; 41(2):178–186

Table 40.1 Organic brain disorders of medium + (GAF 60-1) impairment. First incidence per 1000 years at risk (μ) with 95% confidence intervals (CI)

Age	1947–72				1972–97			
	C	L	μ	95% CI	C	L	μ	95% CI
Men								
15–29	3	8354	0.4	–0.0–0.8	0	1869	0	
30–39	4	5669	0.7	0.0–1.4	2	3862	0.5	–0.2–1.2
40–49	1	5683	0.2	–0.2–0.5	3	5399	0.6	–0.1–1.2
50–59	12	4997	2.4	1.0–3.8	3	5516	0.5	–0.1–1.2
60–69	24	3495	6.9	4.1–9.6	15	4984	3.0	1.5–4.5
70–99	84	2676	31.4	24.7–38.1	60	4445	13.5	10.1–16.9
Total	128	30874	4.2	3.4–4.9	83	26076	3.2	2.5–3.9
			6.4*	5.3–7.5			2.8*	2.2–3.4
Women								
15–29	1	8125	0.1	–0.1–0.4	0	1755	0	
30–39	4	5147	0.8	0.0–1.5	0	3872	0	
40–49	0	4974	0		1	5410	0.2	–0.2–0.6
50–59	5	4699	1.1	0.1–2.0	1	5145	0.2	–0.2–0.6
60–69	11	3671	3.0	1.2–4.8	7	4729	1.5	0.4–2.6
70–99	73	2938	24.8	19.2–30.5	80	5593	14.3	11.2–17.4
Total	94	29554	3.2	2.5–3.8	89	26505	3.4	2.7–4.1
			4.5*	3.6–5.4			2.4*	1.9–3.0

C = First-incident cases. L = Years at risk. * = Age standardized.

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Male and female age-standardized first-incidence rates of dementia and other organic brain disorders every fifth year from 1947–97 are seen in Figure 40.1. In both males and females a trend of decreasing incidences of dementia can be observed from 1947–97, while five-year incidences of other organic brain disorders remained fairly constant through the whole period.

There are a limited number of studies that have tried to ascertain secular trends of dementia incidence. However, in a study from Rochester, Minnesota, no significant change of the incidence of dementia was seen from 1960 to 1984^{17,18}. One difference from the Lundby study was the shorter length of the observation period. A long period of study might be needed to be able to see a slow change over many years¹⁸.

The Lundby population offers an opportunity to study the rates of dementia and other organic brain disorders during a period of great transition in society and development of public health. This transition includes changes of lifestyle (e.g. food, smoking) and increased availability of medical care (e.g. antihypertensive and antidiabetic treatment) as well as changes in the physical environment. Thus, the decrease of organic brain disorders in both male and female subjects may be the result of a healthier lifestyle and availability of treatments protecting against the development of organic brain lesions.

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Clinical Features of Alzheimer's Disease: Cognitive and Non-cognitive

Oludamilola Salami and Constantine G. Lyketsos

Johns Hopkins School of Medicine and Johns Hopkins Bayview, Baltimore, USA

Alzheimer's disease is best described as a neurodegenerative brain disease that causes a clinical dementia syndrome. It is the most common neurodegenerative disorder, accounting for over 60% of dementia cases in late life. Alzheimer's dementia is estimated to affect over 4 million Americans and 21 million persons worldwide¹.

The dementia associated with Alzheimer's disease is heterogeneous and diverse. Symptoms and signs vary with the progression and severity of the illness. Progressive cognitive decline with impaired ability to function in the person's usual environment is regarded as the hallmark of the clinical syndrome. Memory is invariably affected. There is also dysfunction in other domains of cognition including language, visuo-spatial, perception, recognition, praxis and executive function. Non-cognitive neuropsychiatric symptoms (NPS) are universal over the course of illness and are themselves diverse. These include affective, perceptual, behavioural, motivational and personality changes. Alzheimer's disease is usually indolent in its early course. Progression of the disease is associated with loss of independent function. The impact on sufferers, caregivers and other loved ones is often profound. Estimates of life expectancy in Alzheimer's disease range from 3 to 9 years². The mortality rate associated with Alzheimer's dementia is on the order of 10.6 deaths per 100 000 person-years in the population³.

Alzheimer's disease and delirium are clinical syndromes with similarities in clinical features and may be co-morbid. In the early stages of Alzheimer's disease, the key differences are the acute onset, fluctuating symptoms and the prominent sleep-wake cycle fragmentation which are seen in delirium and not in Alzheimer's disease. However, advanced Alzheimer's disease is difficult to differentiate from delirium, except by the clinical history⁴. This section focuses on the clinical presentation of Alzheimer's disease, and the occurrence of its clinical features along a spectrum from early disease to the advanced stages.

COGNITIVE SYMPTOMS

Impairment in cognitive function is the core feature of Alzheimer's disease. Several areas of cognition may be affected and the degree of impairment varies with illness severity (Table 41.1).

Memory

Disturbance of memory is regarded as the hallmark of Alzheimer's disease. Memory impairment is, however, not always the initial symptom. Affective symptoms may often precede memory disturbance⁵. It is important to note that the spouse or close relatives of most patients with Alzheimer's disease are usually the ones who bring the memory deficits to clinical attention, not the patients themselves. Early memory symptoms heralding the onset of dementia include difficulty with the registration and retention of new information, leading to repeating questions or comments. There may also be difficulty manipulating stored information associated with working memory. Delayed spontaneous recall of recently acquired information is impaired in early stages⁶. Immediate recall, recognition and registration of information become increasingly affected with progression of illness. As these symptoms worsen, memory dysfunction affects daily function, which is important in differentiating dementia from memory decline associated with normal ageing. Individuals with early Alzheimer's disease may develop difficulty recalling recent tasks, events, directions and appointments.

Those with advanced education or high intellectual reserve may be able to adapt for some time with minimal impact on their daily function. Some resort to memory cues, such as taking notes or keeping journals, to compensate for decline in memory. In moderate to severe stages, long-term memory becomes impaired. There may be inability to accurately recall details of familiar historic events and personal information, including names of family members, birthdays, special occasions or other aspects of declarative memory.

Language

Both oral and written impairments of language are found in Alzheimer's disease. In the early stages, fluent dysphasia may predominate, often in a pattern similar to transcortical sensory aphasia. Characteristic deficits at this stage include diminished vocabulary and word finding difficulty. Individuals with early dementia often have difficulty selecting words and may lose track during conversations⁶. Word repertoire shrinks and use of language

Table 41.1 Cognitive symptoms associated with Alzheimer's dementia

Memory (working, declarative and procedural impairment)
Language (aphasia, alexia, agraphia, aprosodia, acalculia)
Visuo-spatial dysfunction, recognition impairment or agnosia
Execution of previously learned movements or praxis
Executive dysfunction (planning, sequencing, abstraction, set shifting, organizing)

becomes more simplistic, often described as circumlocutory. There may be paraphasic errors with incorrect word substitutions.

In advanced disease, impaired comprehension and word finding difficulties are more pronounced. The ability to communicate effectively becomes impaired. The patient's speech may become non-fluent with mainly short simple phrases or words. Echolalia and palilalia may also occur as affected individuals develop complete loss of verbal expression. These deficits may extend to reading and writing ability. Some affected individuals may retain their ability to understand and respond to non-verbal and emotional cues.

Visuo-spatial Function

Visuo-spatial cognitive impairment and non-verbal visuo-spatial information processing are the characteristic visuo-spatial disturbances observed in Alzheimer's disease. Visual discrimination, visual recognition and visuo-spatial attention deficits may also occur, but less frequently. Although subtle impairments may be seen with early Alzheimer's disease, deficits occur more commonly in moderate to severe stages of dementia and often become progressive. There may be impairment in ability to synthesize, integrate and organize visual sensory stimuli or other environmental information. There may also be difficulty developing strategies for complex construction. Some persons with Alzheimer's disease have impaired right-left orientation and defective re-visualization, which involves internally re-visualizing and imagining a named object and then describing it accurately when prompted. Some may have difficulty with the synthesis of parts of an object into a whole and then properly identifying the whole (classic agnosia). Patients may also have difficulty copying or drawing objects and, with further progression of the illness, lose the ability to construct complex figures or diagrams. Rarely patients present with reduplicative paramnesia, involving the belief that they are in two or more locations simultaneously. Reduplicative paramnesia, more often seen following head injury, can also be regarded as a misidentification syndrome.

Praxis

Impairments with planned motor movements are closely related to executive dysfunction. These deficits are usually seen in advanced stages of Alzheimer's disease dementia. Ideomotor and ideational apraxias may occur earlier. Ideomotor apraxia is characterized by inability to execute learned movements when prompted despite intact comprehension, sensation, motor strength and coordination. There may be difficulty in organizing and sequencing of movements involved in executing an action, e.g. pantomiming combing one's hair or brushing teeth. Individuals with Alzheimer's disease may

exhibit motor perseveration and poor limb positioning. Ideational apraxia is the inability to perform an action comprised of several steps. An example is pantomiming the act of getting dressed or changing the batteries in a remote control. Given the profound limitations to daily function from apraxia, these symptoms can be very distressing to both patients and care providers. There may also be difficulty recalling the ability to perform previously learned tasks such as driving, using utensils, toileting and self-care.

Executive Dysfunction

Impairment of executive function may result in cognitive, mood, behavioural and personality changes. The latter are discussed later as part of NPS. The cognitive symptoms of executive dysfunction are closely related to higher intellectual capacity and involve several aspects of higher intellectual function, including planning, sequencing, abstraction, set shifting and organizing. Features of executive dysfunction arise commonly early in the course of Alzheimer's disease, and may be the primary reason why functioning becomes impaired and care is sought. There is often loss of generative thought, and inability to plan or organize several mental tasks simultaneously without the use of aids. Individuals who previously did not require daily to-do lists to successfully perform tasks may have progressive difficulty completing activities.

It is important to note that there are age-associated declines in executive function; however, the mental flexibility that allows for the adaptive skills in the absence of dementia is often absent with Alzheimer's disease. Ability to solve problems mentally is affected early. In addition, there may be impairment in symbolic and abstract thinking. Thoughts become more concrete and patients may have difficulty accurately interpreting proverbs. Poor response inhibition (e.g. impaired Stroop colour-word interference test), reduced ability to sustain and divide attention, and perseveration of sequential motor tasks can also be seen in Alzheimer's disease at any stage of dementia or in the clinical prodrome to dementia.

NON-COGNITIVE NEUROPSYCHIATRIC SYMPTOMS ASSOCIATED WITH ALZHEIMER'S DISEASE

Neuropsychiatric symptoms such as depression, apathy, agitation and delusions are nearly universal in dementia associated with Alzheimer's disease. Over time, over 98% of individuals with Alzheimer's disease experience at least one NPS disturbance during the course of their illness⁷. In Alzheimer's disease, the presentation, severity and frequency of these symptoms may fluctuate with progression of the illness. NPS can be classified based on individual symptoms or clusters of frequently co-occurring symptoms⁸. The Neuropsychiatric Inventory (NPI) helps distinguish neuropsychiatric symptoms and signs into 12 domains: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, and appetite and eating abnormalities⁹ (Table 41.2).

NPS may be further differentiated based on a hierarchical approach into clusters of affective disturbance, psychotic disturbance, sleep disturbance, apathetic syndrome and executive dysfunction syndrome⁸.

NPS with Prominent Affective Disturbance

Symptoms of disturbed mood are the most common non-cognitive symptoms seen in Alzheimer's disease. These include depression,

Table 41.2 Other neuropsychiatric symptoms associated with Alzheimer’s dementia

Behavioural disturbance and personality changes (apathy, aggression, agitation, disinhibition and aberrant motor behaviour)
Mood disturbance (depression, anxiety, irritability)
Psychomotor abnormalities (sleep disturbance, appetite dysregulation)
Perceptual disturbance (delusions, hallucinations, illusions)

anxiety, irritability, agitation and elation. Depression is the most common mood symptom with an estimated five-year cumulative prevalence of 77%, and an average point prevalence of 31%¹⁰ (Figures 41.1 and 41.2). Depressive symptoms which may also present in the context of a typical major depressive episode are often part of an atypical affective syndrome occurring in Alzheimer’s disease referred to as ‘depression of Alzheimer’s disease’ (dAD)¹¹ or ‘affective disorder associated with Alzheimer’s disease’¹². Depression is often co-morbid with apathy. More than 40% of apathetic Alzheimer’s disease patients present with depression and 56.4% of those with depression also present with apathy¹³. Other symptoms associated with depression in Alzheimer’s disease include impaired sleep, anhedonia, poor concentration, diminished energy and appetite disturbances.

Depressive symptoms may herald the onset of Alzheimer’s disease. Mood symptoms are more common in mild to moderate than in advanced dementia¹³, although this apparent difference may be a result of difficulties evaluating the mental state of patients with advanced disease. Differentiating Alzheimer’s disease with depression from other forms of late life depression (e.g. major depressive disorder) may be challenging as the symptoms overlap. Apathy, anxiety, diminished motivation, sleep disturbance and appetite dysregulation are examples of overlapping symptoms. However, the sustained subjective dysphoria seen with major depressive disorder is not characteristic of depression in Alzheimer’s disease. Furthermore, unlike individuals with major depressive disorder, depressed patients with Alzheimer’s disease may not report hopelessness, worthlessness and suicidal thinking but rather endorse symptoms of irritability, anxiety, and diminished interest and motivation¹⁴. Less commonly, elation and mood lability may present in Alzheimer’s disease. These mood changes are rarely sustained and are often attenuated by redirection. Delusions may occur in the context of either an affective disturbance or a psychotic disturbance. Delusions are rare in late-life depression but occur in over 30% of patients with dAD.

Individuals with Alzheimer’s disease have diminished insight as the disease progresses; however, in the early stages they may become demoralized. Feelings of demoralization often resolve as they adjust to the disease or lose insight with illness progression. Appetite dysregulation affects an estimated 37.8% of patients with Alzheimer’s disease¹⁵. These symptoms are more prominent with

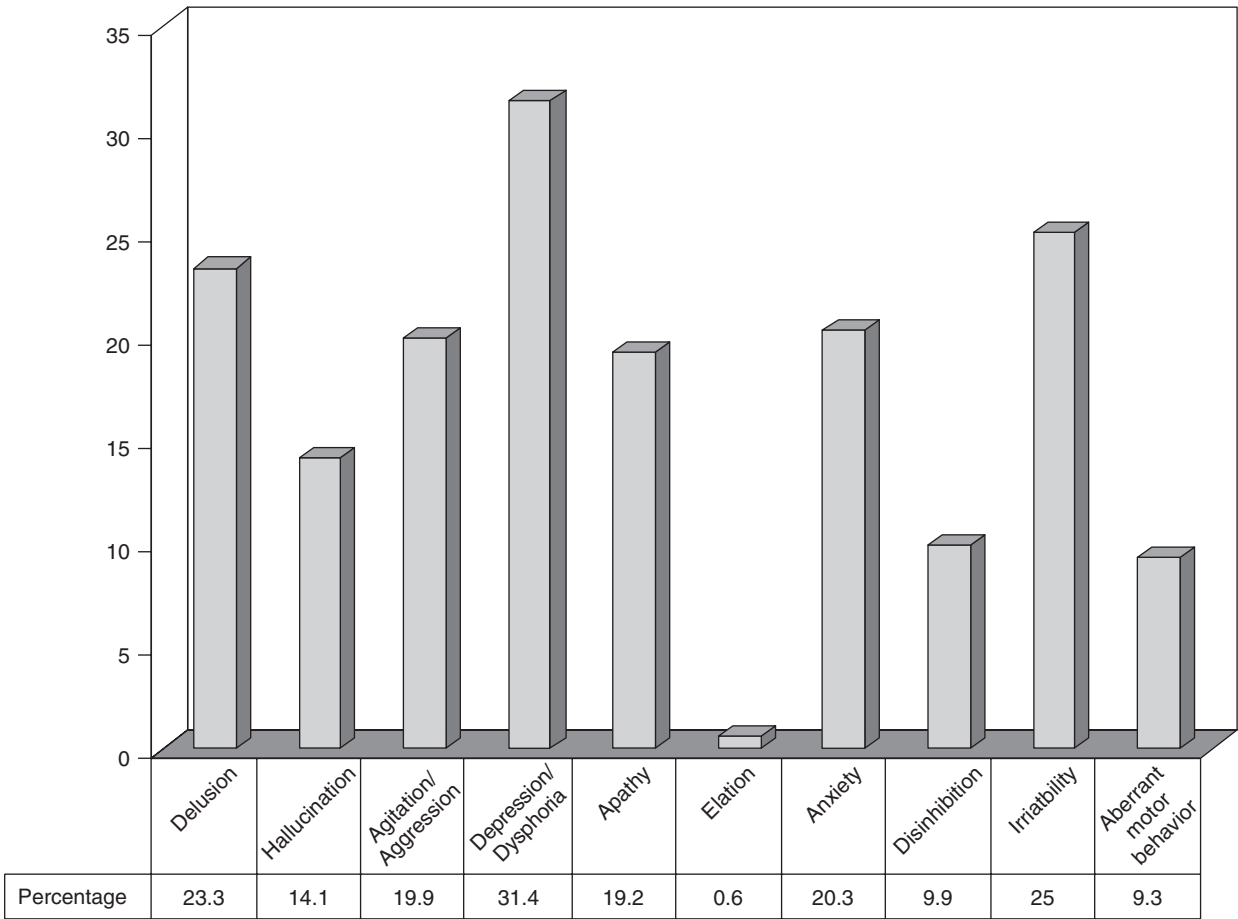


Figure 41.1 Point prevalence of neuropsychiatric symptoms in a community-based US sample¹⁰

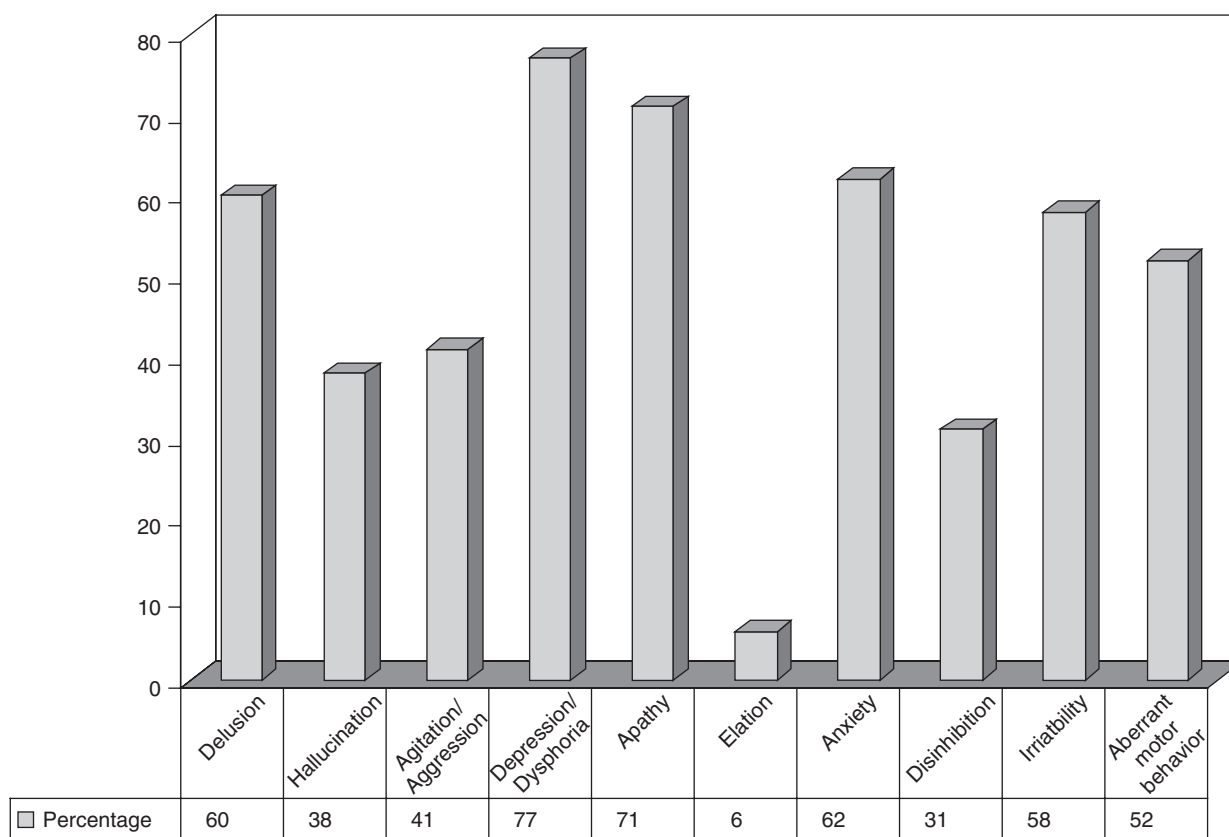


Figure 41.2 Five-year period prevalence of neuropsychiatric symptoms in a community-based US sample¹⁰

severe Alzheimer's disease. With progressive decline in independent function, individuals with Alzheimer's disease often exhibit irregular nutritional intake. Behavioural disturbances including irritability, agitation and disinhibition may have a greater impact on eating patterns and the quality of nutritional intake than the level of cognitive impairment¹⁶. Furthermore, there may be loss of appetite secondary to degeneration of hypothalamic regions associated with feeding and satiety. Nevertheless, without adequate supervision, those with advanced dementia have difficulty maintaining adequate daily nutritional support.

Agitation and aggression in Alzheimer's disease often manifest as emotional excitability, irritability, resistive behaviours, shouting or physical aggression. The estimated prevalence of agitation in Alzheimer's disease is 20–25%¹⁰. Agitated behaviours are not unique to Alzheimer's disease and may also be a part of other late-life conditions, including primary psychotic, depressive or substance use disorders and unrecognized pain. Agitation may also be provoked by environmental stimuli. Agitation and aggressive behaviours occur more commonly with advanced Alzheimer's disease. These behaviours are often seen in institutionalized Alzheimer's disease patients and frequently precipitate institutionalization in those living in the community.

NPS with Prominent Psychotic Disturbance

Delusions are a common neuropsychiatric symptom of Alzheimer's disease with an estimated point prevalence of 23%¹⁰ and a prevalence range of 15–70%¹⁷. The wide range in rates may be due to different

definitions of psychotic disturbance in Alzheimer's disease¹⁸. Delusions are unshakable false beliefs that are out of context with the individual's social and cultural background, while hallucinations are false sensory perceptions that are not simply distortions or misinterpretations of actual stimuli. Delusions in Alzheimer's disease have been associated with older age, male gender and a lower level of education¹⁹. Delusions occur more frequently than hallucinations. The most common types are poorly developed paranoid delusions and misidentification syndromes. The features of paranoid delusions are often related to theft, believing personal objects have been misplaced or stolen, and infidelity. Some characteristic misidentification syndromes may include the belief that family members have been replaced by imposters (Capgras syndrome) or that a stranger (often a misidentified close family member) inhabits their homes (phantom boarder). They may also express the belief that they have been removed from their homes and placed in a foreign environment. There may be differences in cognitive deficits among patients with delusions or delusional misidentification. Patients with delusions often have significantly greater impairment of recent memory, while those with delusional misidentification may have greater impairment of receptive language function. Patients with delusions or delusional misidentification are more likely to have some insight into their psychotic symptoms, unlike those who experience visual hallucinations.²⁰ Delusions in Alzheimer's disease may be associated with depression, aggression, agitation and anosognosia²¹.

Hallucinations are less common in Alzheimer's disease than delusions, occurring in 13–16%¹⁷ of patients with Alzheimer's disease at any point and may occur in up to 38% of these individuals over

a cumulative five-year period¹⁰. Visual misperceptions are the predominant type of hallucinations in Alzheimer's disease. However, if visual hallucinations occur early in the illness, dementia with Lewy bodies should be considered. There is an increase in cognitive impairment, functional decline, placement in institutionalized care and death associated with delusions and hallucinations²². Delusions and hallucinations are seen more often in the moderate stages of Alzheimer's disease and may persist and often recur over the course of the illness¹⁷.

Illusions are not often reported in Alzheimer's disease and clinical evidence describing the features of illusions in this disease is limited. There is, however, some evidence that visual illusions, if present, may worsen with progression of Alzheimer's disease²³.

Sleep Disturbance

Sleep disturbance in dementia is associated with significant caregiver distress and may precipitate institutionalization of community dwelling individuals due to its burden on caregivers. Nocturnal insomnia presents a background for unsupervised and potentially unsafe behaviours such as wandering and pacing and may precipitate serious risk of harm to themselves and others. Environmental stimulation may also play a role in aetiology or propagation of sleep problems in dementia. An estimated 59.2% of those with advanced dementia have some evidence of sleep disturbance, with insomnia, excessive daytime somnolence and napping being most prevalent²⁴. Other symptoms include increased nocturnal awakenings and fragmented sleep. Insomnia is more common in patients with mild and moderate dementia while daytime sleepiness is more frequently associated with severe dementia²⁴. Objective assessments of sleep using wrist actigraphy and polysomnography indicate that individuals with Alzheimer's disease in long-term care facilities may have increased total sleep time, increased sleep latency, increased REM sleep latency, less sleep efficiency, increased N1 non-REM sleep and decreased REM sleep²⁵.

Apathetic Syndrome

Degeneration of the anterior cingulate gyrus and adjacent medial frontal lobe structures with disruption of the frontal and subcortical circuits is associated with apathy. Apathy is one of the most prevalent psychiatric phenomena in Alzheimer's disease, affecting an estimated 75% of patients over the course of illness¹⁰. Features of apathy commonly seen include both emotional and motor phenomena. There is decreased emotional range, reduced motivation, diminished volition to initiate new tasks and a decrease in goal-directed behaviour. Comparisons may be drawn with depressed individuals; however, unlike depression, persons with Alzheimer's disease are not distressed or concerned with these symptoms. In rare cases, with severe dementia, there may be severe apathy in which individuals are awake but do not interact with the environment. They do not eat spontaneously unless fed, and do not attend to personal hygiene or maintain voluntary control over bowel and bladder functions.

Executive Dysfunction Syndrome

Changes in behaviour, mood and personality are often associated with the late stages of Alzheimer's disease. It is, however, not uncommon for these symptoms to present early in the clinical course. Other possible underlying causes, particularly the frontotemporal dementias, should be considered if behavioural and personality changes are

seen early in the disease. Disinhibition, environmental dependency and verbal or motor perseveration are less prevalent than most other neuropsychiatric symptoms and present more frequently in the late stages of the illness²⁶. Behavioural disinhibition and aberrant motor behaviours frequently precipitate placement into a nursing or assisted living home. Pacing and wandering are behaviours seen with increasing frequency with worsening dementia and may also precipitate placement into institutionalized care.

Other Clinical Features

With progression of Alzheimer's disease, there is an increasing risk of falls. This may be related to impairment in balance and gait, or poor coordination caused by the neurodegenerative process. Falls may also occur due to the effects of medications, orthostatic hypotension from cerebrovascular and cardiovascular dysfunction, and environmental hazards²⁷. Falls may be associated with scalp injury, subdural haematoma, traumatic brain injury and rarely skull fractures.

In individuals with severe physical debility who have limited ambulation or are bed-bound, there is a significant elevated risk of decubitus ulcers. Alzheimer's disease may also be a predisposing factor in delirium or infections, particularly of the respiratory and genitourinary tract.

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Neuropsychological Assessment of Dementia and Alzheimer's Disease

David Aaron Maroof and Cynthia A. Munro

Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, USA

INTRODUCTION

Clinical neuropsychology can be conceptualized as both the *study* of affective, behavioural and cognitive manifestations of brain function and the *application* of assessment procedures in quantifying these interrelated processes to inform decisions regarding the causes for dysfunction. The term *neuropsychology* has also been described as a 'merger between experimental psychology and neurological sciences for studying relationships between the brain and behavior'¹ (p. 139). Assessment procedures used by neuropsychologists are tasks that tap various domains of cognition, including, but not limited to, aspects of attention, processing speed, language, visuospatial skills, memory and executive functioning, as well as those assessing mood and aspects of personality. Responses to these tasks provide scores that are used to quantify an individual's functioning in these domains. While we cannot physically observe cognition, we can infer its integrity with the use of standardized psychometric tests. Quantification of an individual's optimal cognitive ability, considering his or her emotional status and personality characteristics and then determining whether one's optimal cognitive ability represents disease, is the cornerstone of the neuropsychological assessment of dementia. In so doing, we improve diagnostic accuracy of dementia above routine clinical evaluation². How we accomplish this is the focus of this chapter.

We have divided this chapter into five sections. First, we will provide a brief introduction to the field of neuropsychology. Second, we will discuss the role of the clinical neuropsychologist in the assessment of dementia. Third, we provide an overview of the basic patterns of cognitive test performance in dementia. Fourth, we discuss some common misconceptions about the practice of neuropsychology. Finally, we present some of the current trends in the neuropsychological assessment of dementia.

INTRODUCTION TO NEUROPSYCHOLOGY

Neuropsychology is an amalgam of many disciplines, influenced by neuroanatomy, neurophysiology, neurochemistry, neuropharmacology, psychology and neurology³, as well as philosophy, physiology and anatomy⁴. Psychometric theory and application, as they relate to appropriate use of data analyses in test construction and the development of normative data, are the very linchpins of neuropsychological

assessment and substantiate the theoretical and conceptual networks of the discipline.

The nexus between current neuropsychological theory and practice harks back to ancient philosophical thought³. Ideas such as aestheticism (e.g., is a theory appealing?), rationalism and empiricism still fuel the practice of clinical neuropsychology⁵. Glozman⁶ discusses the influence of Russian contributions dating back to the late 18th century from psychiatrists and neurologists and attributed many changes in neuropsychological practice – including combining both quantitative and qualitative approaches, expansion to include social and personality variables and increasing nosological patient groups – to this influence. A main theme that Glozman⁶ noted was '...not so much diagnostic but prognostic...neuropsychological assessment should rather emphasize the subject's strengths which are important...and predict his/her ultimate integration into society' (p. 177). The need for a systematic, valid and reliable method of measuring the manifestations of brain function emerged. Test construction thus came on the heels of conceptual and theoretical models of brain function and organization.

Delineating the inception and progression of various neuropsychological tasks is beyond the scope of this chapter. However, we have selected to discuss one very commonly used method for assessing executive functioning to exemplify the manner in which some of our tests have been developed. Executive functioning is a cognitive process involving one's ability to adapt and respond effectively to environmental demands, novel situations and ultimately deduce efficient and effective ways for completing them. Several 'tributaries' of executive functioning have been promulgated, including sequencing behaviours, abstraction, organization and planning. Eling and colleagues⁷ report on the influence of Narziss Ach who designed a paradigm for observing concept formation in the early 20th century. Nonsense words (on cards) were attached on various geometric figures of different shapes and sizes and once these cards were removed, the individual was required to deduce how the words related to the features of the objects. The quintessential element of this task is that one must discover the sorting principle. Goldstein and Scheerer¹ underscored the abstract elements of this task, in which one must be able to abstract from a concrete object, while maintaining insight into other potential 'choices'. The Wisconsin Card Sorting Test (WCST)⁸ was developed on the basis of these principles. Brenda Milner⁹ ultimately demonstrated that lesions in the

dorsolateral prefrontal cortex resulted in shifting problems (i.e., perseverating) and subsequent research has repeatedly confirmed that damage to the frontal cortex is associated with poor performance on this task¹⁰.

Integrity of the perforant pathway (the principal source of input to the hippocampal formation) is essential for normal hippocampal function. In Alzheimer's disease, it is the pathological changes in this pathway that preclude its normal operation of acquisition of contextual knowledge, presumably due to a disconnection among the hippocampal formation and input from sensory-specific and multi-modal association cortices¹¹. However, as the neuropathology spreads beyond the medial temporal lobe structures to the association cortices of the frontal, temporal and parietal lobes, higher order cognitive deficits result¹². Regarding cognitive assessment in Alzheimer's disease, it is the juxtaposition of the neuropathological changes along the disease trajectory with administration of specific tests chosen to assess the associated cognitive deficits that is the cornerstone of clinical neuropsychology. The application of statistical methodology provides the intellectual spadework for clinical practice, as the interpretation of test performance requires the understanding of statistical principles underlying test construction and interpretation.

THE ROLE OF THE CLINICAL NEUROPSYCHOLOGIST

The advent of neuroimaging in the 1970s changed the clinical neuropsychologist's role from that of lesion detection to one of description of the cognitive sequelae of disease¹³ and/or diagnosis of disease for which imaging is uninformative. In general, there is a chasm between knowledge gleaned from neuroimaging and information gathered through neuropsychological examination. Imaging tells us *what* (e.g. cerebrovascular accident), *where* (e.g. anterior cerebral artery) and *how* (e.g. ruptured aneurysm), whereas neuropsychological examination tells us the consequences, including *how much* (degree of deficit) and *in what way* (memory, language, etc.) functioning has been affected.

Neuropsychological assessment in dementia depends on the context of the referral question. In some cases, the neuropsychologist's role is to determine whether cognitive impairment exists and if so, to assist with the differential diagnosis of its cause. In other cases, diagnosis of the disease causing the dementia has been established and the neuropsychologist is asked to determine areas of cognitive strength and weakness, to assist with the development of compensatory strategies. Neuropsychological assessment is also used to track disease progression through repeated examinations, at times determining whether changes in medication are associated with changes in cognition. In still other cases, neuropsychological assessment provides objective data to assist in determining whether a patient is competent to make independent decisions regarding medical, financial or other matters. Recommendations regarding whether a patient should cease driving or working are also informed by neuropsychological assessment. Thus, the context of the referral, even within the narrow scope of dementia assessment, is important to the information that is provided by the neuropsychologist.

RECOGNIZING PATTERNS OF NEUROCOGNITIVE FUNCTIONING IN THE DEMENTIAS

It is quite often the case that clinical neuropsychologists must disentangle ambiguous complaints of declines in cognitive function.

Memory complaints, for example, often dissemble the extent and typology of cognitive deficits. What can present as a memory deficit may be related to the bigger picture of a breakdown in semantic knowledge (e.g. naming), or difficulties with executive function that can affect one's ability to carry out a series of everyday tasks. The pattern of performance exhibited on a neuropsychological examination provides information with regard to these core and peripheral deficits and in conjunction with a comprehensive anamnesis, offers etiological significance.

The cortical-subcortical distinction proffers a heuristically useful model for describing the pattern of neuropsychological performance in various patient groups, despite observations that this is an oversimplified dichotomy^{14,15}. This distinction was engendered by the observation of different clinical presentations in patients with cortical compared to subcortical disease¹⁶. Although the prototypical cortical dementia is that caused by Alzheimer's disease, other diseases, such as frontotemporal lobar degeneration and Creutzfeldt-Jakob disease, are also associated with cortical pathology. Far greater in number, diseases causing subcortical dementia comprise, among others, progressive supranuclear palsy, Parkinson's disease and Huntington's disease and are associated with pathological changes involving the thalamus, basal ganglia and related brain-stem nuclei. Cortical diseases typically develop similar cognitive footprints, including deficits in language, learning and praxis, whereas patients with subcortical dementia typically demonstrate impaired attention/concentration, processing speed and executive function, as well as apathy and depression. Although the cortical/subcortical dichotomy is simplistic and does not account for disorders with both cortical and subcortical features (e.g. cortical-basal degeneration¹⁷), this distinction remains useful in the differential diagnosis of dementia.

In clinical practice, the neuropsychologist must make several determinations when the question of dementia is being considered. After the tests are administered and the scores are obtained, these scores are compared against a normative sample; that is, a sample of individuals, typically of the same age, but sometimes of the same race, sex and education as the patient. This comparison yields standardized scores (percentiles, *z*-scores or *t*-scores) for each raw score. Upon examination of these standardized scores, the neuropsychologist must consider several questions. First, is the examination normal or abnormal? Second, if it is abnormal, does the examination indicate the presence of a cognitive disorder or dementia? Third, is the pattern of cognitive test performance suggestive of cortical or subcortical involvement? Fourth, what disease is underlying the cognitive disorder?

Abnormal scores on individual tests can be defined by several means. In some cases, a score that is obtained by fewer than a particular proportion (often 2%) of the normal population is considered to be abnormal. However, in a large battery of neuropsychological tests, obtaining several scores that are in this 'impaired' range is quite normal¹⁸. In other instances, an abnormal score is one that is unexpected given a particular patient's premorbid ability. That is, if a patient has limited education or sensory deficits that preclude his or her ability to perform some aspects of a task, then an abnormal score might not represent a decline from premorbid ability. Likewise, if a patient has superior premorbid intellectual functioning, a score in the borderline range on a memory test might be considered an abnormal score for that individual.

A second determination is then made regarding whether the presence of one or more abnormal scores constitutes an abnormal exam. This inference requires one to incorporate other information, such as

the patient's or informant's complaints and the overall pattern of test scores. As already mentioned, the presence of one or more abnormal scores often occurs across a battery of neuropsychological tests in normal healthy adults. Thus, the neuropsychologist must determine whether the pattern of abnormal scores is clinically meaningful. This determination is informed by the clinician's knowledge of patterns of test scores that occur in conditions causing dementia. Incorporating measures of emotional functioning are also useful in informing the clinician's determination of whether an abnormal examination is the product of disease or is psychogenic in nature. The practice of interpreting neuropsychological test results is therefore an integrative process, incorporating the patient's history, complaints and test data. Results from neuroimaging and neurological examination, if available, are also considered.

MISCONCEPTIONS ABOUT THE NEUROPSYCHOLOGICAL ASSESSMENT OF DEMENTIA

The assessment of patients with dementia is often multidisciplinary, involving neurologists, psychiatrists, neuroradiologists, geriatric practitioners and/or family practice physicians. Among non-neuropsychologists, several misconceptions regarding the practice of our discipline appear pervasive. We describe several of these misconceptions, as they can hinder one's understanding of the information provided by the neuropsychologist.

Cutoff Scores

Perhaps a result of epidemiological studies that use various scores – such as a Mini Mental State Examination Score of 24 or below – to exclude individuals who are likely to have cognitive difficulties, the notion that a particular score on a given test can be used to indicate dementia is a common misconception. Such scores, when used for research purposes, are often chosen because they are uncommon in healthy individuals. A score that is equal to or below the 2nd or 10th percentiles, that is, a score that represents poorer performance than what 98% or 90%, respectively, of individuals score, are common 'cutoff' scores for research. However, many factors render these cutoff scores inappropriate for use in clinical practice: premorbid ability, effort and number of tests administered all determine whether a particular score is abnormal. Thus, it is inappropriate to apply a cutoff score to an individual, or to use phrases such as 'he scored below the cutoff for dementia', as such scores differ, depending on the individual. For this reason, the use of norms is a cornerstone of the practice of neuropsychology. Such norms are crucial to answering the basic question, 'is this test score normal or abnormal?' Which demographic factors should be considered in the development of normative tables is a topic with particular currency in the field.

Singularity of Domains Assessed by Particular Tests

Another misconception about the practice of neuropsychological assessment is that each test taps a singular ability that is subserved by a discrete brain structure. In practice, two patients might perform poorly on the same task, but for different reasons. For example, if a patient is unable to copy a complex figure, it might be due to poor visual perception, difficulty with constructional praxis or problems

with executive functioning. By administering a battery of tests that assesses these domains in various ways and examining the pattern of test performance, we can then determine which domains are impaired in each patient. It is important to recognize, therefore, that a particular test may require intact functioning in several cognitive domains. It follows that failure to perform a test does not necessarily imply impairment in a single domain.

In addition to the fact that various cognitive processes can subserve performance on the same task, it is also the case that functional networks account for the existence of similar cognitive impairments among individuals with different sites of lesions¹⁹. A common misconception is that executive functioning is determined by integrity of the frontal lobe. Whereas several executive tasks have been associated with frontal lobe activity²⁰ and have been shown to be impaired in patients with frontal lobe lesions²¹, executive dysfunction can occur in the context of abnormal functioning in other areas as well²².

Association between Premorbid Ability and Cognitive Test Performance

A third misconception is that individuals with superior premorbid ability should perform in the superior range on all cognitive measures. This logic often leads to the false conclusion that average test performance represents impairment in high-functioning individuals. However, when this notion is tested empirically, it is simply not the case. On the contrary, individuals of above-average intellectual functioning perform better than those with average intelligence on approximately one-third of measures in a test battery. Individuals with lower IQ scores do perform significantly worse, however, than individuals with average intelligence on most measures²³. Thus, whereas low scores would be expected for individuals with lower intelligence, higher scores on all measures should not be expected among individuals with higher levels of intellectual functioning. While it is possible that average performance across all tests in a domain may represent a decline from premorbid ability in an individual with complaints in that domain, we cannot know this. In such cases, it is important to consider other factors and perhaps even then, the only way we can know whether disease exists is to repeat the examination after some time (usually one year or so) to determine if there is decline in test performance that would suggest the presence of disease.

Time Course of Recovery from Cognitive Deficits in Depression

Depressed individuals can demonstrate cognitive dysfunction in the absence of demonstrable neuropathology²⁴ and these deficits appear to be more pronounced in depressed elderly compared to younger individuals with depression^{25,26}. The most consistently documented deficits among elderly patients with depression involve psychomotor speed, executive functioning and memory for newly learned information^{27,28}. Thus, the prototypical cognitive deficits resulting from depression resemble those seen in 'subcortical' dementia²⁹.

A common misconception concerning the cognitive deficits associated with depression is that they resolve coincident with remission of low mood. Longitudinal studies have shown, however, that cognitive deficits remain during episodes of symptom reduction and even during remission³⁰. The more effort a task requires for success, the less well individuals with depression tend to perform on it³¹. Indeed, some evidence suggests that the relationship between

depressive symptoms and performance on many cognitive tests is largely mediated by impairments of effortful processing^{28,32}. In a study by Hammar and colleagues³³, depressed patients were impaired on cognitively demanding tasks (those requiring effortful processing) when symptomatic and their impairments persisted even after six months, despite significant improvement in symptoms of depression. Similarly, Nebes and colleagues²⁴ found that depressed elderly patients whose mood symptoms responded to treatment with an antidepressant medication (paroxetine or nortriptyline) showed no greater improvement over baseline performance in any cognitive domain than untreated healthy control subjects on five follow-up examinations taking place over 12 weeks. These studies and others suggest that the cognitive impairment observed among depressed elderly patients may be an enduring feature³⁴. Nevertheless, longitudinal assessment of depressed patients can assist in the differential diagnosis between depression and dementia, based on whether there is progressive cognitive decline over time.

RECENT TRENDS IN THE NEUROPSYCHOLOGICAL ASSESSMENT OF DEMENTIA

The evolving field of neuropsychology is witness to numerous developments in the field of dementia and its treatment. These developments have led to changes in the questions we are asked to address and the approaches we use to conduct our evaluations of patients with dementia.

Early Detection of Neurodegenerative Disorder

It is the deliberate use of neuropsychological testing that parallels the course of neuropathology that informs our choice of tests. In so doing, the neuropsychologist makes inferences regarding whether a pattern of test results relates to a pathological process suggestive of a particular disease. However, very early in the course of disease, our tests are not as sensitive in detecting abnormality as they become later in the course of disease. The goal of detecting and distinguishing from among the potential incipient dementias has implications both for prognosis and in determining whether to start relevant disease-specific treatments¹². This goal has increasing currency in light of recent studies suggesting that some factors, such as diet and exercise, may act as modifiers to the risk of developing dementia and progression of mild cognitive impairment to dementia³⁵. Thus, being able to detect the very subtle cognitive changes that are the earliest manifestation of disease has gained more interest in recent years and includes as an objective the detection of a transitional state between normal ageing and dementia. This transitional state has been given several appellations, the most common in the United States being mild cognitive impairment (MCI)³⁶. Attempts at identifying this state have included the refinement of diagnostic nomenclature and increased sensitivity of neurocognitive tests to detect abnormality.

Because many of our tests do not have 'ceiling' effects – that is, even normal healthy individuals do not earn perfect scores on them – the tests themselves are sufficiently difficult for even those with subtle cognitive problems. The interest, therefore, is in improving the diagnostic sensitivity of these tests. One way to do this is by improving the similarity between the normative sample and the patient we are assessing. The use of demographically adjusted scores (discussed in the following sections) is one method of achieving this.

Clinical neuropsychologists sometimes reach an impasse when faced with attempting to detect cognitive changes in the behavioural

variant of frontotemporal dementia (FTD). Specifically, the initial symptoms generally include changes in personality and social interaction, as well as disinhibition³⁷. Torralva and colleagues³⁸ demonstrated that while cognitive measures of memory, attention, visuospatial analysis, executive function and language did not significantly differ in patients diagnosed with the behavioural variant of FTD compared to normal healthy individuals, the authors' executive and social cognition battery did distinguish the groups. It is commonly thought that traditional testing environments may fail to induce executive deficits because of the inherent structure provided by the examination process. As such, the development of assessment tools that elicit abnormal behaviour is a challenge for the field.

The Use of Demographically Adjusted Test Scores

Over the past century, neuropsychologists have interpreted individual test scores by comparing an individual's test scores to a normative sample. The field has seen recent controversy regarding the composition of the norms we use. Specifically, which demographic variables should be considered is a matter of debate. The reason we use a normative sample is to determine the degree of deviation from the average, healthy individual, presumably because the patient was pre-morbidly similar to the average, healthy individual. Typically we choose to compare our patient with a sample of comparable age, due to the influence of age on many of our tests. It is sometimes desirable, however, to compare our patient with an individual who is comparable also in education level, due to the effects of education on test performance. Other normative samples include race and sex as well. Brickman and colleagues³⁹ point out that the value of neuropsychological assessment is contingent on the psychometric properties of the individual tests. If African Americans, for example, have been shown to perform on average lower than Caucasians, a test based on data from the latter group will cause an increase in false positives (i.e. diagnosing someone as impaired, when in fact he or she is performing within normal limits). Such comparisons allow us to determine how similar our patient is to healthy individuals of the same demographic. A similar approach involves the calculation of a predicted score based on a patient's demographic information^{40,41}. Both methods take into account demographic variables in informing the decision about whether a particular score is normal or abnormal and improve the sensitivity of our measures in identifying cognitive impairment. Silverberg and Millis⁴² have shown that adjusting scores can actually *decrease* the usefulness of test performance for predicting functional outcomes, such as the ability to work. If, for example, a 90-year-old individual is normal compared to other nonagenarians with regard to psychomotor speed, we may interpret his score as normal. However, given that the typical 90-year-old individual is much slower than the typical middle-aged individual, we may interpret the elder's score as rendering him unable to perform tasks that require fast processing speed (e.g. being an air-traffic controller). Thus, whether to use demographic adjustments depends upon the question we seek to answer.

CONCLUDING COMMENTS

The field of neuropsychology, influenced by such disparate areas of study as philosophy, neuroanatomy and psychology, is heavily reliant on statistical methods to substantiate its theoretical and conceptual frameworks. Psychometric theory and application, as they relate to

appropriate use of data analyses in test construction and the development of normative data, are the very linchpins of clinical practice. Neuropsychological assessment in patients with suspected dementia provides an important source of diagnostic information, resulting from the empirically based choice of test batteries and the use of statistical methods to interpret these batteries.

Although the role of the clinical neuropsychologist has evolved and depends upon the context of the evaluation, the information provided through neuropsychological assessment remains valuable in the differential diagnosis of dementia and improves diagnostic accuracy above routine clinical examination. The cortical/subcortical distinction, despite its being an oversimplification, remains a useful reference in the decision tree for individual cases. Faulty assumptions about our field relating to how we define abnormality, what our tests measure and the nature of cognitive dysfunction in the presence of low mood, can lead to misunderstandings about what our clinical evaluations can offer.

Current trends in the neuropsychological assessment of dementia include, as in other fields, detection of the very earliest manifestation of disease. Increasing the sensitivity of our tests with the use of increasingly sophisticated statistical methods has resulted from the goal of improving our ability to detect subtle cognitive problems. It is not only the application of knowledge of neuropathological changes and clinical presentation of the various diseases causing dementia that distinguishes neuropsychology as a discipline. It is also the dovetailing of sound clinical judgement with appropriate statistical methodology that is required for good clinical practice.

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Genetics of Alzheimer's Disease

Lynn M. Bekris¹, Chang-En Yu^{1,2}, Thomas D. Bird^{1,2} and Debby Tsuang^{1,2}

¹*Departments of Medicine, Neurology and Psychiatry and Behavioral Sciences,
University of Washington School of Medicine, Seattle, WA, USA*

²*Geriatric Research, Education and Clinical Center and Mental Illness Research, Education and Clinical Center,
University of Washington School of Medicine, Seattle, WA, USA*

INTRODUCTION

Prevalence and Incidence

Alzheimer's disease (AD) is the most common irreversible, progressive brain disease. It is characterized by a gradual loss of memory and cognitive skills. AD accounts for over 50% of all dementia cases and it presently affects more than 24 million people worldwide. Moreover, over 5 million new cases of AD are reported each year and the incidence is likely to increase as a greater proportion of the population ages¹.

AD prevalence and incidence strongly suggest that age is the most influential known risk factor. Indeed, AD prevalence increases significantly with age and AD incidence increases from 2.8 per 1000 person years for people between 65 and 69 years to 56.1 per 1000 person years for people who are older than 90 years². Approximately 10% of persons older than 70 years have significant memory loss and more than half of these individuals have probable AD. An estimated 25% to 45% of persons older than 85 years have dementia³. The duration of disease is typically 8 to 10 years, with a range from 2 to 25 years after diagnosis.

The disease is divided into two subtypes based on the age of onset: early-onset AD (EOAD) and late-onset AD (LOAD). EOAD accounts for approximately 1% to 6% of all cases and ranges roughly from 30 years to 60 or 65 years. On the other hand, LOAD, which is the most common form of AD, is defined as AD with an age at onset later than 60 or 65 years. Both EOAD and LOAD may occur in people with a positive family history of AD. Approximately 60% of EOAD cases have multiple cases of AD within their families and of these familial EOAD cases, 13% are inherited in an autosomal dominant manner with at least three generations affected^{4,5}. Early-onset cases can also occur in families with late-onset disease³. With the exception of a few autosomal dominant families that are single-gene disorders (see below), most AD cases appear to be a complex disorder that is likely to involve multiple susceptibility genes and environmental factors^{3,6–9}.

Clinical Symptoms

Both EOAD and LOAD present clinically as dementia that begins with a gradual decline of memory and then slowly increases in severity until the symptoms eventually become incapacitating. Other common symptoms are confusion, poor judgement, language disturbance, agitation, withdrawal and hallucinations. Rare symptoms include seizures, parkinsonism, increased muscle tone, myoclonus, incontinence and mutism. Death commonly occurs from general inanition, malnutrition and pneumonia³. Treatment of AD with cholinesterase inhibitors and memantine may result in slowing of cognitive decline in mild to moderate dementia cases, but overall, most patients experience only clinically marginal improvement in measures of cognition and in global assessments of dementia^{10,11}.

Clinical Diagnosis

Currently, the diagnosis of AD is based on clinical history and neuropsychological tests. The *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV), criteria for diagnosing dementia requires the loss of two or more of the following: memory, language, calculation, orientation or judgement¹². The Mini-Mental State Examination (MMSE) helps to evaluate changes in a patient's cognitive abilities. In addition, a diagnosis of probable AD necessitates the exclusion of other degenerative disorders associated with dementia, such as frontotemporal dementia (including frontotemporal dementia with parkinsonism-17 and Pick's disease), Parkinson's disease, diffuse Lewy body disease, Creutzfeldt-Jakob disease and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)¹³. Discriminating AD from other forms of dementia is usually done through clinical history and neuroimaging³. In addition, other possible causes of dementia need to be excluded, especially the treatable forms of cognitive impairment, such as impairment due to depression, chronic drug intoxication, chronic central nervous system infection, thyroid disease, vitamin deficiencies (e.g., B12 and thiamine),

central nervous system angitis and normal-pressure hydrocephalus³. Individuals who do not meet these criteria but have short-term memory loss, have only minimal impairment in other cognitive abilities and are not functionally impaired at work or at home are considered to have 'mild cognitive impairment'¹⁴.

Neuropathological Diagnosis

A definitive diagnosis of AD requires a clinical assessment of probable AD, as well as postmortem confirmation, with the presence of two histopathological features: neurofibrillary tangles and amyloid plaques^{15–17}. Before autopsy confirmation, expert clinicians correctly diagnose AD between 80% to 90% of the time¹⁸. Even though plaques and tangles are often found in cognitively normal age-matched controls, the density and the distribution of these attributes are more severe in patients with AD, according to standardized histological assessments¹⁵. Amyloid plaques are extracellular with a cross-beta structure that is characteristic of dye-binding (neuritic amyloid plaques contain thioflavin S and Congo red-positive

fibrillar deposits with both A β 40 and A β 42 present)^{19,20}. The major component of amyloid plaques is amyloid beta (A β), which can be stained and detected using A β antibodies^{21,22}. The most common form of A β in humans is 40-amino-acids long and is called A β 40. A 42-amino-acid-long fragment, A β 42, is less abundant than A β 40 and differs only in that it has two additional amino-acid residues at the C-terminus. A β 42 is associated with AD²³.

A β is derived from the amyloid precursor protein (APP) by the action of two aspartyl proteases. First, α -secretase (non-neurotoxic 'normal' cleavage) or β -secretase (potential neurotoxic 'abnormal' cleavage) cleave APP (Figure 43.1) and second, γ -secretases cleave APP^{24–26}. Upon cleavage by α -secretase, APP releases a large soluble APP alpha fragment (sAPP α) and a membrane-bound C-terminal 83-amino-acid fragment (C83); whereas upon cleavage by β -secretase, APP releases a large soluble APP beta fragment (sAPP β) and a membrane-bound C-terminal 99-amino-acid fragment (C99)^{27,28}. The C99 fragment is subsequently cleaved by γ -secretase to release A β and an APP intracellular domain (AICD)^{29,30} (Figure 43.1). Thus, depending on the point of cleavage

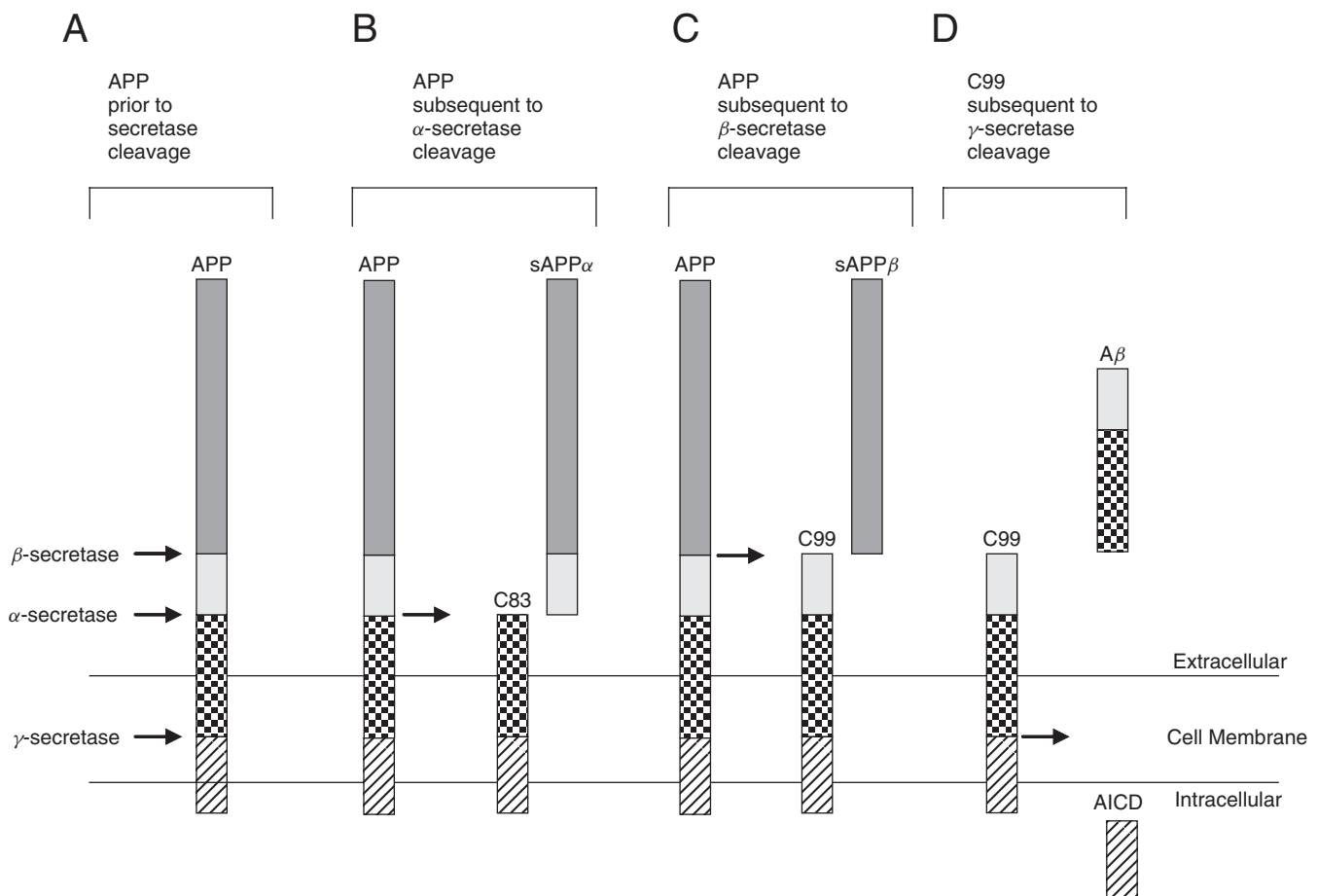


Figure 43.1 APP cleavage. The APP protein can be cleaved by three different secretases; α , β or γ (panel A). Subsequent to 'normal' α -secretase cleavage, sAPP α is produced and released into the extracellular space and the C83 peptide remains in the cell membrane (panel B). Subsequent to β -secretase cleavage, sAPP β is produced and released into the extracellular space and the C99 peptide remains in the cell membrane (panel C). Subsequent to β -secretase cleavage, the C99 peptide is 'abnormally' cleaved by γ -secretase to yield an A β peptide and the AICD peptide (panel D). Scale is approximate

Source: Reproduced from Bekris, Yu, Bird & Tsuang (2010). The Genetics of Alzheimer's and Parkinson's Disease. In: A. Lajtha (Ed.), Handbook of Neurochemistry and Molecular Neurobiology, 3rd edn. Neurochemical Mechanisms in Disease, Vol. 36. New York: Springer-Verlag. With kind permission of Springer Science+Business Media

by γ -secretase, two main forms of $A\beta$ are produced, consisting of either 40 or 42-amino-acid residues ($A\beta_{40}$ or $A\beta_{42}$). The proportion of $A\beta_{40}$ to $A\beta_{42}$ that is formed is particularly important in AD because $A\beta_{42}$ is far more prone to oligomerize and form fibrils than the more abundantly produced $A\beta_{40}$ peptide. Indeed, although it appears that the production of $A\beta$ isoforms is a normal process of unknown function, in a small number of individuals, an increased proportion of $A\beta_{42}$ appears sufficient to cause EOAD^{16,31}.

Neurons bearing neurofibrillary tangles are another frequent finding in AD brains^{32,33} and the temporal and spatial appearance of these tangles, which contain hyperphosphorylated tau, more closely reflects disease severity than does the presence of amyloid plaques^{34,35}. Tangles are formed by hyperphosphorylation of a microtubule-associated protein known as tau, causing it to aggregate in an insoluble form. However, neurofibrillary tangles are also found in other disorders, such as frontotemporal dementia and progressive supranuclear palsy. Moreover, these tangles are not necessarily associated with the cognitive dysfunction and memory impairment that is typical of AD and mutations in the gene that encodes the tau protein (*MAPT*), a main component of neurofibrillary tangles, has not been genetically linked to AD²².

GENETICS OF ALZHEIMER'S DISEASE

Introduction

Overall, more than 90% of AD cases appear to be sporadic and to have a later age at onset of 60 to 65 years (LOAD)³⁶. Although twin studies support the existence of a genetic component in LOAD, no causative gene has been yet identified. Indeed, the only gene that has been consistently found to be associated with sporadic LOAD, across multiple genetic studies, is the apolipoprotein E (*APOE*) gene^{37–41} (Table 43.1). However, many carriers of the *APOE* risk allele ($\epsilon 4$) live into their 90s, which suggests the existence of other LOAD genetic and/or environmental risk factors that have yet to be identified. To this end, several unreplicated genetic variants have been reported and these findings suggest that there may be five to seven major LOAD susceptibility genes^{3,42,43}. For a catalogue of candidate gene association studies, please refer to the AlzGene online database (www.alzforum.org/res/com/gen/alzgene/default.asp).

Genes Associated with Autosomal Dominant Alzheimer's Disease

AD1: Amyloid precursor protein (APP)

Inheritance and clinical features In the 1980s, Kang and colleagues purified both plaque and vascular amyloid deposits and isolated their 40-residue constituent peptide ($A\beta$), which subsequently

led to the cloning of the *APP* type I integral membrane glycoprotein from which $A\beta$ is proteolytically derived⁴⁴. The *APP* gene was then mapped to chromosome 21q, which accounted for the observation that Down syndrome patients (trisomy 21) develop amyloid deposits and the neuropathological features of AD when in their 40s^{22,45–47}.

Since then, over 32 different *APP* missense mutations have been identified in 85 families. Interestingly, most of these mutations are located at the secretase cleavage sites or the *APP* transmembrane domain on exons 16 and 17 (Figure 43.2). Information regarding *APP* mutations are available in the NCBI database and the Alzheimer Disease Mutation Database (www.molgen.ua.ac.be/ADMutations)⁴⁸. Mutations within *APP* account for 10% to 15% of early-onset familial AD (EOFAD)^{3,49–51}, appear to be family specific and do not occur within the majority of sporadic AD cases. The majority of these EOFAD mutations are in or adjacent to the $A\beta$ peptide sequence (Figure 43.2), the major component of amyloid plaques^{52,53}. Most cases containing *APP* mutations have an age of onset in the mid-40s and 50s⁵⁴.

Gene location and structure Sequences encoding APP were first cloned by screening cDNA libraries⁴⁴. The initial full-length cDNA clone encoded a 695-amino-acid protein (APP695)⁴⁰ and consisted of 18 exons. The *APP* gene, located on chromosome 21q21, is alternatively spliced into several products, named according to their length in amino-acids (i.e., APP695, APP714, APP751, APP770 and APP563) and expressed differentially by tissue type whereby the three isoforms that are most relevant to AD are restricted to the central nervous system (APP695) or expressed in both the peripheral and CNS tissues (APP751 and APP770)^{44,55–61}.

Gene function and expression APP is a type-I integral-membrane protein⁴⁴ that resembles a signal-transduction receptor. It is expressed in many tissues and concentrated in the synapses of neurons. Its primary function is not known, though it has been implicated in neural plasticity⁶² and as a regulator of synapse formation⁶³. APP is synthesized in the endoplasmic reticulum, post-transcriptionally modified in the golgi (N- and O-linked glycosylation, sulfation and phosphorylation) and transported to the cell surface via the secretory pathway. APP is also endocytosed from the cell surface and processed in the endosomal-lysosomal pathway^{64,65}. APP and its byproduct $A\beta$ have been found to be translocated inside mitochondria and implicated in mitochondrial dysfunction^{66–68}.

Proteolysis of APP by α -secretase or β -secretase leads to the secretion of sAPP α or sAPP β . This proteolysis generates C-terminal fragments of 10 kDa and 12 kDa, respectively, which are inserted into the membrane. These fragments can be cut by γ -secretase to

Table 43.1 Alzheimer's disease (AD) genes. AD genes are located on four different chromosomes and are associated with autosomal dominant or sporadic inheritance

AD loci	Gene symbol	Gene name	Chromosome	Inheritance
AD1	<i>APP</i>	Amyloid Precursor Protein	21q21	Autosomal Dominant
AD2	<i>APOE</i>	Apolipoprotein E	19q13.32	Sporadic
AD3	<i>PSEN1</i>	Presenilin 1	14q24.2	Autosomal Dominant
AD4	<i>PSEN2</i>	Presenilin 2	1q42.13	Autosomal Dominant

Source: Reproduced from Bekris, Yu, Bird & Tsuang (2010). The Genetics of Alzheimer's and Parkinson's Disease. In: A. Lajtha (Ed.), Handbook of Neurochemistry and Molecular Neurobiology, 3rd edn. Neurochemical Mechanisms in Disease, Vol. 36. New York: Springer-Verlag, Table 1. With kind permission of Springer Science+Business Media

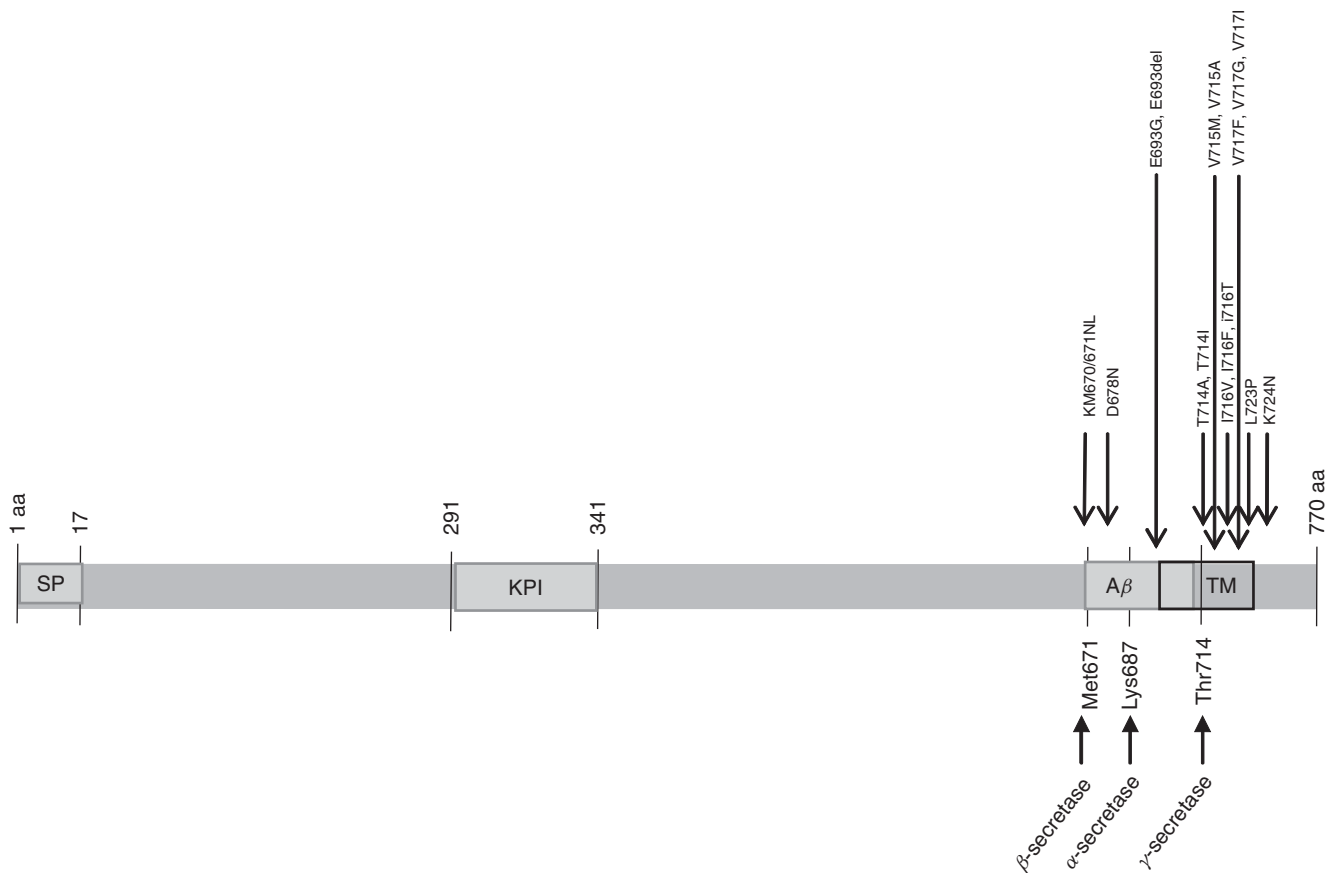


Figure 43.2 AD1: *APP* structure and mutations. SP: Signal peptide. KPI: Kunitz protease inhibitor domain. A β : Amyloid beta. TM: Transmembrane domain. Scale is approximate

Source: Reproduced from Bekris, Yu, Bird & Tsuang (2010). *The Genetics of Alzheimer's and Parkinson's Disease*. In: A. Lajtha (Ed.), *Handbook of Neurochemistry and Molecular Neurobiology*, 3rd edn. Neurochemical Mechanisms in Disease, Vol. 36. New York: Springer-Verlag. With kind permission of Springer Science+Business Media

extracellularly release the A β peptide⁶⁹ and intracellularly release a cytoplasmic fragment identified as AICD⁷⁰ (Figure 43.1). The majority of EOFAD mutations alter this processing of *APP* in such a way that A β 42 levels are changed relative to other A β isoform levels^{71,72}. The function of these *APP* proteolytic fragments is still unclear.

The missense *APP* 'Swedish' mutations (*APPSW*, *APPK670N*, *M671L*) and the 'London' mutations (*APPLON*, *APPV717I*) are examples of *APP* mutations that lead to increased A β production and development of AD^{73,74}. Transgenic mouse models of such *APP* mutations (*PDAPP*, *Tg2576*, *APP23*, *TgCRND8* and *J20*) have been developed⁷⁵. Each of these mouse models have different *APP* expression levels and different neurological abnormalities^{75,76}. For example, the *Tg2576* mouse model that carries the 'Swedish' mutation has high *APP* levels, high A β levels and cognitive disturbances⁷⁷ that are progressive and start as early as six months of age⁷⁸.

Genetic variation *APP* transcripts have been identified in which exons 7, 8 and 15 are alternatively spliced. *APP695*, the predominant isoform in neurons⁷⁹, contains exon 15 but excludes exons 7 and 8. The *APP751* isoform and the *APP770* isoform both encode Kunitz-type protease inhibitor (KPI)-containing forms of *APP*^{58–60,80}, are present in both peripheral tissue and neurons and contain exon 16 and 17 but exclude exons 7, 8 and 15. The gene region that encodes the portion of *APP* that is cleaved to produce the A β peptide is located

within exons 16 and 17 of the *APP770* splice variant⁸¹ (Figure 43.2). Other splice variants have been observed that are missing exon 15 in various combinations with exons 7 and 8; these splice variants are referred to as *L-APPs*^{80,82}. A number of studies have indicated that alternative splicing of exons 7 and 8 is modulated in brain during ageing and possibly during AD^{82–87}. Even though the function of *APP* and its various splice variants is unknown, differential expression of these splice variants between tissues may imply functional differences. It is important to note that while most of the described splice variants contain A β -encoding sequences, two additional rare transcripts, *APP365* and *APP563* do not, implicating additional functionally important variability in *APP* isoform function^{55,88}.

The first described and best characterized *APP* mutation (*V717I*) is located within the transmembrane domain near the γ -secretase cleavage site⁷³ (Figure 43.2). Other substitutions have since been identified at this site and several groups have reported the *V717I* mutation in families who are unrelated to the initial London family. Many other *APP* mutations have since been identified, especially near the γ -secretase cleavage site, and the bulk of these mutations have been associated with modulation of A β levels. For example, a C-terminal *L723P* mutation was identified in an Australian family; this mutation is reported to generate an increase of A β 42 peptide levels in CHO cells⁸⁹. The majority of EOFAD mutations alter processing of *APP* in such a way that the relative level of A β 42 is

increased by increasing A β 42, decreasing A β 40 peptide levels or increasing A β 42 while decreasing A β 40 peptide levels^{71,72}.

AD3: Presenilin 1 (PSEN1)

Inheritance and clinical features Linkage studies established the presence of an AD3 locus on chromosome 14⁹⁰, and positional cloning led to the identification of mutations in the presenilin-1 (*PSEN1*) gene, which encodes a polytopic membrane protein⁹¹. Presenilins are major components of the atypical aspartyl protease complexes that are responsible for the γ -secretase cleavage of APP^{92,93}. Mutations in *PSEN1* are the most common cause of EOFAD. Indeed, *PSEN1* missense mutations account for 18% to 50% of autosomal dominant EOFAD cases⁹⁴. Over 176 different *PSEN1* mutations have been identified in 390 families. *PSEN1* mutations appear to increase the ratio of A β 42 to A β 40 and thereby result in a change in function that leads to reduced γ -secretase activity⁹⁵. It has been suggested that deposition of A β 42 may be an early preclinical event in *PSEN1* mutation carriers⁹⁶.

Defects in *PSEN1* cause the most severe forms of AD, with complete penetrance and an onset occurring as early as 30 years of age. However, there is a wide variability in age of onset as other *PSEN1*-associated AD cases have a mean age of onset greater than 58 years. *PSEN1*-associated AD is an autosomal dominant neurodegenerative disorder characterized by progressive dementia and parkinsonism, notch signalling modulation and A β intracellular domain generation^{16,97}. There is also considerable phenotypic variability in *PSEN1*-associated AD cases, including some patients who develop spastic paraparesis and other atypical AD symptoms. Some of these variable clinical phenotypes have been associated with specific mutations. Neuropathological studies often confirm the clinical diagnosis of AD with measurement of amyloid plaque and Braak stage (as described above) as well as other neurodegenerative changes in other brain areas according to the presence of specific *PSEN1* mutations^{98,99}. For example, researchers found that the clinical and neuropathological features of a Greek family with a *PSEN1* mutation (N135S) included memory loss when the family members were in their 30s, as well as variable limb spasticity and seizures. Upon neuropathological examination of these family members, the diagnosis of AD was confirmed and there was also histological evidence of corticospinal tract degeneration⁹⁹. Moreover, a *PSEN1* mutation (I143M) that lies in a cluster in the second transmembrane domain of the protein has been described in an African family with an age at onset in the early 50s and a short duration of illness of six to seven years. These family members were diagnosed upon autopsy with severe AD pathology characterized by neuronal loss, abundant A β neuritic plaques and neurofibrillary tangles and degeneration extending into the brain stem¹⁰⁰.

Gene location and structure *PSEN1* is located on chromosome 14q24.2. It consists of 12 exons that encode a 467-amino-acid protein that is predicted to traverse the membrane 6 to 10 times; the amino and carboxyl termini are both oriented toward the cytoplasm¹⁰¹.

Gene function and expression *PSEN1* is a polytopic membrane protein that forms the catalytic core of the γ -secretase complex^{92,102}. Gamma-secretase is an integral membrane protein typically found at the cell surface, but it may also be found in the golgi, endoplasmic reticulum and mitochondria^{92,103}.

PSEN1, nicastrin (Nct), anterior pharynx defective 1 (Aph-1) and presenilin enhancer 2 (PSENEN) are required for the stability and activity of the γ -secretase complex^{104–108}. This complex cleaves many type-I transmembrane proteins, including APP and Notch^{92,109}, two proteins in the hydrophobic environment of the phospholipid bilayer of the membrane¹⁰⁷.

PSEN1 knockout (KO) mice are not viable¹¹⁰ but a conditional *PSEN1* KO mouse model, where the loss of the gene is limited to the postnatal forebrain, found that KO mice exhibited mild cognitive impairments in long-term spatial reference memory and retention¹¹¹. These findings suggest that presenilins play a role in cognitive memory. Moreover, knockin mice with missense mutations of the endogenous murine *PSEN1* have high A β 42 levels and perform poorly on the object recognition test^{112,113}. Double *PSEN1*/APP transgenics have been developed and these transgenic suggest that *PSEN1*, APP and mutations within these genes play a role in the production of A β ^{76,114}.

Genetic variation To date, there have been 176 *PSEN1* mutations reported (Figure 43.3). A comprehensive list of *PSEN1* mutations is available through the NCBI database (www.molgen.ua.ac.be/ADmutations). The majority of these mutations are missense mutations. These missense mutations cause amino-acid substitutions throughout the *PSEN1* protein and appear to result in a relative increase in the ratio of A β 42 to A β 40 peptides; this increase seems to occur through increased A β 42 production, decreased A β 40 production, or alternatively, a combination of increased A β 42 production and decreased A β 40 production⁷¹. For example, individuals that carry the *PSEN1* L166P mutation can have an age at onset in adolescence, and *in vitro* studies indicate that this mutation induces exceptionally high levels of A β 42 production as well as impaired notch intracellular domain production and notch signalling⁹⁸.

AD4: Presenilin 2 (PSEN2)

Inheritance and clinical features A candidate gene for the chromosome 1 AD4 locus was identified in 1995 in a Volga German AD kindred with a high homology to the AD3 locus (*PSEN1*); this gene was later named presenilin 2 (*PSEN2*)^{51,115,116}. In contrast to the mutations in the *PSEN1* gene, missense mutations in the *PSEN2* gene are a rare cause of EOFAD, at least in Caucasian populations. The clinical features of *PSEN2*-affected families appear to differ from the clinical features of *PSEN1*-affected families in that the age of onset in these family members is generally older (45–88 years) than for some family members with *PSEN1* mutations (25–65 years). Furthermore, the age of onset is highly variable among *PSEN2*-affected members of the same family, whereas in families with *PSEN1* mutations, the age of onset is generally quite similar among affected family members, and it is even similar among people from different families with the same mutation^{5,51,91,116}. Missense mutations in the *PSEN2* gene may be of lower penetrance than in the *PSEN1* gene and therefore may be subject to the modifying action of other genes or environmental influences^{51,117}.

Gene location and structure The *PSEN2* gene is located on chromosome 1 (1q42.13) and was identified by sequence homology and then cloned^{115,116}. *PSEN2* has 12 exons and is organized into 10 translated exons that encode a 448-amino-acid peptide. The *PSEN2* protein is predicted to consist of nine transmembrane domains

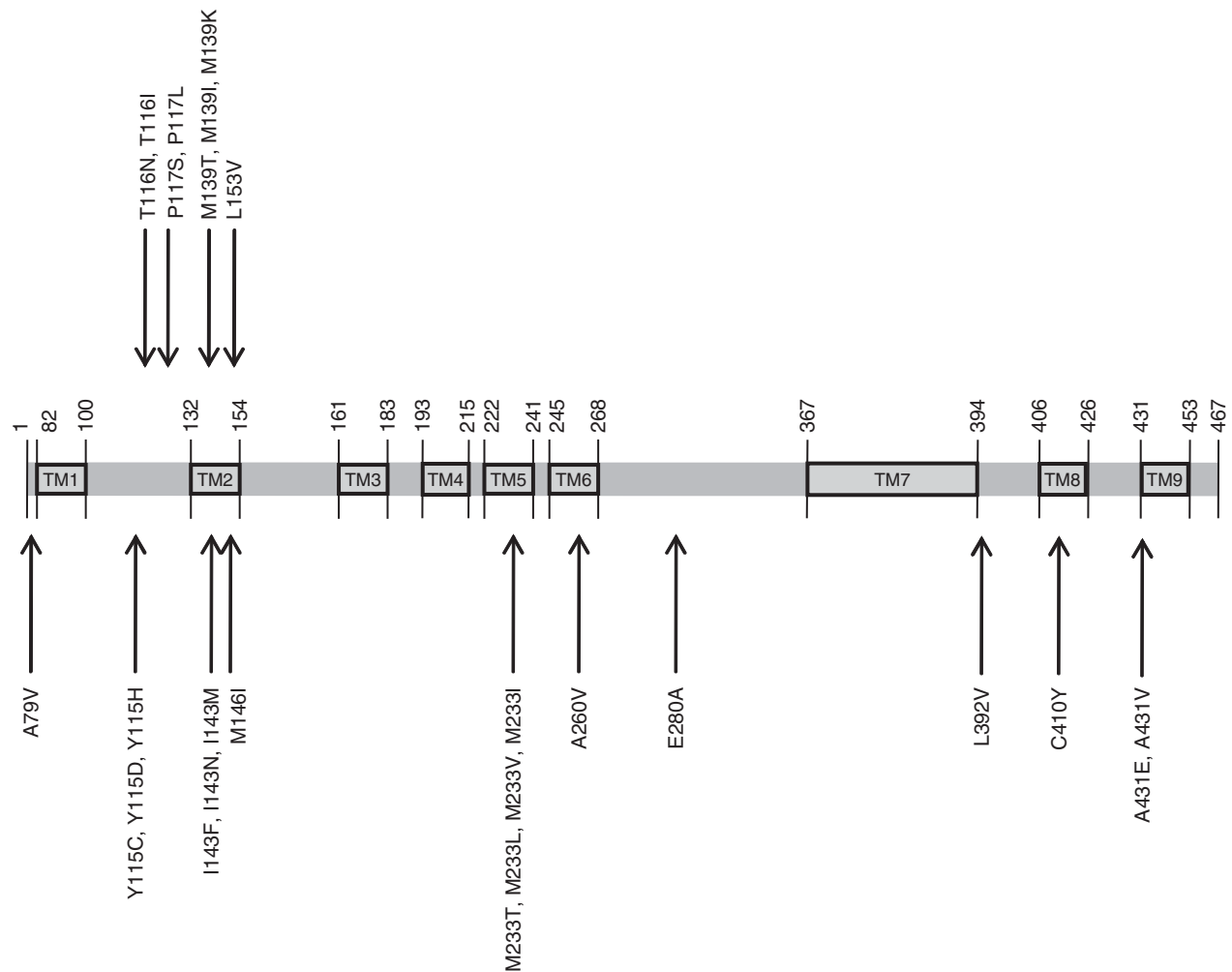


Figure 43.3 AD3: *PSEN1* structure and mutations. Thus far, there have been at least 123 mutations in the *PSEN1* gene described, of which a few are shown. For a more complete list of *PSEN1* mutations see www.molgen.ua.ac.be/ADMutations. TM: Transmembrane domains. Scale is approximate

Source: Reproduced from Bekris, Yu, Bird & Tsuang (2010). The Genetics of Alzheimer's and Parkinson's Disease. In: A. Lajtha (Ed.), Handbook of Neurochemistry and Molecular Neurobiology, 3rd edn. Neurochemical Mechanisms in Disease, Vol. 36. New York: Springer-Verlag. With kind permission of Springer Science+Business Media

and a large loop structure between the sixth and seventh domains (Figure 43.4). *PSEN2* also displays tissue-specific alternative splicing^{115,116,118–120}.

Gene function and expression Like *PSEN1*, *PSEN2* has been described as a component of the atypical aspartyl protease called γ -secretase, which is responsible for the cleavage of $A\beta$ ^{92,93}. *PSEN2* is expressed in a variety of tissues, including the brain, where it is expressed primarily in neurons¹²¹. *PSEN2*-associated mutations have been reported to increase the ratio of $A\beta_{42}$ to $A\beta_{40}$ ($A\beta_{42}/A\beta_{40}$) in mice and humans^{71,95}, indicating that presenilins might modify the way in which γ -secretase cuts APP.

APP processing at the γ -secretase site has been reported to be differentially affected by specific presenilin mutations. For example, *PSEN1*-L166P mutations cause a reduction in $A\beta$ production whereas *PSEN1*-G384A mutations significantly increase $A\beta_{42}$. In contrast, *PSEN2* appears to be a less efficient producer of $A\beta$ than *PSEN1*²³. The functions and biological importance of presenilin

splice variants are poorly understood, but it appears that differential expression of presenilin isoforms may lead to differential regulation of the proteolytic processing of the APP protein. For example, aberrant *PSEN2* transcripts lacking exon 5 appear to increase the rate of production of $A\beta$ peptide¹²², whereas naturally occurring isoforms without exons 3 and 4 and/or without exon 8 do not affect production of $A\beta$ ¹²³.

Genetic variation Mutations in *PSEN2* are a much rarer cause of familial AD than are *PSEN1* mutations; *PSEN2* mutations have been described in six families, including the Volga-German kindred where a founder effect has been demonstrated^{48,51,115,116}, whereas *PSEN1* mutations have been found in 390 families. To date as many as 14 *PSEN2* mutations have been identified. One of the first mutations to be identified was a point mutation located within the second transmembrane domain that resulted in the substitution of an isoleucine for an asparagine at residues 141 (N141I)¹¹⁵. Most recently, a V393M mutation

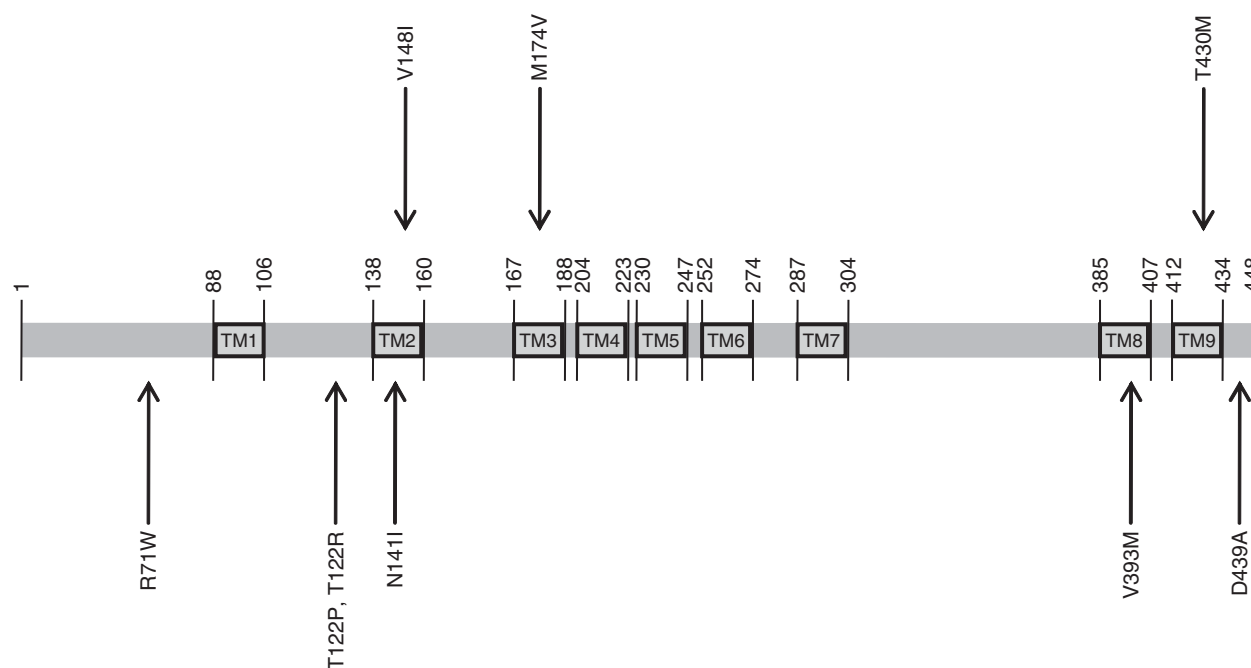


Figure 43.4 AD4: *PSEN2* structure and mutations. Thus far, there have been at least 16 mutations in the *PSEN2* gene described, of which a few are shown. For a more complete list of *PSEN2* mutations see www.molgen.ua.ac.be/ADMutations. TM: Transmembrane domains. The V393M novel mutation was most recently found in one case¹²⁴. Scale is approximate

Source: Reproduced from Bekris, Yu, Bird & Tsuang (2010). *The Genetics of Alzheimer's and Parkinson's Disease*. In: A. Lajtha (Ed.), *Handbook of Neurochemistry and Molecular Neurobiology*, 3rd edn. Neurochemical Mechanisms in Disease, Vol. 36. New York: Springer-Verlag. With kind permission of Springer Science+Business Media

located within the seventh transmembrane domain has been described¹²⁴ (Figure 43.4). A comprehensive list of *PSEN2* mutations is available through the NCBI database (www.molgen.ua.ac.be/ADMutations).

Genes Associated with Risk in Sporadic Alzheimer's Disease

AD2: *APOE*

Inheritance and clinical features The *APOE* gene has been associated with both familial late-onset and sporadic late-onset AD in numerous studies of multiple ethnic groups. The *APOE* $\epsilon 4$ genotype is associated with higher risk of AD¹²⁵, earlier age of onset of both AD¹²⁶ and Down syndrome (where there is an additional copy of chromosome 21 carrying the *APP* gene)¹²⁷ and a worse outcome after head trauma¹²⁸ and stroke, both in humans¹²⁹ and in transgenic mice expressing human apoE4¹³⁰. The frequency of the *APOE* $\epsilon 4$ allele varies between ethnic groups, but regardless of ethnic group, *APOE* $\epsilon 4$ -carriers are more frequently found in controls, and *APOE* $\epsilon 4$ + carriers are more frequently found in AD patients^{39–41,131–140}.

Gene location and structure The *APOE* gene is located on chromosome 19q13.2 and consists of four exons that encode a 299-amino-acid protein. The *APOE* gene is in a cluster with other apolipoprotein genes: *APOC1*, *APOC2* and *APOC4*. The *APOE* $\epsilon 4$ loci are located within exon 4 of the gene. The three *APOE* $\epsilon 4$ alleles ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$) are defined by two single nucleotide polymorphisms, rs429358 and rs7412, which encode three protein

isoforms (E2, E3 and E4). The most frequent apoE isoform is apoE3, which contains cysteine and arginine at amino-acid positions 112 and 158. In contrast, these positions contain only cysteine residues in apoE2 and only arginine residues in apoE4 (Figure 43.5). The cysteine-arginine substitution affects the three-dimensional structure and the lipid-binding properties between isoforms. In apoE4, the amino-acid substitution results in the formation of a salt bridge between an arginine in position 61 and a glutamic acid in 255; whereas apoE3 and apoE2 bind preferentially to high-density lipoproteins (HDLs), this changed structure causes the apoE4 isoform to bind preferentially to very low-density lipoproteins (VLDLs)¹⁴¹.

Gene function and expression The mechanisms that govern apoE toxicity in brain tissue are not fully understood. Some proposed mechanisms include isoform-specific toxicity, *APOE* $\epsilon 4$ -mediated amyloid aggregation and *APOE* $\epsilon 4$ -mediated tau hyperphosphorylation¹⁴².

The *APOE* polymorphism is unique to humans and has been proposed to have evolved as a result of adaptive changes to diet^{143,144}. It is known that apoE plays an important role in the distribution and metabolism of cholesterol and triglycerides within many organs and cell types in the human body¹⁴¹. Individuals carrying *APOE* $\epsilon 4$ have higher total and LDL cholesterol¹⁴⁵. Moreover, *in vitro* neurons have a cholesterol uptake that is lower when lipid are bound to apoE4 compared to apoE2 and apoE3¹⁴⁶, and apoE4 appears to be less efficient than the other isoforms in promoting cholesterol efflux from both neurons and astrocytes¹⁴⁷.

As the major apolipoprotein of the chylomicron in the brain, apoE binds to a specific receptor and works through receptor-mediated

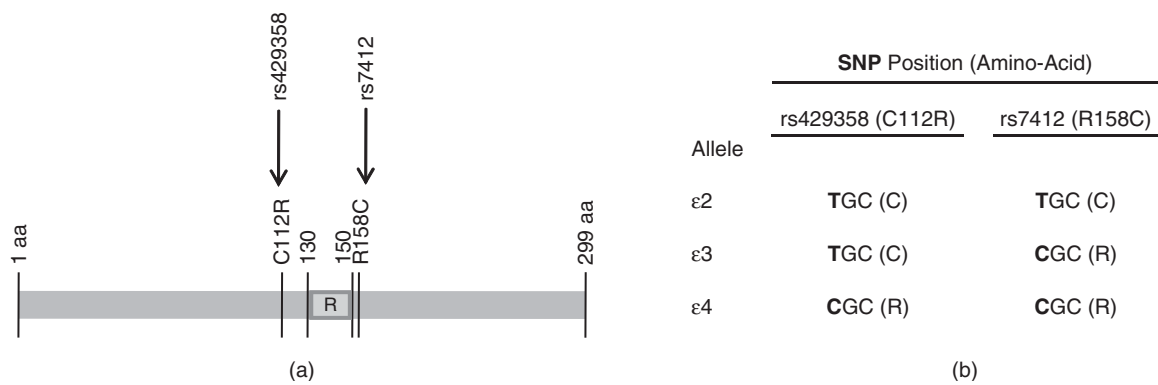


Figure 43.5 AD2: *APOE* structure and single nucleotide polymorphisms (SNPs). The general protein structure of apoE is shown . The two SNPs and corresponding protein locations are shown (rs429358 and rs7412; C112R and R158C) (panel A). R: Receptor binding domain. Scale is approximate. The *APOE* ε2,ε3,ε4 haplotype is shown in panel B
Source: Reproduced from Bekris, Yu, Bird & Tsuang (2010). The Genetics of Alzheimer’s and Parkinson’s Disease. In: A. Lajtha (Ed.), Handbook of Neurochemistry and Molecular Neurobiology, 3rd edn. Neurochemical Mechanisms in Disease, Vol. 36. New York: Springer-Verlag. With kind permission of Springer Science+Business Media

endocytosis to rapidly remove chylomicron and VLDL remnants from circulation; this process is essential for the normal catabolism of triglyceride-rich lipoprotein constituents¹⁴⁸. In the brain, lipidated apoE binds aggregated Aβ in an apoE isoform-specific manner, with apoE4 being much more effective than the apoE3 isoform. Researchers have also proposed that the more efficient binding process of apoE4 enhances the deposition of the Aβ peptide¹⁴⁹.

Brain cells from *APOE* knockout (*APOE*^{-/-}) mice are more sensitive to excitotoxic and age-related synaptic loss¹⁵⁰, and Aβ-induced synaptosomal dysfunction in these mice is also enhanced compared to control animals¹⁵¹. When human apoE isoforms (apoE3 and apoE4) are expressed in *APOE*^{-/-} mice, the expression of apoE3, but not apoE4, is protective against age-related neurodegeneration¹⁵⁰ and Aβ toxicity¹⁵¹. In addition, astrocytes from *APOE*^{-/-} mice that express human apoE3 release more cholesterol than those expressing apoE4; this suggests that apoE isoforms may modulate the amount of lipid available for neurons. Other studies report apoE-specific effects on Aβ removal from the extracellular space whereby the apoE3 isoform has a higher Aβ-binding capacity than apoE4^{152,153}. Animal and *in vitro* models show that, in the brain, astrocytes and microglia are the main producers of secreted apoE^{154,155}. ApoE secretion in human primary astrocytes can be reduced by a combination of cytokines¹⁵⁶; whereas under stress conditions, neurons appear to be the main producers of apoE^{157,158}. In a rodent model, moderate injury has been shown to induce enhancement of apoE levels in clusters of CA1 and CA3 pyramidal neurons¹⁵⁹ and in another rodent model, apoE levels have been shown to increase in response to peripheral nerve injury¹⁶¹.

In addition, individuals carrying *APOE* ε4 have higher amyloid and tangle pathology¹⁶⁰ and an increase in mitochondrial damage¹⁶² compared to those carrying other *APOE* polymorphisms.

Genetic variation The gene dose of *APOE* ε4 is a major risk factor for AD, with many studies reporting an association between gene dose, age at onset¹⁶³ and cognitive decline¹⁶⁴. After age 65, the risk of AD among individuals with a family member with AD increases depending on the number of ε4 alleles present in the affected individual. Risks to family members with the *APOE* 2/2 and 2/3 genotypes are nearly identical at all ages to risks for family

members with the *APOE* 3/3 genotype. Among family members with *APOE* 3/3, the lifetime risk for AD by age 90 can be as much as three times greater than the expected risk found in *APOE* ε4 carriers, suggesting that factors other than *APOE* contribute to AD risk. In addition, a 44% risk of AD by age 93 among family members of *APOE* 4/4 carriers indicates that as many as 50% of people having at least one ε4 allele do not develop AD. There also appears to be a gender modification effect because the risk to male family members with *APOE* 3/4 is similar to that for the *APOE* 3/3 carriers but is significantly less than the risk for the *APOE* 4/4 carriers, whereas among female family members, the risk for the *APOE* 3/4 carriers is nearly twice that for the *APOE* 3/3 carriers^{131,133–140}.

SUMMARY

AD is characterized by an irreversible, progressive loss of memory and cognitive skills that can occur in rare familial cases as early as the third decade. Currently, there is no cure for AD, and treatments only manage to slow down the progression of AD progression in some patients^{10,11}. The early-onset familial forms of AD have an autosomal dominant inheritance linked to three genes: *APP*, *PSEN1* and *PSEN2*, whereas the most common sporadic form of AD, which occurs after the age of 60, has thus far been consistently, across numerous studies, associated with only one gene, the *APOE* gene. The mechanistic contribution of these genes in AD pathogenesis has been studied extensively, but the specific biology involved in the progression of AD remains unclear, suggesting that AD is a genetic and environmentally complex disease.

GENETIC TESTING AND COUNSELLING

APOE ε4 is most highly associated with AD for individuals with a family history of dementia and this association is highest for individuals that carry two *APOE* ε4 alleles (ε4/ε4 genotypes). The ε4/ε4 genotype is uncommon and although the ethnicity of the population may alter the expected prevalence, the genotype occurs in about 1% of normal Caucasian controls. In contrast, the ε4/ε4 genotype

occurs in nearly 19% of familial LOAD populations. *APOE* ϵ 4-associated risk is also found in African Americans and Caribbean Hispanics^{165,166}. Women with an *APOE* ϵ 4/ ϵ 4 genotype have a 45% probability of developing AD by age 73 years¹⁶⁷, whereas men have a 25% risk of developing AD by that age¹⁶⁸. AD risk is also lower for individuals with only one *APOE* ϵ 4 allele (by age 87) or no *APOE* ϵ 4 allele (by age 95)¹⁶⁸. Approximately 42% of persons with LOAD do not have an *APOE* ϵ 4 allele¹⁶⁹. Thus, the absence of the *APOE* ϵ 4 allele does not rule out a LOAD diagnosis. First-degree relatives of a person with LOAD have a cumulative lifetime risk of approximately 20% to 25%, whereas the risk in the general population is 10.4%^{134,170}. It is still not known whether the age of onset of a LOAD patient changes the risk to first-degree relatives of LOAD patients. But the number of additional affected family members most likely increases the risk to close relatives¹⁷¹. Given the low predictive value of the *APOE* ϵ 4 allele, the general consensus is that *APOE* genetic testing has limited value in asymptomatic persons for predicting AD risk^{172,173}. Family history may therefore be a better predictor of LOAD risk¹⁷¹.

In contrast, EOFAD, with an age at onset before 60 to 65 years old, has an autosomal dominant mode of inheritance in which 20% to 70% of cases are estimated to have a *PSEN1* mutation, 10% to 15% of cases are estimated to have an *APP* mutation and *PSEN2* mutations are rare^{172,174}. Indeed, approximately 60% of patients with EOFAD have another known affected family member. The remaining 40% of EOFAD patients may lack a family history because of an early death of a parent, failure to recognize the disorder in family members, or, very rarely, a *de novo* mutation⁵. If an EOFAD patient's parent has a mutant allele, then the risk to the patient's sibling of inheriting the mutant allele is 50%. The child of an EOFAD patient who carries a mutation (*APP*, *PSEN1*, or *PSEN2*) has a 50% chance of transmitting the mutant allele to each of their children.

Testing of asymptomatic adults who are at risk for EOFAD caused by mutations in the *PSEN1*, *PSEN2*, or *APP* genes is available clinically. However, genetic testing results for at-risk asymptomatic adults can only be interpreted after the disease-causing mutation has first been identified in the affected family member. It should be emphasized that testing of asymptomatic at-risk individuals with non specific or equivocal symptoms is predictive not diagnostic. In addition, obtaining results from genetic testing can affect an individual's personal relationships as well as their emotional well-being and it may even cause depression. The principal arguments against testing asymptomatic individuals during childhood are that the testing then removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings and it could have serious educational and career implications. Thus, the general consensus is that individuals who are at risk for adult-onset disorders should not be tested during childhood. Prenatal genetic testing for mutations in the *PSEN1* gene is possible if the *PSEN1* allele has been identified in an affected family member first. Preimplantation genetic diagnosis is also available for families that have a disease-causing mutation. However, parental requests for prenatal or preimplantation genetic testing of adult-onset diseases is rare³.

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Mouse Models of Alzheimer's Disease

Esther Oh, Constantine Lyketsos and Philip Wong

Johns Hopkins School of Medicine and Johns Hopkins Bayview, Baltimore, USA

Advances in the development of animal models of neurodegenerative diseases have accelerated translation of basic science research into application in humans. While many different animal models are currently being studied in research settings, this chapter will focus on transgenic (tg) mouse models of Alzheimer's disease (AD). There are two main types of tg mouse models of AD: models of amyloidosis and/or of tauopathy. These two types represent the two major pathological changes seen in AD, amyloid plaques and neurofibrillary tangles (NFTs). More recently, a model combining both features has been developed, allowing researchers to study their interaction. Important variations are conditional tg mouse models of AD in which the expression of transgenes can be manipulated – induced or inhibited – by external controls, and models in which normal (or endogenous) genes of interest have been deleted from a selected locus ('knock-outs'). The following sections describe representative models in each category, and discuss advantages and disadvantages of each model. Finally, clinical implications of findings from animal studies are discussed.

TRANSGENIC MOUSE MODELS OF AMYLOID-BETA AMYLOIDOSIS

Although human familial AD (FAD) comprises a small portion of AD cases, the identification of genetic mutations associated with FAD in genes coding for the amyloid precursor protein (APP) or presenilin 1 and 2 (PS1, PS2) led to development of the earliest tg mouse models. APP is cleaved by proteolytic enzymes, β - and γ -secretases, to form amyloid-beta ($A\beta$) 40 and 42, the main components of the amyloid plaques¹. Mutations in the APP gene create excess $A\beta$ deposition by enhancing β -secretase cleavage of APP or by altering the pattern of γ -secretase cleavage of APP. This results in a higher $A\beta$ 42 to $A\beta$ 40 ratio, which in turn enhances $A\beta$ fibrillogenesis.

One of the first strategies to create AD-like pathology in mice was to develop tg mouse models that over-express human APP with FAD mutations. While over-expression of APP is not a general feature of AD, this approach led to tg mice with significant $A\beta$ production and deposition over their lifetime. One such tg mouse model, known as PDAPP, uses a platelet-derived growth factor β (PDGF β) promoter to enhance in mice the expression of human APP with V717F mutation². Another early tg mouse model, Tg2576, uses the hamster prion protein promoter (*PrP*) to enhance the expression of human APP with a double Swedish mutation (K670N/M671L)³. Both

models have been extensively studied as models of $A\beta$ amyloidosis (Table 44.1).

Another approach to developing tg AD mouse models involved the insertion of human presenilin genes with mutations known to cause AD into the mouse genome. Presenilins are part of the γ -secretase complex, which is involved in the cleavage of APP along with β -secretase. However, mouse models with PS1 mutations alone do not develop amyloid pathology^{4,5}. When both APP and PS1 mutations are expressed together in tg mice, such as in APP^{swe}/PS1^{dE9} (Table 44.1)⁶, the PS1 mutation increases the ratio of $A\beta$ 42 to $A\beta$ 40, resulting in more $A\beta$ deposition due to the higher fibrillogenic nature of $A\beta$ 42⁷.

Many of the tg mouse models of amyloidosis also develop other pathologies seen in the human disease such as neuritic plaques, gliosis or synaptic loss, allowing for observation of the effect of amyloid on neuronal pathologies. Significantly, monoaminergic neurodegeneration, a feature of the human disease, occurs in at least one mouse model⁸. These models have been very useful to the identification of mechanism-based therapeutics, specifically, anti-amyloid therapies. However, a major limitation is that the amyloidosis models do not develop NFTs, one of the hallmark neuropathological changes seen in AD.

TRANSGENIC MOUSE MODELS OF TAUOPATHY

The amyloid cascade hypothesis¹ proposes that $A\beta$ is an early upstream agent that is followed by excess phosphorylation of tau, an intracellular, microtubule-associated protein. Hyperphosphorylation of tau is thought to lead to the formation of paired helical filaments (PHF), which progress to become NFTs in the neuronal cell body. However, as mentioned above, tg mouse models of amyloidosis do not form NFTs. One reason may be differences in tau isoforms across humans and mice. Six human isoforms of tau exist, each derived from alternative splicing in the brain of the same gene. There are only three isoforms in mice, which may result in a lower propensity for hyperphosphorylation⁹.

There is currently no known tau mutation in AD. However, independent of amyloid plaques, tau inclusions are found in other neurodegenerative diseases such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease (PiD) and frontotemporal dementia (FTD). Therefore, tg mouse models of tauopathy have been created using human mutations in the tau

Table 44.1 Examples of mouse models of Alzheimer's disease

<i>Model</i>	<i>Pros</i>	<i>Cons</i>	<i>Best use of model</i>
PDAPP mice (line 109) ²	Diffuse and neuritic plaques, synaptic loss, astrogliosis and microgliosis; significant impairment on a variety of different learning and memory tests	Some early age-independent memory and behavioural deficits; noncongenic strain background; no NFT or tau aggregates	Studies of passive and active anti-A β immunization; interactions between A β and apolipoproteins
APPswe (Tg2576) ³	Numerous A β plaques, oxidative lipid and glycoxidative damages; memory deficits seen in 9–10-month-old Tg mice	No NTF or tau aggregates; early deficits in Morris water maze with visible platform; noncongenic strain background	Studies of immunotherapeutic approaches; breeding with other AD models; use of NSAIDs and other treatments
Double transgenic mice: Mo/Hu APPswe/PS1dE9 ⁶	Exhibit accelerated A β deposition despite relatively low level of APPswe over-expression; both transgenes are co-segregated; a similar model, line C3-3/S9, shows age-related deficits in behaviour ³¹	Noncongenic strain background; no NFT or tau aggregates	Studies of efficacy of different experimental treatments; breeding of these mice to other transgenic mice is efficient owing to co-segregation of the transgenes
Conditional transgenic mice: rTg4510 ¹⁴	These mice express repressible human FTDP-17 mutation P301L (4R0N tau _{P301L}); progressive age-related NFT, neuronal loss and functional deficits are present; after the suppression of transgenic tau, memory function recovered and neuron numbers stabilized, but NFTs continued to accumulate	No A β accumulation; gross forebrain atrophy, with preservation of hindbrain structures	Studies of reversibility of cognitive and pathological alterations
Conditional transgenic mice: CaMKII α -tTA $\times$ tet-APPswe/ind ¹³	These mice express repressible APP transgene with Swedish and Indiana mutations; they develop progressive amyloid plaques	No NFT or tau aggregates; high expression lines are hyperactive	Studies of reversibility of pathological alterations
Triple transgenic mice: 3xTg-AD PS1, APPswe,tau ¹¹	Amyloid plaque develops before tau pathology, and the regional distribution of amyloid and tau closely mimics human AD pathology; age-dependent decline in both spatial and contextual learning and memory	May be difficult to differentiate the effect of amyloid from tau	Studies of anti-A β immunization; understanding the relationship between amyloid and tau pathology; testing the amyloid cascade hypothesis

Source: Adapted from Savonenko *et al.*, 2005

gene linked to familial frontotemporal dementia with Parkinsonism on chromosome 17 (FTDP-17). One such model, expressing the FTDP-17 mutation P301L, forms NFTs in diencephalon, brainstem, cerebellum and spinal cord. However, this model also has motor deficits due to spinal cord lesions such as fibrillary gliosis and axonal degeneration¹⁰.

More recently, models which reproduce both amyloid plaques and NFTs have been developed, the triple transgenic mice 3xTg-AD, which carry PS1 (M146V), APP (K670N/M671L) and tau (P301L) transgenes (Table 44.1)¹¹. Interestingly, even though both APP

and tau transgenes are expressed to similar levels in these mice, A β deposits emerge prior to tau pathology, consistent with the amyloid cascade hypothesis. Immunotherapy experiments involving direct injection of anti-A β antibodies into the hippocampus showed clearance of A β deposits followed by clearance of earlier (non-hyperphosphorylated) forms of tau. A β deposits re-emerged by 30 days post-injection, with tau pathology re-emerging at a later time point. Injection of anti-tau antibody had no observable effect on either A β or tau deposits. The data from these experiments further support the view that A β precedes tau pathology per the amyloid

cascade hypothesis¹². These triple transgenic models are therefore quite useful for studying the role of tau protein in neurodegenerative diseases, and especially its interaction with amyloid pathology.

CONDITIONAL TRANSGENIC MOUSE MODELS

Researchers have also developed variations of the above models in which the expression of APP, tau or both transgenes are temporally controlled. The approach used, commonly known as the 'tet-off system,' creates a tg model in which administration of a tetracycline analogue, such as doxycycline, turns off transcription of the transgene. Conditional tg models allow study of the effects of temporal variation (early vs. late, short vs. long) in the expression of the transgene. Such systems also model pharmaceutical interventions in which the expression of a transgene is suppressed, allowing assessment of potential treatment effect¹³. They can also test the hypothesis of whether certain structural and biochemical changes are related to the expression of the transgene¹⁴.

A well-known conditional APP tg mouse model is CaMKII α -rtTA $\times$ tet-APP^{swe}/ind (Table 44.1). This model expresses amyloid plaques starting eight weeks of age, and amyloid deposition is severe by six months of age. APP expression is reduced by greater than 95% two weeks after initiation of doxycycline treatment. When doxycycline was given to examine the effects of A β suppression after the onset of deposition, further progression of A β deposition was halted, but there was limited to no clearance of previously deposited amyloid plaques even after six months of treatment. These results suggested that inhibition of A β production may halt further progression of the pathology, but may not clear the pre-existing amyloid plaques¹³.

A tg mouse model with conditional tau expression is rTg4510, in which mutant tau (P301L) expression is suppressed by administration of doxycycline (Table 44.1). This model has age-dependent formation of NFTs, loss of neurons, generalized forebrain atrophy and deficits in spatial memory. While formation of NFTs has been linked to subsequent neuronal loss and cognitive deficits, suppression of mutant tau gene starting at four months of age in these mice did not halt the accumulation of NFTs, even though there was a cessation in the loss of neurons and brain weight¹⁴. In addition, there was improvement in memory function in these mice, despite progressive NFT accumulation. These findings imply that early memory deficits may be due to reversible neuronal dysfunction rather than irreversible development of NFTs or that there may be neuronal remodelling after the mutant tau gene suppression that allows recovery. Another implication from this study is that NFTs may not entirely account for the neuronal loss¹⁴.

Recently, the conditional triple tg mouse rTg3696AB that harbours two human Swedish APP mutations (K670N and M671L) at the β -secretase site, the London mutation (V717I) at the γ -secretase site (APP_{NLI}) and a tau mutation (P301L) has been created. This model shows A β deposits from 4 months of age, and NFTs from 11 months of age. Neuronal loss occurs at 13 months of age. Studies of the effects of transgene suppression, mimicking potential human therapeutic strategies, on pathologic and cognitive behavioural outcomes are in progress¹⁵. This discussion illustrates the advantages of conditional tg mouse models, where temporal variations in the expression of transgenes as well as inhibition of select transgenes can demonstrate the potential role they play in the pathogenesis of neurodegeneration and cognitive behavioural symptoms.

KNOCK-OUT MOUSE MODELS

Knock-out models are mice in which genes of interest have been selectively silenced. They are useful for determining the function of a specific protein or an enzyme, and for studying biological models of the enzyme inhibition.

The APP gene is located on chromosome 21, and has many putative roles. Along with its homologues, the amyloid precursor-like proteins 1 and 2 (APLP1 and APLP 2), APP is thought to have roles in cell adhesion, motility, neuronal survival and neurite outgrowth. Interestingly, one of the APP knock-out mouse models (APP^{-/-}) produces mice that are relatively healthy and fertile, with slightly lower body weight, decreased locomotion and increased reactive gliosis. The ability to maintain a relatively normal litter size was attributed to possible compensation for the loss of APP by its homologues¹⁶. However, subsequent studies revealed behavioural deficit, defective long-term potentiation and GABA-mediated postsynaptic response in these mice¹⁷.

The microtubule-associated protein tau (MAPT) gene is located on chromosome 17q21. In normal human brain, tau is thought to be involved in stabilizing microtubules, which are located predominantly in axons. MAPT knock-out mice (Mapt^{-/-}) do not have overt histological abnormalities. However, they exhibit muscle weakness on a rod walking (balance coordination) or a wire hanging (traction) test. They also demonstrate impaired contextual fear conditioning in foot shock experiments, which are thought to test amygdala and hippocampal functions. However, these impairments in Mapt^{-/-} mice are thought to be due to hyperactivity of the mice rather than due to memory impairment since they exhibit hyperactivity in open fields but have intact spatial learning tasks^{18,19}. As with the APP knock-out models, the lack of significant pathologic deficits in tau knock-out models such as Mapt^{-/-} may be due to compensation by other microtubule-associated proteins that may have overlapping function with MAPT protein¹⁹.

One example of a knock-out mouse model that demonstrates the function of an enzyme while serving as a biological model of enzyme inhibition is the BACE1 knock-out model (BACE1^{-/-}). This model demonstrates the role of the β -site amyloid precursor cleaving enzyme 1 (BACE1) in APP cleavage. Primary cortical cultures from the BACE1^{-/-} mouse embryos have undetectable levels of most A β 40 and 42 species, demonstrating that amyloid is not produced, thus establishing BACE1 as the principal β -secretase in cortical neurons. More importantly, because the BACE1^{-/-} mouse model was viable, this model suggested that it may be possible to develop therapeutic β -secretase inhibitors to reduce A β deposition without mechanism-based adverse effects²⁰.

While abnormal processing of APP and tau may result in neurotoxic substances, such as A β and NFTs, respectively, these knock-out mouse models demonstrate that APP and tau both play important roles in normal neuronal function. In addition, knock-out mouse models of enzymes such as BACE1 demonstrate the biological role of enzymes and the effects of targeting them as part of AD therapy.

DISCUSSION

While Tg mouse models of amyloidosis do not fully reproduce the pathological changes seen in human AD, they have contributed significantly to our understanding of the pathophysiology of AD. Amyloid plaques, along with neurites, neurofibrillary tangles, loss of synapses and death of neurons, are the pathological hallmarks

of AD^{21,22}. Most tg mouse models express either amyloid or tau pathology, although more recent models express both^{12,15}. Many models do not show loss of neurons^{23,24}, a critical feature of human AD. Several explanations have been proposed, including species variability in neuronal vulnerability, lack of key human-type inflammatory factors¹, species variability in amyloid burden, and differences in types of plaques that accumulate in different tg mouse models²⁵. Some tg mouse models also show *age-independent* behavioural deficits *prior* to A β deposition in the brain²⁶, which is different from human AD, in which amyloid deposition begins years before the clinical manifestations are evident.

Model to model variability can also be attributed to the use of different promoters, resulting in different phenotypic expressions. Some tg mouse models have tissue-specific (e.g. brain)¹³ or more broadly expressed³ transgenes, depending on the promoter type. Differences in promoters can also result in differences in transgene expression levels, expression in irrelevant brain areas as well as expression at different times. Differences in background strains can also result in different phenotypic expressions even within the same tg mouse model¹⁹.

Despite limitations, tg mouse models are essential tools for investigating biological mechanisms and assessing potential treatments for AD. AD is characterized by gradual onset and progression of the brain disease over many years. One of the more difficult aspects of human AD research is the long duration of clinical trials, which can become prohibitive due to high patient attrition and costs. In addition, more researchers are focusing their efforts on the period preceding the AD diagnosis, preclinical and mild cognitive impairment (MCI) stages, extending the duration of the study. Tg mouse models have rapid breeding time and lower maintenance costs compared to primate models, allowing accelerated investigation of the mutated gene of interest. This results in shorter lead-time before the development of pathology (e.g. amyloid deposition in the brain) and the resultant behavioural changes. It also enables a researcher to design an intervention and observe pathological and behavioural changes within a short time frame. Many of these models have been used for evaluation of a treatment tool such as immunotherapy²⁷. They are also useful for environmental modifications such as enrichment²⁸ and caloric restriction²⁹, and direct observation of their effects on behaviour as well as on neuropathology.

Many of the tg mouse models develop impairments in learning and memory as assessed by well-established methods including the Morris water maze task^{9,30}. The difficulty of interpreting mouse behaviour partly arises from age-independent behaviours. These behaviours may be due to factors that are unrelated to A β toxicity such as transgene insertion and expression levels, strain background and promoter types⁹. Differences in the timing of behavioural onset in relation to the A β deposition may also be due to the use of different tasks for behavioural testing as well as assessment of behaviour at different stages of learning⁹. Recently, there have been efforts to elucidate potential soluble A β species that may contribute to the behavioural deficits, and that may, in part, explain the age-independent behaviours²⁶.

Some of the difficulties in human AD research arise from heterogeneity within the study population, which introduces confounders. Tg mouse models allow researchers to minimize the biological heterogeneity that may influence the outcome of interest by repeated backcrosses to an inbred breeding strain of mouse model up to at least tenth generation, creating a 'congenic' strain of the model. In conclusion, tg mouse models are useful for studying molecular

mechanisms of a disease as well as for assessing therapeutic effect of drugs or environmental modifications, and continue to make significant contributions towards further understanding of AD.

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Physiological Neuroimaging in Ageing and Dementia: Metabolic and Molecular Scanning

Markus Donix, Susan Y. Bookheimer and Gary W. Small

David Geffen School of Medicine at UCLA, Los Angeles, USA

INTRODUCTION

It is well recognized that in a process of cognitive decline leading to mild cognitive impairment (MCI) and dementia, detection of the underlying changes in brain structure and function will contribute to establishing an accurate diagnosis, with direct implications for pharmacological and non-pharmacological therapy planning. Since the first positron imaging device in 1950 or the first tomographs from single photon emission data in the 1960s, scientific advances in radionuclide development and detection research have led us to look beyond the brain's regional blood flow (SPECT) or glucose metabolism (FDG-PET) into the patterns of amyloid plaque (PIB-PET) and tau tangle brain deposits (FDDNP-PET) or neuronal disintegration (MPPF-PET). With new methods entering clinical settings, we will need to balance our expectations for these new tools against availability and costs. Here we review the current state of metabolic and molecular imaging tools used in ageing and dementia, their utility, promise, as well as potential difficulties in bringing them into common practice. We will first review the basic techniques and then discuss their applications, including practical guidelines and results from the most recent studies reporting sensitivity, specificity and optimal uses.

SPECT

Image Acquisition

Single photon emission computed tomography (SPECT) measures the distribution of radioligands in the brain reflecting regional cerebral blood flow (rCBF), which itself is linked to brain metabolism. The tracer accumulates in proportion to the rate of delivery of blood to a distinct volume of brain tissue. Decades ago to patients this would have meant injection of ^{133}Xe or ^{85}Kr into the carotid artery. Today, within the commercial and experimental available radioligands technetium-99m labelled hexamethylpropyleneamine ($^{99\text{m}}\text{Tc}$ -HMPAO) and ethylcysteinate dimer ($^{99\text{m}}\text{Tc}$ -ECD) tracers are commonly used in brain SPECT imaging. After intravenous injection, these lipophilic compounds quickly cross the blood-brain barrier by diffusion and, due to slow brain clearance, the distribution of the radioligands then remains stable for hours. The underlying multicompartment clearance ('microsphere') model assumes that the tracer is freely diffusible, completely extracted to the brain and 'fixed' without redistribution. The emitted single

photons can be detected by a rotating gamma camera or ring-type imaging system. Spatial resolution is about 10 mm and could reach 5–6 mm using special-purpose detection systems that usually are not available for routine clinical scans.

Spatial resolution in SPECT is only limited by technology (whereas PET resolution also depends on other factors¹; see below) but today SPECT cannot compete with PET on image resolution and begins to lose its uniqueness within other factors. Cost-effectiveness still remains a controversy from a perspective that would take diagnostic accuracy and secondary costs into account; further, PET has become much more available, which also will make it less expensive. Resulting from physics-based differences, the possibility of simultaneous imaging of more than one radioagent is SPECT territory and a growing field of interest. Since all PET tracers share the same energy level, it would be much more difficult to perform simultaneous multiple tracer studies in PET. Signals would have to be separated based upon half-life or kinetics, which seems feasible in the future^{1,2}.

Advanced SPECT technology is heavily reliant on detector improvements, use of hybrid imaging (e.g. SPECT/CT) and incorporation of attenuation or collimator-detector response modelling into image reconstruction algorithms (for review see¹).

The clinical protocol requires the application of 20 mCi (740 MBq) of $^{99\text{m}}\text{Tc}$ -HMPAO or $^{99\text{m}}\text{Tc}$ -ECD 10 to 20 minutes before imaging with HMPAO and 30 to 60 minutes before image acquisition with ECD. Image acquisition itself will take 30 minutes or less. Total radiation exposure is small (about 9 mSv) and in the range from one to three times of the annual natural background.

Memory Impairment and SPECT Imaging

In the field of dementia and related disorders, SPECT has been used widely for both basic science and clinical applications. Alzheimer's disease patients display a characteristic pattern of posterior temporal and parietal perfusion deficits. Sometimes additional reduced frontal rCBF has been detected, associated with behavioural disturbances, such as depressed mood or apathy³. Correlations between neuropsychological performance and rCBF have been reported consistently, especially with focus on language and global functioning⁴. Pharmacological activation studies demonstrated the relationship of, e.g. cholinergic stimulation and rCBF⁵.

In addition to clinical assessment, SPECT studies have been shown to improve diagnostic precision. Jagust and colleagues reported that

a positive SPECT result would increase the likelihood of a diagnosis of Alzheimer's disease by a factor of five⁶. In a meta-analysis, ^{99m}Tc-HMPAO-SPECT could discriminate between Alzheimer's disease, vascular dementia (VaD), frontotemporal dementia (FTD) and normal controls with sensitivities between 66% and 72% and specificities between 76% and 79%. Diagnostic accuracy is improved especially in patients who present with additional signs of cerebrovascular disease or who do not exactly match clinical criteria⁷. Furthermore, SPECT has been shown to be useful predicting the conversion to Alzheimer's disease in patients with MCI⁸.

Measuring cerebral metabolism indirectly using rCBF enhances vulnerability to vascular-related confounders, such as hypertension and other specific cerebrovascular diseases. It has been shown that rCBF differences can be found with respect to gender and advanced age itself⁹. Changes in rCBF are not unique to memory disorders and have been observed in depression¹⁰ and obsessive-compulsive disorder¹¹ as well.

Currently, most clinical SPECT scans are performed in cardiology. ^{99m}Tc-labelled tracers can be used to perform dynamic imaging (e.g. myocardial perfusion SPECT) but in the future, dynamic PET (e.g. ⁸²Rb-based cardiac PET) imaging might have an intrinsic advantage over SPECT since temporal resolution is very closely related to the imaging system's specificity¹.

In addition to regional cerebral perfusion, various neurotransmitter systems have been a target of interest in SPECT tracer development. Dopamine transporter imaging with ¹²³I-2 β -carbomethoxy-3 β -(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane (¹²³I-FPCIT), which can be used in the differential diagnosis of Parkinson's disease, could help to distinguish between dementia with Lewy bodies (DLB) and Alzheimer's disease, if the clinical diagnosis remains ambiguous. Since the cholinergic system is of particular interest in dementia, radiolabelled muscarinic and nicotinic acetylcholine SPECT ligands are currently under investigation in preliminary studies.

PET

Image Acquisition

Positron emission tomography (PET) has more diverse applications in imaging in ageing and dementia, as it can be used to generate images of regional cerebral blood flow (e.g. [¹⁵O]H₂O-PET), metabolic activity (e.g. [¹⁸F]FDG-PET), microstructures (e.g. [¹⁸F]FDDNP-PET) or neurotransmitter receptor distribution (e.g. [¹⁸F]MPPF-PET) in the brain. After being injected intravenously, the isotope emits a positron, which after travelling a few millimetres annihilates with an electron. As a result, two 511 keV gamma photons, moving in almost opposite directions, are produced and then detected using a scintillator material (luminescent when excited by ionizing radiation) in the ring-type scanner. Only coincident arrivals of photons are recognized (within a few nanoseconds' error margin). Because of the peculiar dataset ('coincidence events', each representing a line connecting the two points of detection along which the annihilation occurred) compared to other neuroimaging techniques data, preprocessing and mathematical image reconstruction are challenging. Spatial resolution of PET images is about 3 mm and higher and limited by technological factors (detector-related effects) but also physics-related limitations (positron range and photon non-collinearity)¹. Improvements in PET technology will be seen in both cases. New scintillators for reduction of random coincidences and silicon-based photodetectors will improve detection. PET/MRI

hybrid imaging systems could be used for monitoring patient motion via MRI to incorporate the data in PET image reconstruction, maybe replacing PET/CT in the future^{1,12}. Even ultimate limitations (positron range/photon non-collinearity) have been a target since new statistical reconstruction algorithms could incorporate their probability distributions into image processing or a strong magnetic field (preferably 5 T or higher) of a future PET/MRI system should be able to reduce positron range and therefore enhance scanner resolution¹. Time-of-flight-PET, as one of the most promising technological advances, uses the nanosecond difference of photon arrival times to restrict the position of the positron emission to a subsection of the photons' connection line, which reduces the statistical noise variance in PET reconstruction¹.

PET isotopes usually have shorter half-lives compared to SPECT ligands. The most common PET isotopes are ¹¹C (half-life: 20 min), ¹³N (10 min), ¹⁵O (2 min) and ¹⁸F (110 min). Only a few hospitals have costly on-site cyclotrons, needed to produce them. Third-party suppliers are able to provide ¹⁸F because of its relatively long half-life and therefore clinical use is often restricted to ¹⁸F-labelled ligands. On the other hand, short half-lives allow the safe injection of higher activities, increasing detectable radiation.

The most common clinical application of PET is in resting measures of glucose metabolism, with [¹⁸F]FDG. In the standard clinical procedures, the tracer is injected (usually 5–6 MBq/kg for FDG) after a resting period (15–20 min). [¹⁸F]FDG-PET additionally requires at least four hours of fasting before the scan to minimize competitive inhibition of FDG uptake by blood glucose. About 40 min later (uptake phase) scans are performed (at least 20 min for conventional and 4 min for rapid scan procedures¹³).

The number of PET tracers is rapidly growing and we will focus on today's most promising ligands in the field of memory disorders. Thus, we will not further discuss others that may be relevant in the future, such as [¹⁸F]-BAY94-9172 (amyloid- β plaque labelling ligand, which has been shown to discriminate Alzheimer's disease from FTD patients and healthy controls), [¹¹C]-nicotine (visualization of nicotine binding sites in patients under cholinesterase inhibitor treatment) or [¹¹C](R)-PK11195 (visualization of microglial activation and immune response) (for review see¹⁴). Second, certain techniques, such as PET activation measurements, primarily performed in healthy subjects to identify regional brain activation underlying specific cognitive activities, or regional blood flow measurements with [¹⁵O]H₂O-PET, will not be discussed either because of their decreasing relevance in current diagnostic procedures of memory impairment.

Finally, it must be mentioned that correction for possible confounding parameters is as important as in other neuroimaging techniques. Motion correction must be computed, and limitation in spatial resolution and brain atrophy in the particular patient group discussed here enhances the likelihood of partial volume effects. For adequate correction MRI scans of the subjects should be available.

[¹⁸F]FDG-PET

In PET brain imaging the radiolabelled glucose analogue [¹⁸F]fluorodeoxyglucose ([¹⁸F]FDG) is the most common PET ligand. FDG is transported into cells like glucose but not metabolized after the first step in the glycolytic pathway. Thus, the distribution of [¹⁸F]FDG reflects cerebral glucose metabolism, providing information on the distribution of neuronal loss and synapse dysfunction. Glucose provides energy for neurotransmitter

synthesis, and synaptic dysfunction and neuronal degeneration cause a decline of glucose metabolism in the affected parts of the brain¹⁵.

In patients with Alzheimer's disease most affected brain regions with reduced FDG uptake are temporoparietal association cortex, posterior cingulate cortex, precuneus and variably also frontolateral association cortex¹⁵. These highly reproducible findings provide excellent separation of Alzheimer's disease patients from normal controls. Different FDG uptake patterns can also be observed in Alzheimer's disease patients with early (<65 years) versus late onset of the disease or high versus low education profile¹⁶. Because it is crucially important to identify predictors of future cognitive decline, a growing number of studies is being performed in people carrying risk factors (e.g. genetic) for developing Alzheimer's disease. It has been demonstrated that presymptomatic *APOE4* genotype carriers show abnormal uptake reductions using [¹⁸F]FDG-PET in an Alzheimer's disease-like pattern in the absence of cortical atrophy¹⁷. Although an Alzheimer's disease-like pattern has been found to be predictive for future cognitive decline in normal ageing¹⁸, it remains a controversy if hypometabolism in *APOE4* carriers can be considered a sign of pathology or just a genetic consequence¹⁶.

In patients with MCI, AD-like [¹⁸F]FDG-PET patterns are predictive for conversion to Alzheimer's disease¹⁹. In general, glucose hypometabolism has been reliably observed in MCI subjects, especially in posterior cingulate cortex of amnesic type patients. Metabolic changes in parietotemporal areas seem to be the best predictor for a patient's decline from MCI to Alzheimer's disease¹⁶.

To differentiate Alzheimer's disease from other types of dementia, [¹⁸F]FDG-PET can be helpful in addition to a clinical examination, given the typical metabolic deficit patterns (frontal and anterior temporal and/or mesiotemporal in FTD; similar to Alzheimer's disease but less sparing of occipital and cerebellar cortices in DLB; diffuse cortical and subcortical in VaD); however, accuracy of discrimination has rarely been reported¹⁶.

Today, [¹⁸F]FDG-PET is the best established and growingly available diagnostic tool to observe the metabolic consequences of structural brain alterations in cognitive decline and it is increasingly accepted for reimbursement in countries' medical systems. In today's comparison to SPECT the superiority of PET is evident. Better spatial resolution allows the investigation of smaller brain regions, like the hippocampus, which is of particular interest in the field of memory disorders. In SPECT the occasional loss of the coupling of cortical metabolism and perfusion due to vascular disorders could bias the findings. The effect of hypometabolism shown with [¹⁸F]FDG-PET is generally greater than hypoperfusion effects in SPECT²⁰ and, most importantly, the achievable diagnostic accuracy with PET (sensitivity/specificity: 93%/93% for moderate and 84%/93% for mild [MMSE 24 or higher] Alzheimer's disease versus controls²¹) is higher than with SPECT (66%/79% for Alzheimer's disease versus controls⁶).

Again, an ultimate limitation of studying metabolic patterns is that different diseases could produce the same pattern of metabolic change. As an example, frontal cortical hypometabolism has been reported in both Alzheimer's disease and depression²², and the diverse clinical manifestations of Alzheimer's disease, often including behavioural changes or mood abnormalities, underline the importance of a detailed clinical evaluation preceding brain imaging.

[¹¹C]PIB-PET and [¹⁸F]FDDNP-PET

Direct detection of Alzheimer's disease's histopathological hallmarks, such as amyloid- β plaques and tau tangles *in vivo* using

PET, can be seen as a milestone in PET tracer development. Among more than 10 ligands that have been developed in this respect within the past decade, [¹¹C]N-methyl-2-(4-methylaminophenyl)-6-hydroxybenzothiazole ([¹¹C]PIB) has been most extensively studied. [¹¹C]PIB binds to amyloid- β plaques only, and in several Alzheimer's disease patients who have been followed to autopsy after a [¹¹C]PIB-PET scan, areas of high *in vivo* [¹¹C]PIB retention correspond to postmortem regions showing amyloid- β plaque deposition. Today, the ligand is being used in more than 40 centres worldwide. A disadvantage in terms of commercialization of a [¹¹C]PIB is the short half-life of ¹¹C (20 minutes), which requires on-site cyclotron capabilities, limiting more widespread use. However, in contrast to ¹⁸F-labelled tracers (110 minute half-life), different imaging studies (e.g. [¹¹C]PIB followed by [¹⁸F]FDG) can be performed on the same day.

In Alzheimer's disease patients, [¹¹C]PIB retention is significantly increased in cortical areas compared to controls, particularly in the frontal cortex. [¹¹C]PIB retention has been shown equivalent in patients and controls in areas known to be relatively unaffected by amyloid- β plaques (e.g. white matter, pons, cerebellum)²³. To determine sensitivity and specificity, larger studies will be necessary.

[¹¹C]PIB has also been studied in patients with amnesic MCI. About half of those subjects showed higher [¹¹C]PIB retention compared to controls²⁴. Recent investigations suggest this MCI subgroup might be at a higher risk of Alzheimer's disease conversion and therefore measuring [¹¹C]PIB retention would improve the identification of possible converters. In addition, a good correlation between [¹¹C]PIB and other biomarkers (e.g. CSF A β_{1-42}) has been reported²⁵.

There could also be a possible role for [¹¹C]PIB in the differential diagnosis of dementia. [¹¹C]PIB retention was lower and more variable in DLB and absent in FTD compared to Alzheimer's disease patients²⁶.

In a two-year follow-up analysis, Alzheimer's disease patients showed a pronounced decrease in glucose metabolism, measured with [¹⁸F]FDG-PET, and cognitive decline but surprisingly stable [¹¹C]PIB retention. It has been argued that only a part of amyloid- β plaques might be accessible to exogenous tracer binding or retention could reach an equilibrium state and that additional processes, such as microglial activation and inflammation, should be taken into account in future PET multitracer binding studies²⁷. However, such longitudinal findings of relatively stable levels of [¹¹C]PIB retention²⁷ despite declines in glucose metabolism and cognitive function may limit its utility as a short-term predictor of future cognitive decline.

[¹¹C]PIB-PET has been shown to detect cerebrovascular amyloid in patients with cerebral amyloid angiopathy, a major cause of haemorrhagic stroke. This raises the possibility of extending the future use of [¹¹C]PIB-PET²⁸.

2-(1-([6-([2-[¹⁸F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile ([¹⁸F]FDDNP) is the only molecular imaging probe known to bind to *both* amyloid- β plaques and tau neurofibrillary tangles. Irrespective of its not yet widespread use compared to [¹¹C]PIB, it might be the more promising candidate from a clinical perspective. Moreover, the longer half-life of ¹⁸F could make it more accessible to clinical settings without a cyclotron on site. [¹⁸F]FDDNP has been shown to provide good visualization of plaques and tangles in autopsy-obtained human brain tissue specimens, and it clearly distinguishes between Alzheimer's disease and MCI patients and control subjects. Global [¹⁸F]FDDNP values were more accurate for diagnostic classification than [¹⁸F]FDG-PET or volumetric MRI measurements²⁹. [¹⁸F]FDDNP-PET signal is

highly correlated with cognitive performance, and the agreement between *in vivo* and histopathological postmortem tau and tangle burden maps is remarkable³⁰.

It has become obvious that tau tangle load and not amyloid- β plaque load is associated with age-related cognitive decline³¹. Direct comparison of [¹¹C]PIB and [¹⁸F]FDDNP in the same subjects showed highest [¹⁸F]FDDNP but lowest [¹¹C]PIB binding in the medial temporal cortex of Alzheimer's disease patients, again suggesting that tau tangles are the driving pathological factor in this region³² and maybe in Alzheimer's disease itself.

[¹⁸F]MPPF-PET

Changes in neuronal integrity and neuronal loss are a consequence of the molecular processes in AD pathology and are highly correlated with the decline of cognitive abilities. Therefore, any new possibility to (preferably presymptomatically) detect these changes in brain regions known to be the first affected in the development of the disease (e.g. entorhinal cortex and hippocampus CA1 and subicular fields) would be of interest to contribute to diagnostic precision and our understanding of pathology.

The correlation between neuronal death of large pyramidal cells in hippocampus CA1 field and serotonin 1A receptor density (although glutamatergic, these neurons receive high inhibitory serotonergic input via serotonin 1A receptors) has been studied in rodents using autoradiography³³. With the development of 4-[¹⁸F]fluoro-N-{2-[1-(2-methoxyphenyl)-piperazinyl]ethyl}-N-(2-pyridinyl)benzamide ([¹⁸F]MPPF) as a serotonin 1A receptor binding PET ligand, *in vivo* measurements of receptor density could be performed in humans. Results indicate that [¹⁸F]MPPF-PET clearly distinguishes Alzheimer's disease, MCI and control subjects. Whereas Alzheimer's disease subjects showed the most widespread decrease in [¹⁸F]MPPF binding, with primarily hippocampus but also raphe nuclei being affected, the maybe most remarkable finding was that receptor densities were clearly decreased in MCI patients with only mild cognitive decline³⁴. Despite the fact that the relationship between serotonin 1A receptor density, possible related compensatory and adaptive processes, and disease progression needs to be further examined, [¹⁸F]MPPF-PET, especially in addition to other techniques, such as [¹⁸F]FDDNP-PET, could be a next step to an early and exclusive *in vivo* diagnosis of Alzheimer's disease.

CONCLUDING REMARKS

In the years to come, nuclear medicine techniques will face new competitors. Namely, molecular magnetic resonance imaging, using iron oxide based contrast agents, designed with affinity to receptors or cell surface components may provide molecular pathway or receptor distribution mapping with superior spatial resolution³⁵. Only a few years ago SPECT brain imaging was believed to undoubtedly persist in brain research and diagnostic procedures but today it struggles to survive in a PET environment. But to draw conclusions about whether one imaging technique would overcome another maybe also means to underestimate the next both hardware- and software-based technological advances.

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Computational Anatomy in Alzheimer's Disease

Alex D. Leow¹, Liana G. Apostolova² and Paul M. Thompson²

¹*Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA*
Community Psychiatry Associates, Sacramento, CA, USA

²*Department of Neurology, UCLA David Geffen School of Medicine, Los Angeles, CA, USA*

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, afflicting over 24 million people worldwide. In early AD, short-term memory function is typically among the first to be impaired, followed by a progressive decline in other cognitive functions along with emotional/behavioural disturbances. At present, there is no cure for AD, whose natural course is insidious yet gradually debilitating, and is typically fatal at its most advanced stage, usually due to medical complications. In recent years, scientific interest has also focused on mild cognitive impairment (MCI), a pre-dementia stage that carries a four- to six-fold increased risk of future diagnosis of dementia, relative to the general population^{1–3}.

Many investigators have used MRI and PET imaging to measure longitudinal progression of brain changes in normal aging, MCI and AD, with varying results. As drug candidates that might slow the progression of Alzheimer's pathology began to be developed, the need for robust and sensitive imaging methods to quantify progression of Alzheimer's disease has become increasingly important. As a result, we are starting to see large collaborative multicentre imaging studies on Alzheimer's disease. For example, the National Institute of Aging and pharmaceutical industry funded the Alzheimer's Disease Neuroimaging Initiative^{4,5} (ADNI), with the goal of developing improved methods based on imaging and other biomarkers, for AD treatment trials.

Major advances are occurring in scanning techniques and in image analysis, making it easier to track disease progression with greater power. In studies of hundreds of subjects scanned over time, databases of images can now be combined to visualize the disease trajectory, showing the spread of cortical atrophy, impaired metabolism, and even plaque and tangle accumulation. Ultra-high-field MRI reveals early changes in specific hippocampal subfields^{4,5}, and new PET ligands are emerging to visualize plaque and tangle pathology^{6–9}.

In this chapter, we review several strategies of computational anatomy in mapping brain deficits in AD and early dementia. These strategies include cortical thickness mapping, tensor-based morphometry (TBM) and hippocampal surface modelling. Mathematical concepts from surface modelling, non-linear three-dimensional volume registration, fluid mechanics and multivariate statistics are used across subjects for group and interval comparisons. They can

be exploited to distinguish diseases from normal variations in brain structure, and help yield insights into the dynamics of AD and MCI.

COMPUTATIONAL ANATOMY

Computational anatomy is a general term covering a broad class of mathematical methods that model anatomical structures in images as three-dimensional curves, surfaces and volumes, and combine them across subjects to create statistical maps of brain structural differences.

Cortical Thickness Mapping

In this approach, in order to precisely quantify the amount of tissue loss, overall grey and white matter volumes can be computed from brain MRI scans. Tissue classification methods can assign each image voxel to a specific tissue class. If grey matter maps from many subjects are aligned to a standard three-dimensional digital brain atlas, on which lobar subdivisions have been labelled, regional statistics for subdivisions can be derived. These region-of-interest measures, in conjunction with manual tracings of the hippocampus and other sub-cortical structures, have been the mainstay of morphometric analysis for nearly two decades.

One approach for cortical thickness mapping is presented in Figure 46.1, which shows a computational pipeline for processing MRI scans as described by Thompson *et al.*¹⁰. For each scan, a three-dimensional map is first computed quantifying the distance of cortical grey matter voxels to the grey/white matter interface. Thickness values are calculated from the inner cortical surface to the outer cortical surface, and are plotted at each point on a cortical surface model extracted from the scan. To combine thickness data across subjects (Figure 46.1, second row), a spherical coordinate system is imposed onto each subject's cortical surface. This serves as a reference grid so that thickness data can be compared at a given surface-based coordinate across subjects. If sulcal/gyral landmarks are traced onto the cortical models, data from corresponding cortical regions can be averaged across subjects using a technique known as cortical pattern matching¹⁰ (CPM), where the sulcal pattern is digitized and matched across subjects using a flow field in spherical coordinates. By doing so, an average cortical model can be created

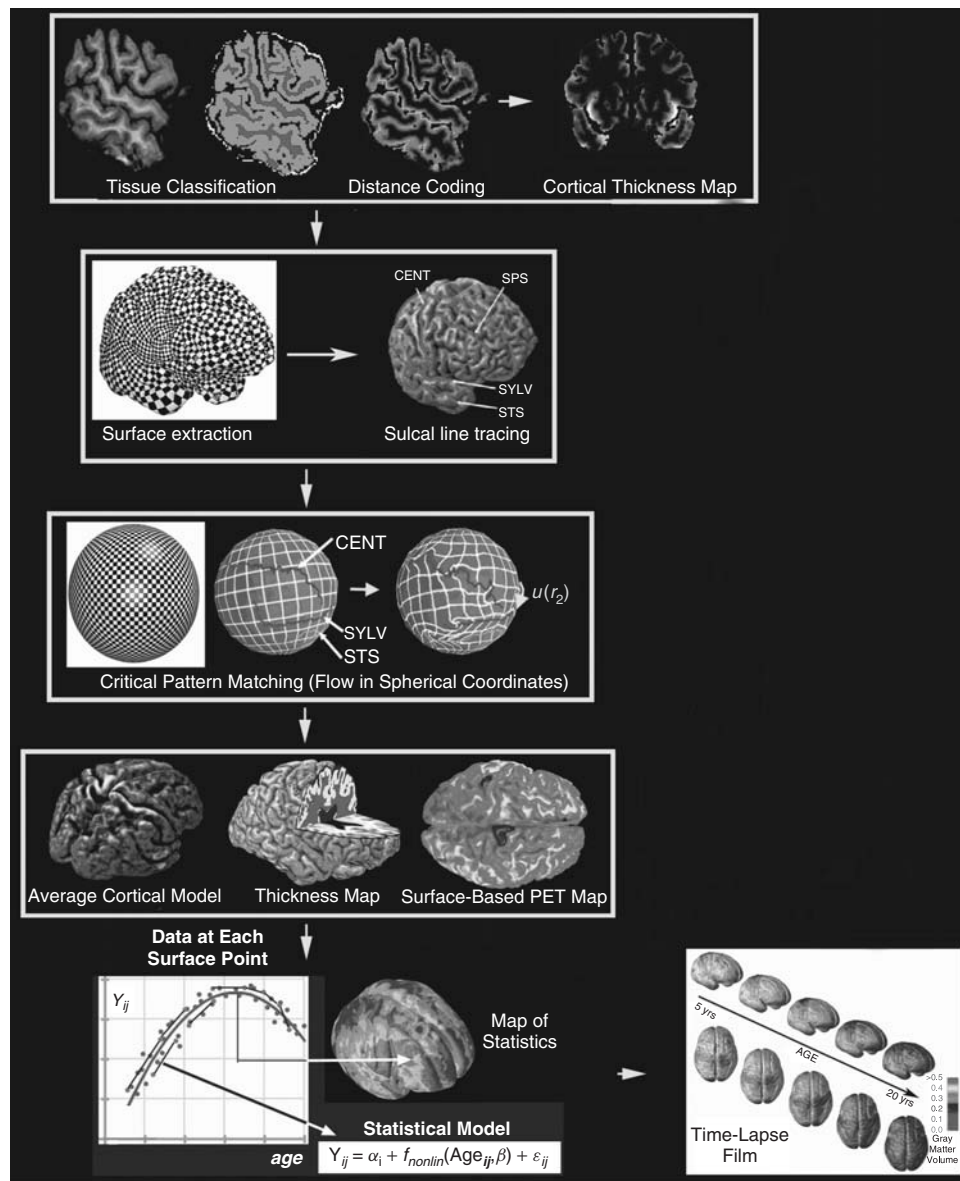


Figure 46.1 Flowchart showing an image analysis pipeline (adapted from¹⁰) that can map changes of various neuroanatomical measures in the cortex, such as grey matter atrophy. Cortical thickness profiles, for example, can be averaged across subjects or compared across time. Tissue classification techniques can be used to identify grey and white matter and to produce cortical thickness maps (row 1). The CPM approach can be applied by tracing sulcal landmarks on extracted brain surface models (row 2) that serve as anchors to guide a flow field matching gyral regions across subjects (row 3). Then maps of cortical thickness, or other cortical signals (such as co-registered PET images, shown here), can be fluidly aligned to an average cortical model (row 4). Statistical models are fitted to data from all the subjects at each cortical point. This can assess whether imaging signals are associated with age (bottom row), or other parameters of interest. Effects of ageing on cortical measures – or changes relative to baseline – may be animated as a time-lapse film to reveal the disease trajectory. A full colour version of this figure appears in the colour plate section

for a group of subjects (such as an AD or MCI population), with well-defined sulcal features in their mean spatial locations (Figure 46.1, fourth row). Moreover, maps of cortical thickness in each individual can be transferred onto this average model while adjusting for the individual gyral pattern differences across subjects. This method allows pixel-by-pixel averaging of values within each delineated region across all subjects, allowing comparisons of patients with controls. Lastly, a statistical model can be fitted to the thickness measures from all subjects at each surface point

(Figure 46.1, bottom row). In brain mapping studies, it is common to fit statistical models to data at each location in an image, to assess effects of age, diagnosis or experimental parameters (an approach known as statistical parametric mapping; SPM¹¹). The results are displayed in the form of a three-dimensional map of statistics, and the overall significance of the map can be colour-coded to show the distribution of atrophy¹⁰.

Cortical thickness mapping is related to several simpler but widely used methods. For example, the ‘boundary shift integral’ technique

quantifies differences between two successive co-registered 3D MRIs by examining the magnitude of the shifting of grey–white junction¹². Before algorithms became widely available for computing cortical thickness accurately from MRI scans, it was more common to compute a local measure of grey matter volume called ‘grey matter density’ (GMD). This is defined, at each point in an image, as the proportion of tissue segmented as grey matter in a small spherical region (typically of 10–12 mm radius) centred at that point^{13,14}. GMD and thickness are highly correlated¹⁵, except at the temporal lobe tips, where cortical curvature is high.

Cortical Maps in AD and MCI

Cortical mapping methods have distinguished patterns of atrophy typical of late- versus early-onset AD¹⁶, and different dementia subtypes¹⁷. Sowell *et al.*¹⁸ applied cortical pattern matching to 176 scans of subjects aged 7 to 87, and compiled trajectories of grey matter thinning, for each cortical point, over the life span. Encouragingly, there was close regional correspondence between the cortical thickness maps created from *in vivo* MRI and the 1929 postmortem data of von Economo. The cortex does not age in a homogeneous way; each cortical region has a somewhat distinctive trajectory^{18,19}. A related study by Gogtay *et al.*²⁰ created a time-lapse map of cortical development from ages 4 to 22, and showed the earliest maturing cortex is least vulnerable to aging and AD.

Apostolova *et al.*²¹ compared grey matter profiles in 26 amnesic MCI and 31 mild AD subjects, showing strikingly greater atrophy in mild AD (Figure 46.2A), conforming to the pattern of spread of AD pathology observed postmortem through the brain. A related VBM study found significantly greater parietal, anterior and posterior cingulate atrophy in mild to severe AD relative to MCI²³.

In Apostolova *et al.*²², we also examined the structural correlates of apathy in AD, by applying cortical mapping to 35 AD patients with and without apathy (Figure 46.2B). Apathy severity was associated with cortical grey matter atrophy in bilateral anterior cingulate (Brodmann area BA 24; $r = 0.39$ – 0.42 , $p = 0.01$) and left medial frontal cortex (BA 8 and 9; $r = 0.4$, $p < 0.02$). A subsequent study found associations between the Boston Naming Test and the animal fluency tests and cortical atrophy in 19 probable AD and 5 multiple-domain amnesic MCI patients who later converted to AD²⁴. The degree of language impairment correlated with cortical atrophy

in the left temporal and parietal lobes, especially in the perisylvian language cortices.

Time-Lapse Maps and the Trajectory of AD

The cortical pattern matching approach may be extended to time-varying or functional imaging data. If longitudinal scans are available, a time-lapse movie of disease progression can be created by fitting a trajectory to cortical thickness, or any other imaging parameter, at each cortical point (Figure 46.1, bottom right)²⁵. A movie ‘frame’ can then be written out for each time-point and the series of frames can be animated. An example of this type of dynamic map may be viewed at www.loni.ucla.edu/~thompson/AD_4D/dynamic.html. Here, a time-dependent model was fitted to cortical grey matter density in 14 AD patients and 12 controls scanned longitudinally for 4 years. Maps of the degree of deficits – either as a percentage or as a significance map – show that the cortex is thinner in medial and lateral temporal lobes in early AD and deficits advance anteriorly to engulf the cingulate and frontal cortex.

Figure 46.3 shows two time-points from this animation, showing that cortical atrophy on MRI proceeds in approximately the same anatomical sequence as plaque and tangle burden in histopathological studies of AD. Plaque and tangle deposition starts in medial temporal regions²⁶ and affects the posterior limbic system first due to its close connections to the posterior cingulate gyrus²⁷. Hypometabolism of the posterior cingulate is observed early in AD, even when no atrophy is detected in this region²⁸. On the other hand, in frontotemporal lobar degeneration, neuronal loss is first observed in the frontal regions closely connected to the anterior cingulate cortex²⁹.

Cortical pattern matching can also be used to understand how amyloid load spreads in the living brain. Braskie *et al.*^{8,30} applied cortical pattern matching to 23 subjects (10 controls, 6 amnesic MCI, 7 AD) scanned with both MRI and [¹⁸F]FDDNP, a recently developed PET ligand sensitive to plaque and tangle pathology^{7,31}. They aligned parametric PET images of amyloid load to MRI scans from the same subjects, textured the PET signals onto the cortex, and combined them across subjects using cortical pattern matching (Figure 46.1, fourth row). They showed that the advancing pathology also follows the classical Braak trajectory for neurofibrillary tangle accumulation. Related work by Mintun *et al.*⁹ and Rowe *et al.*³² with Pittsburgh Compound-B ([¹¹C]PIB) show frontal lobe labelling

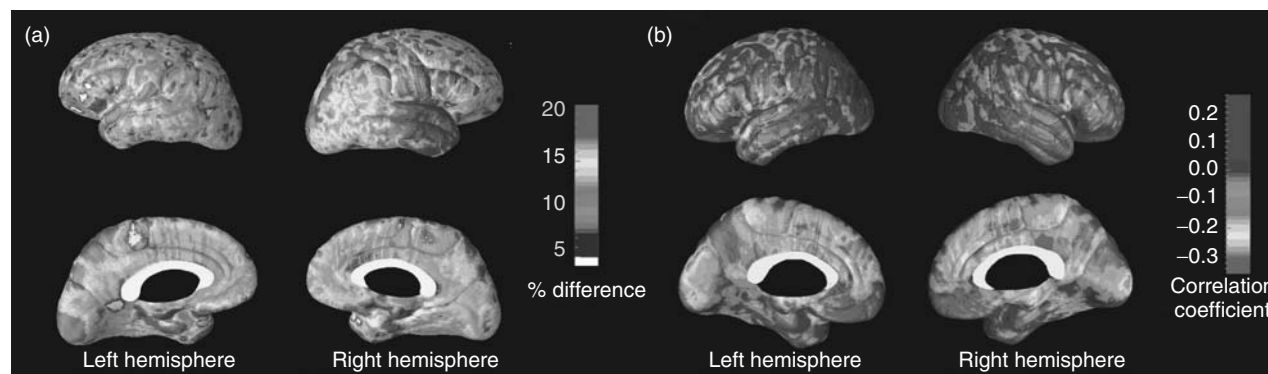


Figure 46.2 (A) Cortical thinning of up to 20% occurs between MCI and AD, in widely distributed cortical areas (greatest tissue loss is coded in red). (B). Grey matter atrophy in the anterior cingulate and supplementary motor cortices is correlated with the presence or absence of apathy in AD. Regions where structural variation correlates with clinical or behavioural differences can be identified using correlation maps such as these (strong associations are shown here in red colours). Data adapted from^{21,22}. A full colour version of this figure appears in the colour plate section

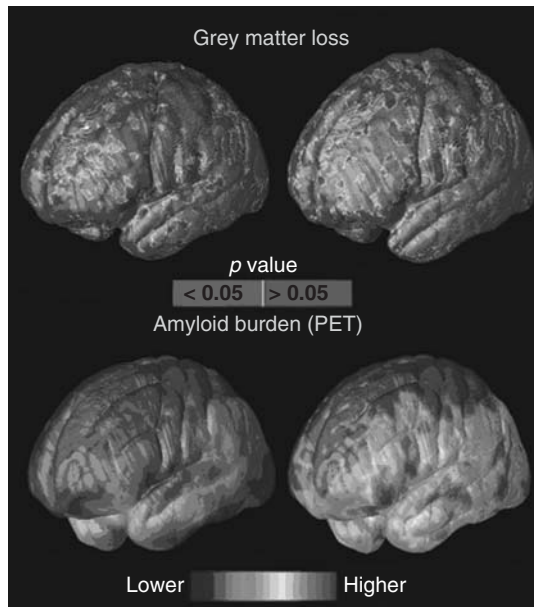


Figure 46.3 Progression of AD based on MRI and [^{18}F]FDDNP PET. On MRI (top row), the areas with grey matter deficits in mild AD (left panel) include primarily the temporal lobe, but in moderate AD (right panel) these deficits have spread to involve the frontal cortex (adapted from a longitudinal study by Thompson *et al.*²⁵). Finally, cerebral amyloid estimated *in vivo* from the PET ligand FDDNP is low in controls, but higher in those with impaired cognition (bottom row; adapted from Braskie *et al.*⁸). The anatomical agreement is striking between these *in vivo* maps and the well-established post-mortem maps for the staging of AD. In all maps, the sensorimotor cortex shows least disease-related degeneration. A full colour version of this figure appears in the colour plate section

early in the degenerative sequence. The PIB progression pattern is consistent with the Braak trajectory for amyloid deposition, which, unlike tangle deposition, shows early increases in the basal neocortex, particularly in frontal and temporal lobes and primarily in poorly myelinated regions such as the perirhinal cortex.

Tensor-Based Morphometry

While the methods described so far provide detailed maps of changes in cortical measures, tensor-based morphometry (TBM) can identify regional volumetric differences in the structure of the brain, both cross-sectionally and longitudinally, from the gradients of the deformation fields that align, or 'warp', images. In a longitudinal design, TBM can track structural changes between serial 3D MRI images, by producing rates of atrophy over time (in percentage points per year). In a cross-sectional design, TBM can compare structural scans of two different groups, such as AD versus controls or MCI versus controls.

Figure 46.4 shows the premise of TBM. If a pair of scans is collected from the same subject over time, they can be aligned with each other, using a fluid transformation that applies compressions and expansions at a local level throughout the anatomy. One class of registration methods models the baseline image as a deformable elastic medium or as a viscous fluid, and applies distributed internal forces to reconfigure the earlier scan to match the later one. The spatial gradient of this transformation (deformed grid in Figure 46.4) provides information on how much tissue is lost over the time interval between the scans, and can be plotted and colour-coded. Applied to a sequence of scans acquired over time from the same patient, these voxel expansion/compression maps¹², also known as Jacobian maps, can reveal the extent and spread of atrophy. They are also amenable to voxel-by-voxel averaging, to make a map of the average voxel-wise atrophy rate.

As part of the ADNI project, Thompson and Leow have applied the TBM approach and analysed the ADNI dataset using both cross-sectional and longitudinal designs. Leow *et al.*³³ studied the serial high-resolution MRI scans (12 months apart) from 40 normal controls, 40 MCI, and 20 AD patients from ADNI. These individual Jacobian maps, representing annual atrophy rates, are then nonlinearly registered to a common template, followed by voxel-wise statistical testing to detect group differences. These maps can also be correlated, on a voxel level, with biomarkers and neuropsychological measures. Moreover, these Jacobian maps can also be summarized on an ROI level to give overall atrophy rates in regions of interest (Figure 46.5; right panel). In the MCI group, temporal lobe atrophy rates were correlated with changes in mini-mental state exam

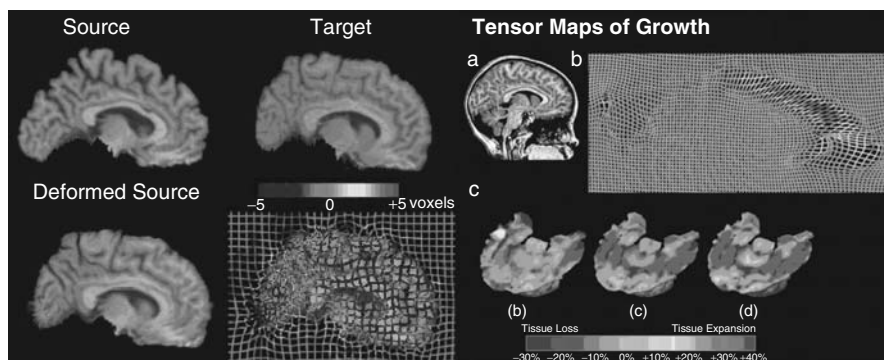


Figure 46.4 Tensor-based morphometry. In TBM, a fluid transformation (*deformed grid*) is applied to a baseline scan (*source*) to reconfigure it (*deformed source*) into the shape of a follow-up scan (*target*). The local expansions (*red colours*) or atrophies (*blue colours*) can be plotted in brain regions such as the corpus callosum (shown in the green box in [a]). Voxel expansions (*red colours*) or contractions (*blue colours*) can be plotted onto a sequence of scans collected from the same subject (shown here in axial view illustrating progressive temporal lobe atrophy in a subject with frontotemporal lobe atrophy) during a degenerative brain disease, emphasizing regions with progressive atrophy. These maps may be averaged across subjects or compared across populations to assess factors that influence degenerative rates in each region of the brain. A full colour version of this figure appears in the colour plate section

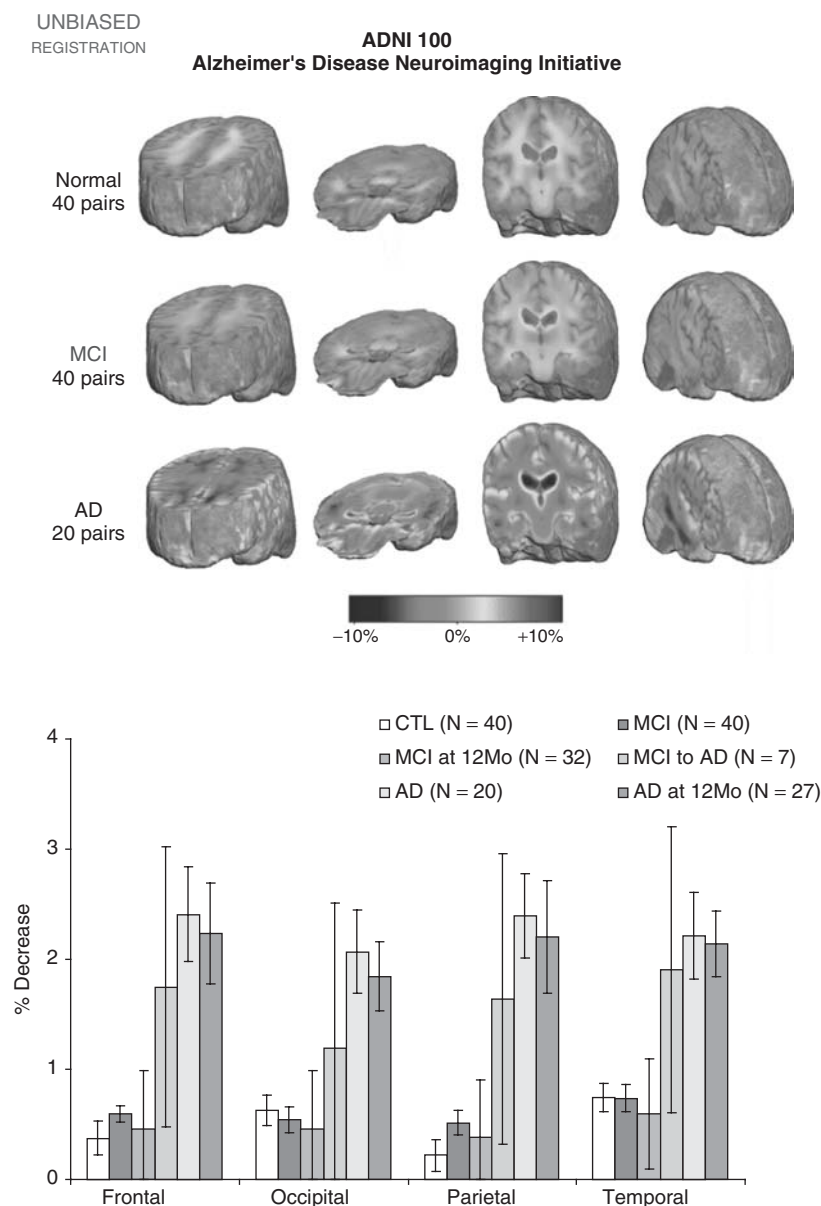


Figure 46.5 (Top panel) average longitudinal tissue atrophy/expansion rate for 40 normal, 40 MCI and 20 AD subjects, using serial MRI scans from the ADNI dataset scanned at 12 months apart. Ventricular expansion (third column) and temporal lobe atrophy (fourth column) are most prominent in the AD group. (Bottom panel) Percentage brain tissue loss from baseline to follow-up within each lobe can be computed by averaging the maps in the left panel for each region of interest (with CSF excluded). The diagnoses for the AD, MCI and CTL groups were determined at baseline. Here, MCI at 12Mo denotes subjects diagnosed as MCI at baseline who did not convert to AD at 12-month follow-up, whereas MCI to AD signifies those who had converted to AD at 12-month follow-up. One MCI subject's diagnosis converted back to control at follow-up, and thus was excluded from the MCI subgroups. The first bar in each group (coloured white) shows mild but significant progressive atrophy in controls. The second bar (turquoise) denotes MCI subjects at baseline, and is followed by bars denoting converters and non-converters. Mean rates are typically higher in the converters, comparable to subjects diagnosed as AD at both time-points, or AD at the last time-point (last two bars). This figure is adapted from the results in³³. A full colour version of this figure appears in the colour plate section

(MMSE) scores, clinical dementia rating (CDR) and logical/verbal learning memory scores. In the AD group, temporal atrophy rates were correlated with several biomarker indices, including a higher CSF level of p-tau protein, and a greater CSF tau/beta amyloid 1–42 (ABeta42) ratio. Temporal lobe atrophy rate was significantly higher in MCI subjects who converted to AD than in non-converters. Serial

MRI scans can therefore be analysed with TBM to relate ongoing neurodegeneration to a variety of pathological biomarkers, cognitive changes and conversion from MCI to AD, tracking disease progression in three-dimensional detail.

Using a cross-sectional design, Hua *et al.*³⁴ computed the statistical maps of group differences using 40 normal controls, 40 MCI subjects

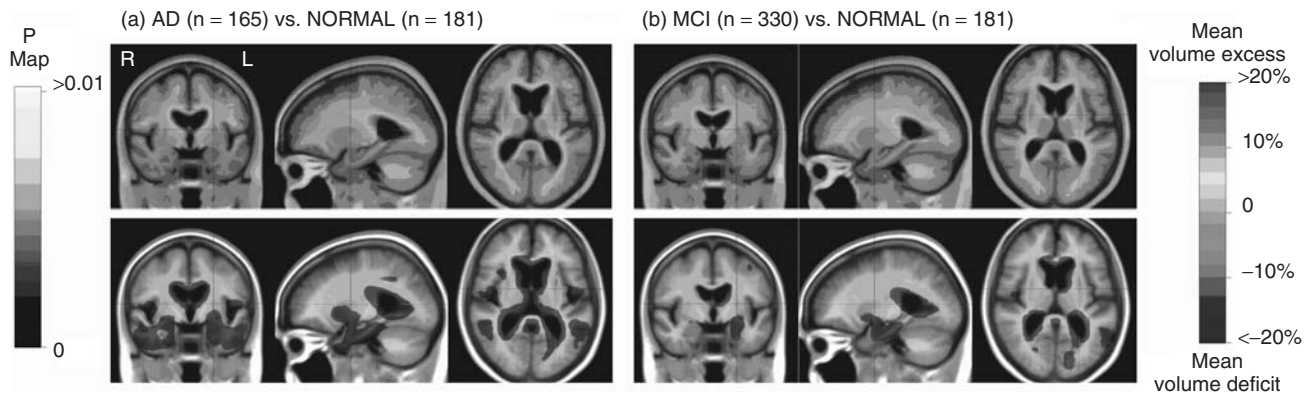


Figure 46.6 3D maps of brain atrophy comparing group differences between MCI ($n = 330$) versus normal ($n = 181$), and AD subjects ($n = 165$) versus normal. The top rows of panels (a) and (b) show the mean level of atrophy as a percentage reduction in volume. The bottom rows show the significance of these reductions, revealing highly significant atrophy in AD but a more anatomically restricted atrophic pattern in MCI. In MCI (b), atrophy is most prominent in the left hippocampus; ventricular expansion is also substantial. When AD is compared with MCI (not shown here), additional temporal lobe degeneration is evident. The overall level of ventricular expansion is about 10–15% for MCI and greater than 20% for the AD group. This figure is adapted from the results in³⁵. A full colour version of this figure appears in the colour plate section

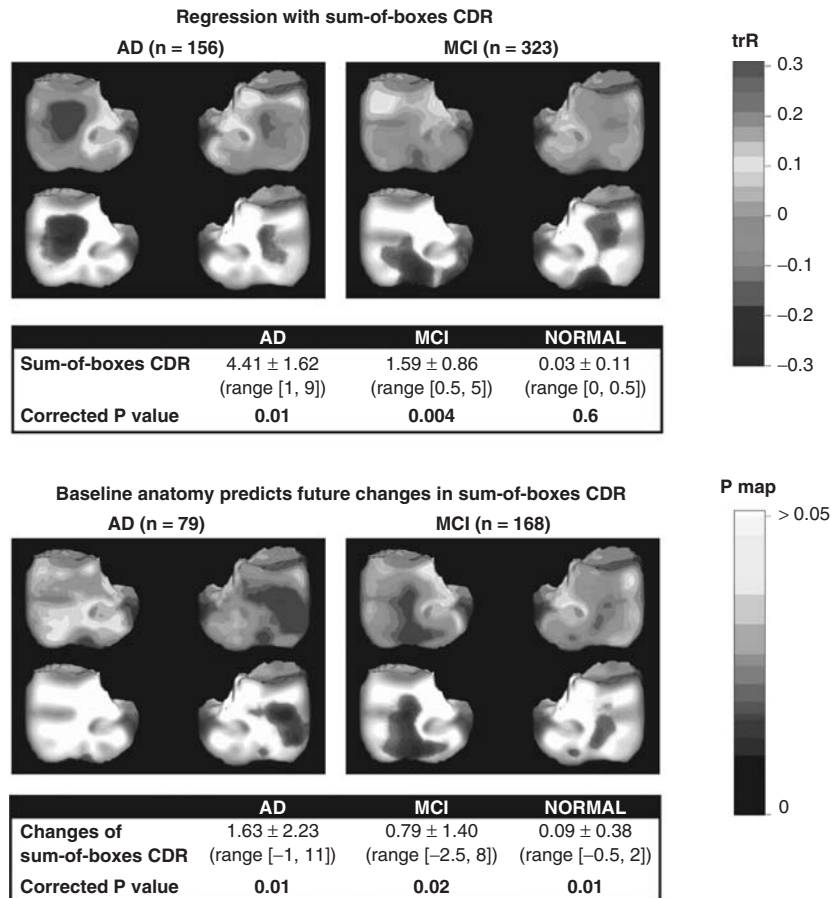


Figure 46.7 Temporal lobe atrophy correlates with sum-of-boxes clinical dementia rating and future clinical decline. Top row negative correlations are detected between temporal lobe atrophy and higher CDR scores at the time of the initial scan (i.e. a higher CDR score correlates with a faster rate of atrophy). The corrected P values in the table (inset) provide an overall estimate of significance, corrected for multiple comparisons. Bottom row atrophy of the temporal lobe also predicts future cognitive decline, as reflected by an increase in CDR scores, which indicates deteriorating cognitive function over the following year. trR denotes partial correlation coefficient. This figure is adapted from the results in³⁵. A full colour version of this figure appears in the colour plate section

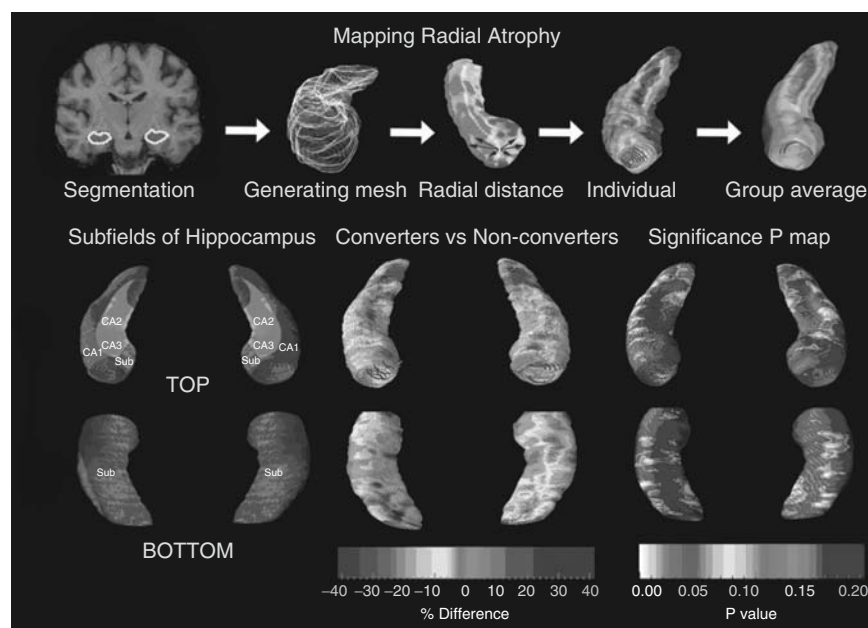


Figure 46.8 Mapping hippocampal atrophy. The radial atrophy mapping method (*top row*) relies on manually or automatically segmenting the hippocampus, computing a 3D parametric mesh model of the structure, estimating the distance between the central core of the structure to each surface point (i.e. the radial distance), and recording radial distance estimates at each surface point to create individual and group average colour-coded maps of the radial distance. These are then statistically compared between groups or conditions. One longitudinal 3D MRI study⁵⁰ compared baseline hippocampal atrophy in MCI subjects who converted to AD versus MCI subjects who remained stable or improved cognitively during three years of clinical follow-up. Greater atrophy at baseline was seen in the CA1 and subicular areas in subjects who subsequently convert to clinically probable AD (*bottom right panels*). The bottom panels show a schematic representation of the hippocampal subfields (*left*), the proportional difference in atrophy levels between converters and non-converters (in percentage points; *middle panels*), and the significance of these differences taking into account normal structural variation (*bottom right panel*). A full colour version of this figure appears in the colour plate section

and 40 AD subjects enrolled in ADNI, and reported widespread medial temporal and limbic atrophy in AD, with a lesser, more restricted distribution in MCI. Moreover, correlation studies showed that atrophy and CSF space expansion both correlated strongly with MMSE scores and CDR.

Hua *et al.*³⁵ increased the sample size and mapped the structural differences between groups using 676 subjects from ADNI (165 AD, 330 MCI and 181 controls). Figure 46.6 visualizes these group differences, revealing highly significant atrophy in AD but a more anatomically restricted atrophic pattern in MCI. These maps can also be correlated with neuropsychological test results or biomarkers. In Figure 46.7, these correlations (between atrophy rates and sum-of-box CDR scores) are plotted on the surface of the temporal lobes. Using this 676-subject sample, baseline temporal lobe atrophy is shown to be correlated with current cognitive performance, future cognitive decline and conversion from MCI to AD over the following year; it predicted future decline even in healthy subjects. In this particular sample, over half of the AD and MCI subjects carried the *APOE4* gene, which increases risk for AD; they showed greater hippocampal and temporal lobe deficits than non-carriers. *APOE2* gene carriers – 1/6 of the normal group – showed reduced ventricular expansion, suggesting a protective effect.

Compared to manual tracing employed in cortical pattern matching, TBM is attractive for clinical trials, as large samples can be studied with no manual interaction. Power is also slightly increased if all brains are aligned to a common brain template that is representative of the mean anatomy of all subjects in the population.

Hippocampal Radial Mapping

Even though TBM can map patterns of atrophic changes throughout the brain, the fact remains that the medial temporal lobe is the site of earliest structural change in AD. The hippocampus, in particular, is one of the most researched brain regions in dementia and aging. In general, studies have shown that AD pathology is associated with hippocampal shrinkage³⁶, and is linked to memory decline. In normal aging, hippocampal volume loss is on average 1.6–1.7% per year^{37,38} while that of the entorhinal cortex is ~1.4% per year³⁹. Much higher hippocampal rates are observed in MCI and AD, with faster atrophy rates in MCI subjects who progress to AD relative to those who remain stable (annual hippocampal atrophy rate for MCI patients who remain stable = 2.8%, for MCI converters = 3.7% and for AD = 3.5–4%³⁶).

In addition to manual tracing on high resolution MRI, several techniques have been proposed for segmenting the hippocampus. A deformable template approach has been proposed that utilizes a pre-defined hippocampal template^{40–43}. Fully automatic methods do not require any user input, and are usually based on extracting and combining some set of image features. For example, Powell *et al.*⁴⁴ used artificial neural networks and Golland *et al.*⁴⁵ proposed to use a large feature pool, and principal component analysis (PCA) to reduce the size of the feature pool. Another fully automated approach for sub-cortical segmentation is FreeSurfer by Fischl *et al.*^{46,47}. FreeSurfer uses a Markov random field to approximate the posterior distribution

for anatomical labellings. Morra *et al.* recently developed a new and powerful hippocampal segmentation approach based on adaptive boosting or AdaBoost. AdaBoost is highly underutilized in medical imaging, although it has generated great interest in pattern recognition and other related fields⁴⁸.

Once the hippocampus is segmented, it can serve as a basis for other advanced surface- or volume-based computational anatomy techniques. In an effort to localize these changes to specific hippocampal sectors, Thompson *et al.*⁴⁹ proposed a radial atrophy mapping (RAM) approach, which creates surface models to represent the hippocampus, imposes a regular grid structure on anatomical models from different individuals, and uses this structure to compute average shape models for different groups. As a local index of atrophy, the distance of each surface point to a centreline threading down the centre of the structure is plotted on the surface (Figure 46.8). Surface-based statistics on this measure can then be used to identify regions where atrophy is associated with diagnosis, cognition, genotype or medication.

CONCLUSION

Here we surveyed a range of computational anatomy methods to monitor dementia progression, each focusing on specific features of the degenerative process. Cortical thickness maps, for example, localize changes relative to gyral and sulcal landmarks, and can be used to create time-lapse movies, but require some time investment in extracting cortical surface models. If data collection is time-consuming and power requirements are high, this approach is still useful even in a clinical trial, as it may detect disease-related changes over short time intervals. Higher-throughput methods, such as TBM and automated hippocampal mapping, are well suited to very large-scale studies. These may be the first mapping methods to routinely analyse databases of images from thousands of subjects. As such, they are natural approaches to use in epidemiological studies of potential risk factors or protective factors that may influence disease onset, conversion or the normal aging process.

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Alzheimer's Disease: Risk Factors and Preventive Strategies

JoAnn T. Tschanz¹ and John C. S. Breitner²

¹*Department of Psychology and Center for Epidemiologic Studies, Utah State University, Logan, UT, USA*

²*GRECC, VA Puget Sound Health Care System, University of Washington School of Medicine, Seattle, WA, USA*

INTRODUCTION

Dementia is a significant cause of disability and mortality among the elderly¹, accounting for nearly 30% of the population-attributable risk of death after age 85². With the continued growth of the world's oldest population segments, the numbers affected by dementia are expected to rise exponentially, reaching 81.1 million by the year 2040³. The most common form of late-life dementia, Alzheimer's disease (AD) accounts for about 50% of dementia among people in their 60s, but may represent as much as 80% in those over age 80^{4,5}. The annual cost of caring for one person with AD is estimated to range from \$9000 early in the disease course to nearly \$20 000 in mid-course⁶. Given the rapid growth in the proportion of those who survive into the latest stages of AD, in the United States alone, the total annual economic burden of the disorder is estimated at \$100 billion⁷, making it the country's third most costly health condition after cancer and heart disease⁸.

With the exception of familial, early-onset forms of AD, there is no single identified cause of the disorder. Current treatments are largely symptomatic, providing only temporary improvement in cognition and neuropsychiatric symptoms. The past several decades have witnessed an explosion of research into risk and protective factors for AD, which someday may yield effective strategies for prevention. This chapter will review the current evidence for risk and protective factors associated with AD and end with a discussion of preventive strategies.

IMMUTABLE RISK FACTORS

Age and Sex

In discussion of prevention, it is useful to dichotomize those risk or protective factors for AD that are potentially subject to intervention versus others. The latter, immutable risk factors are age, female sex and family history. Family history and genetic risk are reviewed by Tsuang (Chapter 43) and are not addressed here. Age is the single strongest risk factor for AD. After age 65, the prevalence and incidence of the condition appear to double with every five years of additional age until 90⁹, when the rates either plateau or decline. In the Cache County, Utah, population, for example, prevalence

estimates ranged between 0.61% at ages 65–69 to nearly 19% at ages 85–89¹⁰. Incidence rates exhibited a similar trend¹¹. Although data are scarce for persons older than age 90, some studies have suggested a plateau or even a decline in incidence rates in extreme old age.

Second only to age in importance is genotype at the polymorphic locus *APOE* that encodes the cholesterol transport protein apoE. The onset of AD is strongly accelerated among individuals homozygous for allele $\epsilon 4$ (about 2% of most populations), but also tends to be earlier in people with a single $\epsilon 4$ allele (typically 25–30%). These allele-specific modifications in onset result in increased AD incidence at younger ages, which appear as an overall increase in risk estimates that are typically adjusted for age¹².

Sex differences in the prevalence and incidence for AD have also been reported, with higher percentages observed in females in some (e.g. see^{10,11,13,14}) but not all populations (e.g. see^{15,16}). Whether this trend is found in any one study may depend on its relative proportions of very old subjects, among whom rates in women may be disproportionately elevated^{11,14}.

The mechanisms underlying the sex-specific difference in AD risk are of interest, but are presently unknown. Some authors have attributed the difference in risk to the greater longevity of women or the higher prevalence of vascular dementia in men (possibly deterring a diagnosis of AD even in the presence of its characteristic pathology), possible hormonal effects, or even the notion that current cohorts of elderly women have less neural or cognitive reserve than men, owing to fewer years of formal education¹⁷. The last explanation seems to us not only contentious but unlikely.

The increasing risk of AD with age (and in women) may instead reflect a host of background physiological changes that accompany ageing including programmed 'intrinsic' factors such as apoptosis, dysfunction of repair processes by progenitor cells in the dentate gyrus of the hippocampus or vascular endothelium, chromosome telomere shortening which signals apoptosis and damage to mitochondrial DNA (reviewed by Drachman¹⁸). 'Extrinsic' factors that occur as the result of normal wear and tear or exposures that accumulate over the lifetime may also contribute. These processes include oxidative stress and the glycation of proteins which interact with reactive oxygen species to form advanced glycation endproducts (AGE). AGE may trigger inflammatory cytokines that damage the

vascular endothelium. Chaperone proteins that normally repair or eliminate misfolded proteins may fail¹⁸, leading to myelin breakdown. Cortico-cortical association fibres are especially vulnerable, and correspond to brain regions most affected in AD (reviewed by Bartzokis¹⁹). The degree to which individuals experience these age-related changes likely varies according to their genes, environmental exposures and lifestyle factors, at least some of which may be related to biological sex or gender roles.

MODIFIABLE RISK FACTORS

Neural and Cognitive Reserve

The notion of neural and cognitive reserve reflects an underlying idea that the brain can withstand some degree of compromise while still maintaining normal cognitive and behavioural functions through the recruitment of alternative neural networks^{20,21}. Cognitive reserve (first proposed by Robert Katzman) is a concept whereby various cognitive strategies may be used to compensate for deficits. Both forms of reserve are malleable and may be built up through the accumulation of life experiences. Years of occupational and educational attainment are thus seen as predictors of reserve. Theoretically, higher levels of reserve could provide some degree of protection against the expression of clinical AD symptoms in the face of a specified burden of pathological change. Indeed, many epidemiological studies have reported an inverse relation between educational or occupational attainment and risk of AD, but studies have also failed to find this association (reviewed by Stern)²¹. The discrepant results may reflect inadequate assessment, particularly of activities in late life that continue to build neural and cognitive reserve. There is some evidence that stimulating activities in late life may reduce the risk of AD or dementia (see lifestyle factors under preventive strategies). Other explanations are possible, however, particularly when the studies employ two-stage screening and examination for dementia²².

Traumatic Brain Injury (TBI)

Several epidemiological studies have reported an increased risk of AD among persons with a history of head trauma. A meta-analysis of case-control studies reports a 1.8-fold increase in risk among those with TBI with loss of consciousness. Adjusting for other factors, the higher AD risk was found only among men (relative risk of 2.7²³), a result confirmed by a subsequent meta-analysis²⁴. Interactions of TBI with *APOE* genotype have been reported by some²⁵ but not others²⁶. The mechanism underlying the association between TBI and AD is unclear. Studies have reported an increase in beta-amyloid deposition and AD pathology following TBI²⁷, and higher frequency of *APOE* $\epsilon 4$ carriers among those with cortical plaques²⁸. In animal studies, results have varied according to species and genetic variation. Increased beta-amyloid deposition was found later in the course of recovery in rodents, but earlier in pigs. In Alzheimer's PDAPP transgenic mice, beta-amyloid levels increased acutely, but without an increase in deposition, whereas in Tg2576 APP transgenic mice, repeated trauma resulted in greater beta-amyloid deposition²⁹. Compounds that reduce beta-amyloid deposition after brain trauma are under active investigation to reduce the neurocognitive sequelae post injury and the risk of AD (e.g. see^{30,31}).

VASCULAR RISK FACTORS

A number of risk factors for cardiovascular disease have been associated with AD. Hypertension, high cholesterol, diabetes, smoking

and atherosclerosis have all been associated with increased risk. For hypertension, studies report a 1.2- to 4.5-fold increase in risk for AD, depending upon the age at measurement and whether systolic or diastolic measures are taken^{32–35}. The relation between blood pressure and AD may be non-linear, as low diastolic blood pressure in mid-life has also been associated with an elevated risk³³. Elevated cholesterol is associated with a 1.4- to 2-fold increase in AD risk³², diabetes, nearly a 2- to 3.4-fold increase^{34,36,37}, smoking, a 1.6- to 2-fold increase^{34,38} and severe atherosclerosis, a 3-fold increase in risk³⁹. With each additional vascular risk factor, there is a corresponding increase in risk^{34,35}.

Interestingly, some studies report that the relation between cardiovascular risk factors and later dementia risk varies according to the timing of measurement relative to the onset of dementia as well as genotype at *APOE*. Although elevated blood pressure or cholesterol levels predict later AD onset, measurements of each decline prior to the onset of dementia^{37,40}. This phenomenon may explain the negative findings reported by some studies (reviewed by Launer⁴¹). *APOE* genotype may also modify the association between vascular factors and AD. In a large Dutch population study of dementia and cognitive decline, the risk of AD with significant atherosclerosis (two or more indicators of plaques in the carotid artery, thickening of the intima media wall of the carotid artery, or evidence of peripheral artery disease) varied according to *APOE* genotype: among those with at least one *APOE* $\epsilon 4$ allele, the risk of AD was 3.9, and for others, 1.4³⁹. For smoking, increased risk of AD was found only among those without $\epsilon 4$ ³⁸. Further study of the interaction between vascular risk factors and *APOE* genotype is needed.

The mechanism underlying the relation between vascular risk factors and AD risk is unclear. Cerebrovascular pathology is common in AD brains, and includes such changes as amyloid angiopathy, cerebrovascular atherosclerosis, endothelial damage and periventricular white matter lesions⁴². Co-existing vascular lesions occur in approximately 24–28% of individuals with AD^{43,44} and also contribute to the dementia syndrome⁴⁵. However, vascular risk factors may also promote the formation of AD lesions or otherwise contribute to toxic physiological processes. In autopsies of participants of the Honolulu Asia Aging Study, mid-life elevations in systolic and diastolic blood pressure were associated with number of senile plaques and neurofibrillary tangles, respectively^{46,47}. In the absence of dementia, increased plaques and tangles have also been reported in middle-aged hypertensive individuals⁴⁸. Cholesterol has also been found to promote the accumulation of beta-amyloid^{49,50}.

Hypertension damages blood vessel walls and contributes to atherosclerosis⁴⁷. When combined with the diminished elasticity of arterial walls, atherosclerosis reduces the brain's capacity to eliminate beta-amyloid. Normally, beta-amyloid is cleared from brain parenchyma by drainage through the cerebral arteries. A reduction in the elasticity of the arterial walls diminishes the force needed to drain the substance⁵¹. Furthermore, damage to arterial walls may also result in a variety of negative consequences including accumulation of amyloid precursor protein (APP), oxidative stress and dysfunction of the blood–brain barrier⁴⁷.

In addition to increasing the risk for adverse vascular outcomes, diabetes may affect AD risk through other mechanisms. The location of insulin receptors in the hippocampus and temporal cortex implicates insulin's involvement in long-term potentiation and other memory-related functions⁵². Normally, insulin crosses the blood–brain barrier and is thought to promote beta-amyloid clearance. In diabetics, however, insulin resistance and hyperinsulinemia in the periphery can result in reduced brain insulin levels,

therefore affecting the rate of beta-amyloid clearance⁵³. However, at autopsy, several studies report no association between diabetes and AD neuropathological markers^{54,55}, but an association with microvascular infarcts instead⁵⁵. Furthermore, diabetes is associated with the production of advanced glycation endproducts, oxidative stress and inflammation⁵².

Obesity

Obesity is typically measured by body mass index (BMI), which is a ratio of weight to height or kg to metres squared, waist circumference (a measure of central obesity), or a hip-to-waist ratio⁵³. A number of studies have examined the relation between BMI and risk for dementia (reviewed by Gufstafson⁵⁶). A majority of the studies indicates an elevated risk for dementia, and specifically for AD, in those with high BMI. Similar to the effects of blood pressure, the relation between BMI and AD appears to vary according to the timing of measurement in relation to dementia onset. The majority of studies examining BMI 10 or more years prior to dementia diagnosis report an increase in risk. For individuals meeting a definition of obese (BMI ≥ 30) the risk of dementia is approximately two-to-five times that of normal weight individuals. A few studies have reported no association or an increase in AD risk with lower BMI. However, most of those studies have used a relatively short follow-up period (e.g. within five years of dementia onset), and this raises the possibility that weight loss in this context is an indicator of incipient dementia rather than a risk factor⁵⁶.

The relationship between obesity and AD risk may operate through several pathways. First, obesity is a risk factor for a number of other adverse health outcomes including insulin resistance, diabetes and cardiovascular risk factors and conditions, and these in turn are risk factors for AD and vascular dementia⁵³. Second, in the USA, obesity is associated with demographic characteristics that are also associated with AD. These include lower education and socioeconomic status and Hispanic or black race. Third, obesity is associated with higher consumption of dietary fat and calories and lower physical activity levels, which also have been associated with AD⁵³.

Psychosocial Stress

Several studies have reported an association between psychosocial stress and dementia. A prospective, Swedish population-based cohort study of 70 year olds examined the effects of 18 stressful life events experienced in childhood, early adulthood and late adulthood in predicting incident dementia. Death of a parent in childhood and physical illness in a spouse or serious illness in a child in late life were each associated with a 6- to 7-fold increase in dementia risk. Experience of manual labour was associated with a 26-fold increase. The number of risk factors experienced was associated with increasing risk⁵⁷. Similarly, the Cache County (UT) population study reported a 3-fold increase in dementia risk with early-life death of a father⁵⁸. This effect was not observed with mother's death, and it was hypothesized that the association reflected the effects of socioeconomic adversity, limited access to health care and other lost opportunities. Although the outcome examined was all-cause dementia, the predominant form of dementia in this population is AD^{10,11}.

In a case-control study from a large health maintenance organization (HMO) in Washington state, number of siblings was associated with increased risk of AD. The risk increased with each additional child so that having five or more siblings was associated with a 39%

increase in risk, seven to nine siblings with a 72% increase, and 10 or more siblings with more than a 2-fold increase in risk⁵⁹. Residence in the suburbs was associated with a reduction in risk. Drawing from the same HMO database and linking to US Census records and birth certificates, Mocerri and colleagues examined the subsequent risk of AD associated with a number of psychosocial factors. Father's work in unskilled manual labour and number of persons in household were each associated with greater risk. Furthermore, these early life experiences interacted with *APOE* genotype. Among those with one or more $\epsilon 4$ alleles, those whose fathers worked in manual labour had an odds ratio for AD of 2.35 (95% CI = 1.07–5.16), but those without $\epsilon 4$ had an odds ratio of 1.40 (95% CI = 0.78–2.52). Compared to individuals with neither the early-life risk factors nor the $\epsilon 4$ allele, having father's work in manual labour, a household size exceeding six members and having an $\epsilon 4$ allele was associated with an odds ratio of 14.80 (95% CI = 4.90–46) for AD⁶⁰. A similar interaction between *APOE* genotype and early-life risk factors was reported in a large sample of Japanese Americans living in King County, Washington. Here, more than four children in household and smaller head circumference were associated with increased risk of AD among bearers of an *APOE* $\epsilon 4$ allele⁶¹.

Other studies have examined the influence of experiences later in life such as loneliness or lack of social support, the latter of which can potentially mitigate the effects of stressful events. Individuals scoring at the 90th percentile of a loneliness questionnaire exhibited a 2-fold increase in risk for AD as compared to those reporting few feelings of loneliness. The elevated risk for loneliness was also associated with more rapid cognitive decline and persisted when controlling for the effects of social network and activity. Interestingly, these effects were independent of the degree of AD neuropathology⁶².

Additional work has examined personality traits, particularly distress proneness or neuroticism. In a sample of elderly Catholic clergy, distress proneness was associated with increased risk for AD. Because personality traits are considered to be relatively stable, the measure of distress proneness was thought to reflect cumulative, psychological distress experienced over the life span. Relative to those with a low level on this trait, individuals at the 90th percentile exhibited a 2-fold increase in AD risk. The effects remained after statistical control for depressive symptoms and engagement in cognitive activities. Distress proneness was also associated with more rapid cognitive decline, particularly in episodic memory. Again, baseline scores on distress proneness were not associated with degree of AD neuropathology at death⁶³, suggesting that the relationship with dementia works through other mechanisms⁶⁴.

Activation of the hypothalamic-pituitary-adrenal (HPA) axis has been suggested to underlie the association between psychosocial stress and AD. Broadly speaking, this process mobilizes resources in response to a 'stressor' by releasing glucocorticoids that promote energy metabolism and modulate immune functions⁶⁵. However, with chronic and excessive activation of the HPA axis, high levels of glucocorticoids may lead to cell death in regions of the hippocampus, and this phenomenon in turn can diminish the normal inhibitory feedback loop, leading to further activation and release of glucocorticoids. This 'glucocorticoid cascade' (see Sapolsky⁶⁶) has been invoked to underlie the hippocampal damage and corresponding cognitive impairment observed with chronic stress in aged organisms⁶⁶. In relation to AD risk, hippocampal damage from chronic glucocorticoid release may functionally reduce the brain's capacity (reserve) to compensate for the neuronal degeneration that accompanies AD. Alternatively, animal studies suggest that glucocorticoids can directly promote the development of AD-type pathology. In transgenic mouse

models of AD, the administration of an experiential stressor or direct glucocorticoid challenge increased beta-amyloid deposition^{67,68} and tau pathology. Clearly, more research examining the role of stress and physiological changes in the brain is warranted.

Early-life stressors may also have their effects through the limitation of financial resources. Early parental death, lower parental socioeconomic occupations and higher sibling density may limit the financial resources available during critical periods of brain development. Nutritional or environmental deprivation associated with low socioeconomic resources may limit brain growth and maturation, and therefore, neural reserve. Access to health care and educational and vocational opportunities may also be curtailed. In addition, the accessibility of emotional resources may be limited, particularly in the case of early parental death. Such non-normative loss may plausibly result in psychological growth and maturation under less than ideal circumstances, potentially leading to maladaptive coping strategies and stress reactivity, that affect brain development⁶⁹. Later, in the face of AD pathology, less neural reserve and poor coping strategies may result in a lower threshold for the clinical expression of dementia.

STRATEGIES FOR THE PREVENTION OF AD

Any of the modifiable risk factors discussed above may present a potential target for intervention. The following sections will briefly summarize the literature regarding potential strategies to reduce the risk of AD. Some of these strategies involve pharmacological compounds that theoretically reduce AD-related neuropathology, whereas others are intended to build neural reserve or promote cardiovascular health. None of these potential prevention strategies has been proven efficacious, but a number are of sufficient promise to warrant discussion here. These include anti-inflammatory drugs, lipid-lowering agents, hormone replacement therapy, antioxidants and lifestyle factors including diet, social support and engagement in physical, cognitive and social activities.

Pharmacological Interventions

Non-steroidal anti-inflammatory drugs

Interest in the use of anti-inflammatory agents in the prevention of AD began with the observation of a lower-than-expected frequency of AD in patients with rheumatoid arthritis⁷⁰. It was speculated that this association reflected the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs) by patients with this condition. The inverse association of AD and NSAID use has subsequently been examined in numerous observational studies, many of which report a reduction in AD risk among NSAID users. Animal studies provide further support for the possibility that NSAIDs may protect against AD pathogenesis (reviewed by Cole *et al.*⁷¹). Despite early signs of promise, the results of randomized controlled treatment trials have been disappointing. Except for encouraging results of a pilot AD treatment trial⁷², trials with NSAIDs^{73–77}, low dose corticosteroids⁷⁸ and hydroxychloroquine⁷⁹ have shown no benefit. A secondary prevention trial to prevent progression from mild cognitive impairment to AD was not beneficial, and suggested harm in the treatment group⁸⁰. Notably, however, all of these trials tested the effect of the drugs on individuals who already exhibited symptoms of dementia or cognitive deterioration – a topic not addressed by the observational literature on NSAIDs and AD incidence. In fact, recent studies had

suggested that any protection was limited to NSAID use initiated more than two years before AD onset^{81–83}. To date, the only large-scale NSAID primary prevention trial is the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) in which celecoxib or naproxen was tested against placebo in subjects with a family history of AD. Owing to unexpected cardiovascular safety concerns, the treatments were stopped after an average of two years of treatment. Analyses at that time showed no reduction in incidence of AD in participants assigned to either celecoxib or naproxen, but instead a suggestion of increased risk^{84–86}. Compounding the disappointment from these results, a recent community-based study that utilized pharmacy records to assess NSAID exposure showed an *increase* in AD incidence with NSAID use, regardless of the recency of such use. The authors of this study speculated that, because the participants in this study were considerably older than those examined previously, the beneficial effects of NSAIDs might be limited to younger individuals, before the onset of AD neuropathology. Alternatively, they conjectured that NSAID use effected a *delay in the onset* of dementia, thereby increasing the numbers of AD cases in older age groups⁸⁷.

Lipid-lowering agents

Based on observations suggesting an increased risk of AD among those with high cholesterol, the use of lipid-lowering agents such as 3-hydroxy-methyl-glutaryl-CoA reductase inhibitors (statins) have been studied as potential protective agents. As previously mentioned, cholesterol promotes beta-amyloid production^{49,50} and reduction in cholesterol levels might inhibit it⁸⁸. Statins have other effects as well, such as prevention of atherothrombosis or reduction of inflammation.

Several case-control studies have reported a reduction in AD risk among users of lipid-lowering agents, typically with statins^{89–93}. However, most of these studies have been cross-sectional in nature. Prospective studies examining statin use and subsequent dementia onset have been disappointing, with negative findings reported from the Cardiovascular Health Study Cognition Study, the Cache County Study and the Adult Changes in Thought Study^{94–96}. Three published randomized controlled trials have found no evidence of a protective effect against cognitive decline as an outcome^{97–99}. Further research is needed to determine whether the effectiveness of statins may differ by APOE genotype⁹⁴.

Hormone replacement therapies

Several observational studies have reported a reduction of AD incidence among women treated with postmenopausal oestrogen replacement therapy (e.g. see^{100–103}), but negative findings have been reported as well (e.g. see^{104,105}). Oestrogen has noted beneficial neurotrophic and neuroprotective effects (see review by Morrison *et al.*¹⁰⁶). Thus a strong rationale exists for potential protection against AD. However, the results of randomized controlled trials have been disappointing. No benefit was reported in treatment trials with women with AD^{107–109}, with the exception of one study using 17-beta estradiol administered by a transdermal patch¹¹⁰. The well-known Women's Health Initiative randomized controlled trials examined hormone users for the prevention of AD, finding no benefit and a suggestion of harm in both treatment groups^{111–113}. Although these results are disappointing, there is limited evidence to suggest that oestrogen may yield positive effects, but only if administered well *prior to* the onset of AD symptoms, and perhaps when there is little or no accumulated AD neuropathology. Thus, observational

studies in which exposure and case detection were constrained to a 10-year window report no effect for oestrogen replacement therapy^{104,105}, but protective effects have been reported for use exceeding 10 years^{103,114}. Consistent with this notion are studies of cell cultures in which oestrogen protects against apoptotic cell death, but promotes cell death in the presence of beta-amyloid₄₂^{115,116}.

Lifestyle Factors

Diet and nutritional supplements

A number of observational studies have reported certain beneficial effects of nutrients from food sources or dietary supplements. Consumption of fish^{117,118}, intake of omega 3 fatty acids¹¹⁷, a Mediterranean style diet¹¹⁹, light-to-moderate alcohol consumption^{120,121} and the antioxidant vitamins, E and C (e.g. see^{122,123}) have been associated with a reduction in AD risk in observational studies. Inconsistent findings have also been reported, for example, with antioxidant vitamins (e.g. see¹²⁴). The underlying mechanisms are unclear but may involve improvements in cardiovascular health, reduced insulin insensitivity, antioxidant and anti-inflammatory effects, and improvement in neuronal lipid membrane function (e.g. see^{120,125–127}). Furthermore, the associations between nutrients and risk of AD may vary by *APOE* genotype. For example, in some studies, higher total calorie and fat intake was associated with increased risk of AD, but only among those with an *APOE* $\epsilon 4$ allele^{125,128}. This finding is consistent with the observation that moderate intake of saturated fat in mid-life increased the risk of AD among *APOE* $\epsilon 4$ carriers¹²⁹.

Few randomized controlled prevention trials have been conducted with dietary supplements, but two have examined n-3 polyunsaturated fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). As reviewed in Cunnane *et al.*¹²⁷, a four-month trial was conducted with DHA with and without lutein (an antioxidant) vs. placebo. Verbal fluency scores improved in both treatment arms, whereas memory functions improved only in the DHA + lutein arm. A 26-week trial of combined EPA and DHA supplements (1800 mg/day or 400 mg/day) provided no benefit on cognitive outcomes, except that among *APOE* $\epsilon 4$ -positive individuals there was suggestion of improved attention¹³⁰.

A few treatment trials have also been conducted with antioxidant supplements. In a large intervention trial of antioxidants and heart disease, the vitamin E arm of the United Kingdom Heart Protection Study showed no differences after five years, in percent of individuals who developed dementia or who were classified as cognitively impaired on a telephone cognitive screening test¹³¹. Additionally, high dose treatment with vitamin E had no benefit in delaying the onset of AD among those with mild cognitive impairment¹³². These findings appear to contradict those of observational studies. It is commonly conjectured that the latter have been vulnerable to error from a variety of confounding factors, but another possible explanation is that neuroprotective effects are observed only with a combination of lipid-soluble and water-soluble agents such as vitamins E and C in combination¹²³. Additional intervention trials are needed to examine the effectiveness of dietary and supplement interventions for the primary prevention of AD.

Physical activity

Many studies report significant benefits of physical activity with respect to maintenance of cognitive ability (e.g. see^{133,134}) and

a reduction in risk of AD and other dementias (e.g. see^{135–137}). The reduction in risk varies by degree of activity. For example a 50% reduction in cognitive decline was seen in those with high levels of exercise (more than three times per week of moderate to high intensity activity¹³⁵, or more than four activities per week¹³⁶). Interactions between activity and *APOE* status are inconsistent: one study reports reduction in risk among non-carriers of the *APOE* $\epsilon 4$ allele¹³⁶ while another reports greater effects among carriers¹³⁷. Mechanisms purported to underlie the beneficial effects of physical activity on cognitive outcomes include improved cardiovascular health, increased cerebral blood flow and increased attention^{138,139}. A recent randomized controlled trial of individuals aged 50 or older reported significant differences between an exercise intervention as compared with education controls on a global measure of cognitive ability (Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) subscale) and a measure of delayed recall¹⁴⁰. The intervention was conducted over a 24-week period among individuals with subjective memory complaint, and follow-ups were obtained at 6, 12 and 18 months. Improved performance was also observed on a measure of delayed recall and functional ability. Post-hoc comparisons indicated greater effects among those without an *APOE* $\epsilon 4$ allele¹⁴⁰.

Leisure activity

Active engagement in leisure activities in late life may continue to build neurocognitive reserve and thereby reduce the risk of dementia. Several observational studies report beneficial effects of high engagement in leisure-time activities such as social interaction, physical conditioning, volunteer work and cognitive activities such as reading or playing games. In a large community-based study with up to seven years follow-up, greater engagement in total activities was associated with reduced dementia risk (RR = 0.88, 95% CI = 0.83–0.93)¹⁴¹. When activities were combined with accrued reserve (as reflected in educational or occupational attainment), the risk of dementia among those with low accrued reserve and low engagement in late-life activities was approximately 1.9–2.3 times that of high reserve and high engagement in late-life activities¹⁴¹. Similar effects have been reported for those with limited social networks^{142,143}.

The mechanisms underlying such positive effects of leisure-time activities include building of neurocognitive reserve, increased synaptogenesis promoted by stimulating activities and stress reduction associated with greater activity and social support (see review by Fratiglioni *et al.*¹⁴⁴). Although there are no randomized controlled trials of leisure interventions, one large trial examined the effects of a cognitive intervention on cognitive and functional outcomes in elderly individuals. Over 2000 individuals between the ages of 65–94 were randomly assigned to one of four training groups: memory, reasoning, speed of information processing and a no-contact control. The interventions (and booster session) resulted in significant improvements in each of the targeted cognitive domains immediately after training and after two years follow-up¹⁴⁵. No effect was observed on the functional outcome measure, although this was thought to reflect limited change in that domain.

CONCLUSION

The scientific literature identifies numerous risk factors that are putatively associated with AD. These processes are not necessarily specific to the disease, but may be changes associated with ageing that

effectively reduce the neurocognitive reserve and resources built over the life span. Other risk factors may affect vascular factors and neuroendocrine response to stress which are purported to promote AD neuropathology or negatively impact vulnerable brain regions important for learning and memory. The large number of risk factors and biological processes that increase the risk of AD suggests the disorder results from multiple causes. As a result, the search for prevention strategies may similarly need to consider multiple factors.

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Down Syndrome: Genetic and Clinical Overlap with Dementia

Giles M.Y. Tan and Declan G.M. Murphy

Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry at the Maudsley, King's College London, UK

Down syndrome (DS) or trisomy 21 is the most common chromosomal abnormality associated with learning disability and affects approximately 1 per 650–1 000 live births. People with DS are more likely to develop Alzheimer's disease (AD) when compared to the general population. There is a well-established link between the neuropathology of AD and DS^{1,2}.

EPIDEMIOLOGY

Age of onset for dementia is typically between 50 and 55 years with a median age of onset of dementia of 55.5 years and an age range of 45 to 74 years³. Prevalence rates of clinical AD in DS vary substantially depending on the population studied, which ranges from 4% in a community sample⁴ to 88% in an institution-based sample⁵. Many of the studies suffered from small sample sizes especially in the numbers of elderly DS persons included. A population-based study found that prevalence rates of AD increased with age – 8.9% (age 45–49), 17.7% (age 50–54), 32.1% (age 55–59) – up to age 60 years then decreased again – 25.6% (age above 60) – with an overall prevalence of 16.8%. The decrease was possibly accounted for by the increased mortality among the elderly demented DS persons⁶.

While congenital malformations and especially congenital heart defects are the commonest cause of mortality in early life, survival rates for people with DS have improved significantly over the years with advances in medical care and more are now living longer and into old age. Life expectancy was 9 years in 1929 and 12 in 1949 but more recent data indicate that the median age at death has increased from 25 years in 1983 to 49 years in 1997, an average increase of 1.7 years per year studied⁷. Survival beyond 60 years of age has also improved, with 44.4% and 13.6% of live born DS individuals now surviving to 60 and 68 years, respectively⁸. Recent evidence suggests that age, presence of dementia and mobility restrictions predict mortality in DS. When compared with the general population, it was found that impaired mobility, severity of learning disability, the presence of epilepsy and visual impairment, but not cardiovascular risk factors or sex, predicted survival⁹. There is mounting evidence that the presence of the APOE ϵ 2 allele increases longevity¹⁰ while non-demented DS individuals with at least one APOE ϵ 4 allele have increased mortality and up to five times the risks of dying within a 5- to 7-year follow-up period than those without an APOE ϵ 4 allele¹¹.

NEUROPATHOLOGY AND GENETICS

The neuropathological manifestation of AD in DS has been attributed to the triplication and over-expression of the APP gene located on chromosome 21¹². This neuropathology is invariably found in the brains of individuals with DS over the age of 40 years¹³. The characteristic neuropathological changes in AD include the deposition of beta-amyloid (A β) as both extracellular diffuse and neuritic plaques as well as in meningeal and cerebral blood vessels and the intracellular accumulation of neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau in the form of paired helical filaments¹. The accumulation of the diffuse plaques, which contain non-fibrillar amyloid, are commonly seen in DS before age 50 years and are not associated with AD whereas the neuritic plaques, which contain fibrillized amyloid and accumulate most commonly after age 50 years in DS, are associated with neuronal degeneration and loss of function¹⁰. NFTs occur at a later age in DS brains than amyloid plaques¹⁴ and have been associated with dementia status in DS³.

A β , which consists of the two major species A β 1-40 and A β 1-42, is produced from β -amyloid precursor protein (APP) by sequential proteolytic cleavage by β - and γ -secretases¹⁵. Starting from a young age, A β 1-42 precedes A β 1-40 in the course of amyloid deposition in the brains of people with DS¹⁶. Plasma A β levels are also elevated in DS persons from childhood¹⁷. Plasma levels of A β 1-40 and A β 1-42 may be correlated with age in older DS adults¹⁸ and plasma A β 1-42 levels were found to be higher in DS persons with dementia compared to those without in some studies¹⁹ but not others, which found no association between plasma A β 1-40 and A β 1-42 levels and the presence of dementia, APOE genotype or duration of dementia²⁰ or age of onset²¹.

Genetic Factors

Studies in the general population with AD have identified mutations in APP, presenilin 1 (PS-1) and presenilin 2 (PS-2) to be associated with early-onset familial forms of AD and the APOE gene polymorphisms with the more common late-onset AD. However, in DS persons, PS-1 polymorphisms do not appear to have the same detrimental effects and are not associated with the development of dementia²².

Apolipoprotein E, which is involved in cholesterol transport and lipid metabolism and occurs in three allelic forms as ϵ 2, ϵ 3 and ϵ 4

on chromosome 19, has been shown to modulate the risk of AD in the general population²³ with the APOE ϵ 4 allele associated with both late-onset familial and sporadic AD and the APOE ϵ 2 allele conferring a protective effect on the risk of developing AD²⁴. In persons with DS, the relationship between APOE ϵ 4 and risk of AD remains controversial. Some studies have shown APOE ϵ 4 allele to be associated with increased risk of AD in persons with DS^{25,26} while others have not^{27,28}. A recent meta-analysis showed APOE ϵ 4 to be significantly associated with the prevalence of AD in DS²⁹.

The extended tau haplotype occurs in two forms, as H1 and H2, and has been associated with earlier onset of AD in the presence of the APOE ϵ 4 allele in the general population. Individuals with DS are at increased risk of developing dementia before age 45 years if they are heterozygous for the extended tau haplotype. Its lack of association with the APOE genotype suggests that it may be an independent risk factor for early onset dementia in DS³⁰.

The genes for proteins that regulate tau phosphorylation, *DYRK1A* (dual-specificity tyrosine-regulated kinase 1A) and calcipressin, are located on chromosome 21 and their increased expression in DS may promote NFT formation. Furthermore, increased expression of both occur in response to increased A β load and helps explain why NFTs occur at a later stage in the dementia process³¹.

Tetranucleotide repeat in intron 7 of APP (att5-8) has been associated with earlier age of onset of dementia by up to 13 years in DS²¹.

GENDER AND THE ROLE OF OESTROGENS

Women in the general population are at increased risk of developing AD compared with men and oestrogen deficiency has been implicated in the cascade of pathological processes leading to AD. This has been reviewed recently³².

The evidence for the effect of gender on risk of AD in DS is contradictory, with some studies finding no differences in age of onset³³, earlier onset³⁴ or later onset³⁵. Postmenopausal DS women with low levels of bioavailable oestradiol have been found to have an increased risk of developing AD³⁶. The average age of menopause in DS women was younger than in the general population and the age of onset of AD correlated with the age of menopause, hence it has been suggested that oestrogen deficiency may be a possible independent risk factor for AD in DS³⁷.

BRAIN METABOLITES: THE POTENTIAL ROLE OF MYO-INOSITOL

The Na⁺/*myo*-inositol co-transporter gene (*SCL5A3*) is located on chromosome 21 and *myo*-inositol significantly affects neuronal development and survival, neuronal osmolarity, membrane metabolism, signal transduction, protein kinase C activation and amyloid deposition³⁸.

Proton magnetic resonance spectroscopy studies in healthy DS persons have reported significant increases in brain choline and *myo*-inositol, but no differences in brain NAA or creatine, and it has been suggested that the abnormal membrane turnover/degradation and increase in *myo*-inositol reflect a 'predementia' phase in which the neuropathology of AD is accumulating and precedes the loss of neurons^{39,40}. The increased brain *myo*-inositol concentrations in healthy DS persons have been shown to be negatively correlated with overall cognitive and memory abilities⁴¹.

In a study comparing brain metabolites in demented, mild cognitively impaired (MCI) and healthy controls in the general population

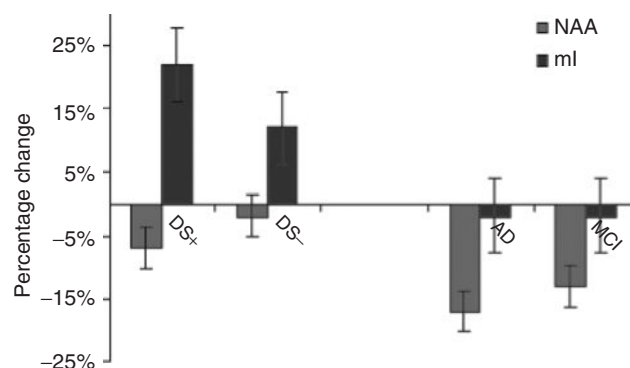


Figure 48.1 The percentage change in unadjusted averages of hippocampal concentrations of NAA and mI by group comparisons (i.e. DS+ to DS-, AD to HC, DS- to HC and MCI to HC)

with demented (DS+) and non-demented (DS-) DS individuals, NAA concentrations were found to be reduced in persons with AD and MCI in the general population but not in either the demented or non-demented DS persons, suggesting that dementia in DS is associated with comparatively small reductions in viable neuronal function (as measured by NAA). In contrast, it was found that brain *myo*-inositol (mI) concentration was only increased in the demented DS group (see Figure 48.1), suggesting that elevated brain *myo*-inositol modifies the risk of dementia in people with DS possibly by interacting synergistically with other risk factors for dementia in this vulnerable population⁴². Research is currently under way to determine if manipulation of brain *myo*-inositol in DS by the use of lithium could offer a novel target for intervention in the dementia process in DS.

OXIDATIVE STRESS

Free radicals produced by metabolic processes are kept in check by antioxidant defences and if this balance is disturbed, results in the highly reactive free radicals reacting with lipids in cell membranes to cause cellular damage, which contributes to neurodegeneration. The genetic locus for Cu,Zn-superoxide dismutase (*SOD1*), a key enzyme in free radical metabolism, is located on chromosome 21⁴³ and has been suggested to have particular relevance to neurodegeneration in DS⁴⁴.

NEUROINFLAMMATION

There is increasing evidence to suggest that cytokines have an important role to play in the development and/or progression of AD in the general population. The inflammatory component of AD is dominated by the presence of activated microglial cells⁴⁵. Studies have shown some support for the hypothesis that cytokines may act as a risk factor for the development of dementia in DS^{46,47}. A small study found positive correlations between serum IL-6 levels with age and severity of AD in people with DS⁴⁸, and there is preliminary evidence to indicate that serum TNF- α levels are elevated in DS persons with AD⁴⁹, suggesting a disease-stage-dependent general activation of the immune system.

NEUROIMAGING

Using magnetic resonance imaging (MRI) based measurements of grey matter atrophy as a surrogate marker of neuronal density,

various neuroimaging studies have described the macroscopic neuroanatomy of DS. More recent studies using sensitive quantitative measures of region-specific atrophy based on high-resolution MRI have suggested that age-specific atrophy in DS resembles the pattern of brain atrophy in the early stages of AD⁵⁰.

In DS persons, overall brain volume including the cerebellum and cerebral grey and white matter, ventral pons, mammillary bodies and hippocampus is reduced whereas the parahippocampal gyrus are enlarged⁵¹. Reductions in cerebral volume are prominent in the frontal and occipital lobes and there is relative preservation of parietal lobe grey and temporal lobe white matter⁵².

As they age, non-demented DS individuals show volumetric reductions in most cortical brain regions⁵³, hippocampus, parahippocampal gyrus and corpus callosum. Demented DS individuals show volumetric reductions in total brain, total grey matter, frontal, temporal and parietal cortices, hippocampus and parahippocampal gyrus and enlarged ventricles when compared to non-demented DS individuals⁵⁰. A recent study showed volumetric reductions of the hippocampus and caudate bilaterally, right amygdala and putamen in demented DS individuals. Hippocampal and caudate volumes both correctly categorized 92% of DS persons without AD as well as 75% and 80%, respectively, of DS persons with AD, suggesting that they may act as markers of clinical AD⁵⁴.

COGNITIVE AND BEHAVIOURAL FEATURES

Pre-Existing Cognitive Ability

Low education and low lifetime occupational attainment have been associated with increased risk of AD in the general population possibly by the lack of cognitive reserve, which hastens the onset of clinical manifestations⁵⁵. In DS persons, higher cognitive functioning has been associated with fewer cases of dementia⁵⁶ and the rate of cognitive deterioration increased with age and degree of pre-existing cognitive impairment⁵⁷.

Executive Dysfunction

The presentation of the early stages of AD in persons with DS differs from that in the general population and is characterized by prominent personality and behaviour changes associated with executive dysfunction rather than declines in episodic memory, which may suggest impairments in frontal lobe functions⁵⁸.

Selective Attention

Progressive impairment in selective attention, as measured by cancellation tasks, has been detected in DS adults in the preclinical stage of AD and the performance in this group could be differentiated from their healthy DS peers who do not go on to develop AD⁵⁹.

CO-MORBIDITY

Physical Health

As in the general population, people with DS experience more health problems as they age. With the onset of AD, there is an increase in the frequency and severity of the co-morbidities. Visual and hearing impairments, gastric concerns, depression, epilepsy, lung disease

and mobility problems have all been reported to be increased in DS with AD compared to those without AD and additionally have also been reported to be associated with the stage of AD, with the co-morbidities being more severe at the later stages of the dementia process⁶⁰. Some of these co-morbidities are significantly more severe in the DS population with AD than those with AD in the general population who do not have DS, e.g. epilepsy⁵.

Maladaptive Behaviours and Mental Ill Health

AD is characterized by progressive decline in cognitive and functional skills and is often accompanied by maladaptive behaviours and psychiatric symptoms. A recent longitudinal cohort study showed point prevalence of mental ill health in non-demented DS adults to be between 10.8% and 23.7% while the 2-year incidence varied from 3.7% to 14.9% depending on the diagnostic criteria used. The highest incidence was for depressive episode and dementia/delirium. Mental ill health was found to be lower in DS when compared with other adults with learning disability⁶¹. An earlier study found that most depressed DS persons were still symptomatic at one year and those with early onset depression were associated with better treatment outcomes⁶².

Non-demented elderly DS persons show less initiative and more apathy compared to individuals with other causes of learning disability, and when compared to younger DS persons, showed more irritation, fear, restlessness at night, sadness, suspiciousness and loss of appetite⁶³. In DS persons with AD, there was a higher prevalence of low mood, restlessness/excessive overactivity, disturbed sleep, being excessively uncooperative and auditory hallucinations, but they were less aggressive when compared to demented learning disabled individuals without DS⁶⁴. In a more recent study, differences in maladaptive behaviours at various stages of dementia were found, with the non-demented DS individuals displaying fewer and less severe maladaptive behaviours than individuals in the early and mid-stages of dementia. Furthermore, those non-demented DS individuals who were transitioning into the early stages of dementia displayed increased aggression, fearfulness, sadness, sleep problems, social inadequacy, stealing and general regressive behaviours⁶⁵.

In a study on referral characteristics, it was found that DS individuals who were referred for specialist dementia assessment showed more behavioural excess, but not deficits, and lower socialization and coping skills when compared to those who were not referred. Their carers also reported the behaviours as having a greater impact on them than on the individual with DS⁶⁶.

DIAGNOSTIC ISSUES

There are significant difficulties associated with diagnosing AD in people with DS. The large intra-individual variability in cognitive functioning, lack of standard diagnostic and methodological procedures and difficulties with obtaining baseline cognitive function with which to assess cognitive and behavioural change in DS persons make early diagnosis of AD especially difficult in this population⁶⁷. Further difficulties arise from the fact that many individuals with DS suffer from underdevelopment of social and cognitive skills and high rates of co-morbidity (e.g. depression and hypothyroidism).

The pre-existing learning disability often results in floor effects on many of the standard assessment tests used, and available screening instruments vary in their reliability⁶⁸. Among the informant-rated instruments, the Dementia Questionnaire for Persons with Mental

Retardation (DMR)⁶⁹, later revised as the Dementia Questionnaire for people with Learning Disabilities (DLD), is widely used in people with learning disability but had variable sensitivity in single assessments and poor specificity in people with DS, while the Dementia Scale for Down Syndrome (DSDS) had good specificity but mediocre sensitivity. Of the direct assessment instruments, the Test for Severe Impairment (TSI) and Severe Impairment Battery (SIB) have been used but require further evaluation in people with DS. More recently, the CAMDEX-DS, a modified version of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) informant interview, has been developed for assessing people with DS suspected of having dementia⁷⁰. As to the different diagnostic criteria in use, the DSM-IV dementia criteria has been shown to be more inclusive than that of the ICD-10, which excluded DS persons with even moderate dementia⁷¹.

TREATMENT

Established antidementia drug treatments for AD in the general population include the cholinesterase inhibitors donepezil, rivastigmine and galantamine as well as the NMDA antagonist memantine. There is limited evidence available on drug therapies for dementia in DS⁷². Recent Cochrane reviews on the subject found only one randomized controlled trial of suitable quality for donepezil, and none for galantamine, rivastigmine and memantine^{73–76}. That study on donepezil suggested some limited benefit of donepezil treatment at 24 weeks⁷⁷, and an open label extension of that study showed that those continued on donepezil showed less deterioration at two years, which may suggest benefits of longer-term use⁷⁸. Drug therapy should form part of the broader multidisciplinary management of persons with DS and AD, incorporating carer support, psychological and behavioural therapies and ongoing assessment of and management of physical and mental health.

CONCLUSIONS

There is considerable neuropathological, genetic and clinical overlap between the AD in DS and in the general population but also some subtle differences. The occurrence of dementia in people with DS is expected to rise proportionately with the increase in their life expectancy. This has implications for health and social care provisions both for them and their carers, and further research into better understanding the neurobiology of the disease in DS and potential treatments for them are warranted.

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The Molecular Neuropathology of Alzheimer's Disease

Orly Lazarov

Department of Anatomy and Cell Biology, The University of Illinois at Chicago, IL, USA

INTRODUCTION

It is yet to be discovered what induces the high vulnerability exhibited by specific groups of neurons in Alzheimer's disease (AD), leading to their progressive degeneration. Vulnerable neurons are located in brain areas that are functionally linked to various forms and aspects of learning and memory, including the hippocampal formation, olfactory system and neocortex (for review see¹). The parahippocampal regions are the earliest to be affected (Braak stages I and II). In particular, the entorhino-hippocampal circuit exhibits an early and significant neuropathology. Neuropathology in this region correlates significantly with degree of dementia. The hallmark lesions of the disease, most pronounced in the affected brain areas, are neurofibrillary tangles and amyloid deposits. Neurofibrillary tangles are intracellular aggregates of bundled paired helical filaments. The principal component of neurofibrillary tangles is hyperphosphorylated tau. The microtubule-associated group of tau proteins consists of alternatively spliced cytoplasmic proteins that bear either three or four microtubule-binding domains and co-assemble with tubulin onto microtubules, where they stabilize these organelles. As such, tau is implicated in numerous critical cellular processes, such as cell proliferation, neuronal maturation, process elongation and axonal transport. Thus, preceding neurofibrillary tangle formation, hyperphosphorylation of tau may interfere with crucial cellular and neuronal functions. The mechanism underlying hyperphosphorylation of tau in AD is not fully understood, as discussed below. Amyloid deposits are aggregates of β -amyloid ($A\beta$) peptides released from a large precursor termed amyloid precursor protein (APP) upon enzymatic cleavage. Upon increase production or fibrillogenic properties, $A\beta$ undergoes conformational changes to form β -sheet structures that tend to form oligomers and subsequently insoluble aggregates. One form of amyloid aggregates is neuritic plaque, an extracellular core of amyloid fibrils surrounded by dystrophic dendrites, degenerating axons and reactive gliosis. Neuritic plaques are abundant in the molecular layer of the dentate gyrus of the hippocampus, the amygdala, the association cortices of the frontal, temporal and parietal lobes, and within certain deep brain nuclei that project to these regions. In addition to neuritic plaques, several other forms of $A\beta$ aggregates exist, including abundant 'diffuse plaques' in the limbic and association cortices and even in non-conventionally affected regions, such as cerebellum. Increased fibrillogenesis and/or levels of $A\beta$ is caused by either

mutagenesis or ageing-linked unknown pathogenesis. In rare, familial, early onset form of AD (FAD), increased fibrillogenesis and/or levels of $A\beta$ are caused by mutations in APP, presenilin-1 (PS1) and presenilin-2 (PS2). These mutations cause misprocessing and trafficking of APP by β -secretase or γ -secretase, the aspartyl protease of which PS is the catalytic core, yielding an increased amount and/or ratio of the fibrillogenic forms of $A\beta$ (e.g. $A\beta_{42}$), that consequently aggregate in the form of amyloid deposits. Both hallmark lesions are the result of misfolding and polymerization of otherwise soluble proteins. The progressive emergence of altered conformations of originally soluble proteins and subsequently insoluble aggregates, intra- and extracellularly, is associated with profound neuronal dysfunction and death.

FAMILIAL ALZHEIMER'S DISEASE-LINKED CENTRAL PLAYERS

Amyloid Precursor Proteins

Amyloid precursor proteins encompass a family of membrane-anchored type I glycoproteins that are ubiquitously expressed and particularly abundant in the brain (for review see²). APP full length are 110–130 kDa proteins that are synthesized in the endoplasmic reticulum. APP maps to chromosome 21 in humans and is transcribed to three isoforms, APP₆₉₅, APP₇₅₀ and APP₇₇₁ with the former being predominantly expressed in neurons and the latter two in glia. APP₇₇₀ is encoded by 18 exons, where exon 17 resembles the membrane-spanning domain. APP₆₉₅ is lacking both exon 7 and exon 8, and is the most abundant APP transcript in the brain. APP₇₅₁ (lacking exon 8), APP₇₁₄ (lacking exon 7) and APP₇₇₀ are expressed in the peripheral and central nervous system. Exon 7 encodes an amino acid fragment that exhibits substantial homology to the Kunitz-type serine protease inhibitor (KPI) while exon 8 shares some homology with the MRC OX-2 antigen. Two additional members of the APP family are amyloid precursor-like protein 1 and 2 (APLP1 and APLP2). They are truncated at the carboxyl terminus and lack the $A\beta$ region. The APLPs map to chromosome 19 in humans. The APLP2 but not APLP1 contains a KPI domain. Nevertheless, neither mutations in APLP1 nor in APLP2 are causative of FAD, supporting the notion that $A\beta$ plays a major role in the disease. Indeed, FAD-linked mutations introduce

amino acid substitutions within or flanking the A β region of APP, around the cleavage sites of α -, β - and γ -secretase. APP undergoes a complex set of tightly linked trafficking and processing. From the endoplasmic reticulum, APP is transported to the plasma membrane through Golgi apparatus. However, only a small fraction of APP molecules reaches the plasma membrane. During this journey APP undergoes multi post-translation modifications of *N*- and *O*-glycosylation, ectodomain and cytoplasmic phosphorylation, and tyrosine sulphation. The presence of the YENPTY internalization motif near the C terminus of APP enables APP endocytosis shortly after it reaches the plasma membrane. Then APP is delivered to endosomes, and a fraction of endocytosed molecules is recycled to the cell surface. Some of internalized APP undergoes lysosomal degradation. During its journey, APP is subject to a complex processing by multiple enzymatic activities (Figure 49.1), most of which are around the 4 kDa region of the A β peptide (for review see¹). In the nonamyloidogenic pathway, APP is cleaved by α -secretase at amino acid 16–17 of the A β region, preventing the formation of A β . In the amyloidogenic pathway, APP is cleaved by the β -secretase enzymatic activity at the carboxyl terminus of the A β region, followed by a cleavage by γ -secretase enzymatic complex at the amino terminus of the A β region, leading to the release of A β .

Following shedding of APP by α - and β -secretase, the soluble product (sAPP α and sAPP β) is released to the extracellular space, while a membrane-anchored fragment is subject to an intramembranous cleavage by γ -secretase, releasing APP carboxyl terminus fragments (AICD) into the cytoplasm. AICD can form a transcriptionally active complex with Fe65 and Tip60. While the role of AICD in regulation of gene transcription is yet to be confirmed, several genes are thought to be regulated by AICD: *KAI1*, the A β -degrading enzyme neprilysin, *LRP1*, and epidermal growth factor (EGF) receptor. Many adaptor proteins with phosphotyrosine-binding domains, including Fe65, Fe65L1, Fe65L2, Mint1 (i.e. X11), Mint2, Mint3, Dab1, and c-Jun N-terminal kinase (JNK)-interacting protein family members bind this motif and the flanking region. Overexpression of these adaptors reduces A β production and deposition in the brains of transgenic mice, suggesting that these adaptors play a role in regulation of APP processing (for review see³). Interestingly, Fe65 serves as a functional linker between APP and LRP in modulating endocytic APP trafficking and A β production. Mutations within the YENPTY endocytosis motif inhibit APP internalization and decrease A β production, suggesting that APP is processed to yield A β following internalization.

The phenotype of mice with homozygous ablation of APP appeared rather mild compared to presenilin-1 knockout phenotype. Some

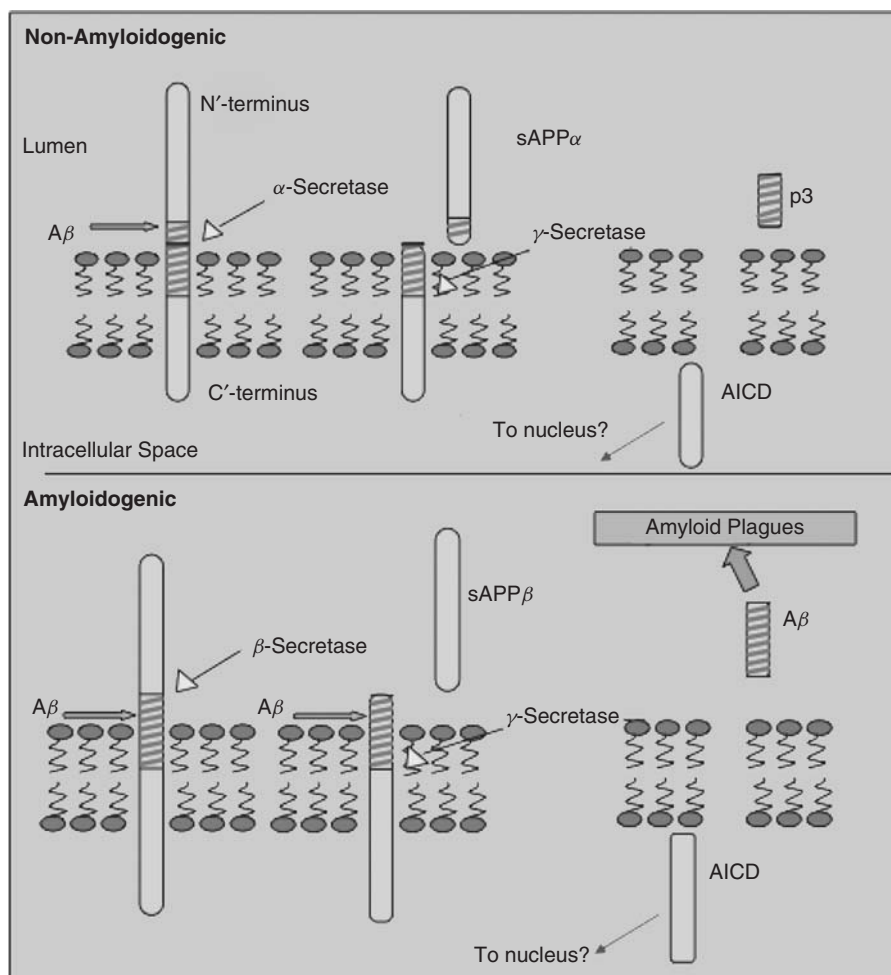


Figure 49.1 Schematic presentation of APP processing in its amyloidogenic and nonamyloidogenic pathways. AICD = APP carboxyl terminus fragments

Image generation by courtesy of Michael Demars

synaptic markers are thought to be reduced in APP-deficient mice, and this reduction correlates with deficits in learning and memory and in synaptic plasticity. APLP2 knockout mice appear normal, while APLP1 knockout exhibit some growth impairments. This mild phenotype might be due to partial functional redundancy among the family members. In support of this notion, *APLP2/APLP1* and *APP/APLP2* double knockouts die right after birth, suggesting that APLP2 functionally overlaps with APP and APLP1. Examination of the central and peripheral nervous system of the double knockout mice confirmed significant deficits in synapse formation, deformed pre- and post-synaptic element distribution, reduced number of synaptic vesicles and aberrant localization of the choline transporter at neuromuscular junctions. Deficiency of all three *App* genes led to death shortly after birth, exhibiting cortical dysplasia suggestive of migration abnormalities of the neuroblasts and partial loss of cortical Cajal–Retzius cells. Taken together, these findings suggest that the *APP* gene family plays important roles in the development of the nervous system, such as synapse formation and regulation of neural progenitor cells.

Presenilins and γ -Secretase

Presenilins (PS1 and PS2) are multipass membrane proteins that are predominantly localized to the endoplasmic reticulum. PS undergo endoproteolysis by an unknown enzymatic activity termed Presenilase, and the resulting amino-terminal and carboxy-terminal fragments that remain closely associated, are thought to be the active form of the protein. PS are thought to play numerous roles in the cell, but are best known for their central role as the catalytic core of the intramembranous, γ -secretase aspartyl protease that cleaves numerous membrane proteins, including APP. γ -secretase is a unique membrane protease complex. Presenilin 1,2 are thought to be the catalytic subunit of γ -secretase. PS contain two essential aspartate residues in putatively adjacent transmembrane domains (for review see⁴). Substitution of either of the two aspartate residues buried within the sixth and seventh transmembrane domains of PS abolishes γ -secretase activity. The proteolytic cleavage, which takes place in the middle of the transmembrane region of the substrate, occurs after ectodomain shedding of the target protein and is amino acid sequence independent. Experiments using transition state analogue inhibitors suggest that γ -secretase has separate sites for substrate binding and catalysis. Another unusual characteristic of the γ -secretase cleavage is the multiplicity of the cleavage sites: one in the middle of the transmembrane domain that creates the carboxy-terminus of A β , and another one that liberates intracellular domain of the substrate into the cytoplasm, for example NICD (notch site-3 cleavage) or APP ICD (AICD ϵ -cleavage of APP). While the composition of the γ -secretase complex is still under intense investigation, three additional proteins, nicastrin, aph-1 and pen-2, have been identified so far as cofactors in the γ -secretase multicomponent complex⁵. Co-expression of these components with presenilin appears to be critical for γ -secretase activity. The first cofactor of the γ -secretase complex to be identified was nicastrin (NCT), a type I membrane glycoprotein comprising 709 amino acid residues in humans. Ablation of NCT in *Drosophila* resulted in embryonic lethality, and knockdown of NCT homolog aph-2 in *C. elegans* resulted in hypoplasia of the anterior pharynx. A point mutation in aph-1 gene identified in *C. elegans* caused an abnormality in anterior pharynx development, similar to that seen in aph-2 mutants. Disruption of the GXXXG motif within the fourth transmembrane domain of APH-1 caused by the mutation

leads to failure in assembly and activation of the γ -secretase complex. Two homologues of aph-1 genes were identified in human aph-1a and aph-1b, both encoding membrane proteins predicted to span the membrane seven times. The identification of presenilin enhancer genes pen-1 and pen-2 revealed that pen-1 is identical to aph-1, while pen-2 encodes a membrane protein that spans the membrane twice. Experiments using RNAi established that suppression of the *Drosophila* homologues of nicastrin, APH-1 or PEN-2 result in the loss of Psn fragments and of γ -secretase activity, as indicated by lack of A β production. Based on systematic examination of downregulation of the different components of the γ -secretase using combinations of RNAi, it is thought that APH-1 and NCT team up to stabilize PS holoprotein, while PEN-2 induces PS endoproteolysis, eliciting maturation of the active form of the γ -secretase complex. Reconstitution of γ -secretase activity in yeast by over-coexpression of human PS1, NCT, APH-1a and PEN-2 in yeast, components which otherwise are not endogenously expressed in yeast, strongly suggests that these four cofactors are sufficient to the generation of γ -secretase activity. In contrast to other known proteases, γ -secretase is composed of a high molecular weight multicomponent complex. However, the stoichiometry of the γ -secretase is still under an intensive investigation. It is yet to be determined what other components are associated with the γ -secretase. γ -secretase regulates the second step in a two-step proteolytic cleavage event of membrane proteins known as regulated intramembrane proteolysis (RIP). This process starts with an ectodomain shedding resulting in the proteolytic processing of membrane proteins to their soluble counterparts. Ectodomain shedding is carried out by members of the ADAM family and matrix metalloproteases, and to a lesser extent by BACE1 and BACE2 (see below). Following shedding, the resulting membrane-bound CTF undergoes a second cleavage event within its transmembrane domain, called intramembrane proteolysis that is catalyzed by the γ -secretase complex.

β -Secretase

A decade ago, the enzymatic activity termed β -secretase that cleaves APP at the N' of the A β region was identified as the aspartyl protease β -site APP cleaving enzyme I (BACE1; also known as memapsin and Asp2) (for review see⁶). A 501 amino acid type I membrane protein, BACE1 resides on the cell surface and in intracellular compartments of the secretory pathway, with its active site within the lumen of these compartments. BACE1 is predominantly expressed in neural tissues with the highest activity level exhibited in neurons. Genetic ablation of BACE1 provided an explicit evidence that BACE1 is the principal neuronal protease required for cleavage of APP at the +1 and +11 site of A β and the main β -secretase in the brain. BACE1 cleaves APP in its extracellular domain at a site close to the membrane surface, the Asp+1 residue, generating a secreted APP ectodomain, soluble APP β (sAPP β), and a membrane-bound APP C-terminal fragment of 99 amino acid residues (C99). This highly sequence-specific cleavage is a prerequisite for A β formation and is followed by endoproteolysis within the transmembrane domain of C99 by γ -secretase, yielding A β . BACE1 also cleaves the APP homologues, amyloid precursor-like proteins, APLP1 and APLP2. BACE1 exhibits classical characteristics of an aspartyl protease with two active site motifs. Mutating either aspartic acid inactivates the protease. A signal sequence (residues 1–21) and a pro-peptide domain (residues 22–45) are in its N-terminus, and are removed post-translationally. Near its C-terminus (residues 455–480) there is a single transmembrane

domain and a palmitoylated cytoplasmic tail. Possible regulators of BACE1 may include several stress-induced transcription factors that bind to its promoter, such as Sp1, GATA-1, AP1, AP2, CREB, oestrogen and glucocorticoid receptors, NF κ B, STAT1, HIF-1 and HSF-1. Other potential regulators are several cytokines, such as IL-1, and A β itself (for review see⁶). BACE1 cleavage of APP is the first critical step for A β production. Therefore, alterations in BACE1 activity manifests in changes in levels of A β production. Indeed, FAD-linked Swedish mutation in APP causes enhanced BACE1 activity, leading to increased A β production and amyloid deposition. In that regard, age-dependent increase in BACE1 activity occurs in the brains of mammals, and correlates with levels of A β . Likewise, an increase in BACE1 activity is detected in AD and correlates with amyloid deposition and A β_{1-x} and A β_{1-42} production. Apparently a mild increase in BACE1 expression results in a significant elevation in A β levels until a plateau is reached. In turn, increased levels or ratio of A β_{1-42} may trigger an upregulation in BACE1 activity. As BACE1 is primarily enriched in neurons, it is expected that amyloid plaque-induced elevated BACE1 level is manifested primarily in neurons. An additional contribution of increased BACE1 activity is expected from activated glia, especially at the stage of disease in which inflammation in the brain is upregulated. Intriguingly, reduced BACE1 activity ameliorates amyloidosis and memory impairments in FAD mice. Thus, cross-breeding BACE1 KO mice with FAD-linked mice exhibiting high levels of A β and amyloid deposition abolished any traces of A β formation or aggregation and learning and memory impairments. Nevertheless, it should be noted that BACE1 knockout mice exhibit some abnormalities in cognitive and emotional functions, such as spatial and reference memories and impairments in temporal associative memory, suggesting that BACE1 is required for some aspects of hippocampal memory, and that a complete inhibition of the enzyme may have unfavourable cognitive side effects. Recent studies show that APP is modulated by the interaction of BACE1 with the neurite growth inhibitor Nogo, a member of the reticulon protein family and a component of myelin, which may imply that BACE1 plays a role in myelination. In support of that, high BACE1 expression levels are observed in early postnatal stages when myelination takes place. Like APP, BACE1 cycles between compartments of the secretory pathway and BACE1 activity resides in both the endosomes and secretory pathway. The immature precursor of BACE1 is synthesized in the endoplasmic reticulum (proBACE1). Through the addition of complex carbohydrates and the removal of the propeptide domain, ProBACE1 rapidly matures into a 70 kDa form, which undergoes extensive post-translational modifications. The majority of BACE1 is produced as an integral membrane protein, while a minor portion of BACE1 undergoes ectodomain shedding. Inhibition of shedding does not influence processing of APP at the β -site. However, co-expression of APP and the soluble ectodomain of BACE1 in cells increase the generation of A β , suggesting the enhanced BACE1 ectodomain shedding may enhance amyloidogenic processing of APP. Mature BACE1 localizes largely within cholesterol-rich lipid rafts. BACE1 is capable of forming stable homodimers that exhibit enhanced catalytic activity.

α -Secretase

In its non-amyloidogenic cleavage pathway, APP is cleaved by α -secretase. This cleavage takes place within the A β domain at Leu+17, thus preventing A β formation. Evidence suggests that

BACE2 cleaves APP at a novel θ -site Phe+19 and Phe+20 sites of APP, downstream of the α -secretase cleavage site⁷.

α -secretase cleavage produces sAPP α ectodomain, and an APP-CTF, C83, which in turn is cleaved by γ -secretase to form a 3 kDa fragment, p3. While an increase in non-amyloidogenic APP metabolism was shown in some studies to be coupled to a reciprocal decrease in the amyloidogenic processing pathway, as α - and β -secretase compete for the same APP substrate, other studies show that these activities may not necessarily be coupled. The identity of α -secretase is unknown. Four putative enzymes were shown to have α -secretase activity: TACE (TNF- α converting enzyme), ADAM (a disintegrin and metalloprotease domain protein)-9 and ADAM-10, and BACE 2^{8,9}. BACE2 is an aspartyl protease and a homologue of BACE1. The amino acid sequences of BACE1 and BACE2 are ~45% identical and 75% homologous. BACE2 is expressed at low levels in most human peripheral tissues, but very low or undetectable levels in the brain. *In vitro*, BACE2 can cleave APP at the β -secretase cleavage site⁹. However, it seems that BACE2 functions mainly as an alternative α -secretase and as an antagonist of BACE1. In support of that, BACE2 is not upregulated as a compensatory mechanism following downregulation of BACE1 and its overexpression reduces A β production in neuronal cultures.

A β MISFOLDING AND OLIGOMERIZATION, SYNAPTIC FAILURE AND MEMORY LOSS

γ -secretase can cleave APP in multiple sites, leading to the formation of numerous size forms of A β . The main form is A β_{40} , however, A β_{38-43} have been identified as well. While its physiological role is yet to be determined, it is important to note that under normal conditions, A β is secreted from neurons throughout life. The most abundant 40 amino acid species (A β_{40}) is not thought to be harmful, whereas the less abundant A β_{42} variant aggregates faster and is thus linked to disease neuropathology (for a review see¹⁰). It is not clear how the addition of the two amino acids at the C-terminus of A β changes the properties of the peptide in a way that makes it more aggregation-prone. However, it is thought that an increase in the A β_{42} /A β_{40} , an upregulation of A β levels and/or reduced A β degradation or clearance lead to neuropathology. A β_{42} tends to generate soluble oligomers that can range in size between dimers to dodecamers. These oligomers were found in human brains lacking amyloid deposits or fibrillary tangles, suggesting that accumulation of oligomeric species of A β occur early in the disease. Many studies have shown that FAD-linked transgenic mice with amyloid pathology have impairments in learning and memory paradigms including acquisition of long-term spatial memory, spatial reversal learning, utilization of spatial working memory, acquisition of social recognition memory, object recognition memory and contextual fear conditioning (for review see¹¹). In some cases, the severity of the impairment has been correlated to A β levels in the brains of individual mice and treatments that reduce A β levels (e.g. immunization with A β or A β antibodies) can reverse learning deficits. Most of these tasks are dependent on the hippocampus and deficits in hippocampal synaptic plasticity, i.e. long-term potentiation (LTP) in the transgenic mice are possible causes for the learning impairments (for review see¹¹). However, the cues used in these learning paradigms are complex and require processing in multiple brain networks before reaching the hippocampus. This makes it difficult to establish where and how in the brain learning breaks down in the affected animals. Several studies have reported impairments in hippocampal LTP in FAD-linked

transgenic mice. However, the role of A β deposition and the presence or absence of amyloid plaques remains unclear. Some studies have reported impaired synaptic function or LTP deficits prior to amyloid deposition, some deficits only after amyloid deposition, and some preserved LTP in the face of extensive amyloid deposition. These disparate results no doubt reflect strain-specific differences in transgene expression and other factors. Most studies agree that functional synaptic density, measured electrophysiologically, is reduced in hippocampus of mice with extensive A β deposits. This accords with other indicators of synaptic degeneration and the toxic effects of A β monomers, oligomers, protofibrils and fibrils on synapses. Compelling evidence for the role of soluble A β oligomers in memory loss was provided by studies showing that a single intraperitoneal injection of anti-A β antibodies can reverse memory impairments in APP transgenic mice without affecting amyloid deposition, suggesting that the antibodies target soluble A β . In support of that, recent evidence suggests that these are the oligomeric forms of A β that are cytotoxic, interfering with numerous cellular functions as well as interfering with aspects of learning and memory and synaptic function. Synaptic dysfunction takes place before synaptic loss, which precedes neuronal loss.

MEMORY LOSS, ALTERATIONS AND IMPAIRMENTS IN NEUROGENESIS

Neurogenesis and Alzheimer's Disease: Cross-Talk and Effects

The contribution of impaired neurogenesis to memory disorders and to AD in particular is increasingly acknowledged. In the adult brain there are two discrete areas where neural stem cells are maintained and differentiate into new neurons and glia throughout life: the subventricular zone (SVZ), adjacent to the walls of the lateral ventricle, and the subgranule layer (SGL) of the dentate gyrus. Both neurogenic areas are part of the olfactory-hippocampal and entorhino-hippocampal circuits that are most affected in AD. Neurogenesis in the adult brain plays a role in numerous aspects of learning and memory (for review see¹²). Numerous studies have suggested that the rate of neurogenesis in both SVZ and SGL declines with age, raising the possibility that reduced neurogenesis may account for, at least in part, impaired learning and memory and cognitive deterioration in the elderly (for example see¹³). Examination of neurogenesis in brain tissue of AD patients revealed increased expression of immature neuronal marker proteins. However, these observations have been challenged recently. Other reports suggest that in the aged and AD brain, there is a dramatic decline in both proliferative capacity of progenitor cells and in the pool of NSCs in the SGL, and that this decline may be attributed to loss in growth factors (for review see¹⁴). Information obtained using animal models of the disease reveals that the vast majority of studies using transgenic mice harbouring FAD-linked mutant PS1 report that neurogenesis is impaired on a steady-state level and upon enriched environment stimulation (for review see¹⁵). Nevertheless, the interpretation of observations obtained in transgenic mice harbouring FAD-linked APP variants is challenging. This may result in the fact that APP is processed to numerous metabolites, that convey different effects on neurogenesis as described below. It is important to keep in mind that the organization composition and dynamics in the neurogenic niches may change as AD progresses, according to the dynamics of neuropathological cues, such as oligomeric A β and amyloid deposition. Another fascinating aspect of the cross-talk between AD and neurogenesis, adding

another level of complexity, is that players that cause FAD regulate neurogenesis, as discussed in the next paragraph.

PS1 Regulates Embryonic and Postnatal Neurogenesis

γ -secretase cleaves other membrane proteins in addition to APP, such as the receptor tyrosine kinases ErbB4, IGF-1R and insulin receptor, as well as of the neurogenic signals Notch1, L1 and E-cadherin (for review see¹⁵). A large number of these substrates are neurogenic signalling that regulate embryonic and postnatal neurogenesis, suggesting that alterations in PS1/ γ -secretase expression, activity or function may directly affect neurogenesis. In support of that PS1 is a homologue of the *C. elegans* sel-12 – a protein that plays a major role in cell-fate decisions. Recent evidence suggests that PS1/ γ -secretase acts as a tumour suppressor in epithelia and that epidermal growth factor receptor (EGFR) levels inversely correlate with PS1/ γ -secretase activity. Intriguingly, EGFR signalling plays a major role in regulation of neural stem proliferation, migration and survival (for review see¹⁶). PS1 is further implicated in the Wnt/ β -catenin signalling pathway that regulates adult hippocampal neurogenesis. The first indication that PS1 may play a role in neurogenesis has been provided by experiments in mice with genomic deletions of *PSEN1* exhibiting severely abnormal somitogenic and neurogenic processes in the brain. These mice die in late embryogenesis. This has hampered further studies of the role of PS1 in a natural brain setting in postnatal life. Some studies in transgenic mice harbouring FAD-linked PS1 variants reveal that expression of FAD-linked mutant PS1P117L, PS1M146V or conditional ablation of PS1 in the forebrain induce impaired hippocampal neurogenesis. In addition, experience of mice in an enriched environment does not upregulate neurogenesis in transgenic mice harbouring PS1 mutant variants. In contrast, other studies suggest that expression of FAD-linked PS1A246E enhances proliferation of progenitor cells in the adult DG. However, these animals express mutant PS1 ubiquitously, including in fully mature neurons. Further studies using mice expressing mutant PS1 in the neurogenic areas solely will be needed to determine the role of PS1 in postnatal neurogenesis.

TAU HYPERPHOSPHORYLATION, AXONAL TRANSPORT, KINASE AND PHOSPHATASE ACTIVITY

Another inevitable cause of synaptic degeneration is impaired communication synapse-cell body, which may result in dysfunctional axonal transport. APP is axonally transported by anterograde fast axonal transport (FAT) in both peripheral and central nerves (for review see¹⁷). Interference with the tightly regulated and complex trafficking of APP might have detrimental effects on its processing and consequently on neuronal homeostasis. A large body of evidence supports the notion that axonal transport is impaired in neurons harbouring FAD-linked mutant PS1 (for review see¹⁸). Thus, for example, budding of endoplasmic reticulum- and trans-Golgi network (TGN)-derived APP-containing vesicles is increased in PS1-deficient cells, or cells expressing a dominant negative PS1 D385A variant. In addition, increased steady-state levels of APP were observed on the surface of cells lacking PS1 or expressing PS1 D385A, while vesicle biogenesis and the extent of cell-surface APP is reduced in membrane preparations from cells expressing FAD-linked PS1 variants. Other recent studies show that the PS1-interacting protein phospholipase D1 plays a role in PS1-regulated APP trafficking in neuronal cultures. Significantly, FAT of both

APP and Trk receptors is markedly impaired in the sciatic nerves of transgenic mice expressing FAD-linked PS1 mutants, accompanied by a reduction in both steady-state levels and accumulation of kinesin-1 in nerves of mice expressing mutant PS1 relative to nerves of mice expressing human wild-type PS1¹⁹. These findings are consistent with and extend previous observations that expression of FAD-linked PS1 mutants in embryonic cultured neurons leads to increased glycogen synthase kinase 3 (GSK-3) activity and reductions in kinesin-1-based transport of selected membrane proteins¹⁸. Taken together, the evidence suggests that expression of FAD-linked PS1 variants leads to deficient supply of both neurotrophin receptors and presynaptic membrane components at nerve terminals, resulting in compromised neuronal function. This evidence further implies that misregulation of phosphatase and kinase activity might underlie impaired axonal transport. In that regard, misregulation of phosphatase and kinase activity may underlie hyperphosphorylation of tau. Tau is a multifunctional microtubule-associated protein that plays major roles in the assembly of microtubules, the stabilization of microtubules against dynamic instability, axonal transport and in polymer interaction with other cytoskeletal filaments. The equilibrium between phosphorylations and dephosphorylations of tau modulates the stability of the cytoskeleton and consequently axonal morphology and transport. Recent studies provide interesting information concerning the course of tau pathology in relation to amyloid pathology in the 3XTg-AD mice and shed new light on the pathological effects of tau hyperphosphorylation and aggregation (for review see²⁰). Function-associated phosphorylation sites of tau are reportedly on serine and threonine, suggesting the role of serine and threonine kinases and phosphatases in AD. For example, the epitope at Ser-396/Ser-404 of tau, thought to be preferentially phosphorylated by GSK3, is hyperphosphorylated in AD. There are more than 10 serine/threonine protein kinases that have been shown to phosphorylate tau *in vitro*. According to the motif-specificity, these kinases can be divided into two major groups, i.e. the proline-directed protein kinases (PDPKs) and nonproline-directed protein kinases (NPDPKs). Among these kinases, GSK-3 β is among the most implicated in the abnormal hyperphosphorylation of tau in AD brains. Glycogen synthase kinase 3 (GSK3) is a component of the WNT signalling pathway, which plays a major role in adult neurogenesis, microtubule dynamics and fast axonal transport²¹. GSK3 is inactivated by phosphorylation at serine 9 (Ser9) in its N'-terminus. Among GSK3's numerous substrates are PS1, β -catenin, tau and kinesin-I light chains (KLC) (for review see²²). Previous studies suggest that FAD-linked PS1 mutations affect GSK3 kinase activity in transfected cell lines. Significantly, phosphorylation of KLC by GSK3 promotes the release of kinesin-I from membrane-bound organelles, leading to a reduction in fast anterograde axonal transport²¹. A separate study showed an interplay between cyclin-dependent kinase 5 (Cdk5), previously shown to be central for tau phosphorylation and GSK3 β in mice overexpressing p25. While Cdk5 activity increases APP processing, GSK3 β activity induces tau phosphorylation. Interestingly, inhibition of Cdk5 activates GSK3 β activity. Cdk5 is activated by factors like p35 and p39, and is involved in tau phosphorylations in neurogenesis. Cdk5 activation is concomitant with degeneration of hippocampal neurons and tau hyperphosphorylation, while its inhibition is neuroprotective, suggesting that misregulation of Cdk5 activity plays a role in the formation of neurofibrillary tangles. Recent intriguing studies shed light on a possible role for casein kinase 2 (CK2) activation in the pathogenesis of the disease. Future studies will determine the

sequence of events in these signalling pathways in the course of the disease.

PERTURBED CALCIUM HOMEOSTASIS AND INTRACELLULAR CALCIUM SIGNALING

As a primary resident of the ER, it may not be surprising that dysfunctional PS affect ER calcium dynamics on multiple levels, imposing mostly 'gain of function' effects on these processes (for review, see^{23,24}). This effect on intracellular calcium homeostasis may also be associated with altered glutamate uptake, leading to neurotoxicity. Expression of FAD-linked mutant PS results in increased ER calcium release in fully mature neurons (for review see²³). Mutant PS enhance IP₃-mediated calcium release from the ER stores, as well as perturb calcium entry through store-operated channels. In addition, it appears that ryanodine receptor (RyR) function is predominantly upregulated. IP₃R alterations or direct effects of mutant PS on endoplasmic reticulum store levels may play a role in the observed calcium dysregulation as well. Nevertheless, it should be noted that mutant PS have also shown a reduction in ER calcium load and ER release with SERCA inhibition. Thus it is not clear whether all mutations have the same effect on ER calcium regulation. Overexpression of mutant PS increases IP₃ channel activity in suboptimal and saturated IP₃ levels by prolonging the channel open time, while wild-type PS mildly affect IP₃ channel activity. PS physically interact with IP₃ receptors and thus modulate them directly. IP₃ receptors modulate gating activity and affect overall calcium dynamics. Indeed, fibroblasts derived from mutant PSK11 mice exhibit increased sensitivity to IP₃ receptor agonists. A recent report suggests that mutant PS reduces endogenous calcium leak from the ER, which may result in an increased ER calcium load and overfilled ER stores. Presenilin knockout cells exhibit perturbed ER calcium stores. Overexpression of PS accelerates the sequestration of cytosolic calcium, an effect that can be blocked by pharmacological inhibition of SERCA, suggesting that PS modulate SERCA function. In support of that, PS1KO/PS2KO cells exhibit a phenotype similar to SERCA KO, suggesting that PS may interact and modulate calcium influx into the endoplasmic reticulum via SERCA, and calcium extrusion from the endoplasmic reticulum via interactions with the ryanodine and IP₃ receptors as well as through endogenous leak channels. While a link to A β regulation is provided by studies suggesting that knocking out IP₃ receptor or SERCA results in a dramatic reduction in A β production further studies will be required in order to determine the intracellular sequence of events that lead to calcium imbalance and subsequently neuronal death.

OXIDATIVE STRESS

Oxidative stress refers to circumstances in which oxidant production surpasses the endogenous antioxidant capabilities of the cell, leading to damage of the tissue. Such conditions occur either following increased production of cellular oxidants and/or decreased concentrations of cell antioxidants including glutathione, vitamin E, ascorbate, the glutathione peroxidase system, superoxide dismutase (SOD) and catalase. Overproduction of reactive oxygen and nitrogen species such as superoxide, hydrogen peroxide, nitric oxide and peroxynitrite occurs in AD and is considered to mediate cell damage and subsequently death (for review see²⁵). Studies suggest that A β induces the formation of high concentrations of oxygen and nitrogen-reactive species and a depletion of endogenous antioxidants. In brain tissue

from AD patients, there are increased levels of markers of oxidative stress including oxidized proteins, membrane lipids, DNA and nitrotyrosine immunoreactivity. Additionally, antioxidants including vitamin E, idebenone, uric acid and glutathione are effective in preventing $A\beta$ neurotoxicity *in vitro*. $A\beta$ induces the generation of reactive oxygen species, including the generation of hydrogen peroxide, peroxy radical and superoxide that in turn may initiate a series of secondary reactions. As oxidative stress might have an accumulative effect that is environment and ageing linked, it may contribute to the initiation and development of neuropathology in sporadic AD.

GENETIC LINKS AND RISK FACTORS UNDERLYING LATE-ONSET SPORADIC AD

Ageing is the greatest risk factor for sporadic Alzheimer's disease, and the vast majority of AD cases are the sporadic late-onset form. The cause of late-onset AD is unknown. Several genetic loci have been identified that predispose individuals to late-onset AD (for review see²⁶) and it has been suggested that some of the encoded polypeptides might play roles in modulating the clearance and/or degradation of $A\beta$ peptides. For example, studies that have implicated the low-density lipoprotein receptor-related protein (LRP) in regulating the efflux of $A\beta$ from the brain to plasma have received support from the identification of DNA variants in LRP, apolipoprotein E (ApoE) and α -2-macroglobulin (α 2M) in late-onset AD. LRP was recently identified as a substrate of BACE1. Polymorphisms in the apolipoprotein E (apoE) gene show the most significant effects on relative genetic risk of sporadic AD. The ϵ 4 isoform (Cys112-Arg) of apoE is associated with increased risk of developing AD, while ϵ 2 (Arg158-Cys) is associated with protection from the disease compared to the normal ϵ 3 allele (for review see²⁷). ApoE binds to members of the low-density lipoprotein receptor family (LDLR) (for review see²⁸). These receptors are known to function in cholesterol and lipid transport and as signal transducers. Numerous reports established that LDLR linked cellular signalling pathways modulate AD pathology. Reelin and its homologue F-spondin are recognized by the very-low density lipoprotein receptor (VLDLR) and apolipoprotein E receptor-2 (apoE-R2), two members of the LDLR family. Interestingly, mice lacking reelin, double-knockouts lacking VLDLR and ApoER2 and mice lacking disabled-1 (Dab1) exhibit tau hyperphosphorylation. Based on that it was suggested that the reelin-ApoE receptor complex initiates a signalling cascade that regulates phosphorylation of tau by GSK3. F-spondin and reelin are thought to regulate APP processing through their interaction with APP and ApoER-2. ApoER-2 has also been shown to be neuroprotective during ageing, and F-spondin was reported to protect against $A\beta$ toxicity. Other LDLR family members including LRP1, LRP1B and LR11/sorLA have also been shown to modulate APP processing. Furthermore, DNA variants have been identified in a gene on chromosome 10, encoding insulin degrading enzyme (IDE), a ~110 kDa thiol zinc-metalloendopeptidase shown earlier to degrade several peptides, including insulin, glucagon, atrial natriuretic peptide and TGF α . Interestingly, IDE-deficient mice exhibit increased levels of $A\beta$ in the brain, and transgenic overexpression of IDE results in reduced $A\beta$ burdens in brains of transgenic mice that develop $A\beta$ deposits. Finally, numerous studies during the last 10 years have reported the beneficial effect of the experimental model 'enriched environment' on AD neuropathology, including reductions in $A\beta$ levels and deposition and learning and memory (for review see¹¹), suggesting that genetic environmental factors play in concert to induce or prevent sporadic AD.

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Neurochemistry of Alzheimer's Disease

Paul T. Francis

King's College London, Wolfson Centre for Age-Related Diseases, UK

INTRODUCTION

Alzheimer's disease (AD) is characterized by gross and progressive impairments of cognitive function, which are often accompanied by behavioural disturbances such as aggression, depression, psychosis, apathy and wandering. Cell and synapse loss together with neuronal dysfunction affecting a number of neuronal systems are considered to result in the development of these typical symptoms of the disorder. In particular, non-cognitive behavioural symptoms are also considered to relate to structural and functional alterations in neurotransmission. Carers find behavioural disturbances difficult to cope with and the presence of such behaviours in AD patients often leads to the need for institutionalization¹. The challenge has been to identify changes in specific neurotransmitter systems that underlie cognitive impairment and particular behavioural problems and to develop rational therapeutic strategies.

NEUROCHEMICAL CHANGES IN ALZHEIMER'S DISEASE

The majority of biochemical studies of AD have relied on information derived from postmortem brain, which typically represents the late stage of the disease (8–10 years after onset of symptoms). In these studies there is considerable evidence of gross brain atrophy, histopathological features and multiple neurotransmitter abnormalities affecting many brain regions. However, investigations of biopsy tissue taken from AD patients 3–5 years (on average) after the onset of symptoms indicate that a selective neurotransmitter pathology occurs early in the course of the disease².

Acetylcholine

Changes affecting many aspects of the cholinergic system in patients with AD have been reported since the initial discovery of deficits in choline acetyltransferase activity in postmortem brains^{3–5}. In biopsy samples from AD patients, presynaptic markers of the cholinergic system were also uniformly reduced². Thus, choline acetyltransferase activity, choline uptake and acetylcholine synthesis are all reduced to 30–60% of control values. The clinical correlate of this cholinergic deficit in AD was, until recently, considered to be cognitive dysfunction. Such a conclusion was supported by clinicopathologi-

cal studies in AD and parallel experiments in non-human primates or rodents, which demonstrated disruptive effects of basal forebrain cholinergic lesions on cognitive functions. Furthermore, cholinergic deficits in AD occur to the greatest extent in cortical areas primarily concerned with memory and cognition – the hippocampus, adjacent temporal lobe regions and select frontal areas. Such studies led to the 'cholinergic hypothesis of geriatric memory dysfunction'⁶.

Neuropathologically, loss of neurons from the nucleus of Meynert (nbM; Ch4 cholinergic nucleus) is well documented in AD, although the extent of the loss reported varies from moderate to severe, and it has been suggested that in AD cholinergic dysfunction exceeds degeneration⁷. Detailed analysis of subpopulations of cholinergic perikarya in the nbM have been reported by Mesulam and Geula⁸, who identified selective cell loss in Ch4p (the posterior section projecting to temporal cortex). In the intermediate sector, Ch4id, which includes projections to the frontal cortex, neuron loss is not as extensive, consistent with the moderate loss of cholinergic enzyme activity.

On the basis of the above evidence, neocortical cholinergic innervation appears to be lost at an early stage of the disease and this is supported by a study in which the cholinergic deficit (reduced ChAT activity) has been related to Braak staging⁹. Braak stages I and II are considered to represent the earliest presentation of AD, with neurofibrillary tangles in the entorhinal cortex, and a 20–30% loss of ChAT activity was reported in brains from patients at these stages of AD¹⁰. However, another study using the Clinical Dementia Rating Scale (CDR) suggests that the greatest reduction in markers of the cholinergic system occurs between moderate (CDR 2.0) and severe (CDR 5.0) disease, with little change between non-demented and the mild stage (CDR 0–2)¹¹. Finally, tau and tangle pathology occurs in cholinergic neurons of the nbM during normal ageing and to a greater extent in patients with mild cognitive impairment (MCI), indicating functional changes in cholinergic neurotransmission¹².

There has been a recent shift of emphasis regarding the clinical significance of cholinergic deficits. Non-cognitive or neuropsychiatric, in addition to cognitive, symptoms also appear to have a cholinergic component¹³. For example, visual hallucinations relate to neocortical cholinergic deficits¹⁴, such deficits (e.g. loss of ChAT) being greater in dementia of Lewy bodies (DLB), where hallucinations are common, than in AD, where they are less common¹⁵. Reductions in cortical ChAT activity in patients with dementia, in addition to correlating with cognitive decline, are also related to overactivity and aggressive behaviour¹⁶.

Glutamate

Approximately 70% of cortical neurons use glutamate as a neurotransmitter and hence the glutamatergic system plays an important role in all regions of the cortex and hippocampus. Evidence for a pivotal role of glutamate in learning and memory is long-established²; indeed, it is likely that any function of a particular cortical region will depend on glutamate neurotransmission at some level. Loss of synapses and pyramidal cell perikarya (both considered to be markers of glutamatergic neurons) from the neocortex of AD patients correlate with measures of cognitive decline². From a biochemical perspective studying the glutamatergic system is more difficult since the amino acid is present at high concentrations in all cells. However, certain proteins related to glutamatergic neurotransmission provide vital clues to the status of this system in AD. For example, reduced glial glutamate uptake is reported in AD¹⁷, probably reflecting oxidative damage to the transporters^{18,19}. Additionally, there is loss of the vesicular glutamate transporter (VGluT) in several cortical regions^{20,21}. Such changes are likely to generate an elevated baseline level of glutamate at the synapse, triggering inappropriate Ca^{2+} influx. These raised background levels of glutamate impair the usual detection of physiological signals (low signal-to-noise ratio), disrupting normal cognitive processes²². Furthermore, the disruption of vesicular glutamate transport results in less glutamate being stored in presynaptic vesicles, reducing the level of signal upon neurotransmitter release²⁰.

In addition, soluble oligomers of beta amyloid ($\text{A}\beta$) can reduce glutamatergic transmission by inducing the internalization of NMDA receptors²³. This pathological effect has been shown to disrupt NMDA-induced receptor currents, inhibiting long-term potentiation (LTP – synaptic plasticity) and signalling to downstream targets such as Akt (also known as protein kinase B)^{23–25}.

Other Neurotransmitters

Using biopsy samples from AD patients, serotonergic and some noradrenergic markers are affected, whereas markers for dopamine, γ -aminobutyric acid (GABA) or somatostatin are not altered. When postmortem studies of AD brain are considered, many neurotransmitter systems, including GABA and somatostatin, are involved or are affected to a greater extent². Based on postmortem studies, however, changes in serotonergic neurotransmission may be linked to the behavioural disturbances of AD, such as depression, rather than cognitive dysfunction. For example, patients with AD who were also depressed had lower numbers of serotonin re-uptake sites in the neocortex than did patients without this symptom²⁶. Furthermore, both reduced serotonergic^{27,28} and increased noradrenergic activities and sensitivity^{29,30} have been linked to aggressive behaviour.

Neurotransmitter Receptors

Many neurotransmitter receptors appear to be unaltered in AD; however, studies have demonstrated a reduction in the number of nicotinic and muscarinic (M2) ACh receptors, most of which are considered to be located on presynaptic cholinergic terminals. Despite continuing, often unconfirmed, reports of changes in one or more of the muscarinic receptor subtypes (M–M5), it is generally agreed, on the basis of autopsy studies, that the M1 subtype is unchanged until later in the disease, when it may decline, probably in relation to cholinceptive (postsynaptic) neurodegeneration. The status of the

other subtypes is not clearly established, primarily due to the lack of specific pharmacological labels. Results using antibodies against the different receptor subtypes, while specific, are complicated by discrepancies between the distribution and density of immunoreactive proteins and localized functional receptors. With respect to muscarinic receptor coupling to G-proteins, most studies using a variety of investigative procedures have identified some degree of uncoupling, especially to the M1 receptor^{31,32} that correlated with cognitive decline.

A highly consistent receptor abnormality in AD is the loss of the nicotinic receptor^{33,34}, which appears to primarily reflect loss of the $\alpha 4$ -containing subtype (generally associated with $\beta 2$) as opposed to $\alpha 3$ or $\alpha 7$ subtypes³⁵. Immunohistochemically, loss of $\alpha 4$ and $\beta 2$ reactive fibres has been observed in temporal cortex, associated with reactive neuropil threads, tangles and plaques³⁶.

The density of 5-HT_{2A} receptors was reduced in AD patients compared to age-matched controls and this reduction also correlated with the rate of decline of Mini-Mental State Examination (MMSE) scores, suggesting that loss of neocortical 5-HT_{2A} receptors may predict for faster cognitive decline³⁷. By contrast, density of 5HT_{1A} receptors in frontal cortex was negatively correlated with cognitive decline³⁸, consistent with an inhibitory action of these receptors on cortical pyramidal function². It is interesting to note that in temporal cortex loss of 5-HT_{1A} receptors was associated with aggressive behaviour³⁹.

NEUROCHEMICAL BASIS FOR APPROACHES TO TREATMENT

Biochemical studies of postmortem brains from AD patients showing evidence of a substantial presynaptic cholinergic deficit, which correlated with cognitive impairment⁴⁰, together with the emerging role of ACh in learning and memory⁶, clearly suggested a rational approach to treatment. However, more recent studies have identified a role for the cholinergic system in attentional processing rather than simply memory.

A prediction of the cholinergic hypothesis is that drugs that potentiate central cholinergic function should improve cognition in AD patients. There are a number of approaches to the treatment of the cholinergic deficit; however, the use of acetylcholinesterase inhibitors is the most well developed approach to the treatment of AD to date⁴¹.

During the late 1980s and early 1990s, the first cholinomimetic compound, tacrine, underwent large-scale clinical studies and established clearly the benefits of cholinesterase inhibition treatment in patients with a diagnosis of probable AD. Tacrine was subsequently approved for use in some, but not all, countries. Statistically significant, dose-related improvements on objective performance-based tests of cognition, clinician- and caregiver-rated global evaluations of patient well-being and also quality of life measures have been reported⁴². Unfortunately, potentially serious adverse side effects have limited the use of this compound.

A so-called second generation of cholinesterase inhibitors has been developed, including donepezil, rivastigmine and galantamine⁴¹. Such compounds demonstrate a clinical effect and magnitude of benefit of at least that reported for tacrine, but with a more favourable clinical profile⁴³. Furthermore, evidence is emerging from clinical trials of cholinomimetics that such drugs may improve the abnormal non-cognitive, behavioural symptoms of AD⁴⁴. The cholinesterase inhibitors physostigmine, tacrine, rivastigmine and metrifonate have variously been reported in placebo-controlled trials

to decrease psychoses (hallucinations and delusions), agitation, apathy, anxiety, disinhibition, pacing and aberrant motor behaviour, and lack of cooperation in AD. The most recent studies indicate that cholinesterase inhibitors have the greatest effect on apathy and mood in AD, rather than agitation and aggressive behaviour^{45,46}.

Targeting the acknowledged glutamatergic deficit in AD has been more problematical since direct agonists would be expected to be toxic and there is no analogous enzyme (cf. cholinesterase) to inhibit. Indirect approaches such as AMPAKines, positive modulators of the AMPA glutamate receptor, have undergone clinical trials with mixed results^{47,48}. The only licensed treatment targeting this system is the NMDA glutamate receptor antagonist memantine. In clinical trials this drug has been shown to improve cognition and activities of daily living^{49,50} and some troublesome behaviours, in particular agitation and aggressive behaviour⁵¹. It is proposed that the cognitive benefits of this drug flow from improving 'signal-to-noise ratio' at NMDA receptors⁵² while the improvement in behaviour may be because of inhibition of the hyperphosphorylation of tau⁵³.

CONCLUSIONS

In AD many different pathological manifestations, such as cortical and subcortical β -amyloidosis (plaques), abnormal tau (tangles and dystrophic neurites), neuronal and synapse loss and various transmitter deficits, provide an increasingly complex framework for clinical-neuropathological correlations. Based upon detailed knowledge of the neurochemical changes that occur in AD, two main symptomatic treatments have emerged, cholinesterase inhibitors and memantine. These drugs provide some benefit to patients and in particular the improvements in behaviour are important to carers. Such therapy is all that is available at present and may well still be required as new therapies designed to slow disease progression come into the clinic.

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Antemortem Markers

Susan J. van Rensburg¹, Felix C.V. Potocnik², Maritha J. Kotze² and Dan J. Stein³

¹*Division of Chemical Pathology, National Health Laboratory Service, Cape Town, South Africa*

²*Faculty of Health Sciences, Stellenbosch University, Cape Town, South Africa*

³*Department of Psychiatry and Mental Health, University of Cape Town, South Africa*

INTRODUCTION

It has become increasingly clear that the disease process of Alzheimer's disease (AD) is multifaceted. Because AD appears to be a complex disorder involving several genes interacting with environmental influences, it is difficult to single out any one factor as the root cause of the disease. Apart from the familial forms of the disease, in which the gene mutations have been elucidated, many post-translational factors are involved in the process of neurodegeneration, in the formation of plaques and tangles and in the development of an inflammatory state of the brain. Although some of these have been found to be altered in AD patients compared with controls, very few markers suitable for antemortem diagnostic purposes have emerged, since many of the alterations are not specific for AD, while others pertain only to subsets of AD¹.

While it has been argued that the most powerful antemortem marker in AD is a clinical diagnosis based on an adequate range of observations², such diagnosis is at present largely one of exclusion. An ideal biological marker would allow for greater specificity and sensitivity than a clinical diagnosis on its own, and be readily obtainable. While neuropathological biopsy diagnosis of AD allows high specificity and sensitivity, it is typically only available postmortem.

The neurobiological alterations present in AD may be reflected in changes in cerebrospinal fluid (CSF) neurotransmitters or neurochemicals, or changes in systemic tissues including blood constituents. It should be borne in mind, however, that CSF measurements are influenced by a variety of factors, including CSF gradients, age, gender, diurnal and seasonal variations, state of the blood–brain barrier, blood contamination, contributions from the spinal cord, phase of illness, psychomotor activity, stress and diet. Measurement of blood constituents may also reflect concentration differences due to diurnal rhythms and other factors.

In this chapter on antemortem markers, we will briefly review neurotransmitters, neurochemistry and systemic pathology. We will also briefly address findings in brain imaging, and genomic and proteomic methods.

NEUROTRANSMITTERS AND NEUROCHEMISTRY

The Cholinergic System

Cholinesterase inhibitors (ChEIs) were introduced for the treatment of AD following the discovery that cholinergic neurons were depleted, and that cholinergic function was significantly decreased in the basal forebrain of AD patients³. Interestingly, the latter research group recently reported that ChEIs increased the phosphorylation of tau protein⁴, resulting in a possible decrease in long-term clinical responsiveness to ChEIs. The depletion of membrane choline may also play a role⁵. CSF markers of cholinergic function, as well as erythrocyte and plasma choline, have been studied as biomarkers for AD, but have not yielded consistent results⁶. Studies, however, indicate differences in the dynamics of RBC choline uptake, consistent with a vulnerability of cholinergic neurons in patients with AD⁷.

The Noradrenergic System

Autopsy studies of AD brains demonstrate that loss of cells in the locus coeruleus (LC), the major nucleus of origin of noradrenergic fibres, may undergo even greater degeneration than the nucleus basalis of Meynert⁸. This raises the question whether the degeneration of the noradrenergic system would provide markers for AD. Reduced noradrenaline (norepinephrine; NE) in autopsy samples of AD brains has been a fairly consistent finding, although it may be hypothesized that increased activity and turnover of the noradrenergic system may compensate for cell loss and that a limited number of NE cells remain highly active in AD patients. Loss of NE innervation would in addition lead to peripheral effects, such as decreased control of vasoconstriction⁸. Some patients with advanced AD have biochemical and physiological indices of noradrenergic hyperactivity, including higher heart rate and blood pressure. Severe neuronal loss in advanced AD may lead to a compensatory increase in LC firing rate, contributing to symptoms such as pacing, agitation, insomnia and weight loss. Haglund *et al.*⁸ developed a scale for the evaluation of LC degeneration in patients with AD, vascular dementia

and non-focal ischaemic deep white matter disease (WMD), as part of the ongoing Lund Longitudinal Dementia study. They found that LC degeneration was significantly higher in AD than in vascular dementia cases, and that there was a significant correlation with white matter pathology severity. However, there was no correlation between the degree of LC degeneration and duration of dementia or AD pathology⁸.

The Serotonergic System

Numerous autopsy studies of AD brains have suggested a serotonergic deficit. Although there have been reports that the major serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), is unchanged in the CSF of AD patients, most studies indicate a reduction in CSF 5-HIAA. In a study by Stuerenburg *et al.*, CSF 5-HIAA correlated with CSF A β 42, but not with CSF tau. There was also a significant positive correlation between CSF 5-HIAA and homovanillic acid (HVA) in AD, but neither 5-HIAA nor HVA could differentiate between mild cognitive impairment (MCI), depression and AD⁹.

Although CSF measures of monoamines have not proven sufficiently specific and sensitive for clinical diagnosis, the degree of pineal calcification (DOC) can be used as an intra-individual melatonin deficit marker¹⁰. Melatonin, the pineal hormone biosynthesized from serotonin, declines with age and more so in AD patients due to calcification of the pineal gland. Mahlberg *et al.*¹⁰ measured the DOC, as well as the size of uncalcified tissue, with computed tomography (CT) in 279 consecutive memory clinic outpatients. The DOC was significantly higher in AD than in patients with other types of dementia, depression or controls, while the size of uncalcified pineal tissue in AD patients was significantly smaller than in patients of the other three groups¹⁰.

Wu and Swaab found that pineal melatonin secretion and pineal clock gene oscillation were disrupted in AD patients, as well as in non-demented controls with early signs of AD neuropathology (neuropathological Braak stages I–II), in contrast to non-demented controls without AD neuropathology¹¹. Furthermore, a functional disruption of the suprachiasmatic nucleus (SCN) was observed from the earliest AD stages onwards, as shown by decreased vasopressin mRNA, a clock-controlled major output of the SCN.

Taken together, measures of neurotransmitter systems have not provided sufficient sensitivity and specificity to be used for diagnostic purposes in the clinic. Nevertheless, such work has been useful in investigating the pathophysiology of AD.

SYSTEMIC PATHOLOGY

It is possible to view AD as a systemic illness. Thus, if AD were a genetic disorder, then disturbances at the molecular level may be expressed in non-neural tissue, with systemic effects. Using blood cells for biomarkers has the added advantage of being relatively non-invasive, and techniques such as flow cytometry provide a convenient platform for such analyses. Uberti *et al.* found that the expression of a conformational mutant of p53 in mononuclear cells was significantly higher in AD patients compared to non-AD subjects. The expression of mutant p53 did not, however, correlate with the duration of illness or disease severity¹².

Zainaghi *et al.* found that an alteration of amyloid precursor protein (APP) fragments in platelets, as measured by Western blot analysis, correlated with cognitive decline in patients with AD¹³. Platelets contain more than 95% of circulating APP and enzymatically produce

both soluble APP and amyloid-beta peptides. It was found that the ratio of 130- to 110-kDa APP fragments in platelets from patients with AD was significantly lower compared to patients with mild cognitive impairment and elderly controls. There was no difference between the latter two groups. The alteration in APP also correlated with membrane fluidity of the platelets¹³.

Membrane fluidity of platelets as a biomarker for AD has been extensively studied. Increased fluidity was demonstrated in patients with AD compared to patients with vascular dementia and elderly controls. Only about 50% of AD patients, however, demonstrate this abnormality. Increased platelet membrane fluidity (PMF) appears to be a familial trait, and the subgroup of AD patients in whom it manifests suffers from an earlier onset and a more rapidly progressive decline. In a prospective longitudinal study evaluating PMF as a putative risk factor for AD, 9 of 330 people with increased PMF (initially asymptomatic first-degree relatives of probands with AD) developed AD after 7.5 years¹⁴. On a biochemical level, it was found that free radical induced lipid peroxidation increased the fluidity of platelet membranes, providing a possible mechanism underlying increased PMF¹⁵. This putative marker of AD would hence also be subject to modulation by environmental factors such as a diet rich in antioxidants.

In fibroblasts, abnormalities in enzymatic activity, glucose metabolism, abnormal calcium metabolism, impaired DNA repair as well as potassium channel dysfunction¹⁶ have been observed. While studies on blood cells and fibroblasts have advanced our understanding of the mechanisms relevant to AD, they are not sufficiently sensitive or specific for clinical use, once more raising the question of environmental influences.

Protein Abnormalities

The hallmark lesions of Alzheimer's disease are neurofibrillary tangles, which contain tau protein, and the plaques with deposition of β -amyloid (A β). Given that the clinical phase of AD may be preceded by a 15–30 year period of deposition of amyloid and tau protein, markers to predict the development of AD should ultimately be obtainable. Several studies have found increased levels of tau protein (total tau as well as phosphorylated tau) and decreased levels of A β (1–42) in CSF¹⁷, while the ratio of these two measures has been found to be a highly sensitive discriminator of AD from normal ageing. Maddalena *et al.* found that the ratio of CSF phospho-tau to A β 42 was significantly increased in patients with AD and provided high diagnostic accuracy in distinguishing patients with AD from healthy control subjects (sensitivity, 86%; specificity, 97%), subjects with non-AD dementias (sensitivity, 80%; specificity, 73%), and subjects with other neurological disorders (sensitivity, 80%; specificity, 89%)¹⁸.

Inflammation

Neuropathological findings in AD brains demonstrate an inflammatory response, including activated microglia. Several studies have measured concentrations of inflammatory markers such as C-reactive protein (CRP) and cytokines in the blood and CSF of AD patients. In the Framingham study, peripheral blood mononuclear cell (PBMC) cytokine production was related to the risk of incident AD. It was concluded that higher spontaneous production of IL-1 or TNF-alpha by PBMCs may be a marker for the future risk of AD in older

individuals. These data strengthen the evidence for a pathophysiological role of inflammation in the development of clinical AD¹⁹. Although these markers are too non-specific for AD diagnosis, drugs aimed at diminishing inflammation and the activity of microglia are currently still being investigated.

A range of other research areas in AD can conveniently be mentioned in this section. These include studies of visual system dysfunctions, olfactory deficits, extrapyramidal dysfunction, atypical dermatoglyphic patterns, altered sweat response, abnormal glucose tolerance and vitamin B12 deficiency. Such work, although interesting, has not yet led to a sensitive and specific antemortem marker.

Environmental Factors in Alzheimer's Disease

Although AD has been linked to a genetic aetiology, studies with monozygotic twins revealed variability in age at onset of as much as 9, 15 or 20 years²⁰. This led to the suspicion that some environmental factor(s) ingested from food and water, or a deficiency of some protective element, or increased oxidation status resulting from stress²¹ may accelerate disease expression in susceptible individuals. Several metals have been investigated in AD in the hope of finding a marker for the disease. Iron metabolism is altered and levels of the iron transport protein transferrin are decreased in the serum of AD patients. Previous reports of elevated levels of the iron binding protein p97 (melanotransferrin) in AD patients were not confirmed in a later study²². Blood mercury levels are significantly raised in AD patients²³ and zinc and copper are decreased in AD compared to controls. Decreased activity of the copper-containing protein ceruloplasmin may be linked to iron deposition in the brains of patients with AD²⁴. Although CSF diagnostic markers A β 42, tau and phospho-tau correlate with lower plasma copper and ceruloplasmin levels in AD patients, supplementation with copper has not improved cognition in AD²⁵, whereas in our experience supplementing AD patients with zinc improves cognition, especially if augmented by vitamins A and D²⁶.

Wu *et al.* investigated the effect of infantile exposure to lead on markers of AD-like pathology in monkeys, and found that epigenetic imprinting in early life influenced the expression of AD-related genes with the effect that a causative environmental marker could be undetectable by the time of disease expression²⁷. Indeed, to date environmental markers have insufficient sensitivity and specificity to serve as useful in the diagnosis of AD.

BRAIN IMAGING

There has been considerable interest in the use of brain imaging in the diagnosis of AD and follow-up during drug trials. Initial promising neuroimaging candidate markers obtained from CT scans and MRI have been confirmed and extended with new techniques, such as measuring hippocampal and entorhinal cortex volumes, basal forebrain nuclei, cortical thickness, deformation-based and voxel-based morphometry, as well as the use of diffusion tensor imaging tractography and functional MRI²⁸.

There are ongoing attempts to validate MR and PET imaging and other biomarkers for use in clinical trials to distinguish between elderly controls, subjects with mild cognitive impairment, and subjects with AD²⁹. C-11 Pittsburgh compound B (PIB) PET (amyloid imaging) represents a particularly promising avenue of exploration, potentially providing a direct window on the pathological processes that underlie AD. A combination of PET, MRI and mutation analysis

of APOE ϵ 4 has been found to be effective in determining grey matter volume and quantification of A β plaque load for patient inclusion and follow-up in anti-amyloid therapy trials³⁰. High-resolution PET also allows *in vivo* visualization of changes in amyloid after administration of Pittsburgh Compound-B, and microglial activation after administration of [18F]fluoroethyl-DAA1106³¹.

GENOMICS AND PROTEOMICS

Advances in genomic and proteomic methods raise the question of whether these may provide clinically useful antemortem markers. The greatest potential impact arguably lies in the detection of early stages of the disease, monitoring of AD progression, and assessment of response to existing and future active and preventative treatments.

Genomics has to date not been helpful in providing accurate diagnostic markers for AD. Structural genomic studies indicated that more than 200 genes may be involved in the pathogenesis of AD. Mutations in the *APP*, *PSEN1* and *PSEN2* genes directly associated with the amyloid cascade account for AD in much less than 5% of affected patients. The most consistent susceptibility factor for late-onset AD³², the ϵ 4 allele of the *APOE* gene, underlies dementia in 40% of Caucasian patients with late-onset disease; however, the APOE ϵ 4 allele does not (yet) influence dementia progression in sub-Saharan Africans³³. Could this indicate that effects of the environment on individuals may change their susceptibility to AD and the expression of genes involved with AD predisposition, causing divergent results when putative markers are compared in different populations? Notably, alcohol consumption increases the risk of dementia specifically in those individuals carrying the APOE ϵ 4 allele³⁴.

Another genetic marker, a genetic variant of transferrin, TfC2, has an increased allele frequency in AD in some populations^{35,36}, but not in others, such as a French population of the Bordeaux region³⁷. TfC2 is associated with diseases attributed to free radical damage, therefore it could be hypothesized that increased dietary intake of antioxidants in certain populations would be protective against the effects of the oxidative allele. The predominantly Mediterranean diet and red wine, which is consumed in the Bordeaux region of France, is known to be antioxidative. Robson *et al.* found that carriers of TfC2 and the C282Y allele of the haemochromatosis gene were at a five times greater risk of AD, while co-inheritance of APOE ϵ 4 conferred an even higher risk of AD in cases from the OPTIMA cohort in the UK³⁸. In the Bordeaux study, in contrast, such an effect was not observed.

While genomics may not at present provide a reliable diagnostic marker for AD, it is estimated that genetic variation accounts for between 20% and 95% of the variability in therapeutic response in AD patients. The pharmacogenetic response in AD depends on the interaction of genes involved in disease pathogenesis (such as APOE ϵ 4) and genes involved in drug metabolism (such as the cytochrome P450 [CYP] system). The CYP2D6 enzyme isoforms affect the metabolism of more than 20% of drugs used to treat CNS disorders, and gene variation may cause drug side effects. Of the four genotype-related metabolizer types defined by CYP2D6, the extensive and intermediate metabolizers are the best responders, while the ultra-rapid and poor metabolizers are the worst responders to pharmacologic treatments in AD.

Genetic markers not suitable for diagnostic purposes may therefore still be useful in providing knowledge of the disease process, for disease prognosis and to guide treatment, e.g. to detect responders to

treatment with ChEIs by testing for the *APOE* genotype. The incorporation of pharmacogenetic protocols into AD research and clinical practice potentially helps to optimize therapeutics by developing cost-effective pharmaceuticals and improving drug efficacy and safety.

Gene expression profiling with microarrays has also yielded some useful evaluations of pathomechanisms and systemic manifestations in AD, using blood mononuclear cell (BMC) transcriptomes of sporadic AD subjects and aged-matched controls. The AD BMCs exhibited a significant decline in the expression of genes concerned with cytoskeletal maintenance, cellular trafficking, cellular stress response, redox homeostasis, transcription and DNA repair, as well as those genes which may impact on $A\beta$ production and the processing of tau. The microarray results also revealed gender differences in the levels of altered gene expression³⁹.

Proteomic research has not fared better than genomics when it comes to providing markers for the diagnosis of AD. Several markers that were initially promising (such as complement factor H precursor and alpha-2-macroglobulin) did not provide the specificity and sensitivity required for biomarkers⁴⁰. In a European task force consensus document, it was also stated that no marker had been validated to reliably measure a change in response to therapy, not even the rate of change in hippocampal volume⁴¹. It was recommended that future trials should include assessment of biomarkers in order to advance our knowledge about their usefulness. Proteomics is an attractive technique for prospecting protein biomarkers, since it involves plasma proteins and peptides that are readily obtained.

Ravid has commented that although plasma could be a useful source of markers, it is also one of the most complex media to work with¹⁷. Dealing with sample-to-sample variations, variations among individuals, and separating 'noise' from a true signal require the processing of thousands of samples. Moreover, only 13% of peptides reproducibly change significantly with the changes in the patient's disease state. Some new technologies that are being used to deal with the complexities of the plasma proteome include a combination of mass spectrometry, affinity chromatography and liquid chromatography to produce unbiased identification and quantification of signature peptides. This author has confirmed that the gap between discovery and diagnostics is still wide. Some of the outstanding issues include finding ways to reduce the costs associated with the validation of biomarkers or proteomic platforms, demonstration of biomarkers' clinical significance, minimizing technical complexity, gaining regulatory approvals, and reaching pharmaceutical levels of reproducibility and sensitivity. He also emphasized the need for collaboration between different disciplines.

Zellner *et al.*, on a more optimistic note, have predicted that the constraints on proteomics will be overcome by developing more advanced technologies, including the design of AD-related protein panels, on which established markers such as tau and $A\beta_{42}$ will be used in combination with novel markers. Laser capture microdissection and fluorescence saturation labelling will overcome the limitations of homogeneous sample collection⁴².

CONCLUSION

It is clear that a number of difficulties face the researcher interested in finding an antemortem marker for AD. Many of the techniques used in this search have important limitations: for example, CSF measurements are influenced by a variety of factors; brain imaging findings often show group differences only; and genetic and proteomic studies reveal multiple small effects. Diagnosis of AD, even

at autopsy, may not always be definitive, leading to heterogeneity of patient samples. In addition, AD may be a heterogeneous disorder, certainly with different manifestations in the older age group. A marker may be present in a control with the AD trait who has not yet developed AD; and if a marker is related to the severity of AD, it may not distinguish between mild cases and controls. Other dementias may overlap with AD not only in phenomenology but also in pathogenesis, and therefore display similar markers. There are also mixed cases, where patients, for example, have both AD and vascular dementia. In addition, biomarkers are currently only of value when they form part of the clinical diagnostic work-up of the patient, emphasizing the expertise of the clinician and collaboration between disciplines.

Nevertheless, the work discussed here does suggest that some combination of measures may ultimately correlate strongly with biopsy diagnosis. Measures from molecular and genetic biology and brain imaging seem particularly promising and are consistent with our growing knowledge of neurochemistry and neuropathology. Genomic and proteomic advances have the potential to ultimately translate into clinically meaningful biomarkers and to result in advances in patient care.

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Pharmacological Therapies in Alzheimer's Disease

Martin Steinberg and Constantine G. Lyketsos

Johns Hopkins Bayview Medical Center, Baltimore, MD, USA

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that causes deterioration in cognition and functioning and is associated with a high frequency of neuropsychiatric co-morbidity. The emotional and financial costs of AD for patients and their caregivers are enormous. To date, no treatment is available to cure the disease or halt its progression, nor is any disease-modifying. Available symptomatic therapies, which include cholinesterase inhibitors and memantine, attenuate cognitive and functional decline and may also improve neuropsychiatric symptoms. This chapter will review the rationales for these therapies, summarize research pertaining to their cognitive, functional and neurobehavioural efficacy, and discuss current prescription and monitoring guidelines. Available evidence concerning the use of unapproved therapies such as vitamin supplementation and *Ginkgo biloba* will also be discussed.

RATIONALE FOR CHOLINERGIC THERAPIES

The deteriorations in cognition and function that occur in AD have been linked to the degeneration of numerous neuronal systems. Evidence is especially strong, however, for an association between these symptoms and the loss of cholinergic neurons. Therefore, increasing available levels of brain acetylcholine may be expected to attenuate decline in AD. Three approaches to increasing cholinergic transmission have been subject to research: increasing availability of the chemical precursors of acetylcholine (e.g. lecithin), enhancing cholinergic transmission by direct receptor stimulation, and inhibiting the breakdown of acetylcholine at its receptor site^{1,2}. Early studies involving the use of acetylcholine precursors were not encouraging. Lecithin, phosphatidylcholine and acetyl-L-carnitine were ineffective, with the former also causing significant body odour^{1,2}. While modest cognitive and behavioural benefits were demonstrated in trials of two cholinomimetic agents, milameline and xanomeline, the frequent occurrence of sweating, gastrointestinal symptoms and syncope limited their usefulness². While the first two strategies have to date been unsuccessful, both efficacy and safety have been established for cholinesterase inhibitors, which increase the availability of acetylcholine for neurotransmission by inhibiting the enzyme acetylcholinesterase. Four cholinesterase inhibitors are currently approved by the FDA for the treatment of AD. Three of these are discussed in detail below. The fourth, tacrine, is now rarely used due to both its complex titration schedule and risks of hepatotoxicity.

DONEPEZIL

Cognitive Benefits

A reversible acetylcholinesterase inhibitor, donepezil has been FDA-approved since 1997 for the treatment of mild to moderate Alzheimer's disease. In one double-blind, placebo-controlled study of 468 participants with mild to moderately severe Alzheimer's disease³, those in the donepezil group improved significantly compared to placebo on a 70-point cognitive battery. The improvement, however, was modest: 2.5 points in the 5 mg/d group and 3.1 in the 10 mg/d group. On the 30-point Mini-Mental State Examination (MMSE), this improvement was 1.0 and 1.3 points respectively. On a scale of global impression of function, 32% and 38% respectively in the donepezil group improved, compared to only 18% with placebo. Correlation was found between clinical improvement and the degree of red blood cell acetylcholinesterase inhibition. Comparable benefits were found in additional trials up to 24 weeks⁴. In an open-label extension trial of two 15–30 week studies⁵, benefits were observed to possibly persist for up to 2.8 years. Donepezil's benefits have been demonstrated in the nursing home setting⁶, and in one study⁷, treatment delayed nursing home placement by 18 months. A one-year, double-blind study⁸ found donepezil to be both cost effective and to reduce the time caregivers spent providing care by 400 hours annually. The sustained benefits of long-term treatment remain controversial, however. One study suggested no significant benefits compared to placebo persisting after three years⁹, while another study¹⁰ did demonstrate sustained benefits over three years, particularly in participants who began treatment immediately, as opposed to receiving placebo for the first year.

Donepezil's benefits have been found to extend to the severe stages of AD as well. In one six-month, placebo-controlled, double-blind study of participants with MMSE scores less than or equal to 10¹¹, those receiving donepezil performed better on measures of cognitive function and activities of daily living. In 2006, donepezil received FDA approval for the treatment of severe AD and is currently the only acetylcholinesterase inhibitor approved for treatment during all disease stages.

Side Effects

Donepezil's side-effects profile and those of the other marketed cholinesterase inhibitors are similar. Gastrointestinal symptoms

Table 52.1 Common and less common side effects of cholinesterase inhibitors and memantine

<i>Medication class</i>	<i>Common side effects</i>	<i>Less common side effects</i>
Cholinesterase inhibitors	Nausea Vomiting Diarrhoea	Anorexia Muscle cramps Insomnia Nightmares Bradycardia Syncope
Memantine	None	Dizziness Constipation Headaches

(e.g. nausea, loose stool) are most common and usually mild and transient, though in some cases these symptoms can be severe. Patients sometimes experience vivid nightmares; discussion of this with patients and caregivers is important as they may not automatically associate these unpleasant experiences with a medication side effect. Muscle cramps and diaphoresis may also occur. Due to its cholinergic properties, caution should be used in patients with pre-existing bradycardia. These cholinergic effects are the likely cause of the most serious side effect, syncope, which may occur in 1% of patients. Table 52.1 displays common and less common side effects for donepezil and other approved AD therapies.

Dosing

The starting dose of donepezil is 5 mg/d. The dose is usually increased to 10 mg/d after four weeks. Side effects are dose dependent and should be monitored. Some clinicians have found doses of 15 mg and 20 mg/d to be tolerated and to confer additional benefit; however, these doses have not been systematically studied and are unapproved. Table 52.2 displays typical dosing guidelines for donepezil and other approved AD therapies.

GALANTAMINE

Cognitive Benefits

Galantamine was FDA approved in 2001 for the treatment of mild to moderately severe AD. A reversible, competitive inhibitor of

acetylcholinesterase derived from the snowdrop variety of daffodils, galantamine is also an allosteric modulator of nicotinic acetylcholine receptors. Although nicotinic receptors may increase cholinergic transmission, any additional cognitive benefits specifically conferred by this mechanism remain theoretical. In one six-month, double-blind, placebo-controlled study¹² of 636 participants with mild to moderate AD, those treated with galantamine at doses of 24 mg/d and 32 mg/d scored 3.9 and 3.8 points higher on the 70-point ADAS-Cog scale than those in the placebo group. At the end of a 6-month, open-label extension with all participants receiving 24 mg/d, ADAS-Cog scores for those treated for the entire 12 months with 24 mg/d remained stable, with less benefit seen in those who started on 32 mg/d and then decreased to 24 mg/d, possibly due to a rebound effect. Although the six-month, double-blind phase showed no benefit on the Disability Assessment for Dementia (DAD) measurement of activities of daily living (ADLs), at the end of the open-label extension, ADL scores for participants receiving galantamine remained at pre-treatment baseline. A later double-blind, placebo-controlled study of 653 participants demonstrated the benefit of galantamine on DAD scores¹³. In a 36-month, open-label trial of galantamine¹⁴, the 194 participants with mild to moderate AD were assessed as experiencing 50% less cognitive decline than would be expected without treatment. An extended-release form of galantamine was FDA approved in late 2004, and has been shown to have similar bioavailability to the immediate-release galantamine. The benefits of galantamine in severe AD are less certain than is the case for donepezil. In a recent placebo-controlled, double-blind study of 407 participants with severe AD, those treated with galantamine demonstrated improvement in cognitive function, but not in activities of daily living. Galantamine remains approved for treatment of mild to moderate AD only. Galantamine is also currently the only acetylcholinesterase inhibitor available in generic form.

Dosing

The starting dose for immediate-release galantamine is 4 mg twice daily. This is increased after one month to 8 mg twice daily. Depending on response, patients can remain at this dose, or increase to 12 mg twice daily after one month. Extended-release galantamine is begun at 8 mg/d and is increased to 16 mg/d after one month, with the option after at least one month to increase to 24 mg/d. Galantamine should be taken with food to reduce gastrointestinal side effects.

Side Effects

The side effects of galantamine are essentially identical to those of donepezil (see above). Gastrointestinal side effects may be slightly more frequent with galantamine than donepezil. For many patients, however, the cost savings due to its availability in generic form may offset this minor disadvantage.

RIVASTIGMINE

Rivastigmine was approved in 2000 and, unlike donepezil and galantamine, is a reversible inhibitor of both acetylcholinesterase and butyrylcholinesterase. Although research suggests that butyrylcholinesterase plays a role in acetylcholine breakdown in AD, as is the case for the allosteric nicotinic properties of galantamine, the clinical significance of this additional mechanism of action remains

Table 52.2 Starting and optimal treatment doses for cholinesterase inhibitors and memantine

<i>Medication</i>	<i>Starting dose</i>	<i>Optimal dose</i>
Donepezil	5 mg daily	10 mg daily
Galantamine	4 mg bid immediate release 8 mg daily extended release	12 mg bid immediate release 24 mg daily extended release
Rivastigmine	1.5 mg bid immediate release 4.6 mg/24 hours for patch	6 mg bid immediate release 9.5 mg/24 hours for patch
Memantine	5 mg daily	10 mg bid

unclear. Like galantamine, rivastigmine is currently approved for the treatment of mild to moderate AD. In a placebo-controlled, double-blind study of 725 participants with mild to moderate AD¹⁵, the treatment group was randomized to either 1–4 mg/d or 6–12 mg/d, and more participants in the 6–12 mg/d group improved by ≥ 4 points on the ADAS-Cog; improvement compared to the other groups was also seen in a scale of progressive deterioration. Nearly a quarter of participants discontinued the higher dose treatment due to side effects, however, mostly gastrointestinal. In a study demonstrating similar clinical outcomes¹⁶, only 55% tolerated the 12 mg/d dose. In a 26-week, open-label extension of a 26-week, double-blind study of rivastigmine at 6–12 mg/d¹⁷, participants treated with rivastigmine for the entire 52-week study duration had improved cognition compared to those initially receiving placebo. Open-label data suggest benefit for rivastigmine over even longer durations. Using a baseline-dependent mathematical model, Small *et al.*¹⁸ demonstrated that patients treated with rivastigmine for up to five years experienced less decline on the MMSE than would be expected in a modelled untreated group.

Since 2007, a rivastigmine 24-hour transdermal patch has also been approved by the FDA for the treatment of mild to moderate AD. The efficacy of the transdermal patch appears to be similar to that of 12 mg/d oral rivastigmine, with three-fold fewer gastrointestinal side effects¹⁹.

Side Effects

While oral rivastigmine has been associated with a high occurrence of gastrointestinal side effects, with the 24-hour transdermal patch, these side effects now appear comparable to those of donepezil and galantamine. Side effects otherwise are similar to donepezil (see above) and galantamine. Rare cases of oesophageal rupture have been reported, and restarting rivastigmine at higher than the minimum dose after several weeks or more off from the medication may place patients at increased risk for this. Oral rivastigmine should be taken with food.

Dosing

Oral rivastigmine is usually begun at 1.5 mg twice daily. At minimum two-week intervals, the dose is gradually increased in 1.5 mg twice-daily increments up to a maximum dose of 6 mg twice daily. Increasing the dose titration intervals from two weeks to four weeks may decrease side effects, and rivastigmine should be taken with food². The rivastigmine 24-hour transdermal patch is started at 4.6 mg/24 hours, and after one month can be increased to 9.5 mg/24 hours. Switching from oral rivastigmine to transdermal patch typically does not require delay, and most patients taking 9–12 mg of oral rivastigmine daily can immediately switch to the 9.5 mg/24 hours patch².

COMPARATIVE EFFICACY AND TOLERABILITY

Several studies have compared the efficacy and tolerability of cholinesterase inhibitors in the treatment of AD. In one 12-week, open-label study of donepezil and oral rivastigmine in the treatment of mild to moderate AD²⁰, similar improvements were noted in both groups on the ADAS-Cog. Tolerability favoured donepezil. Only 47% of the rivastigmine group remained on the maximum dose (6 mg twice daily), compared to 88% for donepezil (at 10 mg/d). The

rivastigmine group was also twice as likely to discontinue treatment due to side effects (22% vs. 11%). Another study compared donepezil to oral rivastigmine in 994 participants with moderate to moderately severe AD over a two-year period²¹ and found that while cognitive benefits were similar, the rivastigmine group performed better in activities of living and daily functioning, though only in the intention-to-treat population. Although adverse events, especially gastrointestinal, were more frequent with rivastigmine during the titration phase, no difference was evident in the maintenance phase, and serious adverse events were nearly identical at 32%.

In a 52-week comparison of donepezil and galantamine in 182 AD participants²², galantamine treatment trended to fewer declines in MMSE score and, in the subgroup of participants with MMSE scores between 12 and 18, fewer declines on the ADAS-Cog. Although no difference was found in performance of activities of daily living, caregivers from the galantamine group reported larger reductions in burden. In contrast, a recent meta-analysis of comparison trials among acetylcholinesterase inhibitors found that, while cognitive profiles among the three were similar, the relative risk of global response favoured donepezil and rivastigmine over galantamine (relative risks 1.63 and 1.42 respectively). Adverse events were lowest for donepezil and highest for rivastigmine, although with the introduction of the rivastigmine transdermal patch, which has improved tolerability, this difference may be less relevant. In interpreting the above inconsistent research, clinicians would be wise to consider Farlow and Boustani's² observation that the companies sponsoring comparison trials often have conflicts of interest, and the results 'must be judged with caution'.

SWITCHING ACETYLCHOLINESTERASE INHIBITORS

Given the similar mechanisms of action among acetylcholinesterase inhibitors, it might be anticipated that patients failing to benefit from one of these agents would be unlikely to benefit from switching to another. Research, however, has suggested that non-responders may benefit from such a medication change. Most studies have focused on a switch from donepezil or galantamine to rivastigmine and have been open label, which limits interpretation of results. In one recent study²³, 270 participants with mild to moderate AD who had not adequately responded to donepezil were immediately switched to rivastigmine and followed for 26 weeks. Seventy percent of these donepezil non-responders either improved or showed no deterioration in global functioning, although only 69% completed the trial and 54% experienced at least one adverse event, mostly gastrointestinal. One hundred and forty six of these participants entered a 26-week, open-label extension¹⁶ in which rivastigmine was generally well tolerated, and 80% completed the trial. Similar results have been found in other studies of non-responders who switch from donepezil or galantamine to rivastigmine²⁴. Unfortunately, no published research has evaluated switching from another acetylcholinesterase inhibitor to donepezil or galantamine; nor has any study evaluated the benefits of a medication change for rivastigmine non-responders.

PRESCRIBING AND MONITORING ACETYLCHOLINESTERASE INHIBITORS

When to Begin

All acetylcholinesterase inhibitors are approved for the treatment of mild AD. Some research points to the benefits of starting treatment as early as possible after the diagnosis is made; in several

clinical trials, participants who began on placebo and switched to a cholinesterase inhibitor were never able to 'catch up' to study peers who received treatment all along²⁵. In patients who do not yet meet criteria for dementia but are diagnosed with mild cognitive impairment (MCI), evidence does not support the use of cholinesterase inhibitors. Potential benefits have been described as 'minor, short-lived and associated with significant side effects'²⁶. If a clinician chooses to begin a cholinesterase inhibitor in an MCI patient (e.g. at the patient's request), disclosure to the patient about the limited known benefits as well as side-effect risks is essential.

Which Cholinesterase Inhibitor to Choose

As reviewed above, limited comparison data are available and research suggests that the three medications are roughly equivalent in efficacy. Most clinicians decide which drug to use based on side-effect profile and patient convenience. For a patient vulnerable to gastrointestinal upset, for example, donepezil may be preferable as gastrointestinal symptoms are likely mildest. If cost is a concern, galantamine is currently the only cholinesterase inhibitor available as a generic. The rivastigmine 24-hour transdermal patch might be an appropriate choice for patients who do not wish to or have difficulty taking oral medication. Because oral rivastigmine is associated with frequent gastrointestinal symptoms and confers no benefit over the patch, it is now uncommonly prescribed.

How Long to Continue Treatment

Guidance in this regard is limited. Most studies demonstrating benefit after six months of treatment have been open label; instead of placebo-controlled, participant outcomes are compared against the expected outcomes of a theoretical untreated cohort. Many clinicians, including the authors, recommend a trial of at least six months, with use of at least one and preferably several outcome measures (e.g. MMSE, opinion of caregivers)¹. If no clear improvement or stabilization is evident after six months, a trial off the medication should be strongly considered, with close observation for decline and a plan to reinstate treatment if such occurs. Reinitiation should occur promptly, as some research suggests that after a washout of more than several weeks, patients may not regain full treatment benefits after restarting the drug²⁷. If no difference is seen off the medication, consideration should be given to switching to another cholinesterase inhibitor. As reviewed above, most available evidence supports the benefit of switching to rivastigmine from another cholinesterase that has not provided benefit.

MEMANTINE

Rationale

Glutamate excitotoxicity may play an important role in the death of neurons in AD. It is hypothesized that injured glutamate-producing neurons release excessive amounts of glutamate, resulting in injury and death to downstream neurons. This likely occurs via glutamate's activation of calcium channels, leading to influx of calcium into downstream neurons. Memantine, a non-competitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor of glutamate, is believed to protect these neurons by preventing the glutamate-mediated cascade of neuronal damage.

Cognitive Benefits

Memantine has been FDA approved since 2003 for the treatment of moderate to severe Alzheimer's disease. In one 28-week, placebo-controlled, double-blind trial of memantine at 20 mg/d in 252 participants with moderate to severe AD²⁸, participants treated with memantine had improved outcomes compared to placebo on measurements of global assessment of change, activities of daily living and cognitive functioning. Another placebo-controlled, 12-week study in participants with moderately severe dementia (either AD or vascular dementia) found memantine use to be associated with a significant decrease in care dependence²⁹. A 24-week, open-label extension of the above-mentioned 28-week study³⁰ demonstrated benefits both in participants who remained on memantine for the entire study duration and those who switched from memantine to placebo. One study suggests that the addition of memantine to donepezil may confer additional advantages in cognition, activities of daily living, global outcome and behaviour³¹. A more recent study suggests that addition of memantine to a cholinesterase inhibitor delays time to nursing home admission³². A third study of memantine addition to a cholinesterase inhibitor, however, found no benefit over placebo³³. Although some evidence suggests benefits in mild AD, memantine is not FDA approved for this purpose.

Side Effects

Memantine is well tolerated by most patients and side effects are uncommon. These can include dizziness, constipation and headaches. The presence of severe renal impairment is a contraindication, and the dose should be reduced in the presence of moderate renal insufficiency.

Dosing

Memantine is started at 5 mg/d and the dose is increased by 5 mg/d weekly until a total dose of 20 mg/d is reached, typically using a commercially available 'titration starter pack'. After initial titration, memantine is administered in a divided dose of 10 mg twice daily.

Prescribing and Monitoring Memantine

A memantine trial should be considered in patients with moderate to severe AD who are able to tolerate such. Memantine can be prescribed in combination with a cholinesterase inhibitor which, as indicated above, may confer additional advantages. Negligible guidance exists as to how long to continue a memantine trial. Most clinicians, including the authors, recommend re-evaluating use every six months, as with the cholinesterase inhibitors. Because cognitive measures (i.e. MMSE) are less useful in advanced dementia, increased emphasis should be placed on the report of caregivers, including professional providers in the assisted living and nursing home setting.

NEUROPSYCHIATRIC EFFECTS OF CHOLINESTERASE INHIBITORS AND MEMANTINE

Neuropsychiatric symptoms (e.g. apathy, agitation, delusions) are nearly universal in patients with Alzheimer's disease, with over 90% experiencing at least one such symptom over the illness course. While these symptoms are often distressing to patients

and caregivers, conventional treatments such as antipsychotics, antidepressants and mood stabilizers are often inadequately effective or cause significant side effects. Studies reporting positive neurobehavioural effects of cholinesterase inhibitors and memantine are therefore of particular interest. In a study by Holmes *et al.*³⁴, 134 participants with mild to moderate AD and significant neuropsychiatric co-morbidity (defined as a neuropsychiatric inventory (NPI) score >11) were randomized to donepezil or placebo for 12 weeks (following a 12-week, open-label donepezil trial). At the end of 12 weeks, NPI scores were 6.2 points lower in the donepezil group compared to placebo. Similar improvement has been demonstrated in trials of galantamine³⁵ and rivastigmine³⁶. Another 12-week study of 272 AD patients with significant agitation³⁷, however, showed no benefit with donepezil treatment compared to placebo. In studies showing positive benefits of donepezil, apathy and mood symptoms appear most likely to respond. The addition of memantine to a cholinesterase inhibitor may confer additional benefit. In a 24-week, placebo-controlled, double-blind study of 404 participants with moderate to severe AD³⁸, those treated with memantine and donepezil demonstrated improvement on the NPI compared to those treated with donepezil alone. Memantine's benefits were most pronounced on agitation, eating behaviour and irritability.

Despite the above encouraging findings, cholinesterase inhibitors and memantine currently have at best a limited role in the treatment of neuropsychiatric symptoms in AD. Although most clinical trials report positive treatment effects, these effects are typically modest. Heterogeneity among studies also exists regarding which symptoms are most likely to respond³⁸, making decisions to target a specific neuropsychiatric symptom with an antidementia drug difficult. Another factor limiting the applicability of these findings to clinical care is that, in most published studies, improvement of neuropsychiatric symptoms was a secondary outcome. A review by Cummings *et al.*³⁹ notes that of 13 placebo-controlled, double-blind trials, only 4 included behavioural change as a primary outcome. For these reasons, the authors do not recommend cholinesterase inhibitors as first-line treatment for any neuropsychiatric symptom causing severe distress. However, in situations where symptoms are mild to moderate in severity and an immediate intervention is not required, a trial of a cholinesterase inhibitor or memantine is a reasonable first step before resorting to pharmacotherapy (e.g. antipsychotics, mood stabilizers) that carries higher side-effect risks. An antidementia drug trial may be particularly appropriate for apathy and irritability both because studies suggest that these symptoms may be most responsive and because alternative effective pharmacotherapy options are especially limited.

ALTERNATIVE THERAPIES FOR ALZHEIMER'S DISEASE

The cholinesterase inhibitors and memantine are currently the only FDA-approved treatments for AD. Various unapproved alternative treatments which have been proposed include vitamin B12, folic acid, vitamin E, *Ginkgo biloba* and serotonergic augmentation with serotonin-specific re-uptake blockers (SSRIs). None of these treatments are supported by sufficient evidence to be recommended by clinicians. Patients and caregivers often inquire about these, however, and they are reviewed below.

Vitamin B12 and Folate

Elevated homocysteine levels have been linked to Alzheimer's disease, and studies have demonstrated an association between

high levels of homocysteine and cognitive dysfunction even in the non-demented elderly. Because vitamin B12 and folate are linked to reduction in homocysteine levels, they have been proposed as treatments for AD. Unfortunately, trials to date do not support clinical benefit. A recent double-blind trial of 409 participants with mild to moderate AD randomized to placebo or high-dose vitamin supplementation (folate, B6 and B12)⁴⁰ demonstrated that, although vitamin supplementation was associated with decreased homocysteine levels, no clinical improvements were evident. This is consistent with prior studies showing no cognitive benefit from folic acid supplementation with or without vitamin B12⁴¹. Vitamin supplementation in the above study was also associated with an increase in depression reaching marginal significance. Thus, vitamin B12 or folate cannot be recommended as treatments for AD.

Ginkgo Biloba

Oxidative stress has been linked to the neuropathological changes in AD, and *Ginkgo biloba* has been proposed as a putative therapy due to its antioxidant properties; recent evidence suggests some anti-amyloid aggregation effects as well. Despite these theoretical rationales, clinical benefits are unclear. One placebo-controlled, double-blind study of 513 participants with mild to moderate AD⁴² found no difference between placebo and treatment groups. However, the authors note that this study may have been compromised by the negligible decline observed in the placebo group. Also, participants with neuropsychiatric symptoms did appear to benefit cognitively compared to placebo. A recent Cochrane review⁴³ of 36 trials describes the evidence for ginkgo as 'inconsistent and unreliable'. Ginkgo is generally well tolerated, but carries a small risk of intracranial bleeding. The authors do not recommend use of ginkgo to treat AD, but would not strongly discourage patients who wish to take it¹.

Vitamin E

Similar to *Ginkgo biloba*, vitamin E has antioxidant properties hypothesized to be of benefit in treating AD. One placebo-controlled, double-blind trial suggested that high-dose vitamin E (2000 international units daily) may slow functional decline in moderate AD⁴⁴. These findings have been considered controversial because clinical significance was found only after adjustment for higher MMSE score in the placebo group. More recent findings have suggested that high-dose vitamin E may be associated with a small increased mortality risk in the elderly. The authors therefore do not recommend vitamin E supplementation in AD, but would not discourage patients wishing to start vitamin E in doses of 1000 international units daily or less.

SSRI Augmentation

Although acetylcholine is the neurotransmitter most highly linked to the cognitive deficits of AD, other neurotransmitters are presumed to play important roles as well. Despite uncertainty about the relationship between serotonin and cognition in AD, some clinicians have observed a modest increase in functional performance in patients treated with SSRIs². In a study by Mowla of 122 participants with mild to moderate AD⁴⁵, cognition improved equally whether subjects were treated with rivastigmine or rivastigmine plus fluoxetine. However, those treated with the combination therapy performed better in activities of daily living and global functioning.

Some of the functional improvement clinicians report with SSRI treatment may actually reflect improvement in underlying depression; Lyketsos *et al.*⁴⁶, for example, found functional decline to be attenuated in depressed AD participants who responded to antidepressant therapy.

FUTURE THERAPIES FOR AD

To date, only symptomatic pharmacotherapies are available for the treatment of AD. Despite the consistently demonstrated efficacy of these medications, their benefit remains frustratingly modest in degree. Current research focuses on the development of novel therapeutic strategies which are disease modifying. Although the pathological mechanisms leading to neuronal loss in AD remain only partially understood, abnormal amyloid processing appears to be a crucial early step. When amyloid precursor protein (APP), which is normally cleaved by alpha secretase, is instead cleaved by beta and then gamma secretase, insoluble extracellular amyloid plaques occur. These plaques have been implicated in neuronal death. Some treatments under development therefore aim to either inhibit beta or gamma secretase, or to enhance alpha secretase activity. Other proposed treatments target the aggregation of amyloid into plaques. Neprolysin, an amyloid-degrading enzyme, is one such target under study. Immunotherapies have also been designed with the intent to clear abnormally processed amyloid from the brain. Although an early clinical trial of an active amyloid-beta vaccine was discontinued after several participants developed meningoencephalitis, modified versions of this vaccine believed less likely to have this adverse effect have since been developed and are being tested.

Neurofibrillary tangles of phosphorylated tau protein are another hallmark AD pathology. These tangles are hypothesized to cause neuronal death by interfering with microtubule function. Proposed therapies to promote microtubule stability include tau kinase inhibitors and the anticancer compound paclitaxel. Although still in early development, viral vectors to deliver genes to modify AD neuropathology are another hopeful area of research.

The results of recent clinical trials for novel AD therapies have unfortunately been discouraging. The failure to demonstrate benefit may at least in part reflect that some AD therapies will work best in certain 'subtypes' of the disease, in certain stages of severity, or in individuals with specific characteristics (e.g. gender, apolipoprotein E status). Increasing attention has therefore focused on biomarkers, which may differentiate which patients are most likely to benefit from different therapies. Such biomarkers may also assist in determining drug response in pre-symptomatic patients, serve as outcome measures in clinical trials of symptomatic patients, and aid in determining whether further development of a treatment is warranted⁴⁷.

CONCLUSION

Although a cure for AD remains elusive, available symptomatic therapies may slow cognitive and functional decline, delay the need for a higher level of care and decrease caregiver burden. Donepezil is currently approved for the treatment of all AD stages, galantamine and rivastigmine for mild to moderate AD, and memantine for moderate to severe. These medications are typically well tolerated. Severe side effects are more common with cholinesterase inhibitors and are mostly gastrointestinal in nature. Although none of the available pharmacological treatments can presently be recommended as

a first-line therapy for any neuropsychiatric symptom, some patients may experience behavioural benefits, especially in regards to mood and apathy. Negligible evidence exists for vitamin supplementation, *Ginkgo biloba* or SSRI augmentation as treatments for AD. When a patient or caregiver inquires about beginning an unapproved therapy, a careful discussion of the available evidence and potential risks is warranted. Current research focuses on the development of treatments which are disease-modifying. The investigation of valid biomarkers for AD may be pivotal in determining which treatments are most promising, and in which subgroups of AD patients they are most likely to be effective.

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Behavioural Management in Alzheimer's Disease – Pharmacology

David A. Merrill and David L. Sultzer

Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA and VA Greater Los Angeles Healthcare System,

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INTRODUCTION

Behavioural symptoms are common in patients with Alzheimer's disease (AD) and contribute substantially to morbidity^{1–3}. As many as 80% of Alzheimer's patients develop behavioural changes, typically with increasing frequency as the disease progresses⁴. Estimates range from between 30–50% for delusions or hallucinations and up to 70% for agitated or aggressive behaviors⁵. Behavioural symptoms have long been known to contribute to caregiver distress^{5,6}. More recent work has found that 46% of caregivers cite dementia-related behaviours as a primary reason for institutionalization⁷. Behavioural symptoms in patients with AD significantly increase direct costs of care, a cost which may be lessened by appropriate psychopharmacological management^{8,9}. In this chapter, descriptions of the most common behavioural disturbances observed in AD and other dementias are provided, followed by examples of common measurement tools used in research to study these symptoms. The currently available pharmacological options for treating the behavioural symptoms of dementia are then reviewed, highlighting areas in which data can help guide targeted treatment of specific symptoms. This chapter concludes with a discussion of general treatment principles, intended to aid clinicians in an era when there are not clearly benign and beneficial treatment options available to address the ongoing severe and complex behavioural symptoms of dementia¹⁰.

The psychosis of AD typically consists of delusions, misidentification syndromes and, less frequently, visual or auditory hallucinations^{3,11}. Delusions of dementia tend to be simple, non-bizarre and often reflective of misinterpretation of the environment. The delusion of stealing is most prevalent, followed by persecutory delusions, delusions of reference, infidelity, grandiosity and somatic delusions¹². Delusions are more common in moderate stages of the illness and are associated with greater cognitive impairment. Likewise, hallucinations are rare in the early stages of AD and become more common in the later stages¹³. The most common misidentification syndromes include failure to recognize one's home ('this is not my home' phenomenon), the belief that strangers are living in the home (phantom boarder syndrome) and imposter loved ones (Capgras phenomenon)¹⁴. Psychosis in AD clearly represents a syndrome distinct from schizophrenia in elderly patients, with only

rare presence of first-rank Schneiderian symptoms and a higher rate of eventual remission of psychosis. In contrast to treatment of older adults with schizophrenia, antipsychotic treatment of psychosis in AD, described in detail below, is characterized by lower doses of medication, shorter duration of treatment and greater vulnerability to extrapyramidal symptoms (EPS).

Agitation in dementia has been defined as inappropriate verbal, vocal or motor behaviours not judged by an outside observer to result directly from the needs or confusion of the agitated individual. Increasing agitation is associated with advanced dementia, pre-morbid aggression and rapid decline. AD patients often also develop depression and anxiety, which in general are managed with antidepressant medications. While these topics will not be addressed in depth during this chapter, it is important to note that, similar to the contrast between schizophrenia and the psychosis of AD, substantial differences exist between primary mood and anxiety disorders versus dementia-related psychological symptoms in terms of aetiology, manifestations and treatment response.

Several standard neuropsychiatric symptom rating scales are used, primarily in research settings, to categorize the common behavioural and psychological symptoms in dementia (BPSD) (Table 53.1). Four of the most widely used general rating instruments include the Neuropsychiatric Inventory (NPI), the Brief Psychiatric Rating Scale (BPRS), the Neurobehavioral Rating Scale (NBRS) and the Cohen–Mansfield Agitation Inventory (CMAI). The NPI measures the frequency and severity of 12 psychiatric symptoms on the basis of caregiver report¹⁵. The items are delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, sleep disturbance, and appetite and eating disorder. The BPRS measures the severity of 18 psychiatric and behavioural symptoms, typically scored by a trained clinician after a semi-structured patient interview and collection of additional information from caregivers¹⁶. The NBRS has 28 items, covering areas including agitation (aggression, agitation, hostility) and psychosis (suspiciousness, hallucinations, delusions) and is completed by an observer on a 7-point scale¹⁷. The CMAI rates the frequency of 29 agitated behaviours in four factors on 7-point scales¹⁸.

Table 53.1 Neuropsychiatric symptom rating scales

Agitated Behavior Inventory for Dementia (ABID)
Agitation-Calmness Evaluation Scale (ACES)
Alzheimer Disease Assessment Scale, non-cognitive portion (ADAS-noncog)
Bech-Rafaelsen Mania Scale (BRMS)
Behavior Observation Scale for Intramural Psychogeriatric Patients (GIP)
Behavior Rating Scale for Dementia (BRSD)
Behavioral Pathology in Alzheimer Disease Rating Scale (BEHAVE-AD)
Brief Psychiatric Rating Scale (BPRS)
Caregiver Burden Questionnaire (CBQ)
Clinical Global Impression of Change (CGIC)
Clinical Global Impression Scale (CGIS)
Clinicians Interview Based Impression of Change plus caregiver input (CIBIC-plus)
Cohen-Mansfield Agitation Inventory (CMAI)
Hamilton Rating Scale for Depression (HAM-D)
Iowa Caregiver Stress Inventory (CSI)
Neurobehavioral Rating Scale (NBRS)
Neuropsychiatric Inventory (NPI)
Neuropsychiatric Inventory-Nursing Home version (NPI-NH)
Neuropsychiatric Inventory minus 5 'mood' items (NPI-NM)
Overt Aggression Scale (OAS)
Positive and Negative Syndrome Scale-Excited Component (PANSS-EC)
Revised Memory and Behavior Problem Checklist (RMBPC)
Screen for Caregiver Burden (SCB)
Social Dysfunction and Aggression Scale (SDAS-9)

When approaching behavioural disturbances in dementia, the overall preferred approach to management includes: (i) assessing to characterize the specific psychiatric or behavioural symptoms; (ii) developing an appropriate set of nonpharmacological behavioural interventions; and (iii) considering medication treatment if there are immediate safety concerns or insufficient response to behavioural interventions. To date, there are no FDA-approved medications for behavioural management of AD. The largest amount of available evidence studying psychosis and/or agitation associated with dementia suggests a modest efficacy of antipsychotic medications in symptom reduction, in the context of these medications now carrying a 'black box' warning regarding use in elderly patients with dementia. What follows is a review of the options available for pharmacological management of behavioural symptoms of dementia. See Tables 53.2 and 53.3 for dosing and side-effect information for agents discussed below.

Table 53.2 Dosage and adverse effects of atypical antipsychotics in dementia

Medication	Initial dose (mg/day)	Usual dosage range (mg/day)	Sedation	Hypo-tension	Anti-cholinergic	EPS	Weight gain
Risperidone	0.5	0.5–2	++	++	+/-	+	++
Olanzapine	2.5–5	5–10	+++	++	+	+	+++
Quetiapine	25	25–250	++	++	+/-	–	++
Aripiprazole	5	5–15	+	+	+/-	–	+/-

ANTIPSYCHOTIC MEDICATIONS

Efficacy Trials

The majority of data examining the psychopharmacological management of behavioural symptoms in dementia exist for the use of antipsychotic medications. Historically, short-term (6–12 week), double-blind, placebo-controlled, randomized controlled trials (RCTs) were completed using standardized neuropsychiatric symptom rating scales. These trials have been reviewed in depth in prior publications; here, the reader is referred to Table 53.4 for a summary of published trial results.

In total, efficacy trials of antipsychotic medications have demonstrated a modest benefit for treatment of agitated behaviour and psychosis in AD and other dementias. However, there is heterogeneity of these findings, with multiple studies also showing no benefit of antipsychotic treatment on primary or secondary outcome measures. Efficacy trials in this arena have typically had high placebo response rates, underscoring the likely importance of several general effects, including the passage of time, increased attention and the expectation of therapeutic intervention. Medication benefit has further been counteracted by adverse events.

As discussed in more detail at the end of this chapter, the decision to use medication and antipsychotic medications in particular should be made in parallel to the process of ongoing optimization of the social and environmental setting of each patient. Concerning results from meta-analyses and a recent large effectiveness trial underscore the importance of completing a thorough individualized risk-benefit analysis prior to initiating psychopharmacological management of behavioural disturbances in dementia with antipsychotic or other medications. However, despite the potential risks involved, antipsychotic medications continue to be used to manage particularly severe and persistent symptoms in patients with dementia, due in large part to a lack of available alternative with substantial supporting evidence.

Meta-Analyses

Schneider *et al.* reported a meta-analysis of RCT data on the efficacy and adverse effects of atypical antipsychotic medications for dementia¹⁹. Using a combination of published and drug company data, they reported on 15 RCTs (three on aripiprazole, five on olanzapine, three on quetiapine and five on risperidone) with a total of 3353 patients assigned to active treatment versus 1757 patients treated with placebo. The majority of patients had AD (87%), were female (70%) and averaged 81 years of age. Mean MMSE score was 11. Eleven trials were conducted in nursing homes and four were completed on outpatients. While approximately half of included trials were designed to recruit subjects with psychosis and the other half agitation, the authors found that most studies had a mixture of

Table 53.3 Dosage and adverse effects of other agents in dementia

<i>Medication</i>	<i>Initial dose (mg/day)</i>	<i>Usual dosage range (mg/day)</i>	<i>Common adverse effects</i>	<i>Precautions</i>
Cognitive enhancers				
Donepezil	5	5–10	Nausea, diarrhoea	Bradycardia
Galantamine	8	16–24	Nausea, diarrhoea	Bradycardia
Rivastigmine	3	6–12	Nausea, diarrhoea	Bradycardia
Memantine	5	10–20	Sedation	Dose reduction with kidney impairment
Antidepressants				
Citalopram	10	10–40	Nausea, diarrhoea	Hyponatremia, EPS
Sertraline	25	50–200	Nausea, diarrhoea, insomnia	Hyponatremia, EPS
Trazodone	25	50–200	Sedation, orthostasis	Priapism (rare)
Mood stabilizers				
Divalproex sodium	125–250	250–1000	Nausea, sedation	Liver function abnormalities, thrombocytopenia, pancreatitis
Carbamazepine	50–100	200–1000	Nausea, sedation, ataxia	Hyponatremia, pancytopenia, drug interactions

patients with psychosis and agitation, a subject pool likely to reflect typical clinical populations.

After combining the trials, symptomatic efficacy was observed for aripiprazole and risperidone while olanzapine was not associated with efficacy overall. The available quetiapine trials used different selection criteria and outcomes and thus could not be statistically combined. In general, there was heterogeneity of findings across trials. Larger effect sizes were seen in patients without psychosis (vs. with psychosis), for those in nursing homes (vs. outpatients) and in patients with more severe cognitive impairment (MMSE less than 10). Approximately one-third of subjects dropped out of the trials, without significant difference between drug and placebo groups. The most common adverse events were somnolence and urinary tract infections or incontinence; increased incidence of extra-pyramidal symptoms and gait abnormalities were seen with risperidone and olanzapine. The authors noted a significant risk for cerebrovascular events, especially with risperidone. In addition, an increased risk for overall death was observed, which will be discussed in more detail below.

Two meta-analyses of typical antipsychotic medications found that neuroleptics are significantly more effective than placebo for behavioural disturbances in dementia, albeit with a small effect size and without differential efficacy between particular agents. For example, results from a meta-analysis of six studies comparing thioridazine with another neuroleptic and five studies comparing haloperidol with another neuroleptic, did not show that these two medications differed significantly from comparison medications²⁰. In another meta-analysis, Lonergan *et al.* examined five RCTs comparing haloperidol to placebo and found that aggression decreased among patients with agitated dementia treated with haloperidol; other aspects of agitation were not affected significantly in treated patients, compared with controls²¹.

A recent meta-analysis of patients with psychosis of AD from four large placebo-controlled clinical trials of risperidone in dementia demonstrated that risperidone significantly improved scores on the BEHAVE-AD Psychosis subscale and CGI scale compared with placebo²². Secondary analyses demonstrated that patients with more severe symptoms showed a more pronounced response to treatment with risperidone compared with placebo than those patients with less severe symptoms. Extra-pyramidal symptoms and somnolence were

more frequent with risperidone than placebo ($p = 0.04$). Cerebrovascular adverse events and all-cause mortality were observed more frequently, although not statistically significantly, with risperidone versus placebo.

Effectiveness Data: NIMH CATIE-AD Trial

The National Institute of Mental Health (NIMH) Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE–AD) project compared the effectiveness of antipsychotic medications versus placebo in treating AD-associated psychosis or agitated/aggressive behaviour²³. CATIE–AD included outpatients in usual care settings and assessed treatment outcome on several clinical measures over nine months. Initial CATIE–AD treatment (olanzapine, quetiapine, risperidone or placebo) was randomized and masked, yet the protocol allowed medication dose adjustments or a switch to a different treatment at any time on the basis of the clinician's judgement. The primary CATIE–AD phase 1 outcome was time to discontinuation of the initially assigned medication for any reason, which was intended as an overall measure of effectiveness that incorporated the judgements of patients, caregivers and clinicians about therapeutic benefits in relation to undesirable effects.

The two primary hypotheses were that (i) there would be pair-wise differences between the three antipsychotic treatment groups and the placebo group in the time to discontinuation for any reason and (ii) among antipsychotic medications that were different from placebo, none would be inferior to the others. The results revealed no pair-wise treatment differences in all-cause discontinuation. The benefits of olanzapine and risperidone, i.e. longer times to discontinuation for lack of efficacy in comparison to placebo (Kaplan–Meier estimate of median time: olanzapine, 22.1 weeks; quetiapine, 9.1 weeks; risperidone, 26.7 weeks; placebo, 9.0 weeks), were offset by shorter times to discontinuation due to adverse effects in the antipsychotic groups (discontinuations due to intolerability: olanzapine, 24%; quetiapine, 16%; risperidone, 18%; placebo, 5%)²⁴. The mean last prescribed medication dose was 5.5 mg/day olanzapine, 56.5 mg/day quetiapine and 1.0 mg/day risperidone.

A secondary data analysis of phase 1 in CATIE–AD found that some clinical symptoms improved with atypical antipsychotic

Table 53.4 Published randomized double-blind, placebo-controlled trials of atypical antipsychotics for dementia related psychosis or agitation

Study	Medication(s)	Sample size	Length (weeks)	Primary outcome(s)	Secondary outcomes	Primary outcome significance	Results/Comments	Adverse events (AEs)
Katz <i>et al.</i> ⁶⁵	Risperidone (0.5–2 mg/d)	625	12	BEHAVE-AD (50% reduction)	BEHAVE-AD psychosis subscale, CMAI, CGIS	Yes	Significant primary outcome (50% or more reduction of BEHAVE-AD in 45% of risperidone 1 mg group and 50% of 2 mg group compared to 33% of placebo group)	More EPS with risperidone 2 mg; dose-dependent increase in somnolence
De Deyn <i>et al.</i> ⁶⁶	Risperidone (mean dose: 1.1 mg/d), haloperidol (mean dose: 1.2 mg/d)	344	13	BEHAVE-AD (30% reduction)	BEHAVE-AD, CMAI	No	Negative primary outcome – no difference between groups; several positive results for secondary outcomes of risperidone vs. haloperidol and placebo	More somnolence with risperidone than placebo; more EPS with haloperidol than risperidone or placebo
Street <i>et al.</i> ⁶⁷	Olanzapine (5, 10 or 15 mg/d)	206	6	Sum of NPI-NH agitation/aggression, hallucinations, delusion scores	NPI-NH, BPRS	Yes	5 mg and 10 mg but not 15 mg had a significant effect on the primary outcome; only 5 mg yielded improved NPI-NH total score	Somnolence and gait disturbance were increased significantly; not EPS
Meehan <i>et al.</i> ⁵⁹	Olanzapine (2.5 or 5 mg IM), lorazepam (1 mg IM)	204	24 h	PANSS-EC	CMAI, ACES	Yes	Significant mean change in primary outcome at 2 and 24 h for both olanzapine doses; lorazepam with significant effect at 2 h but not 24 h	Not significantly different across groups
Brodsky <i>et al.</i> ⁶⁸	Risperidone (mean dose: 1.0 mg/d)	345	12	CMAI total aggression score	CMAI, BEHAVE-AD, CGIS, CGIC	Yes	Risperidone improved CMAI-aggression subscale more than placebo (4.4 point difference, $P < .001$); similar results for other outcomes	Sedation, urinary tract infections with risperidone

Table 53.4 (continued)

Study	Medication(s)	Sample size	Length (weeks)	Primary outcome(s)	Secondary outcomes	Primary outcome significance	Results/Comments	Adverse events (AEs)
De Deyn <i>et al.</i> ⁶⁹	Olanzapine (1–7.5 mg/d)	652	10	NPI-NH psychosis subscale, CGIC	NPIH-NH total and item scores	No	No significant difference on primary outcome between any olanzapine dose and placebo	Weight gain, anorexia and urinary incontinence
Ballard <i>et al.</i> ⁷⁰	Quetiapine (50–100 mg/d), rivastigmine (6–12 mg/d)	93	26	CMAI	SIB (Severe Impairment Battery)	No	Rivastigmine, quetiapine and placebo equivalent	Statistically significant negative effect on cognition with quetiapine
Deberdt <i>et al.</i> ⁷¹	Risperidone (mean dose: 1.0 mg/d), olanzapine (mean dose: 5.2 mg/d)	494	10	NPI, CGIS		No	Improvement regardless of treatment group	EPS with risperidone, weight gain and higher rate of discontinuation due to AEs with olanzapine
De Deyn <i>et al.</i> ⁷²	Aripiprazole (5, 10 or 15 mg/d)	208	10	NPI psychosis subscale, BPRS	BPRS	No	No difference in NPI psychosis subscale decline between aripiprazole (–6.5) and placebo (–5.5). BPRS psychosis and core subscale scores improved significantly with aripiprazole vs. placebo	Mild somnolence, not associated with falls or injury; no increase in EPS
Mintzer <i>et al.</i> ⁷³	Risperidone (mean dose 1.0 mg/d)	473	8	BEHAVE-AD psychosis subscale, CGIC		No	Both placebo and risperidone improved without significant difference	Somnolence occurred significantly more with risperidone
Tariot <i>et al.</i> ⁷⁴	Quetiapine (mean dose 97 mg/d), haloperidol (mean dose 1.9 mg/d)	284	10	BPRS total, CGIS	BPRS factors, NPI	No	All groups improved without significant differences on primary outcomes	Somnolence with quetiapine and haloperidol; EPS with haloperidol

Table 53.4 (continued)

Zhong <i>et al.</i> ⁷⁵	Quetiapine (100 mg/d or 200 mg/d)	333	10	PANSS-EC	NPI-NH, CMAI	Yes	No significant effect on primary outcome with 100 mg group alone or when combined with 200 mg group, but a significant effect with the 200 mg/day group alone; no effect of quetiapine on CMAI	No	No significant difference in primary or secondary outcomes	Quetiapine did not worsen Parkinsonism; trend towards decline on a measure of daily functioning CVAEs were present with aripiprazole ($N = 7$) but not placebo ($N = 0$) No differences between groups
Kurlan <i>et al.</i> ⁷⁶	Quetiapine (mean dose 120 mg/d)	40	10	BPRS score		No				
Mintzer <i>et al.</i> ⁷⁷	Aripiprazole (2, 5 or 10 mg/d)	487	10	NPI-NH psychosis subscale	NPI-NH total; CGIS, BPRS, CMAI	Yes	Aripiprazole 10 mg/d but not 2 or 5 mg/d significantly improved the primary outcome			
Paleacu <i>et al.</i> ⁷⁸	Quetiapine (mean dose 200 mg/d)	40	6	NPI, CGIC		No	Reductions in NPI did not differ between placebo and quetiapine; CGIC did decrease significantly in the quetiapine ($P = 0.009$) but not placebo ($P = 0.48$) group			
Streim <i>et al.</i> ⁷⁹	Aripiprazole (mean dose 9 mg/d)	256	10	NPI-NH psychosis subscale, CGIS	NPI-NH total, BPRS total, CGIC, CMAI	No	No significant difference in co-primary outcomes; improvements in several secondary outcomes			Somnolence increased (14% vs. 4% placebo), no increase in EPS

medications²⁵. Data from the last phase 1 observation indicated greater improvement with olanzapine or risperidone on NPI total scores and the BPRS hostile suspiciousness factor, as well as for risperidone alone on the BPRS psychosis factor and the CGIC. There was worsening with olanzapine on the BPRS withdrawn depression factor. Among patients continuing phase 1 treatment at 12 weeks, there were no significant differences between antipsychotic medications and placebo on functioning, care needs or quality of life, except for worsened functioning on an activities of daily living (ADL) scale with olanzapine compared to placebo. These results suggest that specific symptoms, rather than global changes, may be more realistic treatment targets for antipsychotic medications when used in dementia and that anger, aggression and paranoia may improve preferentially with treatment. These and other treatment guidelines will be discussed in more detail at the conclusion of the chapter.

Analysis of the entire 36-week trial revealed that, metabolically, atypical antipsychotic use was associated with a significant weight gain (0.08 lb/week) and increase in BMI (0.02 kg/m² per week), with the likelihood of weight gain increasing with longer use of antipsychotic medication²⁶. In sub-group analysis, change in weight reached significance for olanzapine (0.12 lb/week) and quetiapine (0.14 lb/week), but not risperidone (0.10 lb/week); similar findings were present for BMI. When examined by gender, these changes in weight and BMI were significant in women (0.14 lb/week and 0.02 kg/m² per week, respectively), but not in men (−0.02 lb/week and −0.003 kg/m², respectively). Further analysis revealed unfavourable overall changes in HDL cholesterol (−0.19 mg/dl/wk) and waist circumference (0.07 inches/wk) with olanzapine.

Cognitively, patients declined significantly over the course of the trial (e.g. mean total decline in MMSE 2.4 points); a decline apparently increased by antipsychotic treatment²⁷. Patients on antipsychotic medications declined more than patients on placebo on all 11 cognitive measures completed in the study, though the majority of differences between active treatment groups and placebo were non-significant. Statistically significant differences included greater decline on the MMSE in the olanzapine group, greater decline on the BPRS cognitive subscale in the quetiapine group and greater decline on a cognitive summary score in the risperidone and olanzapine groups.

Safety Issues with Antipsychotic Medications

Usual side effects of antipsychotic medications include sedation, hypotension, anti-cholinergic effects, extrapyramidal symptoms and weight gain. The general frequency of these side effects varies based on the dose and agent used, as listed in Table 53.2.

Two major safety issues concerning antipsychotic use in dementia, namely cerebrovascular adverse events (CVAEs) and risk of death, have come into focus over the last several years. In 2003, the FDA issued a warning about CVAEs (e.g. stroke, transient ischaemic attack), including fatalities, in patients (mean age 85 years; range 73–97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of CVAEs in patients treated with risperidone compared to patients treated with placebo: in combining data from three controlled trials of risperidone, 12 of 744 (1.6%) risperidone-treated patients compared to 4 of 562 (0.7%) placebo-treated patients developed serious cerebrovascular events. Risperidone prescribing information was adjusted to include this risk. A similar warning was issued for olanzapine and aripiprazole by the manufacturers based

on similar data. For example, in a pooled analysis of five controlled trials of olanzapine in patients with dementia, 15 patients of the 1178 randomly assigned in the trials to receive olanzapine suffered CVAEs (1.3%), compared with 2 out of the 478 randomly assigned to placebo (0.4%). For the subgroup of patients who had vascular dementia, there was a five-fold higher likelihood of experiencing a CVA. Overall, a meta-analysis found that pooled rates of CVAEs were 1.9% in atypical antipsychotic treated patients versus 0.9% in placebo-treated patients, yielding an odds ratio of 2.1 (95% CI, 1.2–3.8)¹⁹. Typical antipsychotics appear to be similar to atypical antipsychotics in stroke risk^{28,29}.

Regarding risk of death, in 2005 the FDA reported that atypical antipsychotic medications were associated with a significantly (1.6–1.7 times) greater mortality risk compared with placebo, based on several analyses of 17 RCTs of 5106 elderly patients with dementia³⁰. Most deaths were due to either cardiac or infectious causes, the two most common immediate causes of death in dementia in general. A meta-analysis of 15 RCTs found a risk of death with atypical antipsychotics of 3.5%, compared to 2.3% for placebo, resulting in an odds ratio of 1.5 (95% CI, 1.1–2.2)³¹. Data on typical antipsychotic medications demonstrated a similar elevated risk of death^{31,32}. In 2008, the FDA required manufacturers of typical antipsychotic drugs to make safety-related changes to prescribing information to warn about an increased risk of death associated with the off-label use of these drugs to treat behavioural problems in older people with dementia³³.

These safety concerns are highlighted in warnings now on all antipsychotic medications stating that these drugs are not approved for treatment of dementia-related psychosis. This has resulted in efforts to re-evaluate the prescription of antipsychotic medications to patients with dementia. In addition, there is a renewed level of interest in the discovery and development of alternatives to the use of antipsychotic medications in treating the behavioural disturbances found in dementia, as discussed below.

Antipsychotic Withdrawal Trials

In AD patients initially prescribed antipsychotic medications for treatment of behavioural disturbance for at least three months, the DART-AD trial found no significant difference between those randomized to receive continued treatment and those receiving placebo (antipsychotic medication discontinued) in the change of global cognitive function on the Severe Impairment Battery (SIB) or behavioural symptoms (as measured by the NPI) after six months follow-up³⁴. A later analysis of this same population found a significantly increased risk of mortality in the patients who continued to receive antipsychotic medications compared to those who received placebo³⁵. A similar lack of negative impact on NPI scores with stopping antipsychotic drug therapy in demented nursing home patients was observed in the briefer four-week BEDNURS trial³⁶.

COGNITIVE ENHANCERS

Cholinesterase Inhibitors

Given the high proportion of patients with advancing dementia placed on cholinesterase inhibitors, several recent studies have examined the possible clinical utility of cognitive enhancers in ameliorating emergent behavioural symptoms. A meta-analysis of

26 trials to quantify the efficacy of cholinesterase inhibitors for neuropsychiatric and functional outcomes in patients with mild to moderate AD found at best a very modest beneficial impact of these drugs³⁷. For neuropsychiatric outcomes, six used the NPI and 10 of the trials used the ADAS-noncog. Compared with placebo, patients randomized to cholinesterase inhibitors improved 1.72 points on the NPI (95% CI, 0.87–2.57) and 0.03 points on the ADAS-noncog (95% CI, 0.00–0.05). For functional outcomes, 14 trials used activities of daily living (ADL) and 13 trials used independent-ADL (IADL) scales. Compared with placebo, patients randomized to cholinesterase inhibitors improved 0.1 SDs on ADL scales (95% CI, 0.00–0.19) and 0.09 SDs on IADL scales (95% CI, 0.01–0.17)³⁷. There was no difference in efficacy among the various currently available cholinesterase inhibitors. Importantly, these trials did not specifically seek to include patients with behavioural disturbance and the findings may best apply to patients with very mild symptoms.

In contrast, a notable recent negative study was the 2007 CALM-AD trial examining donepezil treatment of agitation in AD³⁸. Howard *et al.* examined the potential benefits of cholinesterase inhibitors for behavioural disturbances in 272 patients with AD who had clinically significant agitation and no response to a brief psychosocial treatment programme. There was no significant difference between the effects of 12 weeks of donepezil (128 patients) versus placebo (131 patients) on scores of the Cohen–Mansfield Agitation Inventory (CMAI). Twenty-two of 108 patients (20.4%) in the placebo group and 22 of 113 patients (19.5%) in the donepezil group had a reduction of 30% or greater in the CMAI. Likewise, there were also no significant differences between the placebo and donepezil groups in scores for the NPI, the Neuropsychiatric Inventory Caregiver Distress Scale or the CGIC. An earlier nursing-home study of 208 patients with advanced AD also failed to show a significant benefit of donepezil on total NPI scores, although there was benefit of donepezil on the agitation measure specifically³⁹.

Memantine

Data investigating the behavioural effects of memantine on behavioural disturbances in dementia are limited. A recent exploratory analysis of a 24-week, double-blind, placebo-controlled trial comparing memantine (20 mg/day) with placebo in subjects with moderate to severe AD on stable donepezil treatment was completed⁴⁰. Authors used NPI measurements at baseline, week 12 and week 24, to assess the effects of memantine on behaviour. Treatment with memantine reduced agitation/aggression, irritability and appetite/eating disturbances. While the studies did not seek to include patients with behavioural symptoms and mean rating scores suggested mild symptoms, memantine reduced agitation/aggression in patients who were agitated at baseline and delayed its emergence in those who were free of agitation at baseline.

ANTIDEPRESSANTS

Available data on antidepressants and behavioural disturbance in dementia are limited, but do show some possible benefit. The findings discussed below need to be replicated in expanded study populations before antidepressants can be confidently recommended as alternatives to antipsychotic medications for the treatment of agitation or psychotic symptoms associated with dementia. Adverse effects may be more benign than with antipsychotic treatment, although there is very little comparison data and more complete understanding of the

antidepressant side-effect profile in this population will require larger trial samples.

Citalopram

In a moderately sized study, citalopram was found to be more efficacious than placebo in the short-term hospital treatment of psychotic symptoms and behavioural disturbances in non-depressed, demented patients⁴¹. This study also included a treatment arm with perphenazine, which did not differ from citalopram or placebo groups. In a later study, when citalopram was compared to risperidone, agitation symptoms (aggression, agitation or hostility) and psychotic symptoms (suspiciousness, hallucinations or delusions) decreased in both treatment groups, but the improvement did not differ significantly between the two groups⁴². There was, however, a significant increase in side-effect burden with risperidone but not with citalopram.

Sertraline

An initial small trial of sertraline showed a 38% overall response rate, which was equivalent to placebo and a trend for decreased aggression ($P = 0.08$)⁴³. A later trial of sertraline, in this case added to donepezil treatment, in outpatient AD patients with behavioural problems found no primary effect, but post hoc analyses demonstrated a modest but statistically significant advantage of sertraline over placebo augmentation in mixed-model analyses and in a subgroup of patients with moderate-to-severe symptoms as measured on CGI and NPI scales⁴⁴.

Fluvoxamine

The initial published trial on fluvoxamine use in dementia did not show significant benefit on cognitive functioning or behavioural changes in elderly dementia patients⁴⁵. However, given that fluvoxamine can increase antipsychotic blood levels, another small trial examined fluvoxamine augmentation of perphenazine in AD patients and found that perphenazine plus fluvoxamine was better than perphenazine plus placebo on lowering total BPRS scores⁴⁶.

Trazodone

Sultzer *et al.* 1997 found that trazodone was equally efficacious as haloperidol in reducing agitation and aggression in a small mixed population of inpatient dementia subjects over a 9-week trial period⁴⁷. Further analysis found that the presence of delusions did not predict a greater behavioural improvement with haloperidol treatment than in subjects without signs of psychosis, while mild depressive symptoms were associated with greater improvement in trazodone-treated patients⁴⁸. However, a larger ($n = 149$) randomized, placebo-controlled, multicentre trial comparing the efficacy of trazodone, haloperidol, behavioural management and placebo found modest but non-significantly different improvement in all four groups of the study⁴⁹. Post hoc analysis of placebo responders demonstrated that the reduction observed was of the same magnitude as predicted by regression to the mean; patients exhibiting greater improvement had more severe baseline behavioural disturbances⁵⁰. A small ($n = 26$) study of frontotemporal dementia patients found trazodone to be effective in reducing behavioural disturbances; 10 of the trazodone treated patients had a greater than 50% reduction of NPI scores⁵¹.

MOOD STABILIZERS

Valproate/Divalproex Sodium

Despite preliminary promise, results from controlled trials published to date essentially show very limited effect of valproate/divalproex sodium over placebo in the treatment of behavioural disturbances in dementia. The first RCT published using divalproex sodium in nursing-home patients with agitation and dementia ($n = 56$) found the drug/placebo difference in BPRS agitation scores at the threshold of significance ($P = 0.05$), while differences in CGI did not reach significance ($P = 0.06$)⁵². In a second trial, in aggressive demented inpatients ($n = 42$), there was no primary effect of valproate⁵³. Secondary improvement was shown on restless, melancholic and anxious behaviours – with the caveat that no correction was made for multiple comparisons. A third study of divalproex in nursing-home patients with AD associated agitation ($n = 153$), found no difference from placebo over six weeks of treatment⁵⁴. More recently, Herrmann *et al.* found that valproate was poorly tolerated and significantly worsened agitation and aggression on NPI and CMAI measures in a small population ($n = 14$) of institutionalized AD patients, when compared with placebo treatment for six weeks⁵⁵.

Given the negative results in trials targeting existent behavioural symptoms in dementia, the Alzheimer's Disease Cooperative Study (ADCS) has been conducting a clinical trial to address whether chronic valproate treatment can delay emergence of behavioural symptoms in outpatients with AD. Divalproex sodium has been shown to be better tolerated in these AD patients in doses less than 1000 mg/day, with doses of 1500 mg/day causing worse cognitive performance⁵⁶.

Carbamazepine

Two small positive efficacy trials have been published using carbamazepine to treat behavioural symptoms of dementia. The first involved nursing-home patients with dementia with agitation who showed improvement on BPRS and CGI measures over six weeks when compared to a parallel placebo group⁵⁷. The second examined outpatient AD patients who had failed treatment with antipsychotic medications and again found relatively greater improvement in carbamazepine-treated patients compared to placebo but also a trend for worsened hallucinations⁵⁸.

Other Medications

A few small studies have examined other pharmacological approaches for treatment of behavioural disturbances in dementia, including oral or intramuscular benzodiazepines^{59,60}, diphenhydramine⁶¹, propranolol⁶², buspirone⁶³ and transdermal oestrogen⁶⁴.

GENERAL PRINCIPLES FOR PHARMACOLOGY OF BEHAVIOURAL DISTURBANCES

At the current time, no uniform treatment algorithm can be applied to elderly patients with behavioural disturbance in dementia. However, some general treatment guidelines for medication use can be discussed. Medications should be prescribed only for specifically defined target signs and symptoms. Prior to initiating psychopharmacological management, one must identify underlying contributing factors. Modifiable causes, such as environmental issues or co-morbid

medical conditions, should be addressed and corrected prior to medication treatment. A review of the patient's medication regimen should be undertaken to discontinue unnecessary drugs and those that may dull cognition, such as sedative-hypnotic, opiate and anti-cholinergic medications. Superimposed delirium due to acute change in medical condition or medications is common in patients with dementia and often promotes behavioural disturbances.

Behavioural interventions (see related chapter in this book) should be initiated prior to medication use and monitored for effectiveness and modification throughout the treatment process. Given the known risks of medication use in patients with dementia, only behavioural symptoms that are recurrent and severe should be considered for pharmacological treatment. Examples of such behaviours would include those which put patient or caregiver safety at risk, such as psychosis contributing prominently to behavioural disturbance. Medication management may also be considered for psychotic symptoms that are prominently distressing to the patient or for behaviours that interfere with basic care needs.

The treatment plan should be guided by an individualized assessment of specific symptoms and the possible benefits and potential risks to the individual of a particular intervention. Clinicians should recognize the value of evidence from controlled clinical trials that is derived from studies of specific patient groups and settings, yet must also consider the individual patient's particular circumstances, needs and goals in developing a personalized treatment plan. When initiating psychotropic drug trials, micro-doses may be a good starting point but this needs to be monitored, as some patients respond well to low doses but may need increases over time. In general, the minimally effective dose should be used over the shortest duration of time possible to address the target symptom being treated. Medication effects need to be monitored over time and the treatment adjusted to match ongoing goals. This should include regular attempts at dose reduction and medication discontinuation trials. Lack of improvement or presence of significant adverse effects may require medication discontinuation or switching to another agent within or between classes of psychotropic agents.

Psychopharmacological management works best when coordinated with caregivers and treatment team members in an active collaboration. The consultant model of treatment has been found to be least effective when compared to alternative models such as interdisciplinary treatment teams which include active input not only from treating specialists, but internists, nurses, social workers, therapists and other care partners.

Following the above guidelines, one can typically look for improvement within 2–4 weeks of treatment initiation and if not observed, this requires re-evaluation of target symptoms and treatment goals. Such goals should typically be shared decisions, based on the patient and family values expressed regarding quality of life and other relevant matters. Documented sharing of information regarding known risks and benefits of proposed drug treatments should be completed with patients and caregivers. Information should be delivered in a manner appropriate to each family's education level and knowledge base.

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Behavioural Management: Non-Pharmacological

Jiska Cohen-Mansfield

*George Washington University Medical Center and School of Public Health, Washington DC, USA
Tel Aviv University Herzeg Institute on Aging and Sackler Faculty of Medicine, Tel-Aviv, Israel*

The discussion of non-pharmacological interventions to treat dementia has increased in recent years. Such interventions can be used to reduce agitation and problem behaviours, enhance affect, cognition and activities of daily living (ADL), and reduce delusions and hallucinations. These interventions most often change the physical and social environment of the person with dementia by improving the level and quality of stimulation in the environment, providing social contact, or adapting the environment to increase comfort and ease in daily activities. In this way, non-pharmacological interventions can address unmet needs of persons with dementia and enhance their quality of life.

THEORETICAL FRAMEWORKS

Several theoretical frameworks describe the manifestations of the behavioural, affective, cognitive and psychotic impairments associated with dementia from an environmental and psychosocial perspective. Three such theories that explain behaviour problems are the behavioural model, the environmental vulnerability model and the unmet needs model. Some of the theories that explain affect include the learned helplessness model and the reduced reinforcement model. There are also various theories relating pain and loneliness to affect. Each theoretical framework has different implications for intervention.

Behaviour

The behavioural model states that a problem behaviour is controlled by its antecedents and consequences. Antecedents include triggers that initiate the behaviour, such as the view of the exit door eliciting an attempt to exit the institution; consequences refer to the reaction to the behaviour, such as when screaming is followed by attention from staff members, a response that reinforces the screaming behaviour. Alternatively, the environmental vulnerability model asserts that dementia results in an increased vulnerability to the environment, which leads to a lower threshold at which stimuli affect behaviour. A stimulus that may elicit an appropriate response in a person without cognitive impairment, such as a movie or magazine, may overwhelm a person with cognitive impairment and therefore generate an inappropriate behaviour. This model is based on the concepts of person–environment congruence¹ and the environment-behavioural model, which suggest that, for optimal functioning, a

match is needed between the person's needs and abilities and the demands of the environment as they relate to those needs and abilities. A related concept is that dementia results in a progressively lowered stress threshold². Accordingly, persons with dementia progressively lose their coping abilities, and therefore perceive their environment as increasingly stressful. Since their threshold for tolerating this stress is also decreasing, anxiety and inappropriate behaviour can result as environmental stimuli exceed the person's stress threshold.

According to the unmet needs model, a person with dementia has difficulty meeting his/her needs because of a decreased ability to communicate needs and provide for oneself. The loss in the ability to communicate and perform tasks. The combination of the loss of ability to communicate and perform tasks, inability to effectively utilize the environment, and deficiencies in individualizing care results in unmet needs^{3,4}. Problem behaviours emerge as an attempt to meet or to communicate those needs.

The different models are not mutually exclusive and may be complementary. An environmental vulnerability may make the person who suffers from dementia more susceptible to environmental antecedents and consequences. The environmental vulnerability may also produce an unmet need when normal levels of stimulation are perceived as over-stimulation. Furthermore, different models may account for different behaviours in different people.

Affect

Depressed affect has been conceptualized as resulting from lack of control and a sense of helplessness, from insufficient level of control over one's environment⁵, or from an insufficient level of reinforcing activities, i.e. pleasurable experiences⁶. Depressed affect has also been linked to loneliness⁷ and to physical pain.

Delusions/Hallucinations

Delusions can represent a misinterpretation of reality, which may stem from actual environmental changes for which the person is not adequately prepared. This may be the case when an older person becomes frightened by a caregiver who comes to get her dressed, and whom the older person may perceive as a total stranger. Hallucinations have been associated with visual impairments, and may therefore represent a natural reaction to sensory deprivation⁸.

INTERVENTIONS

The following describes non-pharmacological interventions used for alleviating behavioural, affective, cognitive and psychotic symptoms of dementia.

Behavioural

Interventions for behavioural problems that are based on the unmet needs model most often focus on three types of unmet needs: need for social support and contact, need for stimulation and activities, and need for relief from discomfort. At the most basic level, providing social support and contact involves talking to persons with dementia, even if the caregiver conducts the majority of the conversation. One-on-one interaction is a potent intervention that can be performed by relatives, paid caregivers or volunteers. Alternatively, simulated social interventions can be useful when live social contact is not available; such interventions include videotapes of family members⁹, simulated presence therapy¹⁰, in which an audiotape of a family member's side of a telephone conversation is played repeatedly to the person with dementia, or commercially produced interaction videos for persons with dementia, in which viewers are invited to sing along to familiar music or to remember past events. Training staff members to view all interactions with those in their care (such as during ADL) as opportunities for social contact is also an opportunity to provide social support.

Pet therapy is another option¹¹, which may include visits with dogs, cats or fish, or simulated pet therapy using plush stuffed animals or robotic pets¹². In addition to interaction with the animal, pet therapy provides a topic for interaction with other people. Dolls have also been used to simulate companions/babies, and massage may be an effective mechanism for social contact with non-verbal persons with advanced dementia.

In order to address the need for activity or stimulation, many different types of activities or stimuli have been used. Stimulation includes music, aromatherapy, touch therapy, 'Snoezelen' programmes, massages and white noise. Structured activities, such as manipulation of objects, sorting, cooking, sewing and sensory interventions, may be helpful. Montessori-based activities are a set of activities based on Maria Montessori's principles¹³, such as task breakdown, immediate feedback, and use of everyday, real-world materials. Other options for activities include exercise, art therapy, including drawing and painting, where participants can express themselves by choosing colours and themes, and adaptations of ADL, like setting the table or cooking.

Activities can include cognitive tasks that can be done individually or within a group. Group examples include 'Question Asking Readings', in which a group reads a script accompanied by questions typed on cards that encourage participants to discuss related topics. Another group memory task is memory bingo, a game in which participants match beginnings and endings of popular sayings, which can also stimulate group discussion¹⁴. Individual cognitive tasks involve sorting cards or objects by category.

An alternative to addressing the need for stimulation by providing stimuli is to accommodate the behaviour that provides activity and stimulation. For example, interventions for accommodating pacing or wandering behaviour include outdoor walks¹⁵ and the use of wandering areas¹⁶. Inappropriate handling or the constant manipulation of objects can be accommodated by providing appropriate materials, such as books and pamphlets for handling, or activity aprons (aprons

that have buttons, zippers and other articles sewn on) as appropriate and safe items for persons to handle. Similarly, rocking chairs and gliding swings have been used to accommodate restless behaviour and provide more acceptable stimulation.

Regarding relief of discomfort, interventions such as pain management, light therapy to improve sleep, and reduction of discomfort by improved seating or positioning and removal of physical restraints have all been related to improvement in behaviour. Changes in the methods and environment of providing ADL have also been associated with reduction in inappropriate behaviours. For example, tape recordings and pictures of birds, flowing water and small animals in baths as well as offering food during bathing have been associated with a decrease of agitated behaviours during bathing. Person-centred showering and towel baths resulted in decreased agitation in comparison with usual bathing routines¹⁷.

In order to provide for the unmet needs of the person with dementia, caregivers need to understand the needs and how to address them. Staff training is a category of non-pharmacological interventions, which includes training in skills such as communication and providing assistance in ADL, or in techniques to handle inappropriate behaviours. Many such programmes focus on improved understanding of the older person and the impact of dementia. Person-centred care and the use of dementia-care mapping are care principles that have been associated with decreased levels of behaviour problems¹⁸. Changing caregiver behaviour through training is, however, a complex and difficult challenge, and often requires ongoing instruction, modeling, monitoring, feedback and support of the caregiver. Therefore, in institutional settings, staff training is closely tied to management.

The most common intervention based on the behavioural theoretical framework is differential reinforcement, which changes the contingencies that are supposed to maintain or reinforce the behaviour. This consists of positive reinforcement contingent on non-agitated behaviour, such as moving the person to a quiet area when agitated for time out, or restriction, where the person is denied goods (e.g. cigarettes), activities or access to a location or another person when agitated. In contrast, reinforcement is provided when not agitated.

The interventions based on the environmental vulnerability theoretical framework include reduced stimulation units, which aim to eliminate the stimuli that, according to the theory, activate the low stress threshold and result in the problem behaviours. These units have been modified to appear less obstructive to those with dementia. They typically have small group sizes at tables for eating and small groups for activities, neutral colours on pictures and walls, no televisions, radios or telephones (except for emergencies), an educational programme for staff and visitors concerning the use of touch, eye contact and slow, soft speech, use of quiet voices by staff at all times, and a consistent daily routine¹⁹.

Affect

Based on the theoretical model of learned helplessness, interventions to decrease depressed affect focus on increasing the older person's sense of control, such as allowing the person to make his/her own decisions about meals or clothes or to care for a plant. The intervention approach based on the alternative theoretical framework of reduced reinforcing events is that of providing older persons with pleasant activities, individualized to the preferences of each person²⁰. Loneliness is highly correlated with depressed affect, and social interventions described above, including both live and simulated social

activities, are also appropriate for improving affect. Group activities can also be used as vehicles to promote social contacts. Additionally, combined interventions that merge outdoor experience with social contact, such as combining a wheelchair bicycle with small-group activity therapy and one-to-one bike rides with a staff member, have been applied to reduce depression in nursing home residents²¹.

Self-affirming interventions also target improving affect. These include reminiscence therapy, which encourages persons with dementia to talk about their pasts, and may utilize audiovisual aids, such as old family photos and objects. Reminiscence can enhance individuals' sense of identity, sense of worth or general well-being²², and may also stimulate memory processes. Validation therapy, in which a therapist accepts the disorientation of a person with dementia and validates his or her feelings, can improve affect by acceptance rather than rejection of the experiences of the person with dementia²³.

Cognition

Several cognitive principles underlie cognitive interventions for persons with dementia. These include: (i) long-term memory is usually maintained better than short-term memory; (ii) procedural memory remains more intact than declarative memory; and (iii) new learning is possible in dementia and is achieved through the same principles as other memory, but often requires more aids or repetition. Cognitive interventions have been used to improve general cognitive function or the performance of specific tasks. Interventions for improving general cognitive function include memory training²⁴, maintaining lifelong habits that have been over-learned through long-term practice, general problem solving, use of mnemonic devices, word games and puzzles, computer programs with cognitive exercises, and/or the use of external memory aids such as notebooks, lists, calendars or alarms. Computer-based memory training has the advantage of adapting to the level of the older person and to the type of cognitive stimulation most needed²⁵. Physical exercise has also been shown to have a positive effect on cognitive performance in older adults with dementia²⁶. For persons with more advanced cognitive impairment, reality orientation has been used, where staff members present orienting information such as information about time, place and person, usually in a group setting²⁷.

The use of cognitive interventions for more specific procedures often includes procedural memory training, using spaced-retrieval (a procedure where a task, such as placing the walker in a specific location, is learned through repetition over increasingly longer retention intervals²⁸), cueing and similar techniques. In the later stages of dementia, memory books, which contain autobiographical, daily schedule and problem resolution information, can assist with communication²⁹. Technological aids, such as the use of electronic memory devices or environmental sensors³⁰, are expected to play an increasing role in the future as prostheses for cognitive losses.

FUNCTION

Non-pharmacological interventions to improve function often include environmental interventions and task simplification. These are used to optimize the performance of activities of daily living by adjusting the surroundings (including physical access, temperature, colour, furniture, wall design and cues) to facilitate the activity for both patient and caregiver. The extent of environmental adaptation varies, from decreasing clutter to providing grab bars or handrails. As a means to decrease the risk of falling, lowering bed height, placing mattresses

on the floor, using hip protectors, improving light on the way to the bathroom, and improving call systems have been used. Enhanced visibility of toilets increased their utilization³¹, and eating behaviour improved with better light and increased contrast between plates and the table³².

An alternative intervention is task simplification or cognitive prosthesis, which utilizes task breakdown, enhanced instruction, modeling, rehearsal, cueing and gradual approximations of a task. The notion of simplifying tasks can also be applied across daily activities, such as by providing consistency in caregiver assignment, which helps orient older persons across different tasks. A combination of these interventions and others has been included in occupational therapy interventions to enhance function in dementia³³.

Delusions/Hallucinations

Non-pharmacological interventions for psychotic symptoms are based on the understanding of the aetiology of the symptom.

- *Misinterpretation of stimuli or reality.* At times, the diagnosed 'delusion' or 'hallucination' is triggered by an environmental stimulus. For example, a loudspeaker system may sound like voices from outside or an image seen through a mirror may be interpreted as someone being in the room. This is facilitated by the combination of sensory deficits and cognitive limitations that occur with dementia giving rise to an incorrect interpretation of an initially vague or unclear stimulus. Interventions to minimize this confusion would most often remove or change the stimulus so as not to elicit the mistaken interpretation. Delusion can also be a representation of reality. Examples are delusions of theft, as theft is common in many nursing homes, or the delusions of abandonment that may occur when a person enters a nursing home. Whether this feeling reflects reality from the point of view of the caregiver is irrelevant, as the move into a strange environment represents abandonment from the point of view of the person with dementia. The goal of interventions to alleviate this feeling is to re-establish trust in the relationship. Older persons may eventually change their perceptions when they become comfortable with their care and when they sense consistent caring by the family, such as with social contact (real or simulated, described above), which may provide a sense of love and familiarity, thus countering the feelings of abandonment and betrayal.
- *Delusion as confabulation in the face of memory loss.* Many delusions are misinterpretations of actual events in the environment. When a person with dementia complains that an object has been stolen, she may be forgetting where she has placed her personal belongings and interpreting her inability to find them as theft. A number of potential solutions can be offered to older persons, including marking personal belongings in clear ways so that they are easily identifiable, attaching a finder such as a KeyRinger™ to a personal belonging, or purchasing multiple inexpensive copies of personal articles so they may be easily replaced when necessary. Similarly, the delusion that a caregiver is an impostor is often the result of an individual's inability to recognize the caregiver. In that case, an intervention should work toward improving the individual's relationship with the caregiver.
- *Other reasons.* Delusions have at times been reported to result from delirium associated with acute medical conditions that should be treated, or from bright light therapy, which, in those cases, should be removed. Delusions have also been linked to depressed

affect in many studies^{34,35}. It is unclear whether the delusions lead to depression or the depression leads to delusions (e.g., through inactivity and isolation), or if both are caused by other factors. Depression may be controlled by treating the depression non-pharmacologically, as described above.

- *Pleasant 'psychotic symptoms'*. At times hallucinations are pleasurable. Some people talk with deceased relatives and derive happiness from these encounters. If a person seems to enjoy such hallucinations and does not suffer any ill effects, an optimal intervention may be to explain this situation to caregivers in a manner that will make the practice acceptable to them.
- *Visual and auditory problems/sensory deprivation*. Hallucinations are more likely to occur in persons with visual problems^{8,35,36}, and may be linked to sensory deprivation³⁷. Additionally, there is evidence that in the absence of the stimulation of sensory areas by external objects, people may experience hallucinations³⁸. Correction of visual problems through medical intervention or through aids such as eyeglasses, enhanced contrast, larger type/object or improved lighting is a first step in addressing hallucinations among persons with visual impairments. To the extent that sensory deprivation may be a contributing cause of hallucinations, sensory stimulation, such as music, massage and aromatherapy, may be beneficial.
- *Cultural differences between caregivers and persons with dementia*. Some behaviours perceived by caregivers as psychotic symptoms may actually be culturally based, such as 'talking' to the dead or singing, or praying in a loud voice.

INDIVIDUALIZATION OF INTERVENTIONS

A crucial principle in applying non-pharmacological interventions to persons with dementia is that of individualizing these interventions to fit the person's needs and abilities. Some of the dimensions to consider in tailoring interventions are listed below:

1. Current and past sense of identity, which usually include some retained aspects of previously held identities, such as work role, family relationship or preference for a certain type of leisure activity.
2. Current sensory abilities, which include visual, auditory, smell and touch modalities. Mechanisms for augmentation of sensory abilities should be explored, including simple ones, such as better fitting eyeglasses, an auditory amplifier, better fitting hearing aids etc.
3. An enhanced understanding of current needs, including social contact of any kind, longing for family, for daytime activity, for stimulation, for physical exercise or for a specific meaningful activity, such as helping or working.
4. Cognitive and communication abilities.

EFFICACY OF INTERVENTIONS

Many reviews have tried to clarify the evidence regarding the efficacy of non-pharmacological interventions, despite many methodological and other difficulties in the research in this area³⁹⁻⁴³. Many non-pharmacological approaches resulted in a statistically and clinically meaningful improvement in the manifestation of behaviour problems, function and affect. With few exceptions, most studies are small and have methodological problems, often due to insufficient funding. There are, however, some larger studies

that used valid comparison groups and showed the efficacy of non-pharmacological approaches⁴⁴. For some areas, however, such as delusions and hallucinations, no studies were found regarding the efficacy of non-pharmacological approaches. While results vary, non-pharmacological approaches to intervention are a promising option when treating specific symptoms and when aiming to improve quality of life in dementia.

PREREQUISITES AND BARRIERS TO THE PRACTICE OF INTERVENTIONS

The actual utilization of non-pharmacological interventions in dementia falls far short of its potential. A number of systemic issues are responsible for this gap. Funding is lacking both for the practice of non-pharmacological interventions and for the acquisition of knowledge about these through systematic research. The commonly used alternative intervention of psychoactive medication is reimbursed, and the underlying structure for its delivery, including physicians, medicine aids, pharmacies, and monitoring and quality control systems, is largely in place. In contrast, the provision of non-pharmacological interventions is generally not reimbursed, and a system for providing them is often absent. Similarly, funding for non-pharmacological research is limited, because, unlike pharmacological interventions, there is no financial entity that is likely to benefit financially from this knowledge. Such limited funding results in many of the studies on these interventions having small samples and other methodological limitations, further limiting the faith in this approach and the willingness to fund it.

Yet, the most obvious barrier to the implementation of the non-pharmacological approaches described is that the current structure of care does not promote such non-pharmacological assessment and intervention. In most cases, the physician prescribes antipsychotic or antidepressant medication based on informant reports. No one in the care system is currently responsible for assessing, observing and analysing inappropriate behaviour or psychotic symptoms in order to determine their aetiology and their impact on individuals' lives. Thus, clinicians most often do not witness the event and do not have the ability to verify or question the interpretation of the diagnosis. The ability of caregivers to provide non-pharmacological interventions is further limited by lack of staff member knowledge, insufficient staffing levels and insufficient support within and outside the care situation. In order to provide non-pharmacological interventions for dementia, the system of care needs to promote an atmosphere and practice of caring that goes beyond what is currently available in most care settings. Attentive listening and observation are needed to differentiate between the various needs expressed by behavioural and psychotic symptoms. Knowledge of the disease, as well as of specific symptoms and their aetiology, meaning and management, will allow caregivers to better understand the individual's behaviours rather than attributing them to resistance, difficult personality, malicious intent, craziness or indifference. Compassion and empathy by caregivers allow them to better understand the needs of the person with dementia and to clarify appropriate avenues for interventions. In order to allow alternative interventions, the system of care needs to promote autonomy and respect for the person with dementia and to maximize flexibility in procedures for caregiver and care-receiver alike. A transformation in the system of care is therefore needed in order to allow an optimal use of non-pharmacological interventions to promote quality of life for persons with dementia.

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Emerging Applications of Gene and Somatic Cell Therapy in Geriatric Neuropsychiatry

Eric Wexler

David Geffen School of Medicine at UCLA, Los Angeles, USA

'Men do not quit playing because they grow old; they grow old because they quit playing.'

Oliver Wendell Holmes

INTRODUCTION

Startling advances in medicine have extended our lives and given us healthier bodies, but not healthier minds. The mere fact that we are living longer consigns more of us to enduring our final years ravaged by diseases like Alzheimer's or stroke, and suffering all the psychiatric manifestations that are part and parcel of these diseases. Currently available treatments do little. Therapies that replace the damaged brain tissue, either by regeneration or by transplantation, are needed. Unfortunately, both a poor theoretical understanding of neuronal generation/regeneration, and a lack of practical tools to effectively deliver these genes to the right cells, in the right amounts, continue to hamper the field of regenerative medicine. Similarly, harnessing the therapeutic potential of stem cell transplants remains a promise unfulfilled because neural stem cells (NSCs) simply do not function properly when transplanted into regions other than those that normally support adult neurogenesis. Worse yet, even those few privileged environments that normally support neurogenesis are rendered inhospitable to newly implanted NSCs by many of the same conditions that make someone a candidate for neural transplantation in the first place.

The idea of transplanting neurons to repair damaged brain is not new; the first trials, using foetal tissue, in Parkinson's patients were performed more than two decades ago. Initial optimism gave way to the harsh reality that this was not the cure many had hoped for. Many hypothesized that more mature cells simply had lost the ability to learn how to adapt to their new host environment. Naturally, waves of enthusiasm have heralded discoveries from foetal NSCs to human embryonic stem cells (hESCs), with their uncanny pluripotency. Still, somatic cell therapy remains an elusive prospect because transplanted cells do not properly engraft, either failing to properly differentiate, dying or not integrating into the local circuitry. Developing therapies that provide real clinical improvement requires leveraging our new-found appreciation of the microenvironment within which neurons normally develop.

Since the field of neural repair remains in its infancy, any review of this field (including this one) must contain a fair degree of educated

guessing about the future, some of which will turn out to be wrong. To minimize the impact this might have, we will focus on communicating the essentials of current thinking in the field, rather than trying to divine what approach(es) will ultimately be successful. To this end we have broken this chapter down into three sections. The first section aims to supply the reader with a historical understanding of early clinical repair trials, highlighting some of their limitations and questions raised. The second section provides a primer on the regenerative capacity of the adult brain. In this section we introduce the concept of an adult stem cell niche. To the clinician, some of these sections may seem technically dense; we have made every attempt to minimize the use of unnecessary jargon. However, the reader should recognize that an under-appreciation of the importance of the niche goes a long way towards explaining the shortcomings of previous trials. Conversely, understanding how disease or ageing alters the functioning of these microenvironments will be absolutely critical for understanding the rationale of any future neuroregenerative therapy trials. The third section introduces the clinical reader to some of the current and emerging tools at the gene therapist's disposal. Finally, we will provide some plausible scenarios where the discussed concepts and tools can be integrated to produce workable future clinical trials. In sum, this chapter should empower the reader with the necessary framework for understanding ongoing developments, rather than trying to divine which approaches will ultimately be successful.

BIRTH OF REGENERATIVE MEDICINE

Molecular strategies for functionally repairing the damaged brain fall into one of three categories: (i) replace/repair circuitry; (ii) potentiate function of remaining cells; and (iii) halt disease progression¹. The cell replacement strategy has the longest track record with the first foetal neuron transplants being reported in 1989². The lion's share of transplantation trials was performed on patients suffering from either Huntington's or Parkinson's disease. However, the technique has also been applied to patients with macular degeneration, stroke and, most recently approved, children with Batten's disease. More recently, there has been some forays into gene-therapy-based approaches. Below we will review the finding from these previous transplantation trials, with an emphasis on calling out those features that are amenable to improvement in future studies.

Parkinson's Disease

Parkinson's disease (PD) is characterized by relatively selective loss of the dopaminergic neurons in the nigrostriatal tract, though all brain regions are ultimately affected in later stages. Nigrostriatal degeneration results in a well-characterized syndrome of progressive rigidity, bradykinesia, tremors, poor gait/balance, and later dementia in many patients. The first human neural transplants involved unilateral stereotactic injection of mesencephalic dopamine neurons, obtained from 7 to 9 weeks gestational age human fetuses, into the putamen of long-term Parkinson's patients^{2–11}. These trials delivered initially encouraging results. Imaging studies (PET or MRI) revealed graft viability and recipients exhibited motor improvement, with reduced medication doses.

Because initial trials were all unblinded, concerns over the placebo effect prompted more sophisticated trials. These included sham surgery and blinded rating of imaging results. In a larger trial reported by Freed and colleagues¹² 40 PD patients, ranging in age from 34 to 75 years old, received either embryonic mesencephalic neuroblasts/neurons or sham surgeries and were followed, double-blind, for the succeeding 12 months. They found that although the transplanted cells survived transplantations, the procedure only seemed to clinically benefit younger (younger than 60 years of age) PD patients. Unfortunately, the more carefully this promising therapy was evaluated, the less 'promising' it appeared¹³. Some patients developed uncontrollable dyskinesia, presumably due to aberrant axon regrowth; many showed limited improvement. However, this approach has fallen out of favour because it neither slows disease progression, nor is it more effective than aggressive medication, and probably less effective than deep brain stimulation.

With a guide to designing future therapies, it is interesting to note that on analysis some transplanted neurons developed Lewy bodies^{14,15}. This finding suggests that merely placing new tissue into an inhospitable (deteriorating) brain is not a viable solution. The most recent regenerative trials for PD have focused on changing this environment by providing additional trophic support. Specifically, there have been attempts to augment glial-cell-derived growth factor (GDNF) levels in the striatum, as this protein has shown a significant ability to protect dopaminergic neurons from a variety of experimental insults. The farthest along trial involved direct infusion of GDNF into the putamen¹⁶. The preliminary results of these studies are again promising, but only time will tell^{16–18}. The current trend in PD trials is towards use of adeno-associated virus (AAV) to deliver and induce production of the therapeutic factor (neurturin, a GDNF-like ligand¹⁹) or enzyme (glutamic acid decarboxylase²⁰; aromatic L-amino acid decarboxylase²¹).

Alzheimer's Disease

In contrast to PD, only one group has made any progress towards applying regenerative medicine to Alzheimer's patients. The two trials differed in their technical approach, but shared the goal of delivering nerve growth factor (NGF), a survival factor for cholinergic neurons, to the brain regions suffering cholinergic neuron loss. Using an *ex vivo* gene therapy approach, they implanted fibroblasts that were engineered to secrete NGF²². The other study used *in vivo* gene therapy, utilizing AAV to induce local NGF production²³. The initial results seem promising, but the long-term benefit and safety is an open question.

Huntington's Disease

Huntington's disease (HD) serves as a model neuropsychiatric disorder, despite being a relatively rare disease (7 per 100 000 persons). A toxic gain-of-function mutation (polyglutamine trinucleotide repeat expansion) in the huntingtin protein causes this dominantly inherited movement disorder. Huntingtin is widely expressed throughout the brain, resulting in personality changes or other psychiatric manifestations that may precede overt motor symptoms by almost a decade. However, it is the striking degeneration of the striatum that burdens patients with its characteristic choreoathetoid movements. Eventually, all patients will suffer major psychiatric symptoms, and if they live long enough, dementia will ensue (DSM-IV; 294.1 Dementia Due to Huntington's Disease).

Transplantation trials in HD were contemplated soon after the purported 'success' of foetal neural transplant in PD patients. These open label trials (i.e. no sham surgery) entailed transplantation of committed neuroblasts from foetal human striatum into the brains of moderately affected HD patients^{24,25} (and later^{26,27}). The results of these trials appeared mixed. Bachoud-Lévi and colleagues reported that on two-year follow-up, three out of five transplant recipients exhibited improvement of both motor and cognitive symptoms^{28,29}. These improvements correlated recovery of metabolic activity in the specific striatal location of the transplants, as well as connected regions of the cortex. In contrast, another group following seven patients used PET to examine graft survival. They found evidence of poor graft survival/function. Moreover, they could not demonstrate a significant relationship between changes in PET and clinical function, forcing them to conclude that there was no benefit from transplantation³⁰.

On longer-term follow-up, Bachoud-Lévi and colleagues found mixed results with regard to improvements in motor symptoms. Among those patients who displayed an improvement at two years, chorea remained stable at an improved level for the following four years³¹. While chorea was improved, dysomnia became steadily more prominent, paralleling the results in PD transplant trials. More encouraging were their observations of limited cognitive decline among initial responders. They showed no worsening on the Mattis dementia rating scale and only slight worsening on the Trails A. Although the relatively small numbers of these follow-up studies makes it difficult to draw any major conclusions, they suggest that transplants in HD may be more beneficial than in PD. Unlike PD, there are very few pharmacological interventions for HD, making an invasive procedure like cell transplant more appealing. Still, it seems apparent that transplantation is not going to become more pervasive until concomitant neuroprotective treatment becomes available. On a more general cautionary note, there are at least two documented cases of tumour formation among patients who have received cell transplants^{32,33}, raising the spectre of additional safety concerns.

REGENERATIVE CAPACITY OF ADULT BRAIN

A Brief History of Adult Neurogenesis

For nearly the entire twentieth century the regenerative capacity of the adult brain was considered to be almost nil. It was dogma that the number of neurons in the adult mammalian brain was fixed near birth. This sentiment was reflected by the great neuroanatomist Santiago Ramón y Cajal, who wrote, 'Once development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In adult centers, the nerve paths are something fixed,

and immutable: everything may die, nothing may be regenerated³⁴. As early as 1897 there was evidence for undifferentiated cells in the adult brain that had the potential to become either neurons or glia; however, this view was not accepted for almost another century. (Charles Gross provides a fascinating historical accounting of this cautionary tale of scientific sophistry and denial³⁵.)

In the early 1990s, Reynolds and Weiss demonstrated that one could easily isolate multipotent progenitors from the adult mouse striatum. These precursors expanded in culture by application of epidermal growth factor (EGF) and then directed towards differentiating into neurons or glia^{36,37}. More than anything, the ease with which other laboratories could replicate their findings ushered in the acceptance of adult neurogenesis. Subsequently, Eriksson and colleagues examined the postmortem brains of cancer patients who received BrdU as part of their chemotherapy regimen. They found that this thymidine analogue, which is incorporated into replicating DNA, was present in adult borne hippocampal neurons³⁸. This elegant study was later extended and replicated, demonstrating a similar neurogenic zone in the subventricular zone (SVZ), neatly paralleling previous animal studies^{39–41}.

The lingering question of why all mammals retain this form of plasticity has yet to be answered satisfactorily. That the hippocampus plays a critical role in short-term memory formation and is implicated in emotional regulation suggests that adult neurogenesis plays an evolutionarily conserved role in these processes. The most straightforward evidence suggests that adult neurogenesis plays a role in memory formation. For example, the two most potent stimulators of adult neurogenesis, exercise and environmental enrichment, increase hippocampal neurogenesis and improve performance on cognitive tasks like the Morris water maze, even among aged animals. These improvements are only seen with tasks that are hippocampus-dependent (e.g. the water maze), but not with hippocampus-independent learning (e.g. active shock avoidance or delayed eye blink) (reviewed by ^{42–45}).

Neural Stem Cells and Their Environment

What is a neural stem cell?

Throughout our lifetime new neurons are generated from nascent precursors termed neural stem cells. ‘Stem cells’ have garnered tremendous popular and scientific attention over the past several years, but this raises the question of what is a neural stem cell? Since the discovery and acceptance of adult neurogenesis over 10 years ago, the field has been mired by confusing language and inconsistent definitions of what it means to be a neural stem cell⁴⁶. In order to avoid such confusion, the following definitions will apply throughout this chapter: a neural stem cell is one that self-renews and has the potential to give rise to multiple cell lineages. Precursors (e.g. adult hippocampal precursor; AHP) are proliferating multipotent cells that do not self-renew. It is often difficult to experimentally distinguish NSCs from multipotential precursors. Therefore, in the absence of data showing that a cell truly self-renews, it is more conservative to refer to multipotent cells as precursors, and not stem cells. In contrast, lineage committed progenitors (e.g. neural progenitors) are rapidly proliferating cells whose differentiation potential is limited to one cell type.

Emergence of adult NSCs

The earliest NSCs begin their life as a thin layer of symmetrically dividing neuroepithelium lining the neural tube. In later embryonic

development, these neuroepithelia become radial glia, which support the migration of migrating neuroblasts. These radial glia persist in the neonatal brain and ultimately transform into an astrocytic subtype with the properties of an NSC⁴⁷. These NSC appear to constitute two preserved germinal centres in the adult mammalian brain, one in the SVZ and the other in the subgranular zone (SGZ) of the hippocampal dentate gyrus. The former migrate through the rostral migratory stream (RMS) to take up residence in the olfactory bulb, while the latter migrate a short distance to form the dentate granule cells⁴⁷.

Neurogenic stem cell niche

The anatomy of these two neurogenic region shares many similarities. Both constitute thin strips containing small clusters of proliferating cells (types A/G, B, C/D) in close opposition to vascular endothelium^{48,49}. The type B cells are slowly proliferating, self-renewing astrocytes that are the real NSCs in these regions. The C (SVZ) and D (SGZ) cells are more rapidly dividing neural progenitors (transit amplifying), while the A (SVZ) and G (SGZ) cells are the immature neurons. The intricacies of the anatomy and the developmental process are far too complex for this discussion and are reviewed extensively elsewhere^{47,49}. What is important is to recognize that the NSCs, their progeny and their blood supply reside in close opposition, creating a somewhat self-contained microenvironment. This specialized milieu is termed the stem cell niche⁵⁰.

Three compartments comprise this niche: ultrastructure, cells and milieu. (i) Ultrastructure: extracellular matrix and other cellular scaffolding maintain the gross cytoarchitecture of specific brain regions. Since guidance molecules are immobilized on these scaffolds, their loss can cause aberrant dendritic arborization and impaired axonal pathfinding of transplanted/regenerating neurons. (ii) Cellular components include NSCs, astrocytes (supportive and immunological), neurons, oligodendrocytes, microglia, and vascular endothelium and smooth muscle. (iii) The milieu is a metastructure composed of the many dynamically regulated, diffusible factors released by the constituent cells. Gradients of these factors are responsible for coordinating: (i) homing of immune cells; (ii) migration of neuroblast during foetal development (or transplanted neural stem cells); and (iii) neuritogenesis and synaptogenesis.

Niche Function

The niche, like a womb, creates a uniquely nurturing environment to support the birth and development of NSCs into full-fledged neurons. In addition to this supportive function, it serves to insulate the NSCs from the greater milieu. The constituent cells create this environment and generate the milieu, and in turn, each is impacted by it. Therefore, no cell is an island (with apologies to John Donne), the fate of each intimately affected by its neighbours. *In toto*, the niche preserves the delicate balance between NSC maintenance and differentiation and directs lineage decisions.

How is the niche regulated?

The SVZ/SGZ niche contains cells in various stages of development, from stem cells to committed progenitors to maturing neurons, as well as vasculature and ependyma (SVZ). As such, the developing NSCs are subjects to a host of intrinsic (e.g. neighbouring

Table 55.1 Niche targets for future gene therapy trials

<i>Secreted proteins</i>	<i>Niche effects</i>
Bone morphogenic protein4 [BMP4]	Astroglial differentiation
Brain derived neurotrophic factor [BDNF] ^a	NPC/neuron survival
Ciliary neurotrophic factor [CNTF] ^a	Astroglial differentiation
CCL5 (Rantes)	NSC quiescence
CXCL12 (SDF1 α)	NPC chemoattractant, NSC
CX3CL1 (Fractaline)	NPC differentiation
Epidermal growth factor [EGF]	NSC/NPC survival and proliferation
Erythropoietin ^b	NPC differentiation
Fibroblast growth factors [FGF-2/FGF-20] ^a	NPC proliferation
Glial-derived neurotrophic factor [GDNF] ^a	Neuron survival
Granulocyte macrophage colony stimulating factor [GM-CSF] ^b	Neuronal differentiation
Hepatocyte growth factor (HGF) ^a	NPC/neuron survival
Insulin-like growth factor 1 [IGF-1] ^b	NPC proliferation, neuron survival
Leukaemia inhibitory factor [LIF]	NSC proliferation and survival
Neurotrophin 3,4/5 [NT3, NT4/5]	Neuron survival
Nerve growth factor [NGF] ^a	Neuron survival
Platelet-derived growth factor [PDGF] ^b	OPC proliferation and survival
Progranulin [PGRN]	Neuronal survival (?), anti-inflammatory(?)
R-spondin [RSPO ^a]	NPC proliferation (?)
Transforming growth factor beta [TGF β]	Neuronal differentiation, anti-inflammatory
Vascular endothelial growth factor [VEGF] ^a	Angiogenesis, NPC/neuron survival
Wnt3,Wnt7a, Wnt8b	NSC/NPC proliferation and survival
Wnt5a, Wnt7b	Neuronal differentiation

NSC, neural stem cell; NPC, neural progenitor; OPC, oligodendrocyte progenitor.

^aUsed in clinical trials.

^bFDA approved (alternate indication).

cells) and extrinsic (e.g. from blood or CSF) cues. These ‘niche players’ represent the prime targets of proposed gene therapy protocols. Formally, there are three forms of signalling at play: (i) externally derived signals conveyed via the blood (endocrine) or CSF (exocrine); these include diffusible factors like muscle-derived IGF-1 or VEGF, or inflammatory cytokines (e.g. interleukin-6, IL-1 β or tumour necrosis factor alpha; TNF α); (ii) paracrine factors produced by local astrocytes or neurons (e.g. BDNF, FGF-2, Wnt, neurotransmitters); and (C) cell-autonomous signalling, which includes autocrine factors like Wnt or PDGF as well as genetically pre-programmed differentiation^{51–53}.

Table 55.1 summarizes some of the most prominent modulators of the adult NSC niche; however, the full panoply of secreted factors influencing the niche is far too extensive for the confines of this chapter (for review see^{54–62}).

‘Normally’ aging niche

Neurogenesis reduces by more than 50% with advancing age. Some of the non-mutually exclusive hypotheses put forth to explain this observation include (i) functional, active downregulation⁶³; (ii) inflammation⁶⁴; (iii) burnout/depletion of stem cells (e.g. secondary to reduced Wnt⁶¹); (iv) niche changes that directly suppress trophic support⁶⁵; (v) reduced circuit activity, which in turn could decrease BDNF/trophic support⁶⁶; (vi) elevated cortisol, which accompanies normal ageing⁶³; (vii) reduced physical activity, which reduces IGF-1, again, limiting trophic support^{67–71}; and (viii) less intellectual stimulation might functionally reduce need for neurogenesis or might limit circuit activity indirectly (intellectual

reserve hypothesis⁷²). Intriguingly, exercise, environmental enrichment, cortisol reduction and inflammatory blockade all improve neurogenesis in older animals to near youthful levels and improve cognition^{73–76}. Therefore, even though the aged brain exhibits lower baseline plasticity, it retains the capacity for regeneration, if properly stimulated. These provide additional scientific unpinning for ongoing trials of their efficacy in patients with cognitive impairment. (The reader should consult⁷⁷ for a systematic review of neurogenesis and ageing. However, for a more general review of age-related plasticity changes, consider^{78,79}.)

Neurogenesis and psychiatric illness

There is conflicting evidence about whether aberrant hippocampal neurogenesis underlies the aetiology of major depression or anxiety disorder. However, there is mounting evidence that neurogenesis is required for the beneficial effects of antidepressants. Without exception, all effective treatments for depression, including all classes of antidepressants, lithium and electroconvulsive therapy, stimulate neurogenesis, while chronic stress, which predisposes depression suppresses neurogenesis in animal models. Similarly, infusion of neurogenic stimulators like BDNF, IGF-1, FGF-2 and VGF produces antidepressant/anxiolytic effects, with the expected delay in onset. More recently, it was shown that ablation of neurogenesis blocks the beneficial effects of antidepressants on mood and cognition^{80–85}.

Niche and neurodegenerative disease

A host of pathologies, many associated with older age, can comprise niche function. Broadly, they do so in three ways: (i) generation of

an actively toxic environment by inflammation, increased expression of trophic antagonists or neurotoxins (e.g. soluble A β); (ii) development of a passively non-permissive environment through loss of trophic support (e.g. reduced BDNF, WNT, IGF-1, VEGF etc.) or vascular insufficiency; and (iii) structural damage from trauma or stroke. Because each neuropsychiatric disease differs in its underlying pathology, lesions to the neurogenic niche will differ as well. Since any cellular replacement/repair strategy requires recreating the niche (see below), an understanding of how the niche is compromised is an absolute prerequisite for the development of effective treatments.

Alzheimer's is the most common progressive neurodegenerative disease. It is characterized by early loss of short-term memory. Hippocampal involvement occurs early in the disease course, unlike PD or HD. As recently reviewed⁸⁶, there are conflicting reports in the literature as to whether hippocampal neurogenesis is increased or decreased early in the disease course^{87–89}. The emerging picture suggests that early on modest cell loss triggers a compensatory increase in neurogenesis, probably via increases in FGF-2. However, the underlying pathology prevents survival of sufficient neurons to have a clinical impact. Later on, neurogenesis is uniformly impaired, paralleling the clinical picture. From the perspective of future therapies, it is interesting to note that exercise and environmental enrichment improve neurogenesis and cognitive performance, despite equal β -amyloid plaque loads^{90,91}.

A common feature of patients with AD, PD, HD and even non-specific mild cognitive impairment (MCI) is that they exhibit significantly impaired olfaction before the onset of more defining features (e.g. abnormal movements in PD)^{92–96}. It is tempting to speculate that the cause is alterations in the SVZ niche, since the primary role of adult SVZ neurogenesis is to supply new neurons to the olfactory bulb. Interestingly, when one examines the SVZ in patients with these three diseases, each displays a unique cytoarchitectural pathology. In AD, there is diffuse cell loss in regions with A β accumulation. In contrast, in PD, there is an SVZ thinning and 30% reduction in NSC proliferation, primarily reflecting a loss of type C (transit amplifying) progenitors and type A (immature) neurons. Examination of the SVZ in HD provides us with the most illuminating observation. The SVZ in HD is more than twice as thick as in age-matched healthy brains, even though AD, PD and HD are all characterized by profound neuronal loss. This increase is due almost exclusively to a doubling in the number of type B cells (radial glia/NSCs). Unlike in stroke patients, it appears that these cells never mature enough to leave the niche, hence never migrating to the lesioned area (i.e. striatum)⁹⁷.

Neurogenesis and stroke

Stroke represents a physiologically unique aetiology of cognitive impairment and mood dysregulation in the elderly. Up until the time of the ischaemic event, baseline regenerative mechanisms are unimpaired, unlike progressive neurodegenerative diseases like AD or PD. For this reason, the post-insult neurogenesis is far more robust than in AD, PD or HD. Initially, neural progenitors from the striatal SVZ migrate towards the area of inflammation created by the infarct. Neurogenesis in the region of the infarct can persist for upwards of four months in both humans and animal models^{98–101}, while the damage in younger patients can be mitigated by administration of erythropoietin¹⁰² or GM-CSF¹⁰³ (as reviewed in¹⁰⁴).

ADVANCED THERAPEUTIC TECHNOLOGIES

The terminology used for describing new technique or technologies can often be confusing; regenerative medicine is no exception. For simplicity's sake, let us define a few of these terms. *In vivo* gene therapy is the introduction of a novel gene into the patient. Most often, the goal is to raise above baseline the endogenous levels of some beneficial protein (e.g. infecting the striatum with a virus that over-expresses GDNF: see above). Somatic cell therapy is where primitive cells are engrafted into a region with the hope that they will integrate and subserve some function. The early foetal tissue transplants were an example of this type of therapy. *Ex vivo* gene therapy is a hybrid of the gene and cell therapy. In this model, cells (e.g. stem cells, fibroblasts) are engineered to express and release the protein of interest. In other words, they serve as living, implantable minipumps. Finally, there are advanced pharmaceuticals, which includes just about everything else. These can be engineered proteins (e.g. recombinant IGF-1 which is FDA approved for use in children with growth defects), small molecules (classic drugs), therapeutic antibodies, vaccines, interfering RNAs etc. In this section we will introduce cutting edge reagents and vectors that are being deployed in the coming generation of neural-repair trials

Cell-based Therapy

Cell-based therapy has received tremendous attention in recent years, as judged by both the volume of published review articles extolling its virtues and the volume of political debate regarding its use. People conceive of these cells as a ready source of spare parts that could be used to replace the damaged tissue. This conceptual simplicity belies quite significant technical challenges.

Newer transplantation trials propose using one of the following types of stem cells: (i) neural stem cells (NSC): possess the ability to differentiate into neurons, astrocytes or oligodendrocytes, but no other tissues; (ii) embryonic stem cells (hESC): blastocyst-derived pluripotent cells can give rise to any cell type in the body (in theory); and (iii) induced pluripotent stem cells (iPSC): pluripotent cells derived from a more mature cell type by genetic reprogramming with a panel of transcription factors. Since iPSCs can be derived from living patients, they hold great prospective value for modelling disease, as well as holding therapeutic potential. However, they are a less than two-year-old technology and many clinicians may be unfamiliar with them. Smith and colleagues provide a fuller discussion comparing and contrasting iPSCs and hESCs¹⁰⁵.

Even though no successful stem cell trial has been completed, the reader should already have a sense that no type of stem cell is the 'magic bullet' many had hoped for¹⁰⁶. Each has significant limitations, as well as advantages, some of which are summarized in Table 55.2. Any pronouncement on which prove to be therapeutically useful would be mere speculation. Instead, the clinician and translational researcher should focus on what it would take to make any therapeutically useful.

First, we need to understand what we expect of these transplanted cells. (i) The transplanted stem cells must differentiate into the proper cell type and subtype (e.g. dopaminergic neurons, rather than glia); (ii) they must migrate into the correct position to integrate with the intact circuitry; (iii) they must survive in an environment already compromised by the underlying disease (i.e. survive immune attack, inflammation, apoptosis secondary to inadequate trophic support etc); and (iv) they need to remain differentiated and not

Table 55.2 Resources for cell-based therapy

	<i>Source</i>	<i>Application</i>	<i>Advantages</i>	<i>Disadvantages</i>
Foetal neural stem cells	Abortus	Replacement	Large expansion capacity Steady supply of tissue Low transformation potential High differentiation potential	Heterologous donor Difficult to sort tissue
Adult NSC	Postmortem brain, biopsy (?)	Replacement	Autologous (potentially)	Limited expansion capacity
Embryonic stem cell	Derived from discarded blastocysts	Replacement	Limited tissue supply Pluripotent	High teratoma risk Heterologous donor Chromosomal instability Religious/political complications Few available lines Potential transformation
Induced pluripotent stem cells	Skin biopsy or hair samples (fibroblast-keratinocyte)	Replacement	Autologous	
Hematopoietic stem cell	Blood sample	Create vascular niche, anti-inflammatory	Easily purified Easily acquired Autologous grafting Autologous	May be useless May not migrate sufficiently
Engineered fibroblast-keratinocyte	Skin biopsy or hair samples	Ex-vivo gene therapy (minipumps)		
Immortalized cell-lines	Mixed	Replacement	Easy to grow	Poor function High tumour risk Archaic technology

NSC, neural stem cell.

malignantly transform as occurred in several early gene therapy and foetal cell trials^{32,107}.

Second, getting transplanted stem cells to differentiate and integrate in non-neurogenic regions represents the greatest technical hurdle that must be overcome (points i and ii above). When foetal NSCs, and later hESCs, were first derived, there was a fanciful belief that being fully plastic (i.e. pluripotent) meant that they could be engrafted into a brain region. Once there they would grow into the region, as the native cells had done during foetal development. Since this was another case of wishful thinking, a limitation common to all three stem cell types is that they will require cellular programming prior to engraftment. As a field, we have made the greatest strides towards converting stem cells into dopaminergic neurons^{1,108,109}. However, even here the programming efficiencies are low, and the developmental programme traversed is poorly understood. (The reader wishing a better understanding of these complexities should consult the following recent reviews^{110,111}.) Unfortunately, even less is known about coaxing these cells to properly integrate into the existing neuronal network. In short, the first few steps in making stem cells therapeutically useful are, truly, big steps indeed.

Third, safety concerns by the FDA and individual IRBs have been the primary holding up to initiation of many stem cell trials. Because hESCs universally form teratomas when injected into animals, it is unlikely that they, in their unadulterated form, will ever be used in human trials. Even the very first clinical trial of an hESC-derived progenitor was on an extended hold by the FDA until early 2009^{112,113}. How real these safety concerns are is a matter of debate, but one that is sure to continue for several years.

Gene Therapy Vectors

W. French Anderson reported in the autumn of 1990 the first gene therapy trial on a patient suffering from a form of severe combined immunodeficiency (SCID). Almost three decades later, the only broadly successful application of gene therapy has been in the treatment of SCID¹¹⁴. It is hard to overstate the disappointment that, with over 1 500 approved clinical trials worldwide (many prematurely aborted), successes are so few and setbacks all too prominent^{115,116}. The darker side of its major 'success' is that in the European trial, four patients who had received retroviral-based gene therapy for X-linked SCID went on to develop leukaemia. These malignancies were

Table 55.3 Most common gene therapy vectors

<i>Vectors</i>	<i>Advantages</i>	<i>Limitations</i>
Virus		
Retrovirus	Integrating	Dividing cells ONLY
Integrating	Broad tropism	Preferential insertion in active genes, particularly those regulating cell proliferation
	Moderate transgene size	High oncogenic potential
	Long-term expression	
Lentivirus	Integrating	Oncogenic potential
Integrating	Infects quiescent cells	Modest diffusion
	Broad tropism	
	Moderate transgene size	
	Long-term expression	
Herpes virus	Large transgene size	High inflammatory potential
Episomal		Transient expression in non-neuronal cells
AAV	High-titres	Smallest transgene capacity
Episomal (90%)	Highly-specific tropism	Highly-specific tropism
Integrating (10%)	Low inflammatory potential	
	Serotype-9 crosses blood–brain barrier	
Adenovirus	Large payload	High inflammatory potential
Episomal	Efficient transduction	Poor diffusion
		Short-term expression
Naked plasmid DNA-liposome ¹³⁹	Large payload	Poor transduction
	Easy to purify	
Blood-brain barrier translocators		
Carrier-mediated peptide transport	IGF-1, EGF	No carrier for most proteins
Receptor-mediated transcytosis	Highly adaptable to different proteins	Unproven in clinical trials
	RMT-BDNF entering clinical trials	
Cell-penetrating peptides	Highly adaptable to different proteins	Unproven in clinical trials
Intranasal delivery	Positive clinical improvement in clinical trials of stroke and Alzheimer's	Highly variable dosing and penetration

the result of the retrovirus preferentially inserting into the promoter of the *LMO2* gene (in two cases), a known T-cell oncogene.

Most gene therapy trials were designed to treat cancer (65%), where the goal is to arrest proliferation and foster death in the target cells. As neuropsychiatrists, our goals for gene therapy are diametrically opposite; preservation of neurons forces us to develop our own 'personalize toolbox'. To illustrate the shortcoming of applying previous trials' technique to problems of neurodegeneration, consider the following. The earliest (and only successful) trials used Moloney murine leukaemia virus (MMLV) based retroviral vectors. Like all oncoretroviruses, they only infect dividing cells, making them almost useless for treating the CNS (i.e. mature neurons do not divide). The alternative for initial trials, adenoviral vectors, can infect CNS, but have demonstrated extremely limited CNS penetration and the potential for severe inflammation. (Such inflammatory induced multi-organ failure led to the high-profile death of a relatively healthy clinical trial volunteer in 1999¹¹⁷.) Together these help to explain why just 1.8% ($n = 27$) of clinical gene therapy trials have been approved for neurological disease, and only half of those for treatment of the brain (see the Gene Therapy Clinical Trials Worldwide database¹¹⁸).

These recognized shortcomings help define the requirements for the next generation of neuro-gene therapy tools. CNS gene therapy vectors must (i) possess the ability to infect non-dividing cells; (ii) carry the gene of interest to the intended target; (iii) be able to express the gene and resist the cell's natural defences, thereby preventing it from

being turned off; and (iv) be safe (i.e. not induce malignancy transformation or severe inflammation, two primary causes of morbidity and mortality in previous gene therapy patients^{107,117}).

Engineered viruses carrying a therapeutic gene remain the mainstay of proposed trials. Lentivirus (HIV-based) and adeno-associated virus (AAV) vectors are the two most popular viral vectors for current trials. They possess the desirable traits of low inflammatory response, good gene transduction and long-term gene expression. Table 55.3 summarizes the strengths and weaknesses of these and other gene therapy vectors (reviewed by^{115,119–123}).

Interfering RNA

Until recently it was thought that most RNA transcribed from our genomes was either translated into protein or incorporated into ribosome function (i.e. rRNA, tRNA). Now, it is believed that much, if not most, RNA is actually regulatory in nature. These short RNA species (RNAi) are able to complex with coding RNAs, thereby regulating protein production. The therapeutic potential of RNAi for treating cancer or HIV has garnered a great deal of press (and the 2006 Nobel Prize). In brief, the utility of RNAi is to reduce expression of some undesired mutant gene (a.k.a. toxic or gain-of-function mutation) like the bcr-abl fusion mutant found in chronic myeloid leukaemia. In psychiatric disease, some examples include AAV-delivered RNAi targeting the tau, and APP mutations found in

AD and frontotemporal dementia (FTD) or mutant huntingtin^{124–126}. At the time of this writing no RNAi-based therapy for a CNS disorder has reached the stage of approved clinical trial; however, this is likely to change in the coming years. This subject has been reviewed extensively elsewhere^{127–129}.

Rethinking Clinical Trials

This section title begs the question, why do we need to change how we conduct clinical trials? Even though the mathematics behind selecting trial sample sizes is well understood¹³⁰, the psychiatry literature suffers from an unfortunately large number of studies being ‘underpowered’ for their purpose (power being the probability of concluding a benefit when there actually is one.) The primary culprit is not academic laziness, but arises from the fact that the statistical design of most trials requires that end-points and sample sizes must be fixed ahead of time. The more complex a trial, the more likely that these *pre hoc* assumptions will be wrong. While space limitations prevent a lengthy discussion of clinical trial design, it is important for the reader to understand that there is an alternative to designing exploratory trials around proving or disproving a null hypothesis. These Bayesian designs provide several advantages, including (i) allowing adaptive sizing of arms, midway in trial; (ii) measuring probabilities for non-directly observable events; (iii) incorporating prior knowledge; (iv) allowing smaller trials with the same statistical power; and (v) cross-arm information sharing, allowing more treatment variables. All of these will be invaluable for future gene therapy trials where such trials will require multifactor treatments and small sample sizes. For a more complete discussion of Bayesian statistics and their application to clinical trial design, the reader is referred to one of the following^{131–136}.

Neural Repair Finds Its Niche: Where Do We Begin Putting All the Pieces Together?

Many would begin by asking the question: what do we want to treat? However, we should ask: what are we willing to treat? It was proposed several years ago to apply gene therapy towards the treatment of anxiety/stress disorder¹³⁷. The great philosopher (and baseball player) Yogi Berra reportedly quipped, ‘In theory there is no difference between theory and practice. In practice there is.’ Many illnesses we confront in geriatric psychiatry could, in theory, be treated with gene therapy or stem cells, but would we? All proposed gene- or cell-based therapy trials are invasive and present a high risk of morbidity. As with our anxiety example, when would we recommend brain surgery with gene therapy over a larger dose of diazepam? The risk versus benefit calculation has always been such that we will only consider these treatments for the worst afflicted patients (i.e. the ones with little to lose). Since these are the hardest patients to treat, we have made the already daunting task of perfecting regenerative therapy even harder.

To resolve our conundrum and bring these therapies into clinical practice, we need to complete many, many more clinical trials. Therefore, we need to make the trials less invasive, and thus less risky, thereby allowing us to treat less sick individuals. An example might be a regenerative trial in patients with early stage HD. Preclinical studies demonstrate that viral cotransduction of BDNF to promote survival and Noggin to block astrocytosis regenerates medium spiny neurons in the striatum¹³⁸. Directly translating these animal studies into a clinical trial would be the ‘sexy’ approach. The theoretical grounds for such a trial are sound, but in practice it would be *extremely* difficult to obtain IRB approval for a two-gene therapy trial. A pragmatic, though less flashy, alternative is to determine whether some combination of available drugs might induce the same regeneration (see Table 55.4). For illustration purposes, we are

Table 55.4 FDA approved drugs with neuroregenerative potential

	Target	NSC	NPC	OPC	Mature neurons/oligos
<i>Drug</i>					
Antidepressants (↑ 5HT/NE/DA)	Increased circuit activity Increased BDNF		S	S	D, S
Indomethacin	Anti-inflammatory			S	S
Lithium	GSK-3 β	P	P	P	
Lovastatin (?)	GSK-3 β (?)		P (?)	P (?)	
Milrinone, rolipram	PDE3/4				D, S
Rosiglitazone	PPAR γ				D
Valproic acid	HDAC GSK-3 β (?)	I	I	I	D, S
<i>Peptide</i>					
IGF-1		P (?)	P, S	P, S	D, S
Erythropoietin					D Angiogenesis (?)
GM-CSF					D
PDGF				D, S	
<i>Other</i>					
ECT	Increased circuit activity Increased BDNF		P	?	D, S
DBS/rTMS	Increased circuit activity		P (?)	?	?

NSC, neural stem cell; NPC, neural progenitor; OPC, oligodendrocyte progenitor.

I, inhibits proliferation; D, promotes differentiation; S, promotes survival; P, increases proliferation.

finalizing the Bayesian framework for such a trial comparing IGF-1 treatment paired with combinations of VPA, lithium, rasaglitazone and indomethacin.

The list of approved drugs with regenerative potential is growing, but is still quite limited. Therefore, most approaches to neuro-repair will ultimately require either gene therapy and/or cell-based therapy. The process needs to be a rational one, not relying on serendipity. In its most basic form it should entail

1. *Careful target selection*: identifying the biological target in need of correction (e.g. loss of dopaminergic nigral neurons);
2. *Payload*: design the actual treatment. A good basis for selecting these comes from our previous discussion of the neural stem cell niche, in health and disease;
3. *Vector/delivery*: engineer a means of getting it to the right place;
4. *Surveillance*: devise a way of monitoring the treatment (i.e. is it working?).

In summary, the best guide for future trials may be simply not to repeat the naïve mistakes of the past, most notable ignoring the essential role of the neurovascular niche in supporting and guiding neural regeneration. If we take such care then future editions of this text will likely contain more discussion of treatments at hand, and less hand-waving about the treatments of the future.

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Vascular Dementia

Ingmar Skoog

*Institute of Neuroscience and Physiology, Unit of Neuropsychiatric Epidemiology,
Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden*

BACKGROUND

Cerebrovascular disorders are generally believed to be the second most common cause of dementia, after Alzheimer's disease (AD). Dementia caused by cerebrovascular disease is often labelled vascular dementia (VaD). AD and cerebrovascular disease often co-exist in the same patient. This condition is termed mixed dementia¹. Cerebrovascular disorders are also associated with cognitive decline which does not reach diagnostic thresholds for dementia^{2–6}. The term vascular cognitive impairment was introduced by Bowler and Hachinski in 1995⁷ to capture the whole range of cognitive dysfunction associated with vascular disease. This term thus includes VaD, mixed dementia and other forms of cognitive decline caused by cerebrovascular and cardiovascular diseases. It is important to recognize that cognitive impairment associated with cerebrovascular or cardiovascular disorders is potentially preventable or treatable.

DIAGNOSTIC CRITERIA AND DEFINITIONS

The most often used criteria for VaD were developed almost two decades ago. ICD-10 was published in 1993⁸, DSM-IV in 1994⁹, and the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria were published 1993¹⁰. These criteria show inconsistencies, and give rise to very different rates of VaD^{11,12}.

Definition of Dementia and Cognitive Decline

Cognitive function declines with increasing age. The decline may be accelerated by a range of insults to the brain, such as AD, cerebrovascular disease, other brain disorders, and various peripheral disorders such as cardiovascular diseases (CVDs). When the cognitive function reaches a certain threshold, and gives rise to difficulties in everyday life, the term dementia is used.

In criteria such as those of the ICD-10⁸ and DSM-IV⁹, dementia is a global decline in intellectual function involving memory, orientation, visuospatial abilities, executive function, language, thinking and often changes in personality and emotions. One problem with these criteria is that they state that memory impairment is mandatory for a diagnosis of dementia. This concept is based on the symptoms of AD,

and misses a large proportion of individuals with severe cognitive dysfunction associated with impairments in activities of daily living (ADLs) and personal function, as cerebrovascular disease may cause significant cognitive dysfunction with relatively preserved memory function⁷.

Definition of Cerebrovascular Disease

Many different cerebrovascular diseases may cause cognitive decline and dementia, including stroke, silent infarcts, ischaemic white matter lesions (WMLs), hereditary cerebral haemorrhage with amyloidosis, granular cortical atrophy, hypertensive encephalopathy, cerebral amyloid angiopathy and cerebral vasculitis (Table 56.1). Most cases of VaD have a mixture of cerebrovascular changes, which could be expected, as different cerebrovascular diseases share similar risk factors. The two most common causes of VaD are stroke and WMLs. However, most criteria highlight clinical strokes in their definitions of cerebrovascular disease. Thus, the definition of cerebrovascular disease is based on the presence or history of focal neurological motor symptom/signs, or brain imaging findings of cerebrovascular disease. DSM-IV lists examples of signs, while the ICD-10 specifies that at least one should be unilateral spastic weakness of the limbs, unilateral increased tendon reflexes, extensor plantar response or pseudobulbar palsy.

The DSM-IV requires that there should be signs *and* symptoms *or* laboratory evidence of cerebrovascular disease (i.e. that brain imaging reveals 'multiple infarctions in the cortex and subcortical white matter'), while ICD-10 requires evidence from history, examination *or* tests of significant cerebrovascular disease (i.e. history of stroke or evidence of cerebral infarction on brain imaging). In the NINDS-AIREN criteria¹⁰, a diagnosis of probably VaD requires that focal signs consistent with stroke *and* relevant cerebrovascular disease by brain imaging should be present. One of the authors of the NINDS-AIREN criteria published a modified version a year later¹³, in which this criterion was changed to focal signs consistent with stroke *or* relevant cerebrovascular disease by brain imaging. The first version is far too strict and underestimates the occurrence of VaD¹¹, since it will exclude individuals without stroke symptoms (including those with silent infarcts or white matter lesions). In a study on 85-year-olds¹⁴, 13% of the demented had VaD based on the first version (i.e. 'focal signs consistent with stroke *and* relevant cerebrovascular disease by

Table 56.1 Causes of vascular dementia

Stroke
Silent infarcts
Ischaemic white matter lesions (WMLs)
CADASIL
Hereditary cerebral haemorrhage with amyloidosis
Granular cortical atrophy
Hypertensive encephalopathy
Cerebral amyloid angiopathy
Cerebral vasculitis

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

brain imaging'), while 47% had VaD with the second version (i.e. 'focal signs consistent with stroke *or* relevant cerebrovascular disease by brain imaging'). In a study conducted on 100 demented patients, the prevalence of VaD was 14% using the first NINDS-AIREN criteria and 76% using DSM-III-R (which uses 'focal signs consistent with stroke *or* relevant cerebrovascular disease by brain imaging')¹². The NINDS-AIREN criteria allow for a diagnosis of 'possible' VaD in patients with dementia and focal neurological signs in whom brain imaging is missing, and in patients with subtle onset and variable course.

Definition of an Association between Cerebrovascular Disease and Dementia

The influence of a stroke or an infarct on the cognitive symptoms is not easy to decide in the individual case, even if epidemiological studies suggest a strong statistical relationship^{6,15–19}. The temporal relationship between symptoms of stroke and onset of dementia is often regarded as strengthening the possibility that the two disorders are related. The recent reports that non-symptomatic infarcts are common in the elderly and related to an increased risk for dementia and stroke^{20,21} may question this statement. The NINDS-AIREN criteria suggest an arbitrary limit of three months for onset of dementia after stroke. However, a stroke which occurred years ago indicates the presence of cerebrovascular disease, including silent infarcts. The NINDS-AIREN criteria allow for a diagnosis of 'possible' VaD in the absence of a clear temporal relationship between dementia and clinical symptoms of stroke.

Both DSM-IV and ICD-10 criteria leave the clinician to decide on whether cerebrovascular disease and dementia are related, as both state that 'CVD should be (reasonably) judged to be etiologically related to the disturbance'. There are no specifications as to what this judgement should be based on.

EPIDEMIOLOGY

Almost all epidemiological studies reporting on the frequency of VaD are concerned with the subtype related to clinically manifest stroke or transitory ischaemic attacks (TIA). The proportion of vascular dementia varies widely between studies: between 15 and 45%. The variation may reflect disparities in diagnostic criteria, or differences in the rate of cerebrovascular disorders in different geographical areas²². It may also reflect differences in the efforts made to detect and diagnose cerebrovascular disease, and if brain imaging has been used. Although the prevalence of dementia is similar in most parts

of the world, there are differences regarding the type of dementia. Stroke-related dementia is traditionally reported to be more common in Finland, the former Soviet Union and Asian countries, including Japan and China, than in Western Europe and the USA, where AD is generally reported to be the most common type of dementia. However, more recent studies report proportions of VaD in China and Japan similar to western countries²³. Whether this is due to changes in diagnostic procedures or in risk factors for stroke is not clear.

Stroke

As mentioned, all criteria for VaD encompass history of stroke. Stroke patients typically have history of stroke or TIA including acute focal neurological symptoms and signs, such as hemiparesis or acute aphasia. Other cardiovascular manifestations, including myocardial infarction and hypertension, are common in the patients. Stroke is most often caused by cortical infarcts due to thromboembolism from extracranial arteries and the heart, and is often related to large vessel disease.

The typical clinical course of stroke-related dementia includes sudden onset, stepwise deterioration and a fluctuating course. In the early stages, the expression of cognitive impairment is variable and depends on the site of the lesions. A large proportion of patients with cerebrovascular disease have a gradual onset of dementia with a slowly progressive course²⁴, with or without focal signs or infarcts on brain imaging, which makes it difficult to differentiate from AD or other types of dementia. It has even been suggested that individuals with cortical strokes show less decline in cognitive function than those with subcortical cerebrovascular disease²⁵.

Stroke is an essential part of most criteria for VaD or vascular cognitive impairment. In line with this, most epidemiological studies report an increased frequency of dementia in individuals with stroke (Table 56.2). In the studies by Tatemichi *et al.*^{15–17}, relatively young individuals with ischaemic stroke had at least nine-times greater risk for dementia than stroke-free controls, and those with dementia had a higher mortality rate and worse prognosis which was independent of stroke severity. Also Pohjasvaara *et al.*¹⁸ reported an increased prevalence of dementia in stroke victims, as well as a decrease in independent living for those with dementia. Lindén *et al.*⁶ reported that stroke victims aged above 70 had an odds ratio (OR) of 4.7 for dementia. The odds for dementia were higher in those aged 70–80 (OR 6.7) than in those aged above 80 (OR 4.8), but the frequency of dementia after stroke was higher after age 80 (34% versus 18%). In addition, 60% of non-demented stroke victims had some cognitive dysfunction, showing that very few elderly stroke victims are free from cognitive disturbances. In a population study on 85-year-olds, Liebetrau *et al.*¹⁹ reported that the odds ratio for dementia in stroke was 4.3, but the prevalence of dementia in those with stroke was

Table 56.2 Prevalence of dementia in stroke patients and in the general population

Age group	Stroke (%)	Population (%)
60–64	10	1
65–69	20	1
70–74	25	2
75–79	30	5
80+	50	20–30

57%. It may be that the increased risk for dementia with stroke decreases with age although the prevalence increases.

The most important risk factors for stroke are hypertension, diabetes mellitus, atherosclerosis, atrial fibrillation, smoking, being overweight, and hypercholesterolaemia, especially high levels of low-density lipoprotein (LDL) cholesterol²⁶. All these risk factors are potentially preventable or treatable. Changing risk factor patterns (e.g. decrease in smoking, more treatment of hypertension) have decreased the incidence of stroke, and may thus decrease the frequency of VaD. On the other hand, more individuals survive after stroke, which may act in the opposite direction. It is not yet known if the prevalence or incidence of VaD is increasing or decreasing.

The pathogenesis of stroke-related dementia has not been established. The main hypothesis is that dementia is related to the location or the volume of the infarcts, but there are also other possibilities. The risk factors for VaD can be divided into stroke-related and non-stroke-related²⁷. The stroke-related are similar to those in stroke, for example male sex, hypertension, diabetes mellitus, smoking and cardiac diseases. Non-stroke-related risk factors are similar to those found in sporadic AD and include higher age, lower level of formal education, family history of dementia and the presence of cerebral atrophy. This combination of risk factors supports the view that stroke-related dementia often is a consequence of both stroke and pre-existing AD pathology. According to neuropathological studies, pure VaD, without any AD brain changes, is rare²⁸.

Silent Cerebrovascular Disease

Most cerebrovascular disease is not related to focal symptoms, aphasia or other distinct clinical manifestation, but may be detected on brain imaging. The relevance of this silent cerebrovascular disease has been debated, but recent research has shown that it is related both to dementia and later manifestations of clinical stroke. The most common 'silent' disorders are silent infarcts and ischaemic white matter lesions.

Silent infarcts

Cerebral infarcts often occur without focal symptoms. The frequency of these so-called silent infarcts increases with age²⁹. These lesions were until recently believed to be benign incidental findings on brain imaging, when researchers from the Rotterdam Study reported that individuals with silent infarcts were at increased risk of developing clinical stroke²⁹ and dementia²⁰. Among 85-year-olds, 10% have silent infarcts on CT, and these lesions double the prevalence of dementia²¹. It is important to detect these lesions, as treatment of vascular risk factors, such as hypertension, may decrease the risk of new strokes and thus potentially delay dementia in these high-risk patients.

Subcortical white matter lesions

Another important cerebrovascular disease causing dementia and cognitive decline is subcortical white matter lesions (WMLs)³⁰. These have been suggested to be the most common cause of VaD. Subcortical areas of both hemispheres are affected by marked or diffuse ischaemic demyelination and moderate loss of axons with astrogliosis and incomplete infarction. In addition, arteriosclerotic changes with hyalinization or fibrosis and thickening of the vessel

walls and narrowing of the lumina of the small penetrating arteries and arterioles are also present^{31,32}. The cortex, the subcortical U fibres and corpus callosum are generally well preserved, probably due to the construction of the blood supply.

The pathogenesis behind WMLs is probably that long-standing hypertension causes lipohyalinosis and thickening of the vessel walls with narrowing of the lumen of the small perforating arteries and arterioles which nourish the deep white matter³¹. Episodes of hypotension may lead to further hypoperfusion and hypoxia-ischaemia, leading to more loss of myelin in subcortical areas. The deep white matter has few collaterals, which makes it more vulnerable to ischaemia than the cortex. Furthermore, myelin is probably more vulnerable than axons to ischaemia³³.

WMLs may be detected on brain imaging. On computerised tomography (CT) scans they appear as low-density areas, and on magnetic resonance imaging (MRI) as hyperdense areas. MRI and CT may not always capture the same changes. WMLs on MRI correspond to several different histological findings, most often *état criblé*, and often show no correlation with cognitive decline and dementia. On the other hand, in 55 cases of WMLs on CT, the histopathological picture described in the previous paragraph was reported at autopsy in 53 of the cases³⁴. Thus, MRI is more sensitive than CT for detecting changes in the white matter, but has a lower specificity.

MRI studies generally report much higher rates of WMLs than CT studies. The Rotterdam population study³ reported that 11% in the age strata 65–69 years, 21% in those aged 70–74 years, 27% in 70–79-year-olds and 54% in those aged 80–84 years had WMLs, and the Helsinki Aging Brain Study³⁵ reported periventricular hyperintensities in 21% of those aged 55–75 years, and 65% in those above that age. A recent population-based neuropathological study reported that 94% of demented subjects had WMLs³⁰.

The cognitive decline related to WMLs is suggested to be due to disconnection of subcortical–cortical pathways, producing a decline in abilities related to subcortical or frontal lobe structures. Subcortical symptoms in individuals with WMLs include psychomotor slowness and retardation^{4,5} and extrapyramidal signs. Frontal lobe symptoms³⁶ include executive dysfunction, apathy, loss of drive and emotional blunting. Other symptoms are bilateral or unilateral pyramidal tract signs, and hemi- or motor anaesthesia, pseudobulbar palsy, depression, early urinary incontinence and early gait dysfunction. Memory dysfunction is often mild.

The dementia often has an insidious onset and a slowly progressive course^{25,31}, which makes it difficult to distinguish from AD. Initially, there may be transient and fleeting attacks of focal neurological symptoms, with a subacute accumulation of deficits. WMLs seldom occur as the sole cause of dementia, and the clinical picture may vary depending on what other causes contribute to the dementia. Punctate WMLs on MRI do not progress, while confluent white matter abnormalities are progressive, and thus more malignant in the long term³⁷.

The main risk factors for WMLs are high age, hypertension, and hypertension clustering factors. It has been suggested that the arterial changes are due to exposure of vessel walls to increased pressure over time. The greater the pressure and/or life span, the more likely are these changes to be present. This may be one reason for the observed increase with age reported in most studies.

It was recently shown that diastolic blood pressure and mean arterial pressure in midlife was related to the presence of white matter lesions in late life, supporting both the theory that long-standing high blood pressure is important and that resistance of the smaller arteries and microvascular network is important³⁸.

Mixed Dementias

The common co-occurrence of AD and VaD is becoming increasingly recognized^{1,30}. This may even be the most common cause of dementia, especially in the oldest ages. As already mentioned, cerebrovascular disease increases the risk of developing dementia^{6,15–19,34}, but to evaluate the relative contribution of cerebrovascular disease towards the dementia symptoms in the individual patient is almost impossible. Cerebrovascular disease may be the sole cause of dementia in an individual; it may be the event that finally overcomes the brain's compensatory capacity in a subject whose brain is already affected by not-yet clinically manifest Alzheimer pathology, and in many instances minor manifestations of both disorders which individually would not be enough to produce dementia may produce it together^{39,40}. On a clinical basis, it is often almost impossible to differentiate mixed dementia from pure VaD. Cerebrovascular disease as a contributing cause of dementia may be overlooked as onset is sometimes insidious, the course gradual, and the infarctions clinically silent or not detectable by brain imaging. Pure VaD may also be overdiagnosed, as the presence of stroke, WMLs or other cardiovascular disease does not mean that they caused the dementia.

Even the histopathological diagnoses of AD and VaD are uncertain. Extensive AD encephalopathy^{41–43} and cerebrovascular disease^{41,44} are reported in individuals with no signs of dementia during life. The MRC-FAS study⁴³, and the Nun Study⁴⁵ both found that only about half of those fulfilling neuropathological criteria for AD were demented during life. Similar results are reported in PET (positron emission tomography) studies using the PiB (Pittsburgh compound B) to detect amyloid deposition⁴⁶. This shows that presence of extensive AD in the brain does not always result in dementia. A substantial proportion of individuals fulfilling the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association) criteria for probable AD or NINDS-AIREN criteria for probable VaD have mixed pathologies^{28,47,48}. Also, WMLs have been described on both brain imaging and at autopsy in about two-thirds of cases of Alzheimer's disease^{32,34,49}. The Nun study⁴⁵ showed that presence of cerebrovascular disease increased the risk that individuals with AD lesions in their brains would express a dementia syndrome, from 57% in those without cerebrovascular disease to 93% in those with 1–2 lacunar infarcts and 75% in those with large infarcts⁴⁵. In addition, patients with VaD may have cholinergic deficits similar to those seen in AD, caused by ischaemia of basal forebrain nuclei and of cholinergic pathways^{50,51}. Also other markers of AD, such as high tau⁵² and low beta-amyloid⁵³ in cerebrospinal fluid may appear in VaD. Finally, similar vascular risk factors have been reported both for AD and VaD⁵⁴, which also may explain the common co-occurrence of these disorders.

DIAGNOSIS

The first step in the diagnostic work-up is to determine the extent of cognitive dysfunction, the nature of this dysfunction, and its consequences. This should be done in all elderly patients with a recent stroke, or other cerebrovascular disease. A simple screening instrument may be used, for example the Mini-Mental State Examination. Other tests include examinations of executive function, the Clock Test, word fluency, naming ability and five-item memory test. It needs to be emphasized that patients with dementia related to CVD are often difficult to test due to language dysfunction.

The second step aims to identify cerebrovascular and other causes of the dementia. In the elderly, there are often multiple causes of dementia, and every contributing treatable cause that can be diagnosed may be important in the treatment of the patient. Besides cerebrovascular disease, other conditions that might contribute to cognitive decline include, for example, cardiovascular diseases, deficiency states, infections and depression. Brain imaging is necessary in this step, not only to identify cerebrovascular disease (white matter lesions and cerebral infarcts), but also to diagnose low pressure hydrocephalus, subdural haematoma, and brain tumours. The examinations should also include careful history-taking, interview of a close informant, neurological, psychiatric and physical examinations, chest X-ray, ECG and biochemical screening. This last includes cholesterol (total cholesterol, s-high-density lipoprotein cholesterol, s-low-density lipoprotein, triglycerides), screening for diabetes mellitus (fasting P-glucose, B-HbA1c), P-homocystein, vitamin B12, a thyroid function test and thrombocytes, leukocytes and haemoglobin. Cerebrospinal fluid (CSF) examinations should be performed for analyses of beta-amyloid, tau protein, inflammation and CSF/blood ratio (for blood–brain barrier function).

An ECG should be performed to detect arrhythmias and other cardiac diseases. A carotis Doppler should be done to detect atherosclerosis in this vessel.

Traditionally AD has been a diagnosis of exclusion and VaD has often been assigned if the patient has a history of stroke thought to be etiologically related to dementia. From a clinical standpoint, it is neither important nor possible to differentiate between AD and VaD in most cases with cerebrovascular disease. Most cases of VaD are probably of a mixed aetiology, and older patients with AD may often have concomitant cerebrovascular disease, which needs treatment. Therefore the diagnostic procedure should detect evidence for AD and cerebrovascular disease and direct the treatment to both disorders.

TREATMENT POSSIBILITIES

The general strategy in the treatment of VaD is to prevent new strokes or infarcts. Detection and treatment of risk factors is essential. Some risk factors are listed in Table 56.3. Treatment of cardiac arrhythmias, diabetes mellitus, hypertension and hypercholesterolaemia is also essential. Regarding white matter dementia, antihypertensive treatment may potentially prevent the changes in the small vessels. Recently it was shown that treatment of hypertension prevented stroke also in individuals above the age of 80⁵⁵. Although no formal studies have been performed, the use of anticoagulant agents, for

Table 56.3 Risk factors for vascular dementia

Hypertension
Atherosclerosis
Arteriolosclerosis
Heart disease (infarction, arrhythmias)
Hypotension
Diabetes mellitus
Hyperlipidaemia
Smoking
Overweight
Hyperviscosity

example low-dose treatment with salicylates, is often used. Patients with VaD often have concomitant AD. In these cases, one should initiate treatment with an acetylcholinesterase inhibitor^{50,56}.

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The Frontotemporal Dementia Syndromes

Mario F. Mendez

VA Greater Los Angeles Healthcare System and David Geffen School of Medicine at UCLA, Los Angeles, USA

INTRODUCTION

The frontotemporal dementia (FTD) syndromes are related disorders resulting from neurodegeneration of the frontal and anterior temporal lobes. In 1892, Arnold Pick, a Prague neuropsychiatrist, described the first known patient and subsequently published a series of three patients with left anterior temporal atrophy^{1,2}. In 1911, Alois Alzheimer, a German neuropathologist, described the characteristic inclusion bodies of what came to be known as 'Pick's disease.' The field was nearly quiescent until the late 1980s when investigators in Lund, Sweden reported on an autopsy series of 158 patients with dementia^{3,4}, 20 (13%) of whom proved to have frontal lobe degeneration. In the past two to three decades, progress has been rapid. In the 1990s, there were several clinicopathological studies of FTD^{5,6} and the eventual demonstration of a linkage of some cases to the tau gene region on chromosome 17⁷. Finally, in the past few years, researchers discovered an association of FTD with mutations in the progranulin gene (*PGRN*) and identified one of the major ubiquitinated proteins in FTD as the TAR DNA-binding protein 43 (TDP-43)^{8–11}.

The three principal FTD syndromes are the behavioural variant (bvFTD), which comprises over half of these patients, and the language-predominant syndromes of progressive non-fluent aphasia (PNFA) and semantic dementia (SD). Although often underdiagnosed^{12,13}, these three FTD syndromes comprise the third most common neurodegenerative dementia after Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). Clinical reports describe frequencies of FTD of 5–13% among dementia outpatients^{14,15}. In possibly the best population-based series, there was a calculated annual (1990–1994) incidence of FTD in Rochester, MN, of 2.2 per 100 000 in the age group 40–49 years, 3.3 for 50–59, and 8.9 for 60–69¹⁵.

On average, the FTD syndromes have a presenile age of onset, are equally common among men and women, and lack a proven ethnic predisposition. The age of onset of bvFTD averages around 57 years with a usual range of 51–63 years, but patients have presented from the 20s to the 80s^{16–18}. The age of onset of SD is similar to that of bvFTD, but PNFA patients are often slightly older¹⁷. FTD syndromes are common among dementia patients with an age of onset of less than 65 years, accounting for approximately 15–20% of young-onset dementias^{18–20}, with prevalences in the 45–64 year age group of 15 per 100 000 in the UK and 6.7 per 100 000 in the Netherlands^{20–22}.

CLINICAL PRESENTATIONS

Behavioural Variant FTD

The clinical syndrome of FTD presents with several 'core' and 'supportive' behavioural changes in mid-life (Table 57.1)^{23–26}. The most common behavioural changes are apathy or decreased spontaneity and interest, and disinhibition or impulsivity^{25,27,28}. Second, bvFTD patients violate social and moral norms, conventions or rules^{25,26}. They may inappropriately touch others or violate their personal space, talk to strangers or children that they do not know, make sexual comments, forgo tact or table manners, and even manifest sociopathic behaviour such as theft. Third, they have 'emotional blunting' with a loss of empathy and awareness of the needs of others. Basic emotional appreciation is decreased, particularly for negative facial or vocal emotions^{29,30}. Fourth, patients lose insight into their behavioural changes and lack self-referential behaviours such as embarrassment or shame. Fifth, they frequently have changes in dietary or eating behaviour, most commonly a carbohydrate craving²⁵. Sixth, bvFTD patients have a range of repetitive behaviours from simple motor stereotypies to complex compulsive-like acts²⁵. Finally, a supportive criterion is neglect or loss of interest in personal hygiene with failure to wash, bathe, groom or dress appropriately. In comparison, psychotic symptoms such as delusions and hallucinations are much less common among bvFTD patients compared to other dementia syndromes^{25,31}.

Cognitive functions

Patients with bvFTD develop frontal-executive deficits. This is reflected in their lack of insight and loss of awareness or distress at their disability or the consequences of their behaviour. Their judgement is abnormal, and they are often concrete on idiom and proverb interpretation. Occasionally, patients have stimulus-bound behaviour such as echolalia and utilization behaviour (grasping and repeatedly using objects that they see or tending to read aloud anything they see). On language examination, bvFTD patients often have progressively decreased verbal output and mutism in advanced stages. They also manifest reiterative speech or verbal stereotypies. In contrast, early bvFTD patients have relatively spared memory with better free recall, cued recall and recognition than

Table 57.1 Behavioural variant frontotemporal dementia

-
- I. Core diagnostic features*
- A. Progressive deterioration of behaviour, cognition or both
 - B. Early apathy or inertia
 - C. Early behavioural disinhibition with abnormal sociomoral behaviour
 - D. Early 'emotional blunting' or loss of sympathy or empathy
 - E. Loss insight or and self-referential behaviours
- II. Supportive diagnostic features*
- A. Dietary or eating behaviour, most commonly a carbohydrate craving
 - B. Repetitive (stereotypic or compulsive) behaviour
 - C. Executive deficits with relative sparing of memory and visuo-spatial functions
 - D. Decline in personal hygiene and grooming
 - E. Brain imaging: predominant frontal and/or anterior temporal abnormality
-

Source: Modified from Neary *et al.*⁶¹

do AD patients^{18,32,33}. Furthermore, they have preserved visuo-spatial skills such as spatial localization and orientation in familiar surroundings^{34,35}. Rare bvFTD patients even have a facilitation of artistic and musical ability³⁶.

On neurological examination, bvFTD patients are usually normal early in their course but can develop primitive reflexes and motor changes as the disease progresses. A major subgroup of bvFTD patients develops parkinsonism, dystonia and ideomotor apraxia, or fasciculations and muscle wasting. Many of those who develop parkinsonism eventually evolve to the related syndromes of progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS)^{37–43}. A second major subgroup of about 10–15% of bvFTD patients develop motor neuron disease (MND), primarily with bulbar and proximal upper extremity impairment^{44–47}.

On neuropsychological testing, bvFTD patients perform particularly poorly on tests of executive functions^{48–52}. They are often impaired on digit span backwards, verbal fluency, Trail Making Test B, and the Tower Test. They do poorly on the Iowa Gambling Task, where they fail to improve when offered monetary rewards⁵³. Patients with bvFTD cannot do tasks of abstraction and have poor verb comprehension relative to nouns^{54–56}. They may be impaired on paradigms where they must infer other people's mental states, thoughts and feelings, referred to as 'theory of mind'⁵⁷, and the ability to process social rule violations is impaired along with their sense of 'personal' morality^{30,58}. In comparison, as previously noted, there is relative preservation of amnesia or visuo-spatial impairments on neuropsychological measures.

Progressive Nonfluent Aphasia

PNFA is characterized by an initial two or more year period of relatively isolated difficulty in verbal expression with agrammatism, difficulty with sentence syntax, shortened phrase length, and motor speech difficulties in the presence of relatively preserved comprehension (Table 57.2)^{59–62}. Patients have difficulty with verbs and with sentence processing⁶³. They also have apraxia of speech, with hesitant, broken and effortful output and phonologic (phonemic paraphasic) errors, particularly in repetition of polysyllabic words. Speech changes include progressive dysarthria with stuttering and

Table 57.2 Progressive non-fluent aphasia

-
- I. Core diagnostic features*
- A. Insidious onset and gradual progression
 - B. Agrammatism
 - 1. Grammatical morpheme and functor word omission
 - 2. Reduced mean length of utterance
 - 3. Phonemic paraphasias
 - C. Motor speech abnormalities
 - 1. Articulatory struggle and stuttering
 - 2. Dyarthria and/or dysprosody
 - 3. Apraxia of speech
- II. Supportive diagnostic features*
- A. Impaired syntactical comprehension
 - B. Impaired repetition
 - C. Alexia and agraphia
 - D. Brain imaging: asymmetric abnormality predominantly affecting left hemisphere
-

Source: Modified from Neary *et al.*⁶¹

oral apraxia⁶⁴. Reading and writing is correspondingly impaired, and patients with PNFA are aware of their language and speech deficits.

In PNFA, there is asymmetric atrophy of the left frontotemporal lobes⁶¹. Magnetic resonance imaging (MRI) with voxel-based morphometry (VBM) and functional imaging reveal marked atrophic changes or hypometabolism and decreased blood flow in the left perisylvian, inferior frontal and anterior insular areas^{59,65}. Most patients with PNFA have frontotemporal neuropathology, but some patients have a language variant of AD at postmortem^{62,66}.

Semantic Dementia

This FTD syndrome produces a multimodal loss of conceptual knowledge, particularly in word comprehension and facial recognition (Table 57.3). In contrast to PNFA, patients with SD have fluent speech and normal grammar but cannot understand words⁶⁷. They have relative preservation of repetition, phonology, syntax, the ability to read aloud and the ability to write orthographically regular words. Their speech output becomes progressively empty, however, as they lose substantive words and their meanings. On testing, they have problems with single word comprehension on pointing commands, word definitions and matching of objects or pictures with words. On reading, there is a characteristic disorder termed 'surface dyslexia' with inability to read irregularly spelled words but preserved ability to sound them out⁶⁸. The rest of their cognitive profile reflects semantic loss in other domains. There may be an impairment in the recognition of familiar faces (prosopagnosia) and impairment of object meaning or identity (object agnosia) that cannot be attributed to naming difficulties. Despite these deficits, SD patients can continue to learn (episodic memory) and have intact visuo-spatial skills⁶⁹.

In SD there is circumscribed atrophy of the anterior inferior temporal gyri⁷⁰. The cortical atrophy involves the left inferolateral temporal lobe and fusiform gyrus, right temporal pole, bilateral ventromedial frontal cortex, and the amygdaloid complex with sparing of the hippocampus⁷⁰. Most SD patients have greater atrophy in the left anterior temporal region compared to the right. The asymmetric involvement is often evident on MRI imaging and correlates

Table 57.3 Semantic dementia: consensus criteria*I. Core diagnostic features*

- A. Insidious onset and gradual progression
- B. Poor confrontational naming, particularly for unfamiliar items
- C. Loss of word comprehension, particularly for unfamiliar items
- D. Intact word repetition
- E. Intact motor speech

AND/OR

- A. Perceptual disorder characterized by
 - 1. Prosopagnosia: impaired recognition of identity of familiar faces
 - 2. Object agnosia: impaired recognition of object identity
- B. Preserved perceptual matching and drawing reproduction

Supportive diagnostic feature

- Brain imaging: predominant anterior temporal abnormality-bilaterally or asymmetric

Source: Modified from Neary *et al.*⁶¹

with relative impairments for word meaning (left temporal lobe) versus prosopagnosia or object recognition (right temporal lobe)⁷¹. The function of the anterior inferior temporal region appears to be to bind information together.

CLINICAL EVALUATION AND DIAGNOSIS

With the exception of the identifiable mutations, there are as yet no definitive tests for the FTD syndromes. In bvFTD, the behavioural changes outlined above usually precede or overshadow any cognitive deficits^{6,18,19,72}. Suspicion for bvFTD arises when there is a change in personality, usually in mid-life^{19,73,74}. Suspicion for PNFA or SD arises when there is new speech or word-finding difficulty in mid-life. Clinical criteria for diagnosing the three main FTD syndromes are the FTD Consensus Criteria (see Tables 57.1–57.3)⁶¹. These criteria have proven imperfect, with about 33–56% of bvFTD patients failing to meet Core Consensus Criteria on presentation (see Table 57.1)^{12,13,75}. They are particularly deficient when it comes to a subgroup of bvFTD patients who lack changes on neuroimaging and who fail to progress after years of follow-up^{50,51,76}. Currently, the FTD Consensus Criteria are undergoing revision by an international team of experts in the field.

Brain MRI can help confirm the presence of an FTD syndrome (Figure 57.1)⁷⁷. Although often normal in early stages^{78,79}, MRI scans eventually show frontal and anterior temporal atrophy, enlargement of the Sylvian fissures, and anterior callosal atrophy^{80–86}. There is temporal polar, amygdalar and lateral temporal and fusiform gyrus involvement but relative sparing of the hippocampi^{83,87–90}. FTD patients may have additional MRI evidence of bilateral caudate atrophy, and others have changes in the substantia nigra and putamen or high signal changes in white matter⁹¹. VBM studies in autopsy-confirmed patients have confirmed the mesial frontal, anterior insular and anterior temporal regional atrophy^{92–96}. Finally, recent studies suggest that the neuropathological variants of FTD may have different patterns of frontotemporal atrophy on neuroimaging^{95,97}.

Functional imaging may be more sensitive than MRI for the diagnosis of FTD. Positron emission tomography (PET) and single-photon emission tomography scans show decreased regional

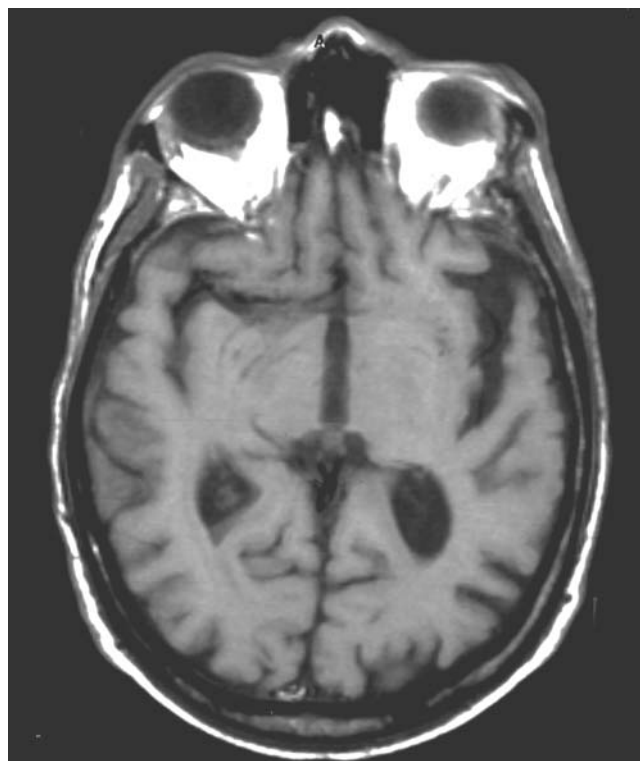
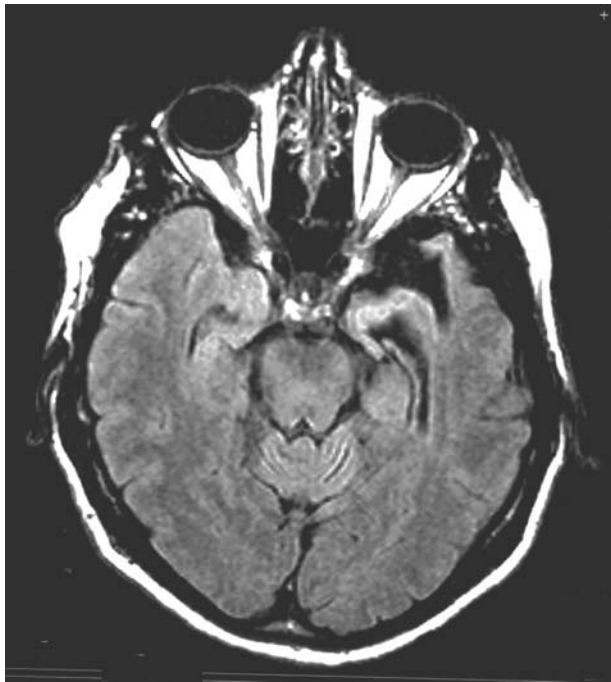


Figure 57.1 MRI (T2-weighted) image of progressive non-fluent aphasia (PNFA). Asymmetric atrophy of the left Sylvian fissure with reciprocal enlargement of the left frontal horn

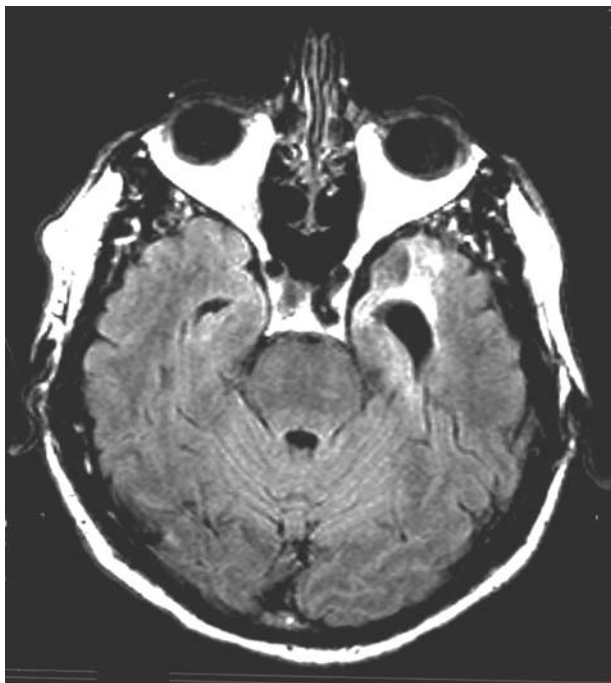
metabolism and cerebral blood flow in the frontal cortex and anterior temporal lobes (Figure 57.2)^{72,82,98,99}. On fluorodeoxyglucose (FDG) PET, glucose uptake is reduced primarily in dorsolateral and ventrolateral prefrontal cortices and in frontopolar and anterior cingulate regions¹⁰⁰. Although PET scan changes are not specific for FTD syndromes¹⁰¹, worsening functional changes over time favour the diagnosis of a neurodegenerative dementia such as FTD^{102,103}. Furthermore, new functional imaging technologies, such as Pittsburgh Compound-B (PIB), hold great promise for distinguishing FTD syndromes from AD and other neurodegenerative disorders with amyloid-related pathology^{104,105}.

There are important brain–behaviour relationships between symptoms and specific regions of involvement in FTD. Patients with bvFTD have greater right than left-sided atrophy^{106,107}. The initial pathology in bvFTD involves the ventromedial frontal cortex, orbitofrontal region and anterior insula^{108,109}. Abnormalities in social and moral conduct correlate with changes in these regions on functional neuroimaging²⁶. Apathy correlates with mesial frontal atrophy on both MRI VBM and on FDG-PET^{28,110}. Disinhibition correlates with atrophy of the subcallosal part of the frontal lobe, orbitofrontal region and adjacent temporal areas^{28,106,110}. PFNA and apraxia of speech correlate with left peri-Sylvian and anterior insular involvement⁹². SD correlates with anterior temporal atrophy^{88,111}. Moreover, in SD, impaired word comprehension corresponds to left anterior temporal atrophy, and right temporal atrophy corresponds to impaired recognition of faces (Figure 57.3).

Most other biomarkers, such as plasma TDP-43 or tau levels, have not yet proven to be clinically useful for the diagnosis of FTD syndromes. Cerebrospinal (CSF) biomarkers hold the most promise for



(a)



(b)

Figure 57.2 FDG-PET imaging of FTD patient. (a) Horizontal and (b) sagittal views demonstrate frontal and anterior temporal hypometabolism

eventually helping distinguish FTD from AD¹¹². Among patients with bvFTD, some have found a significant decrease of CSF tau protein¹¹³, but most report normal or only slightly increased CSF total tau and phospho-tau levels^{114–120}. Overall, the literature indicates significantly lower total tau and tau/A β 42 amyloid ratios in FTD compared to AD. In addition, decreased plasma levels of the

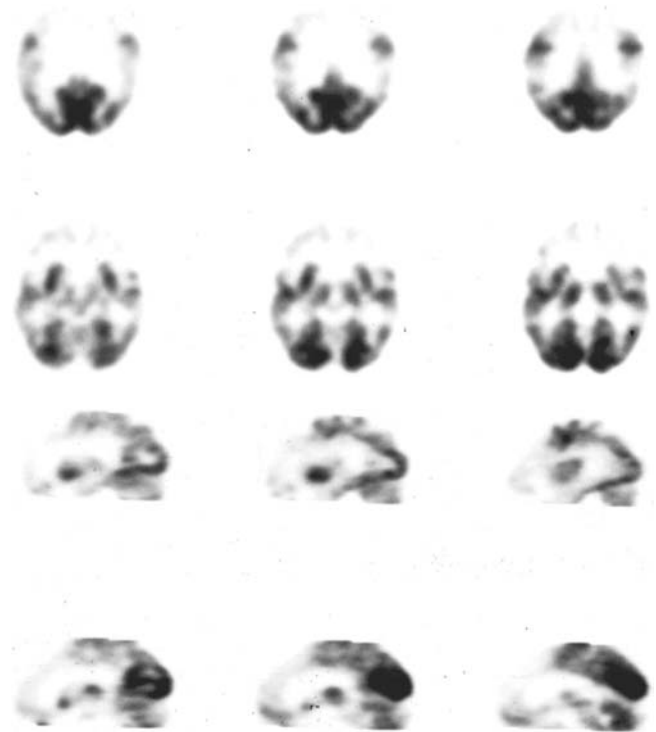


Figure 57.3 MRI (T2-weighted) images from patient with semantic dementia (SD). There is bilateral anterior temporal atrophy disproportionately affecting the left temporal lobe and associated with impaired word comprehension

PRGN protein in FTD patients with these mutations may be useful in screening for this specific genetic form of FTD (see below)¹²¹.

PATHOLOGY AND NEUROGENETICS

There is frontotemporal lobar degeneration on gross pathology. The ventromedial frontal region and the anterior temporal areas have the most severe atrophic changes. Initially, the cortical degeneration is usually asymmetric and involves the mesial frontal regions including the anterior cingulate gyrus and the anterior insula. The frontotemporal cortex has neuronal and synaptic loss and astrogliosis with spongiosis (minute cavities or microvacuolation) of the outer, supragranular (II–III) layers, with variable involvement of subcortical and limbic structures^{122–124}. Specific loss of von Economo neurons occurs in the anterior cingulate and anterior insulae¹²⁴. Finally, the serotonergic and dopaminergic systems are decreased with relative sparing of cholinergic systems^{125,126}.

The FTD syndromes include pathological variants that have intraneuronal inclusions that are either tau-positive or tau-negative, ubiquitin-positive (Table 57.4)¹²⁷. FTD is most commonly due to tau protein, with tau-positive inclusions, or to the neuronal accumulation of TAR DNA-binding protein-43 (TDP-43) protein, with tau-negative, ubiquitin-positive inclusions. Among a cohort of 26 bvFTD patients, there were equal numbers with tau-positive and tau-negative pathology¹²⁸, and among another 74 bvFTD patients, 55% were associated with a TDP-43 proteinopathy^{60,129}. Tau is a microtubule-associated protein (MAPT) that stabilizes microtubules and promotes microtubule assembly by binding to tubulin¹³⁰.

Table 57.4 Frontotemporal lobar degeneration (FTLD) neuropathology^{127,141}

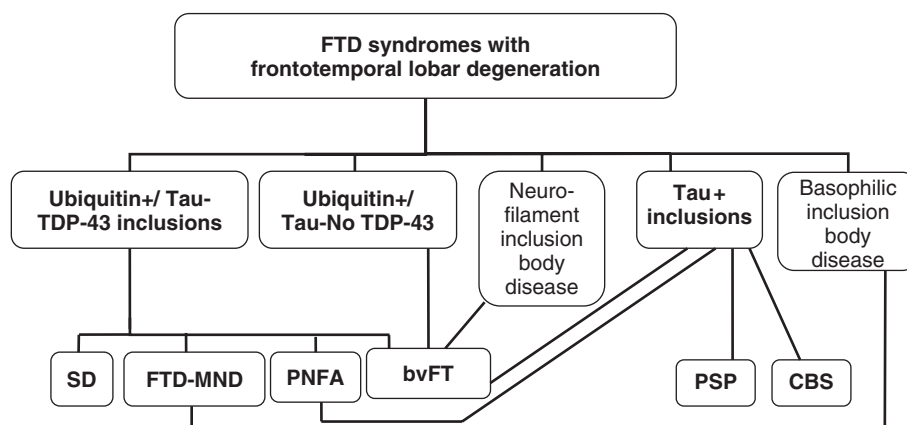
<i>Histopathology</i>		<i>Clinical syndromes</i>	<i>Genetic association</i>
<i>Tau-positive</i>			
FTLD-tau	Intranuclear tau-positive inclusions, e.g. Pick bodies	bvFTD, PNFA, PSP, CBS	<i>MAPT</i> gene abnormalities
<i>Tau-negative, ubiquitin-positive</i>			
FTLD-TDP			
U1	Dystrophic neurites (elongated, long); neuronal cytoplasmic inclusions (few)	SD	None known
U2	Dystrophic neurites (few, short); neuronal cytoplasmic inclusions	FTD-MND, MND	Intraflagellar transport 74
U3	Dystrophic neurites (short); neuronal cytoplasmic inclusions; neuronal intranuclear inclusions	bvFTD, PNFA	<i>PRGN</i>
U4	Dystrophic neurites; few neuronal cytoplasmic inclusions; neuronal intranuclear inclusions	bvFTD	<i>VCP</i>
FTDP-UPS	Ubiquitin proteasome system	bvFTD	<i>CHMP2B</i>
FTDP-U 'atypical'		Very young onset bvFTD	
<i>Tau-negative, ubiquitin-negative</i>			
FTDP-IF	Neuronal intermediate filament inclusion disease		
FTDP-ni	No inclusions	bvFTD	
BIBD	Basophilic inclusion body disease	bvFTD	

It is abnormal if hyperphosphorylated, resulting in a breakdown of microtubules and an impairment of axonal transport. TDP-43 is a nuclear protein whose function is not entirely clear, but appears to have a role in the regulation of transcription and mRNA splicing¹³¹. It is normal for TDP-43 to be ubiquitinated, but it is abnormal when phosphorylated¹³¹.

Many patients with FTD syndromes have the intraneuronal accumulation of MAPT with tau-positive inclusions^{132–134}. Six different isoforms of this tau protein result from alternative splicing, particularly of exon 10, which affects the number of carboxyl-terminal repeats^{135,136}. An FTD 'tauopathy' may result from tau-positive inclusions due to either an imbalance in the ratio

of tau isoforms with 3 or 4 microtubular binding repeats or to the abnormal hyperphosphorylation of tau. A tauopathy underlies nearly half of those with bvFTD, most of those with the PNFA variant, and all who develop parkinsonism, including the related disorders of PSP and CBS^{60,92,128,129,137}.

More than half of patients with FTD syndromes have tau-negative, ubiquitin-positive inclusions which contain TDP-43 (Figure 57.4)^{127,138–140}. TDP-43 is expressed when there is neuronal injury, resulting in caspase-dependent cleavage of TDP-43 and its deposition in insoluble neuronal inclusions. These ubiquitin-positive inclusions include different ubiquitin subtypes (U1–U4) depending on the distribution of ubiquitin positivity (Table 57.4)^{141–144}. About

**Figure 57.4** The relationships among the different pathologic and clinical variants of FTD syndromes with frontotemporal lobar degeneration

a quarter of FTLD-TDP cases are U1, half are U2, a quarter are U3, and a very small number are U4. A ubiquitin-positive, TDP-43 proteinopathy underlies over half of those with bvFTD, most of those with the SD variant, and FTD patients who develop MND^{60,128,129,145}. In addition, abnormal TDP-43 immunoreactivity also occurs in other neurodegenerative disorders including AD^{94,146}.

A small proportion of FTD cases are associated with pathologies other than a tauopathy or a TDP-43 proteinopathy (Table 57.4). Some patients have ubiquitin-positive inclusions without TDP-43. A subset of these shows immunostaining against proteins of the ubiquitin proteasome system (FTDP-UPS). Another subset is ubiquitin-positive, TDP-43-negative without any positive immunostaining to an identified target protein. These 'atypical' FTLD-U patients have a very early age of onset and lack a clear family history for the disorder¹²⁷. Other patients are both tau-negative and ubiquitin-negative. One, known as neuronal intermediate filament inclusion body disease, results from an accumulation of intraneuronal inclusions that are immunoreactive to neurofilament and α -internexin (FTDP-IF)^{127,147,148}. Another has no inclusions whatsoever evident on immunohistochemistry (FTDP-ni). This term replaces the formerly described FTD cases of 'dementia lacking distinctive histology'^{139,140,149,150}. A further subset associated with FTD-MND is basophilic inclusion body disease, which results in the identification of basophilic round neuronal inclusions that show variable immunoreactivity to ubiquitin but are unreactive to other stains (BIBD)^{151,152}.

Some estimates state that 38–50% of patients with FTD may have a positive family history^{153,154}, but direct autosomal dominant inheritance is present in only about 15%¹⁵⁵. These autosomal dominant cases are due to *MAPT* mutations in 7–21% and *PGRN* mutations in 5–26%, both linked to chromosome 17^{10,156–158}.

MAPT mutations may result in neurodegeneration from tau aggregation in neurons and glia resulting in interference with axonal transport^{159,160}. This aggregation often follows from missplicing of exon 10 and the surrounding intronic 'stem-loop'. There are over 40 known potential pathogenic *MAPT* mutations including 27 missense mutations, 4 silent mutations, 2 in-frame single codon deletions and 8 intronic mutations¹⁶¹.

In 2006, researchers reported mutations in the *PGRN* gene in association with FTD and ubiquitin-positive (FTLD-TDP U3) inclusions^{9,10,140,162}. Since then, researchers have found 40 to 50 different *PGRN* mutations that lead to degradation of mutant RNA^{9,156,161}. Progranulin is a 593-amino acid, secreted glycosylated protein. It has many roles, including in brain development, as a growth factor and as an anti-inflammatory agent with functions in wound healing. The relationship between *PGRN* and TDP-43 remains to be elucidated. Paradoxically, investigators have identified mutations in the gene encoding for TDP-43 in familial amyotrophic lateral sclerosis, but not in FTD or FTD-MND families^{163,164}.

In addition to *MAPT* and *PGRN*, there are rare genetic mutations associated with FTD syndromes. Mutations in the valosin-containing protein linked to chromosome 9 result in bvFTD with inclusion body myopathy or Paget's disease (VCP)¹⁶⁵. VCP is an ATPase associated with multiple cellular activity, and, at autopsy, there are widespread ubiquitin- and TDP-43-positive intranuclear inclusions (FTLD-TDP U4)^{141,166}. Mutations in the charged multivesicular body protein 2B (CHMP2B) linked to chromosome 3 result in early onset bvFTD with severe cognitive deficits¹⁶⁷. CHMP2B plays a role in efficient autophagy, and, at autopsy, there are ubiquitin-positive inclusions that are not immunoreactive to TDP-43 but that appear to stain for other ubiquitin proteasome system proteins (FTLD-UPS)¹⁶⁸.

Finally, the clinical bvFTD-like syndrome may result from an alternative transcription of the presenilin 1 mutation associated with familial AD¹⁶⁹.

COURSE AND MANAGEMENT

The duration of FTD syndromes can be quite variable, depending on subtype and the presence or absence of complications, such as parkinsonism or MND. The usual duration of the three uncomplicated syndromes, bvFTD, PNFA and SD, is about 8–11 years with death resulting from terminal pulmonary, urinary tract or decubitus infections or complications^{6,170}. Those with FTD-MND have a much shorter, more malignant course of about 1–3 years¹⁸. There may be a decreased survival if there is an underlying tauopathy, as opposed to a TDP43 proteinopathy¹⁷¹. As FTD syndromes progress, syndromes may transform and evolve. For example, bvFTD or PNFA patients with an underlying tauopathy may evolve to parkinsonism and PSP or CBS. Regardless of phenotypic evolution, all, except for a subgroup of non-progressors ('phenocopies'), eventually accumulate cognitive deficits, develop profound dementia, and have a tendency to late mutism. The non-progressive phenocopies are an enigmatic group of patients who fulfil criteria for bvFTD but show little change in their symptoms over time^{50,51,172}.

The treatment of bvFTD primarily involves managing the behavioural symptoms with psychoactive medications. Selective serotonin-receptor inhibitors, such as sertraline, paroxetine or fluoxetine, can decrease disinhibition–impulsivity, repetitive behaviours and eating disorders¹⁷³. Trazodone or an atypical antipsychotic such as aripiprazole can also help manage significantly disturbed or agitated behaviour, disinhibition or verbal outbursts. Antipsychotics, however, carry some risk in dementia and in bvFTD, and the US Food and Drug Administration has required warning labels because these medications may increase mortality in elderly patients. Moreover, similar to patients with dementia with Lewy bodies, some patients with bvFTD can have an unusual neuroleptic hypersensitivity^{12,174}. The acetylcholinesterase inhibitors, such as donepezil, galantamine or rivastigmine, have not had significant efficacy for patients with bvFTD and can worsen disinhibition or compulsions¹⁶⁹. Memantine, another dementia medication, is under investigation for the treatment of this disorder, but has not yet shown clinically significant efficacy^{175,176}. Most recently, investigators have developed measures for monitoring of clinical drug trials and rational drug treatment for FTD syndromes¹⁷⁷. This approach holds great promise for an eventual treatment that targets the underlying pathophysiology of FTD, particularly the abnormalities in tau protein and TDP-43¹⁷⁶.

The non-pharmacological management of patients with FTD syndromes focuses on behavioural interventions and care of the caregivers. Behavioural disturbances are particularly distressing to caregivers, who are prone to significant depression^{27,178,179}. Family support and education is critical, including the availability of psychosocial counselling and community resources. Some behavioural disturbances may respond to retraining or to rehabilitation techniques^{180,181}, and speech therapy may benefit PNFA and SD patients. Special attention is needed for safety issues among FTD patients¹⁸², and, when hyperorality is present, restrictions are necessary to prevent lethal ingestion behaviours¹⁸³. As immobility occurs, FTD patients, like all advanced dementia patients, become susceptible to pulmonary emboli, aspiration pneumonia, urinary tract infections and decubitus ulcers.

CONCLUSIONS

The FTD syndromes are neurodegenerative disorders that are rapidly being elucidated. Research has now shown that they are clinical, pathological and genetically heterogeneous conditions. The three classic syndromes are bvFTD, with apathy, disinhibition and other behavioural changes, and PNFA and SD, with early predominant language or word comprehension difficulty. These FTD syndromes can be associated or evolve into the parkinsonian syndromes of PSP and CBS or into FTD with MND. In recent years, basic science research has also made great strides in uncovering the underlying neuropathology and neurogenetics of these syndromes. We now know that they are primarily due to abnormalities in tau or in TDP-43 protein and that these may result from mutations of the *MAPT*, *PRGN* or other genes. The future looks extremely promising for the discovery of pathophysiological mechanisms and disease-modifying therapies for the FTD syndromes.

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The Lewy Body Dementia Spectrum (Alpha Synucleinopathies)

J.-P. Taylor and I. G. McKeith

Wolfson Research Centre, Newcastle General Hospital, Newcastle upon Tyne, UK

INTRODUCTION

The alpha synucleinopathies encompass a diverse range of neurodegenerative entities with the common neuropathological hallmark of abnormal accumulation in the brain of aggregates of insoluble alpha-synuclein. Major members of this club include Parkinson's disease (PD), the associated Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), multisystem atrophy (MSA), pure autonomic failure and rapid eye movement (REM) sleep behaviour disorder. The clinico-pathological manifestation of each of these conditions appears to depend upon the pattern of insoluble alpha-synuclein deposition in specific neuronal and glial populations¹.

Of particular relevance to geriatric practitioners, and the focus of the present chapter, are the Lewy body dementias (LBDs) PDD and DLB, given that, combined, these diseases represent the second commonest cause of dementia in the elderly².

NEUROPATHOLOGY OF LEWY BODY DEMENTIAS

As intimated by their appellation, the common histopathological feature of LBDs is Lewy bodies (LBs). These spherical neural inclusions were first described by Friederich Lewy in 1912 in the substantia nigra, locus coeruleus and dorsal nucleus of vagus as well as in the hypothalamus, nucleus basalis of Meynert and sympathetic ganglia of PD patients^{3,4}. However, interest in the role of LB formation in dementia did not arise until the latter half of the twentieth century when Japanese neuropathologists described a number of cases of dementia with severe extrapyramidal signs, who on autopsy had significant cortical LB deposition^{5–8}. These cortical LBs can now be relatively easily visualized by the use of advanced neuropathological techniques including antiubiquitin and, more recently, specific alpha-synuclein immunohistochemical staining.

Histopathologically, LBs are eosinophilic neuronal inclusion bodies whose major constituent is aggregated alpha-synuclein bound together with ubiquitin and neurofilament. Cortical LBs tend to be smaller and less eosinophilic than LBs seen in the brainstem. It has been proposed by Braak and colleagues⁹ that in PD, LBs appear initially in the brainstem and then ascend progressively along the neuroaxis, with this pattern corresponding to the clinical development of parkinsonism. Later cognitive and neuropsychiatric symptoms emerge then as a consequence of LB cortical involvement.

The temporal order of progression appears to be less clear in DLB although neuropathologically three categories, based on LB deposition, have been proposed³: a brainstem-predominant DLB, a limbic (or transitional) DLB, and a predominantly cortical DLB. Correlation of these categories or the distribution of alpha-synuclein with dementia development, extrapyramidal signs or neuropsychiatric symptoms, however, is lacking¹⁰. In addition, current pathological criteria probably do not explain the full range of potential pathological distributions that can occur, as up to 20% of older patients with LBs at autopsy have a cortical predominant pattern of distribution that does not conform to either the Braak or DLB Consortium schemas¹¹.

Neuropathological assessments of DLB are further complicated by the presence of co-existent Alzheimer's disease (AD) pathology as high senile plaque counts are found in 80–90% of DLB cases; this is a comparable level to that found in pure AD. Conversely, LB pathology has been found in the amygdalae of individuals who have widespread AD pathology¹² although these cases seldom display any clinical characteristics of DLB and thus should be regarded separately from LBDs³. These observations have, however, contributed to the sustained belief that AD and LBDs are caused by the same underlying disease as reflected in the use of terms such as 'the Lewy body variant of AD' for these mixed pathology cases¹³. This is inappropriate, since 80–90% of DLB cases neuropathologically do not have the typical AD-associated neocortical neurofibrillary tangles which are now known to be integral to the pathophysiology of AD¹⁴. More recently clinico-pathological data have suggested that the expression of a DLB clinical phenotype is related to the severity of LB pathology and inversely related to the severity of Alzheimer type pathology^{3,15}.

CLASSIFICATION OF LEWY BODY DEMENTIAS

Existing nosological systems such as DSM-IVR have been poorly operationalized with regard to PDD and DLB. PDD in DSM-IV-R is only briefly referenced and its syndromal definition is imprecise requiring the presence of PD with associated cognitive and motoric deficits, executive dysfunction and impairment in memory retrieval, which may be exacerbated by depression. DLB as a disease entity is not even listed in DSM-IV-R and this probably reflects the presumed association with AD as well as the various and confusing diagnostic labels which have been attached to this condition over the years, including Lewy body dementia, Lewy body variant of AD, senile dementia of Lewy body type and diffuse cortical Lewy body disease.

An important step forward to address these issues has been the formulation of operationalized criteria for both PDD¹⁶ and DLB^{5,6} (see Tables 58.1, 58.2 and 58.3), with the latter undergoing a revision in 2005³. These have allowed clinicians to make more precise diagnoses and develop clearer management strategies. From the perspective of research, operational criteria have begun to facilitate in a systemized manner a better understanding of the natural history of these conditions and improved clinico-pathological correlations, as well as allowing clinical trials to be conducted to standards accepted by drug regulatory authorities. Overall, however, it is important to recognize that the criteria for DLB and PDD are still under development and will require further refinement (e.g. neuropathological criteria), as well as being complemented by effective disease biomarkers to improve early detection (see later discussion).

As presented in Tables 58.1 and 58.2, the diagnosis of probable or possible PDD depends primarily upon the presence of core symptoms of (i) diagnosis of parkinsonism, (ii) a dementia with an insidious onset and slow progression in the context of established PD and (iii) the absence of features which could suggest other conditions as the cause of mental impairment¹⁶. The diagnosis of probable PDD depends upon the presence of the core symptoms as well as a cognitive profile typical for PDD (e.g. attention, visuo-spatial) and at least one behavioural symptom (e.g. visual hallucinations). The diagnosis of possible PDD is less rigorous; while still requiring the core features, the associated cognitive impairment may be, for example, atypical; behavioural symptoms may or may not be present and there may be features which make the diagnosis less robust, e.g. evidence for vascular disease on imaging. For a diagnosis of probable or

Table 58.1 Features of dementia associated with Parkinson's disease

I. Core features	
1.	Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2.	A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as: • Impairment in more than one cognitive domain • Representing a decline from premorbid level • Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms
II. Associated clinical features	
1.	Cognitive features: • Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day • Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia) • Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction • Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall • Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
2.	Behavioral features: • Apathy: decreased spontaneity; loss of motivation, interest, and effortful behaviour • Changes in personality and mood including depressive features and anxiety • Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects • Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions • Excessive daytime sleepiness
III. Features which do not exclude PD-D, but make the diagnosis uncertain	
	• Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging • Time interval between the development of motor and cognitive symptoms not known
IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D	
	• Cognitive and behavioral symptoms appearing solely in the context of other conditions such as: - Acute confusion due to a. Systemic diseases or abnormalities b. Drug intoxication - Major Depression according to DSM IV • Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Source: From Emre *et al.* (2007); Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders* 22(12):1689–1707. Reprinted with permission of John Wiley & Sons, Inc.

Table 58.2 Criteria for the diagnosis of probable and possible PD-D**Probable PD-D**

- A. Core features: Both must be present
- B. Associated clinical features:
 - Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
 - The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis
- C. None of the group III features present
- D. None of the group IV features present

Possible PD-D

- A. Core features: Both must be present
- B. Associated clinical features:
 - Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
 - Behavioral symptoms may or may not be present
- OR
- C. One or more of the group III features present
- D. None of the group IV features present

Source: From Emre *et al.* Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders* 22(12): 1689–1707. Reprinted with permission of John Wiley & Sons, Inc.

Table 58.3 Consensus criteria for the clinical diagnosis of probable and possible DLB

1. Central feature (essential for a diagnosis of possible or probable DLB): Dementia defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function and visuo-spatial ability may be especially prominent.
2. Core features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB):
 - Fluctuating cognition with pronounced variations in attention and alertness
 - Recurrent visual hallucinations that are typically well formed and detailed
 - Spontaneous features of parkinsonism.
3. Suggestive features (if one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for the diagnosis of possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone):
 - REM sleep behaviour disorder
 - Severe neuroleptic sensitivity
 - Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging.
4. Supportive features (commonly present but not proven to have diagnostic specificity):
 - Repeated falls and syncope
 - Transient, unexplained loss of consciousness
 - Severe autonomic dysfunction, e.g. orthostatic hypotension, urinary incontinence
 - Hallucinations in other modalities
 - Systematized delusions
 - Depression
 - Relative preservation of medial temporal lobe structures on structural imaging
 - Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
 - Abnormal (low uptake) MIBG myocardial scintigraphy
 - Prominent slow wave activity on EEG with temporal lobe sharp waves.
5. A diagnosis of DLB is less likely:
 - In the presence of cerebrovascular disease evident as focal neurological signs or on brain imaging
 - In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture
 - If parkinsonism only appears for the first time at a stage of severe dementia.
6. Temporal sequence of symptoms:
DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if present). In research studies, when a distinction needs to be made between DLB and PDD, the one-year rule between the onset of dementia and parkinsonism should be applied.

Source: Adapted from McKeith *et al.* Diagnosis and management of dementia with Lewy bodies. Third report of the DLB consortium, *Neurology* 2005; 65: 1863–72. Reprinted with permission from Wolters Kluwer Health.

possible DLB (Table 58.3), consensus criteria demand that the core features of fluctuating cognitive impairment, recurrent visual hallucinations and parkinsonism should be present (two or more core features for a diagnosis of probable DLB and one core feature for a diagnosis of possible DLB). DLB criteria also provide supportive and suggestive features that may make the diagnosis more likely. Clinical assessment of these features is discussed in more detail later.

The development of these criteria has, however, not been without difficulties:

Deciding if it is DLB or PDD

The diagnostic separation of DLB from PDD, on the basis of when the motor features occur relative to the dementia has caused controversy^{17–20}. Currently both the consensus criteria for DLB and PDD recommend that for a diagnosis of PDD, the extrapyramidal motor features need to be present for at least 12 months or more before the onset of the dementia, but if the dementia precedes the motor symptoms or occurred within 12 months of the motor features then the diagnosis should be DLB. This boundary delineation has been considered useful in research for determining the epidemiology and natural history of these conditions as well as providing clinicians with clear categorical labels for diagnosis. However, separation of PDD and DLB on a temporal arbitrariness has no strong clinical or pathological basis. Indeed, as will be discussed below, while minor differences do exist between DLB and PDD, they demonstrate remarkably similar cognitive profiles as well as similar neuropsychiatric features, neuroleptic sensitivities, sleep symptoms, autonomic dysfunction and responsiveness to cholinesterase inhibitors²¹. Overall unitary approaches have proven useful for study of common neurobiological and genetic processes in these conditions, and, indeed, the term Lewy body disease, which encompasses PD, PDD and DLB, and the term Lewy body dementias, which includes PDD and DLB, have been particularly helpful in this regard (see Figure 58.1). Therefore, while separating the dementias, PDD from DLB, avoids confusion clinically and helps stream patients depending upon the clinical setting in which they are first diagnosed (e.g. movement disorder clinics for PDD and dementia clinics for DLB), in certain cases, particularly when the temporal ordering of motor to cognitive symptoms is not clear, the umbrella term LBDs is likely to be more useful (Table 58.4).

Problems with Validation of DLB Consensus Criteria

Neuropathological validation studies using the 1996 DLB consensus criteria⁶ suggested that while the specificity of the clinical diagnosis

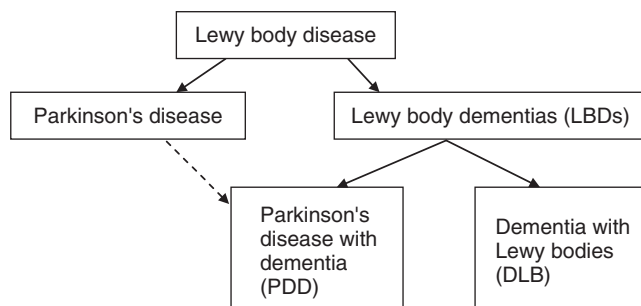


Figure 58.1 Classification of Lewy body diseases

Table 58.4 Key points in classification

- Parkinson's disease with dementia (PDD) should be used to describe dementia that occurs in well-defined Parkinson's
- Dementia with Lewy bodies (DLB) should be diagnosed when the dementia occurs before or concurrently with parkinsonism
- In research, the parkinsonism needs to be present for at least one year before the onset of dementia to make a diagnosis of PDD, but if the dementia occurs within 12 months of the motor symptoms, or indeed precedes it, then the diagnosis should be DLB
- Lewy body disease includes PD, PDD and DLB
- Lewy body dementias (LBDs) are part of the Lewy body disease spectrum and include PDD and DLB

When it is difficult to diagnostically separate PDD from DLB, the generic term LBDs might be more helpful clinically.

of probable DLB, i.e. LB pathology found at autopsy, is high at >80%, the sensitivity $\approx$ 60%, which suggests that many LB pathology cases do not present with the typical features of fluctuations, visual hallucinations or parkinsonism. Difficulties in clinically discerning core symptoms in certain individuals, particularly when the dementia is severe, the fact that significant LB pathology may occur later in the disease course such that its clinical effects are limited, or the co-occurrence of Alzheimer pathology, which modifies the clinical presentation, are all possible explanations for this reduced sensitivity in DLB detection. Importantly, it means that a significant proportion of potential DLB cases are missed; however, biomarkers and, in particular imaging techniques (see below), which enhance sensitivity in atypical/uncertain cases, may help overcome this problem.

AETIOLOGY

The aetiology of LBDs remains unclear. However, a number of biological candidates have been proffered, including LB formation, alpha-synuclein pathology and neurochemical deficits.

LB and Alpha-Synuclein Pathology

Initially LBs were hypothesized as the core neurotoxic lesion involved in the aetiology of LBDs given their association in PD with nigro-striatal dopaminergic cell loss. However LBs are only sparsely distributed in the cortex in LBDs and their density does not appear to correlate strongly with disease duration or symptom²². More recent thinking has been to view LBs as a neuroprotective response by vulnerable neurons attempting to sequester toxic alpha-synuclein species. An earlier stage in the neurodegenerative process appears to be the accumulation of small aggregates of alpha-synuclein. These aggregates, which are enormous in number, appear to be more widely distributed in the brains of patients with PDD and DLB than LBs and their presence in presynaptic terminals is thought to severely impair synaptic function²³. The presence of amyloid beta in the neocortex has also been associated with more extensive alpha-synuclein lesions and thus it has been speculated that amyloid beta may have a role in the genesis of alpha-synuclein deposition in LBDs. This is an intriguing finding as it may provide evidence of a link between LBDs and AD pathology but further work is required to clarify this interaction²⁴.

Recently, a great deal of interest has been focused on the role of the enzyme glucocerebrosidase (GBA) in LBDs. GBA deficiency as a result of an autosomal recessive mutation has long been known to be associated with Gaucher's disease, where there is marked cellular accumulation of the GBA lipid substrate, glucocerebroside. However, it has become evident that while the severe manifestations of Gaucher's occur when there is less than 20% GBD activity, milder heterozygous mutant variants can have little deleterious effect in early life but can cause the later development of PD or DLB (see below for further discussion)²⁵. Currently it is unclear in what way GBA mutations are related to PD and LBDs although it has been speculated that impaired ceramide metabolism (in which GBA is involved) and lysosomal recycling interact with the process of alpha-synuclein formation.

Neurochemical Changes

In addition to the neuropathological changes, there are severe deficits in monoaminergic and cholinergic systems in LBDs (see O'Brien *et al.* for further elaboration²). While the link between nigro-striatal dopaminergic neuronal degeneration and parkinsonism is established, it is also speculated that abnormal dopamine transmission, particularly in the striatum and frontal areas, contributes to the executive dysfunction²⁶. Cell loss in raphe nuclei (serotonin) and locus coeruleus (norepinephrine) may explain the mood symptoms, apathy and attentional dysfunction evident in LBDs. Cholinergic deficits in LBDs have been suggested to contribute to the global cognitive impairment and attentional dysfunction as well as hallucinosis; amelioration of these symptoms by cholinesterase inhibitors (ChEis) strongly supports the involvement of cholinergic dysfunction in LBDs pathology.

EPIDEMIOLOGY

Parkinson's Disease Dementia

The prevalence of dementia in PD has been estimated at between 24% and 31%, and the incidence rate is at least four to six times that of the rate of dementia in age-matched controls^{27,28}. It is becoming increasingly recognized that cognitive impairment is present even in the earliest stages of PD; in two recent studies it was estimated that between 19% and 24% of newly diagnosed PD patients appear to have some degree of cognitive impairment^{29,30}. The nature of these deficits varies, but subtle deficits in executive function, including attention shifting and working memory, as well as deficits in visuospatial function and episodic memory, have been noted. With time there appears to be a broadening and exacerbation of these deficits and it has been suggested that the mean duration from onset of PD to the development of PDD is around ten years; indeed one longitudinal study suggested that the cumulative prevalence was up to 78% after eight years of follow-up³¹. Risk factors for the development of PDD include older age, mild cognitive and attentional impairments at the initial diagnosis of PD, the severity of motor manifestations, and, in particular, the presence of rigidity, postural instability and gait disturbance^{32–35}. While PD incidence is twice as common in men as women it is not clear if male gender predisposes PD patients to the development of PDD. Smoking may also be a risk factor but the presence of apolipoprotein E4 (*APOE4*) genotype, unlike AD, does not appear to be a risk factor for PDD^{36–39}. Recent large-scale autopsy studies have demonstrated that between 4% and 10% of PD patients have evidence for GBA mutations. These individuals tend

to display early-onset parkinsonism and at least half had hallucinations and cognitive decline; it has recently been suggested that GBA mutations represent the most common genetic risk factor for the development of PD or LBDs⁴⁰.

Dementia with Lewy Bodies

Community prevalence figures for DLB have ranged from 0% to 30.5% of dementia cases depending on the sample cohort⁴¹. This wide range can be explained by a small number of studies with low patient numbers, differences in case criteria used and the presence of significant sampling biases. However, studies have suggested approximately 15–30% of all dementia cases meet neuropathological criteria for DLB at autopsy, emphasizing that a significant proportion of DLB cases are probably being missed clinically⁴². There are very few studies examining the incidence of DLB; two longitudinal studies, one US-based and the other Japanese-based, estimated the incidence as 0.57 per 1000 person years and 1.4 per 1000 person years, respectively^{43,44}. Risk factors for DLB are unclear as prevalence studies have been too small. It has, however, been suggested that *APOE4* status reduces survival rate in DLB (as with AD) although its presence has little effect on disease onset or duration⁴⁵. With regard to GBA, an autopsy study that included 95 patients with pathological confirmed DLB noted that 28% of subjects had GBA mutations. Those patients with AD co-pathology had substantially less at 10%, suggesting that GBA mutations tend to lead to more pathologically pure forms of LBDs⁴⁶. There may be an increased prevalence of DLB with older age and some case series have suggested a male preponderance although more recent studies have refuted this. Of note, however, is a recent neuropathological study suggesting that while the prevalence of LBs is almost the same between the sexes, the severity of LB pathology may differ, with males having a more brainstem/limbic pattern compared to a more diffuse neocortical pattern seen in women¹⁵.

CLINICAL FEATURES

LBDs have a distinctive constellation of symptoms and signs, including progressive cognitive impairment, neuropsychiatric alterations, parkinsonism, sleep behaviour disturbances and autonomic dysfunction. In PDD, parkinsonism is the initial complaint with the subsequent development over many years of an insidiously progressive cognitive impairment. Neuropsychiatric symptoms such as visual hallucinations are often initially viewed as a side effect of dopamine replacement therapy, but later, particularly as the cognitive impairment advances, they often arise independent of any anti-parkinson treatment. DLB patients, on the other hand, often have less prominent parkinsonism at initial presentation; instead, they tend to present with an evolving dementia that is often associated with attentional/cognitive fluctuations as well as visual hallucinations. These differences in the clinical presentation of the PDD versus DLB, particularly earlier in the disease course, are likely to relate to the differences in pathological spread and distribution of LBs and alpha-synuclein between the two conditions, as previously discussed. However, symptom and feature convergence occur between PDD and DLB later in the disease course, reflecting the commonality at this point in terms of neuropathology.

Cognitive and Attentional Impairment

Clinicians with experience in LBDs often state that they get an inherent 'feel' of how the cognitive profile of patients with LBDs

differs from that of patients with AD. Patients with LBDs have been suggested to display 'subcortical' features such as bradyphrenia and attentional deficits as well as visuo-perceptual problems (disproportionate to the global cognitive impairment), and this contrasts with the more 'cortical' feel of AD, where language and memory deficits are predominant. Thus on the Mini-Mental State Examination, a patient with DLB or PDD might be well orientated to time and place, score two out of three points on the delayed recall, but be unable to perform the serial sevens or copy the double pentagons.

This clinical impression of a difference is certainly supported by detailed neuropsychological testing. Patients with LBDs tend to perform better on verbal memory tests; indeed, in the early stages of the disease, episodic recall tends to be preserved, in contrast to AD, where short-term memory deficits are the presenting complaint. However, psychomotor speed is much slower in patients with LBDs compared to AD patients. In addition, patients with LBDs tend to have much more marked executive and attentional dysfunction^{47,48} and this appears to be associated with fluctuations in cognitive function. These fluctuations, which may vary in duration in terms of minutes, hours or days, occur in up to 85% of patients with LBDs⁴⁹. Fluctuations in cognition can occur in other dementias, such as AD and vascular dementia, but they appear qualitatively distinct in LBDs, where there appears to be an interruption of awareness that is often associated with transient episodes of confusion and communicative difficulties. Remission of near-normal cognitive function can then occur spontaneously in the absence of clear environmental triggers, suggesting that the fluctuations in LBDs are internally driven. A major problem, however, which has affected the accurate diagnosis of LBDs, is how to clinically define what cognitive fluctuations actually are. In DLB, various caregiver/observer inventories have been created to answer this issue. Importantly, Ferman *et al.*⁴⁹ found that four characteristics of the fluctuations appear to be particularly useful in reliably distinguishing DLB from AD:

- daytime drowsiness and lethargy
- daytime sleep of two or more hours
- staring into space for long periods
- episodes of disorganized speech.

Patients with LBDs also display more marked visuo-perceptual impairments on testing than AD patients, and this may tie in with the finding that there is marked parietal and occipital hypoperfusion in LBDs on functional neuroimaging. Within LBDs, the profile of cognitive deficits is broadly similar in PDD and DLB although it has been suggested that DLB patients suffer more severe executive and attentional dysfunction than PDD patients⁵⁰.

Neuropsychiatric Symptoms

Visual hallucinations are a common symptom in LBDs: 45–65% of PDD patients have visual hallucinations; their occurrence is higher in DLB with 60–80% displaying visual hallucinations¹⁶. These rates contrast with the low rates of visual hallucinations reported in AD (less than 10%) and hence the importance which is attached to the presence of visual hallucinations in the diagnostic criteria for both PDD and DLB. Visual hallucinations also tend to be persistent in LBDs, which helps differentiate them from those which occur in AD or delirium. In terms of phenomenology, the majority of hallucinations tend to be complex and formed, and are typically of people (often children), animals and body parts that are either animate or

static. The hallucinations can provoke emotional responses ranging from amusement through to indifference and outright fear. Insight is often variable and dependent upon the severity of the concurrent dementia although patients often have better insight into the unreality of the episode when it is over. Auditory hallucinations can also occur, but less frequently than visual hallucinations, in about 20% of patients with LBDs. Delusions are very common in DLB patients (rates of up to 78% have been reported) although their prevalence in PDD patients is lower at about 20–25%¹⁶. They are often based around experienced hallucinations and visuo-perceptual disturbances. They are typically complex and bizarre and their content often includes persecutory, spouse infidelity and 'phantom boarder' themes. Misidentification syndromes such as Capgras appear to occur almost exclusively in DLB compared to PDD¹⁶.

Depressive symptoms also appear to be common in PDD and DLB patients although prevalence estimates vary considerably from 7% up to 76% depending upon the population studied and the definition used⁴². It can be difficult to make the diagnosis of depression as the clinical picture is often complicated by associated apathy, bradykinesia and attentional dysfunction.

Sleep disorders, in particular REM sleep behaviour disorder, are frequently associated with LBDs. This parasomnia is characterized by a loss of skeletal muscle atonia during REM sleep and its onset often precedes the onset of LBDs by many years. With associated daytime somnolence and nocturnal restlessness, it has been suggested that REM sleep behaviour disorder may contribute to the cognitive fluctuations and hallucinations seen in LBDs⁴⁹.

Parkinsonism

PD is a prerequisite for the diagnosis of PDD; in contrast, in DLB, parkinsonism is only present in about 25–50% of patients at time of diagnosis, although the majority (75–80%) will go on to develop motor features sometime during their disease course. Postural gait instability with less tremor dominance appears to be the typical presenting motor phenotype in both PDD and DLB⁵¹. Symmetric extrapyramidal symptoms, greater axial rigidity and suboptimal levodopa responsiveness (especially evident in DLB) in comparison to PD are also features⁵².

Autonomic Dysfunction

Autonomic dysfunction that affects both sympathetic and parasympathetic systems is a significant and common feature of PD through to PDD and DLB. The dysfunction leads to a variety of clinical manifestations including orthostatic hypotension, carotid sinus hypersensitivity, reduced secretions (lacrima, mouth, sweat), urinary retention, erectile dysfunction and bowel problems (both constipation and diarrhoea). Orthostatic hypotension and carotid sinus sensitivity occur more commonly in LBDs than AD or age-matched controls^{53,54} and are likely to contribute to the high rates of syncope and falls that occur in this population.

Alpha-synuclein and LB deposition appear to be widespread within the autonomic system. This and the associated acetylcholine deficiency, which impairs effective preganglionic and parasympathetic synaptic neurotransmission, have been speculated as possible causes of the autonomic dysfunction⁵³.

Neuroleptic Sensitivity

Neuroleptics can provoke a severe adverse reaction in 30–50% of patients with LBDs⁵⁵ even when low doses are used. These reactions

can either be acute or subacute and they generally manifest as an abrupt worsening of parkinsonism with associated increased sedation and confusion. The severity of these reactions is such that they can prove fatal within days or weeks. Acute D2 blockade is thought to mediate these effects and they can occur with the use of both typical and atypical antipsychotics⁵⁶.

Gait Instability, Falls and Loss of Consciousness

Gait dysfunction and falls are extremely common in the LBDs; the causes are probably multifactorial and related to motor symptoms, attentional impairments and autonomic dysfunction. Transient losses of consciousness occur in patients with LBDs where they are found mute and unresponsive for several minutes but do not obviously display any focal neurological signs. These may relate to autonomic mechanisms such as orthostatic hypotension or carotid sinus sensitivity although they may be an extreme expression of fluctuating attention and arousal.

CLINICAL DIAGNOSIS

The availability of clear, internationally recognized consensus criteria for both PDD¹⁶ and DLB^{3,5,6} provides a rigorous scaffold on which clinicians can formulate their diagnosis; however, this places an onus on the clinician to:

- Take a detailed history from both the patient and a reliable informant, which is inclusive of the severity of impairment in daily living activities;
- Compile a problem list which will aid management decisions;
- Perform a mental state examination as well as cognitive testing which encompasses multiple domains;
- Carry out a full neurological examination;
- Arrange for appropriate investigations such as brain imaging or assessment of dopaminergic function.

DIFFERENTIAL DIAGNOSIS

Aside from the difficulties of diagnostically separating PDD from DLB there are a number of other differentials that should be considered. Often the question for PD versus PDD is: when does the dementia become clinically evident? To address this, the movement task force⁵⁷ provided a five-point guideline that recommends there should be:

1. a clear diagnosis of PD according to Queen's Square Brain Bank criteria;
2. the PD develops before the onset of dementia;
3. there is a global decline in cognitive efficiency (Mini-Mental State score <26);
4. cognitive deficiency is sufficient to impair daily life;
5. impairment occurs in more than one cognitive domain (e.g. attention, executive, visuo-constructive or memory).

For both PDD and DLB, other atypical Parkinson syndromes such as MSA, progressive supranuclear palsy, and corticobasal degeneration should be considered in the differential. However, for DLB the main differential diagnosis is other dementias, in particular AD; up to 65% of autopsy-confirmed DLB cases also meet the clinical NINCDS-ADRDA criteria for probable or possible AD⁵⁸. Vascular dementias

frequently present with fluctuations in cognition, which can cause diagnostic confusion with DLB. Although rare, Creutzfeldt-Jakob disease should be considered, particularly if myoclonus is evident.

DLB has often been re-elaborated as 'delirium with Lewy bodies'; therefore, intermittent delirium is another important differential; the diagnosis of DLB should therefore only be considered after appropriate clinical investigation to exclude infective, metabolic, medication or other related causes has been carried out. Occasionally DLB may present atypically, initially, as a late-onset delusional disorder or a depressive psychosis. Development of cognitive decline or parkinsonism should raise suspicions of DLB as the underlying cause.

INVESTIGATIONS AND POTENTIAL BIOMARKERS

Electroencephalography

Although not specific, the EEG in LBDs can show generalized slowing with transient temporal sharp waves; indeed, this EEG pattern is incorporated into the supportive features described in the DLB consensus criteria.

Imaging

Generalized atrophy as well as white matter changes occurs in LBDs. However, their presence does not help clinically in making the differential diagnosis. Nevertheless, in DLB there appears to be a relative preservation of hippocampal and medial temporal lobe volume on MRI, which can help differentiate it from AD⁵⁹. Functionally, occipital hypoperfusion has been noted in LBDs in single photon emission computerized tomography (SPECT)/positron emission tomography (PET). However, while specificity in SPECT/PET is often greater than 80% for distinguishing DLB from Alzheimer's, sensitivities tend to be lower. For example, Lobotesis *et al.*⁶⁰ noted a sensitivity of only 68%. An important recent development for the diagnosis of DLB is the visualization of presynaptic dopaminergic deficits in the striatum using ¹²³I-radiolabelled 2 β -carbomethoxy-3 β -(4-iodophenyl)-N-(3-fluoropropyl)nortropane (FP-CIT, trade name DaTSCAN). This technique demonstrates high sensitivity (78%) and specificity (90%) in identifying probable DLB versus non-DLB dementia⁶¹. However, although the current regulatory approval for FP-CIT imaging is in distinguishing probable DLB from AD, this discrimination can often be adequately made on clinical grounds alone. Rather, a longitudinal study has suggested that FP-CIT appears to be much more useful in determining clinically uncertain, i.e. 'possible', cases⁶². In this study of 19 people with an initial diagnosis of possible DLB who subsequently were diagnosed with probable DLB 1 year later, 12 had had abnormal FP-CIT scans at baseline (63% sensitivity).

Another potentially useful imaging modality is that of cardiac scintigraphy with ¹²³iodine metaiodobenzyl guanidine (¹²³I-MIBG); this provides a measure of the degree of postganglionic sympathetic cardiac innervation and it has been used to discriminate PD from other motor disorders such as MSA⁶³. Additionally, ¹²³I-MIBG uptake is markedly reduced in DLB in contrast to non-demented PD patients⁶⁴ and AD patients, and it has been advocated as a means of improving sensitivity in discriminating DLB from AD, particularly if SPECT perfusion imaging is equivocal⁶⁵.

Cerebrospinal Fluid and Plasma Markers

There is increasing interest in the use of cerebrospinal fluid (CSF) and serum markers in the diagnosis of dementias. CSF levels of

alpha-synuclein species and p-tau, as well as a large number of other neurochemicals, have all been mooted as potential markers of LBDs (see Mollenhauer and Trenkwalder for further elaboration⁶⁶), in particular the differentiation of DLB from AD. However, study results have been mixed, with poor replication between studies, variable sensitivities and specificities with frequent overlap in concentration levels between disease groups (e.g. DLB versus AD), and a lack of neuropathological confirmed diagnoses. Recently, serum proteomic array methods, which identify multiple potential diagnostic protein markers, have been used to diagnostically separate DLB from AD⁶⁷, and RNA expression patterns in blood have been suggested to be helpful in the diagnosis of early PD⁶⁸.

Genetics

A large number of genes have been associated with rare forms of familial PD; for example, *LRRK2*, *PINK1*, *SNCA* and *PARK2*, to name a few. As noted previously, GBA mutations appear to be strongly associated with the development of PD and LBDs. However, aside from this, specific gene linkages to PDD and DLB are less clear although a gene-dose effect with triplication of the associated alpha-synuclein gene (*SNCA*) has been suggested to give rise to familial variants of DLB and PDD whereas duplication is associated only with motor PD⁶⁹. However, sporadic LBDs have not been found to be associated with over-expression of alpha-synuclein genes. Butyrylcholinesterase allelic variants in conjunction with the presence of APOE ϵ 4 alleles have been suggested, in individuals who will go on to develop LBDs, to increase the likelihood than they will express the DLB clinical phenotype rather than PDD phenotype, i.e. dementia before the onset of parkinsonism⁷⁰.

Conclusion

Biomarkers are useful in early diagnosis, separation of the disease from other differentials, understanding the natural history of the disease and providing objective biological correlates of treatment response. However, while a number of modalities, including fluid markers and genetics, are potentially promising, they will require significant further research before they are clinically useful. Currently, best evidence probably exists for imaging markers, in particular, FP-CIT SPECT.

COURSE, PROGNOSIS AND PSYCHOSOCIAL EFFECTS

The annual decline in cognitive and motor function scores in DLB and PDD patients is about 10%³⁵. The survival duration from symptom onset (either parkinsonism or dementia) to death is between five and eight years in DLB and PDD patients depending upon the population studied^{71,72}. However, some patients display a much more rapid disease course and adverse predictors may include older age at onset, greater neuropsychiatric symptom severity (hallucinations and depressive symptoms), cognitive fluctuations and the presence of co-morbid Alzheimer pathology. Conversely, a long latency between parkinsonism onset and dementia onset in PDD patients has been suggested to predict longer survival after dementia onset.

The psychosocial impact of LBDs is high: cognitive, neuropsychiatric and motor impairments cause significant difficulties for patients and their caregivers. Nursing home placement is often a frequent outcome and is particularly common when psychotic symptoms are present. One study which examined quality of life indices in DLB

patients suggested that DLB patients had lower quality of life scores and used more resources than AD patients; indeed, almost 25% of DLB patients included had negative scores on the EQ-5D utility index, a level which has been defined as a state worse than death⁷³. Determinants of poor quality of life in DLB patients included the presence of apathy, delusions, poor activities of daily living and absence of a caregiver; cognitive scores had no impact.

MANAGEMENT

Initial diagnosis of AD is often straightforward; in contrast, awareness of LBDs among clinicians and the general public is often very limited and this has previously led to patients being misdiagnosed, given incorrect information and treated inappropriately. Fortunately, the establishment of the consensus criteria, diagnostic neuroimaging and an increasing evidence base for the symptomatic treatment of LBDs has improved this situation. Furthermore, dissemination of knowledge is also now being supported by organizations such as the Lewy Body Dementia Association (www.lewybodydementia.org) and Lewy Body Society (www.lewybody.org).

Overall, LBDs are complex conditions in which there are multiple management issues including those of early diagnosis, treatment of cognitive impairments, assessment and management of neuropsychiatric and behavioural symptoms as well as treatment of parkinsonism, autonomic dysfunction and sleep disorders³. Treatments include pharmacological therapy, but non-pharmacological approaches, psychoeducation to patients and family about the various neuropsychiatric symptoms and a multidisciplinary approach to management which encompasses occupational therapy, good nursing care, and social and carer groups are also very important. Table 58.5 provides a summary of the management approach. However, currently there is insufficient data for evidence-based guidelines for PDD and DLB management although it should be noted that the Third Consortium report by McKeith and colleagues does provide the first authoritative recommendations based on expert consensus for the latter condition³.

NON-PHARMACOLOGICAL TREATMENTS

Systematic evaluation of non-pharmacological interventions in LBDs is lacking. In the case of visual hallucinations, clear explanations as to their origin to patients who still have insight and the caregivers can be helpful. Hallucinations also appear to be exacerbated by visuo-perceptual disturbances, which can be secondary to eye disease or environmental issues; cataract removal, improved illumination and removal of patterned furnishings (e.g. carpets, curtains) that can provoke illusionary experiences all may be helpful. In addition, low levels of arousal and cognitive fluctuations appear to respond to enhanced environmental novelty and improved social interaction.

PHARMACOLOGICAL TREATMENTS

Management of Cognitive Impairments

The profound cholinergic deficits which occur in the central nervous system of patients with LBDs have provided the scientific rationale that restoration of acetylcholine may help ameliorate some of the cognitive and neuropsychiatric dysfunction that occurs in LBDs. Three ChEis – donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl) – which block the breakdown of acetylcholine within the synapse and thus prolong its effect postsynaptically have been used

Table 58.5 Symptom management in LBDs**General management**

Provide psychoeducation to patient and relatives, including explanation of the intrinsic features of LBDs including cognitive effects (attention and cognitive fluctuations), neuropsychiatric symptoms such as hallucinations, and any associated motor symptoms

Establish from the patient and carer which symptoms are most problematic, impair quality of life and need active treatment

Consider firstly what non-pharmacological and social care interventions can be implemented e.g. environmental stimulation for fluctuations; care package and occupational therapy assessment for cognitive and motor impairments

Specific treatment*Cognitive impairment*

Perform baseline assessment of cognitive function; this may need to be done on several occasions given the tendency to fluctuate in LBDs

Review medication chart; stop any unnecessary drugs with a propensity to anticholinergic or sedative effects

Consider, provided there are no contraindications, a gradual introduction of a ChEi; response should be evident within several weeks. This may include specific improvements in test scores, but also be alert to more global improvements in activities of daily living and attention

Memantine, in addition, or as an alternative, should also be considered

Neuropsychiatric symptoms

Treat symptoms only if they are causing distress and/or are functionally impairing; for example, many patients are able to tolerate their visual hallucinations without the need for active treatment

Review any antiparkinson medication; gradually reduce and, if possible, stop the medications in the following order: anticholinergics, amantadine, direct dopamine agonists, COMT inhibitors and L-dopa

ChEi, in addition to their cognitive benefit, may help ameliorate neuropsychiatric symptoms such as visual hallucinations, delusions, and apathy

If psychotic symptoms persist, consider a cautious trial of an antipsychotic:

Warn both patient and carers about the potential for severe adverse reactions

Start low and go slow

Review antipsychotic use regularly, looking for side effects; be alert that most neuroleptic reactions occur in the first two weeks and it may be appropriate to admit patients during this period for monitoring

If parkinsonism is worsened or occurs for the first time (in the case of some DLB patients) stop the antipsychotic

Do not prescribe the antipsychotic for prolonged periods. Regularly re-assess the need for the drug; can alternative interventions be applied now the situation is containable?

Depression may respond to SSRIs or SNRI. Avoid antidepressants with major anticholinergic effects (e.g. tricyclics) as this can adversely affect cognition and cause confusion

Clonazepam may help nocturnal hallucinations and RBD

Motor symptoms

Balance the need for treatment of motor dysfunction versus the potential for exacerbation of neuropsychiatric symptoms; use the minimal antiparkinson medication required for benefit

Autonomic dysfunction/orthostatic hypotension

Discontinue any unnecessary antihypertensives. Orthostatic hypotension may respond to the addition of midodrine or fludrocortisone

in LBDs treatment. There is some evidence for all three medications with regard to improvement in global cognitive function, attentional function and activities of daily living, although to date, only the efficacy of rivastigmine has been examined in large, robust placebo control trials in DLB and PDD patients^{74,75} and as such it is the only ChEi which is currently licensed for treatment in PDD. Nevertheless, there is no evidence to suggest that any one ChEi is better than another⁷⁶. Generally the treatment effect size for cognitive impairment appears to be larger in LBDs than AD and this probably reflects the greater cholinergic deficit seen in the former⁷⁷.

Overall, ChEis are reasonably tolerated in patients with LBDs; notable side effects include gastrointestinal disturbance, urinary frequency, insomnia, leg cramps, hypersalivation and lacrimation. Given the reciprocal interplay between dopamine and acetylcholine in the striatum, one might expect an exacerbation of motor symptoms with ChEi treatment; surprisingly a dose-dependent worsening only occurs in a minority of patients⁷⁸.

There is limited data for the long-term effect of ChEi treatment in LBDs although benefits appear to be sustained for up to two years^{79,80}. However, there is no data with regard to any potential disease modifying effects.

Memantine, which has a low side effect profile, may also be useful treatment in LBDs; a recent study in PDD and DLB patients by Aarsland *et al.* noted some improvement in a clinical global impression of change scale and improved speed on attentional tasks in patients receiving memantine for 24 weeks in comparison to placebo, and within the memantine receiving group there was a 1.4 point improvement in MMSE scores⁸¹.

Management of Neuropsychiatric Symptoms

Visual hallucinations are the most frequently occurring symptom in LBDs and they are often accompanied by delusions, agitation and behavioural disturbance. As noted above for cognition, ChEis have

also been shown to be effective in open-labelled studies for treating visual hallucinations although placebo-controlled data is available only for rivastigmine^{74,75}. Symptom reduction in frequency and intensity seems to be, in part, mediated by improvements in attentional function. Conversely, the presence of visual hallucinations predicts a better cognitive response to ChEi, perhaps as a result of greater cholinergic deficits in those individuals who experience them⁸².

ChEi should be considered first line; however, if they are ineffective it is sometimes necessary to consider the use of an atypical antipsychotic. Clozapine or quetiapine have been advocated in the literature as preferred agents. However, clozapine has notable side effects (e.g. agranulocytosis) and needs regular blood monitoring. Clinical trial data for quetiapine is equivocal; one study noted that while quetiapine did not worsen parkinsonism, it did not have any demonstrable benefits with regard to agitation or psychosis in DLB or PDD patients⁸³.

However, there are substantial risks associated with antipsychotic use. Aside from the high risk of severe neuroleptic reaction, the Food and Drugs Administration in 2008 issued an alert that both typical and atypical antipsychotics are associated with increased mortality in older patients with dementia related psychosis⁸⁴. Additionally both risperidone and olanzapine have warnings about increased risk of cerebrovascular disease⁸⁵. Overall, therefore, a high level of caution needs to be applied to the use of antipsychotics in LBDs.

Treatment of depression and apathy in LBDs is empirical as there is no clear evidence base. Preferred agents include SSRIs and SNRIs with the avoidance of tricyclics given their anticholinergic propensity. Apathy and drowsiness may respond to ChEis, and some have advocated the use of modafinil or methylphenidate although there is no evidence to support the effectiveness of these agents.

Low dose clonazepam before bed may be helpful in the management of associated REM behaviour disorder (RBD) in LBDs⁸⁶.

Management of Parkinsonism

It is well established that antiparkinsonian medications can exacerbate psychotic symptoms in LBDs and often there needs to be a clinical compromise between a relatively mobile and active patient with psychosis and one who is non-psychotic but immobile. In PDD, it is often necessary to have some level of anti-parkinsonian medication given the greater motor impairments that occur in this condition relative to DLB. Medications should be used at the lowest dose possible, and anticholinergic, anticholinergic and direct dopamine agonists should be avoided if possible. In DLB, only a third of patients show significant motor response to L-dopa; therefore treatment of parkinsonism should only be instituted if motor symptoms interfere with function.

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Prion Diseases

Brian S. Appleby

Division of Geriatric Psychiatry and Neuropsychiatry, The Johns Hopkins Hospital, Baltimore, USA

PRION THEORY AND BIOLOGY

Cellular Prion Protein

The native cellular prion protein (PrP^c) is located throughout the human body, predominantly in the brain and gut. PrP^c is a glycosyl phosphatidyl inositol-linked glycoprotein that is anchored on lipid rafts. The tertiary structure of PrP^c is primarily composed of α -helices with few β -sheets. The prion protein gene (*PRNP*) was identified in 1986 and its identification has led to the development of *PRNP* knock-out mice, which do not appear to behave differently from wild-type mice. However, PrP^c null mice exhibit impaired synaptic inhibition and it has been proposed that PrP^c has stress-protective functions. Divalent cations including copper, zinc and manganese have also been shown to bind to PrP^c, though the significance of this is unclear. There has been emerging evidence that PrP^c may be associated with Alzheimer's disease and psychiatric illnesses as part of the stress diathesis.

Pathological Prion Protein

In contrast to the native prion protein, the pathological prion protein's (PrP^{res}) structure is primarily composed of β -sheets that aggregate and form amyloid plaques. The high β -sheet content of PrP^{res} leads to its partial resistance to proteinase K, resulting in proteinase-resistant protein fragments (i.e. PrP^{res}) called prions, which stands for 'proteinaceous infectious particle.'

There are three aetiologies of PrP^{res}: (i) sporadic, (ii) genetic and (iii) acquired. Although the exact mechanism for the formation of sporadic PrP^{res} is unknown, it is widely believed to be the result of a posttranslational mutation. This has recently been demonstrated using *in vitro* protein misfolding cyclic amplification (PMCA) techniques¹. PrP^{res} can also be generated *de novo* by mutations within the prion protein gene (*PRNP*). Lastly, PrP^{res} can be acquired from an outside source and introduced into the body, precipitating the formation of additional PrP^{res}.

Prion Theory (The Protein-Only Hypothesis)

Prions are transmissible agents that lack the nucleic acids that bacteria and viruses use to infect other organisms. In lieu of nucleic acids, the transmissibility of prions is accomplished via an autocatalytic mechanism, a theory coined the 'protein-only hypothesis' (Figure 59.1). This process was first postulated by the mathematician J. S. Griffith

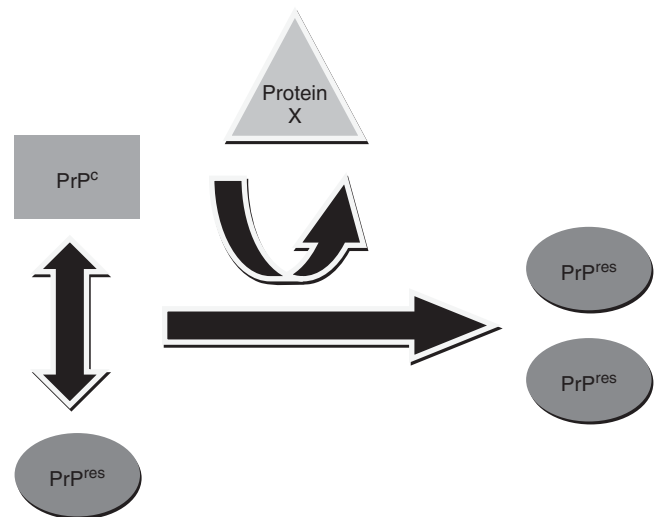


Figure 59.1 The prion conversion process. PrP^{res} replicates via an autocatalytic mechanism. PrP^{res} uses PrP^c as a substrate for the production of further PrP^{res} proteins. An uncharacterized protein (protein X) is postulated to facilitate the transformation process

in 1967² and was later described by Stanley Prusiner, who was subsequently granted a Nobel Prize for his work³. PrP^{res} interacts with PrP^c, using itself as a template to change the conformation of PrP^c into another PrP^{res} protein. Mouse studies have found that the presence of PrP^c is a requirement for the conversion process to occur. As evidence of this fact, PrP^c-null mice do not develop prion disease when they are inoculated with PrP^{res}, as the conversion process does not occur without the PrP^c substrate.

HUMAN PRION DISEASES

Kuru

Human prion diseases, or transmissible spongiform encephalopathies (TSEs), were initially described in detail by Nobel Prize laureate Carlton Gajdusek through his research on kuru⁴. Believed to be a 'slow virus', kuru was an endemic illness in the Fore tribe of Papua New Guinea. Kuru was characterized by rapidly progressive ataxia, oculomotor impairment, myoclonus and dementia with death typically occurring within two years of the illness onset. Gajdusek

later found that kuru was transmitted among the tribe via its cannibalistic rituals of consuming their deceased, particularly their brains. Tribal members who consumed brain matter of relatives with kuru were exposed to the illness and incubated it for several years, sometimes decades, until they eventually developed the illness. It is generally accepted that the kuru epidemic has since subsided and no longer exists.

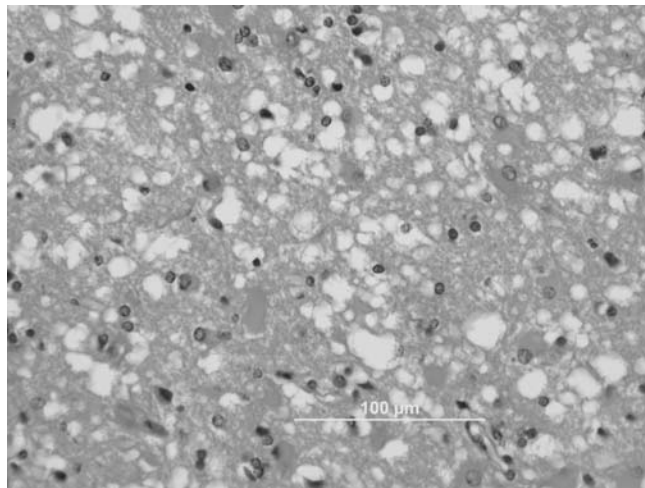
Creutzfeldt–Jakob Disease

The most common human prion disease is Creutzfeldt–Jakob disease (CJD), which was first described by two neuropsychiatrists, Hans Gerhard Creutzfeldt⁵ and Alfons Maria Jakob⁶. Both Creutzfeldt and Jakob described patients with a rapid neurodegenerative illness who

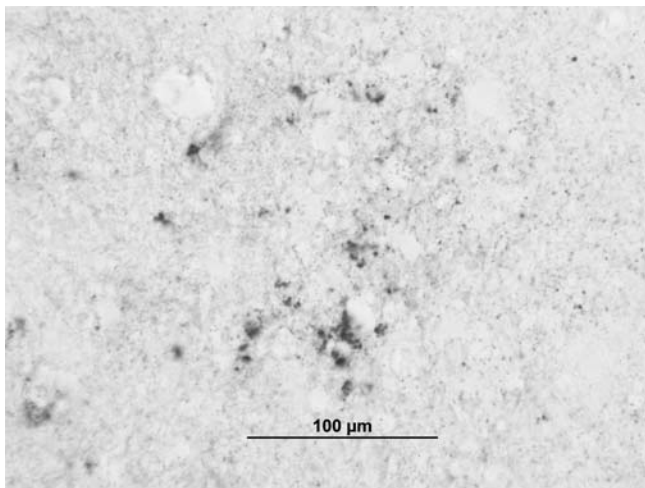
had a spongiform appearance of their brain at postmortem analysis. CJD is recognized at autopsy by the neuropathological triad of astrogliosis, spongiform changes and neuronal death (Figure 59.2a). Immunostaining with monoclonal 3F4 antibodies also shows prion deposition within the brain (Figure 59.2b). Abnormal prion proteins can also be detected by pre-treating brain homogenate with proteinase K and performing Western blot analyses that typically detect proteinase-resistant protein fragments (PrP^{27–30}).

CJD is a rare cause of dementia. The worldwide incidence of CJD is one per million people per year and is slightly higher in females than in males, although the age-adjusted incidence is slightly higher in males. CJD is rare in blacks for unclear reasons, but ascertainment problems may be one reason for the low incidence. Researchers have discovered a genetic propensity towards the development of CJD in relation to the codon 129 polymorphism of the *PRNP* gene. Individuals who are homozygous (Met-Met or Val-Val) at codon 129, especially Met-Met, are more likely to develop CJD. The *PRNP* codon 129 polymorphism is also associated with differences in clinical presentations and survival times.

CJD can be divided by aetiological subtypes. There are three main aetiologies of CJD: (i) sporadic CJD (sCJD), (ii) genetic CJD (gCJD), and (iii) acquired forms of CJD. The latter group includes the iatrogenic transmission of CJD (iCJD) and human transmission of bovine spongiform encephalopathy (BSE) called variant CJD (vCJD). In addition to different aetiologies, these subclasses of CJD also demonstrate different demographic, clinical, diagnostic, neuropathological



(a)



(b)

Figure 59.2 (a) Haematoxylin and eosin (H&E) stain of the temporal cortex and (b) monoclonal 3F4 antibody immunostaining of the hippocampus in a patient with Creutzfeldt–Jakob disease. The neuropathology is characterized by a spongiform appearance, astrogliosis and neuronal cell death. Immunostaining (b) reveals abnormal prion protein deposits (dark brown). A full colour version of this figure appears in the colour plate section

Table 59.1 Characteristics of Creutzfeldt–Jakob disease by aetiological subtypes

CJD subtype	Cases (%)	Mean age of onset (years)	Mean illness duration (months)
Sporadic	85	61	4
Genetic	15	56	14
Iatrogenic	<1	43	11
Variant	<1	32	13

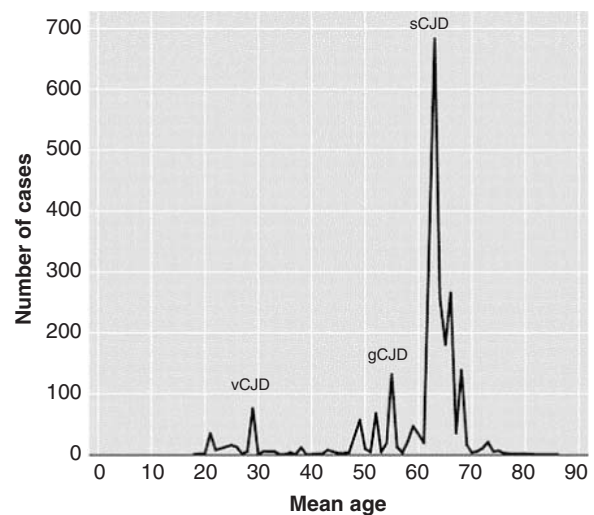


Figure 59.3 Age of onset of Creutzfeldt–Jakob disease. The age of onset follows a bell-shaped curve with a mean age of onset in sporadic CJD (sCJD) of 61 years, 56 years in genetic CJD (gCJD), and 32 years in variant CJD (vCJD). Adapted from Appleby *et al.*⁸

Table 59.2 Presenting symptoms of sporadic Creutzfeldt–Jakob disease

<i>Presenting symptom</i>	<i>Cases (%)</i>
Cognitive impairment	72
Ataxia	44
Visual/oculomotor impairment	35
Mood disorder	28
Vertigo	26
Behaviour/personality change	23
Psychosis/agitation	20
Sleep disorder	18

Source: Adapted from Appleby *et al.*⁸

and molecular characteristics. Table 59.1 lists the characteristics of the CJD subtypes^{7,8}.

Sporadic Creutzfeldt–Jakob disease

The exact aetiology of sCJD is unknown, but is largely believed to be a consequence of a posttranslational mutation of PrP^c. Comprising 85% of all human prion diseases, sCJD is the most common human prion disease. The age of onset follows a bell-shaped curve with a mean age of onset of 61 years (Figure 59.3). The average survival time is four months and a very small percentage of individuals

Table 59.3 Diagnostic test results in sporadic CJD

<i>Diagnostic test</i>	<i>Characteristics</i>
EEG	Periodic sharp wave complexes
CSF analyses	+14-3-3 protein
Brain MRI (DWI/FLAIR)	Hyperintensity in the basal ganglia and/or cortical ribbon

survive for more than two years. Although the cardinal symptoms of sCJD are dementia, ataxia, myoclonus, akinetic mutism and visual disturbances, the clinical presentation is widely variable and can include many different neuropsychiatric symptoms (Table 59.2)⁹.

A definitive diagnosis of CJD is only possible via neuropathological examination; however, various diagnostic tests can aid with an antemortem diagnosis (Table 59.3). CJD is a diagnosis of exclusion; hence, all other possible aetiologies should be considered and ruled out first. An electroencephalogram (EEG) may help to arrive at a diagnosis should it show the classic periodic sharp wave complexes (PSWCs) that are characteristic of CJD (Figure 59.4). A lumbar puncture must always be performed to exclude other causes of encephalopathy but the cerebrospinal fluid (CSF) can also be examined for the presence of the 14-3-3 protein, a native neuronal protein that is a marker of neuronal cell death. Although a sensitive diagnostic test, the 14-3-3 protein is non-specific and can be detected in the

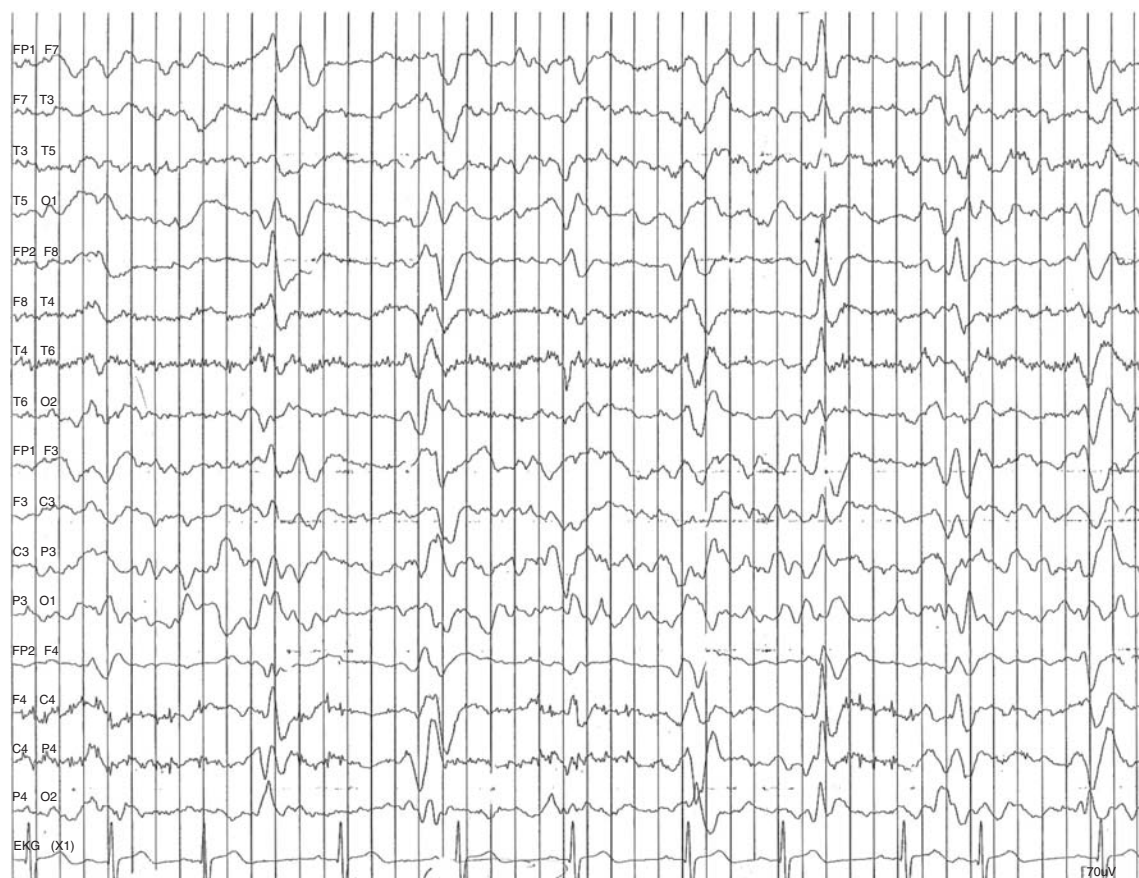


Figure 59.4 Electroencephalogram (EEG) of a sporadic Creutzfeldt–Jakob disease patient. The diffuse and synchronous periodic sharp wave complexes (PSWCs) seen in this EEG are characteristic of CJD

CSF of patients with multiple sclerosis, transverse myelitis and brain tumours. The presence of 14-3-3 in combination with tau is highly specific for a diagnosis of sCJD. Brain magnetic resonance imaging (MRI) can also be helpful in establishing a diagnosis of CJD. Hyperintensity in the cortical ribbon and/or basal ganglia are frequently observed on diffusion weighted and FLAIR image sequences, as shown in Figure 59.5.

Genetic Creutzfeldt–Jakob disease

Genetic CJD accounts for approximately 15% of human prion diseases and it is caused by a pathological mutation in the prion protein gene (*PRNP*) that results in the production of PrP^{res}. To date, over 30 different mutations in the *PRNP* gene are known to result

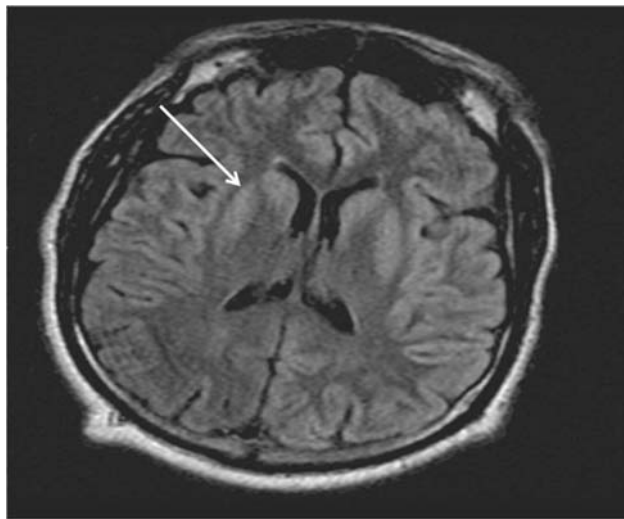
in prion diseases. The majority of mutations are autosomal dominant point mutations, but insertion and deletion mutations have also been described. All mutations demonstrate near complete penetrance by the ninth decade of life. The age of onset is usually mid-life (Figure 59.3) and disease duration is typically longer than other prion diseases and can be several years in duration. Clinical and neuropathological phenotypes vary and are determined by the mutation site, codon 129 polymorphism, and PrP^{res} type¹⁰. Diagnostic test results also differ between mutation types. The most common gCJD haplotype is E200K-129M. Other common mutations and their characteristics are listed in Table 59.5.

Iatrogenic Creutzfeldt–Jakob disease

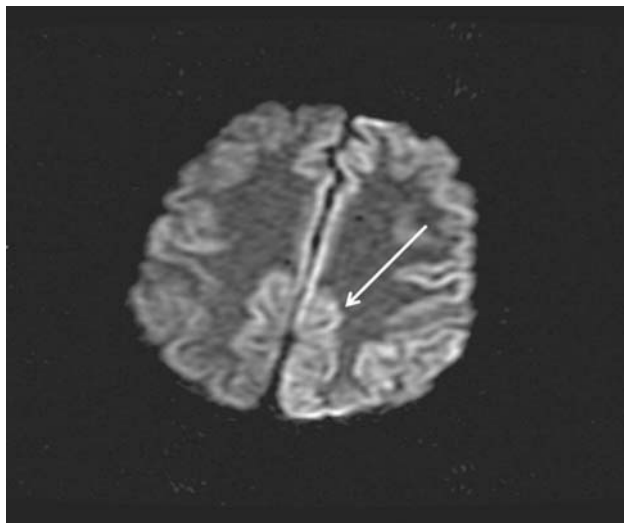
Iatrogenic CJD is pre-empted by the transmission of prions through several possible medical interventions¹¹. Table 59.4 lists the known risk factors for iCJD, including cadaveric dura grafts, gonadotrophins, corneal transplants, neurosurgical depth electrodes and neurosurgical instrument contamination. Direct contact with the central nervous system is necessary for transmission to occur in the majority of cases. Very low levels of prion proteins have been detected in the blood and urine of CJD patients, though the amounts are not significant enough to cause transmission with the exception of vCJD. There have been four recognized cases of vCJD transmission via blood transfusions; three died of CJD and one was pre-symptomatic at the time of death. There has been no known blood-borne transmission of the other prion diseases. Because of iCJD, cadaveric dura mater grafts and corneas are no longer used and neurosurgical instruments undergo extensive autoclaving procedures to prevent the transmission of prions. The ages of onset and survival times are variable given the groups' varied demographic features.

Variant Creutzfeldt–Jakob disease

Although it is the most publicized form of CJD, vCJD is quite rare. Fewer than 300 total cases have been described to date, nearly exclusively in European countries (e.g. UK, France, Spain, Italy and the Netherlands). Variant CJD is caused by ingesting foodstuffs tainted with a form of prion disease found in cows, termed bovine spongiform encephalopathy (BSE). During the 1990s, Bob Will and colleagues at the UK National Creutzfeldt–Jakob Disease Surveillance Centre noted an increased incidence of CJD in younger people, who also exhibited atypical neuropathological features at autopsy. Individuals with vCJD tended to be in their 20s or 30s (Figure 59.3) and had amyloid plaques in their brains, termed 'kuru plaques'¹². Individuals with vCJD primarily presented with psychiatric (e.g. mood and anxiety disorders) and sensory symptoms and their illness duration was typically longer than sCJD. Until December 2008, all cases of vCJD



(a)



(b)

Figure 59.5 Brain magnetic resonance imaging of a patient with Creutzfeldt–Jakob disease. (a) Basal ganglia hyperintensity is seen on FLAIR sequences and (b) hyperintensity in the cortical ribbon is seen on diffusion-weighted imaging

Table 59.4 Risk factors for iatrogenic Creutzfeldt–Jakob disease

Risk factors

Dural mater grafts
Cadaveric gonadotrophins (e.g. hGH, hCG)
Corneal transplants
Neurosurgical depth electrodes
Neurosurgical instrument contamination

Table 59.5 Clinical characteristics and EEG findings of familial prion diseases by mutation

<i>PRNP genotype</i>	<i>Clinical characteristics</i>	<i>EEG findings</i>
E200K	Rapidly progressive dementia, ataxia and myoclonus	PSWCs
V210I	Memory impairment, behavioural changes, and ataxia	PSWCs
D178N-129V	Cognitive impairment, depression and irritability	Lack of PSWCs
D178N-129M (fatal familial insomnia)	Insomnia, dysautonomia, pyrexia and dementia late in illness	Loss of sleep architecture
P102L (Gerstmann–Sträussler–Scheinker disease)	Gait and limb ataxia, nystagmus and dysarthria	Slowing

have been homozygous for methionine at codon 129 (129Met-Met), which led many to believe that the *PRNP* codon 129Met-Met genotype was necessary for the development of vCJD. Many researchers cautioned that, similar to iCJD, the codon 129 polymorphism may affect incubation period and that other polymorphisms may also be at risk, though they may display a prolonged incubation period. With the discovery of the first codon 129 Met-Val vCJD case in December 2008¹³, many are concerned that there may be another cluster of vCJD cases from the 1990s BSE exposure.

Fatal Familial Insomnia

Fatal familial insomnia (FFI) is a hereditary prion disease first described by Pierluigi Gambetti and colleagues¹⁴. FFI is caused by the D178N-129M mutation of the *PRNP* gene in contrast to one of the more common gCJD mutations, D178N-129V (Table 59.5). The different haplotypes differ in their codon 129 polymorphism of the mutant allele, resulting in different clinical and neuropathological phenotypes. FFI typically occurs in mid-life with the onset of progressive insomnia, fatigue, dysautonomia (e.g. labile blood pressure and pulse, pyrexia) and hypervigilance. Dementia typically does not manifest until late in the disease. EEGs and sleep studies show a characteristic loss of sleep architecture, including the absence of sleep spindles and K complexes. The neuropathology of FFI also differs from conventional CJD in that spongiform changes are found predominantly in the thalamus. There have also been several cases of sporadic fatal insomnia (sFI) described in the literature.

Gerstmann–Sträussler–Scheinker Disease

Gerstmann–Sträussler–Scheinker disease (GSS) is the least common heritable prion disease and it is caused by several different mutations in the *PRNP* gene, the P102L mutation being the most common¹⁵ (Table 59.5). The initial symptoms of GSS include global cerebellar impairment (e.g. limb and gait ataxia, dysmetria, scanning speech). The survival time of individuals with GSS can be several years in duration. The unique pathological prion protein, Pr^{7–8}, is also a characteristic feature of GSS.

SAFEGUARDS

Despite the name ‘transmissible spongiform encephalopathies,’ prion diseases are not infectious in the usual clinical environment. Only universal precautions are necessary when providing routine care to individuals with prion diseases. Prion precautions, which consist of special autoclaving and sterilization procedures, are necessary when

there is exposure to the central nervous system. Scenarios in which prion precautions would be necessary include neurosurgery, post-mortem examinations, and general surgery in individuals who have a family history of familial prion disease and suspected vCJD. In the United States, individuals who have a relative who has been diagnosed with a prion disease or those who spent time in the UK during the 1990s cannot give blood.

In relation to the zoonotic forms of acquired prion disease, care must be taken when handling central nervous system tissue of any mammal. Consuming brain matter, which is considered a delicacy in some cultures, is a high-risk activity for acquiring prion diseases. Not all animal prion diseases are transmissible to humans. Scrapie, a prion disease in sheep, has not been demonstrated to cross the animal–human species barrier. Some prion diseases in other species, such as cows, have shown the potential for human transmission. Because of vCJD, national governments and agricultural regulatory agencies should prohibit the return of ‘downer cows’ into the feed. Genetic forms of BSE have recently been discovered, strongly discouraging any re-feeding of animals as they have the potential to be presymptomatic carriers of prion disease. Chronic wasting disease (CWD), a prion disease that is rampant in cervids (e.g. deer and elk), has recently become a concern in the US. Researchers have estimated that up to 30% of deer in certain locales are incubating CWD. Although cervid to human transmission of CWD has not been demonstrated in the laboratory, hunters are encouraged to have their game tested for CWD prior to its consumption.

TREATMENTS

Unfortunately, human prion diseases are invariably fatal with no current treatment or cure. Several investigational treatments have been and are currently being explored. Carsten Korth, a psychiatrist who trained in Stanley Prusiner’s laboratory, discovered the antiprion effects of chlorpromazine and other phenothiazine antipsychotics that led to the two largest clinical trials in prion diseases to date¹⁶. Korth uncovered that many compounds with antiprion activity were based on tricyclic structures with an aliphatic side chain at the middle ring moiety. Chlorpromazine, imipramine and quinacrine were among these compounds, quinacrine having approximately 10-fold greater antiprion activity compared to the others. This discovery led to two major trials of quinacrine for the treatment of CJD: PRION-1, a UK trial with negative results, and a quinacrine trial at the University of California at San Francisco (UCSF), the results of which have not been published. Besides quinacrine, several other compounds are being investigated as potential treatments for prion diseases, including intraventricular pentosan polysulphate (PPA) and doxycycline. Both compounds exhibit antiprion activity *in vitro*, although human

studies have demonstrated that neither drug will likely be a cure. Future studies are planned to examine the use of antiprion protein antibodies, gene therapy and iRNA.

Until better treatments are available for individuals with prion disease, the clinician is left with the all-important symptomatic treatment of the disease. Certain symptoms can be particularly upsetting to the patient and the family. Myoclonus, especially startle myoclonus, can greatly decrease quality of life, yet can be easily managed with behavioural interventions (e.g. decreased touching, turning and decreased sensory input in general) and benzodiazepines or anticonvulsants. Both drugs can also address seizures, which are sometimes present in the end stages of the illness. Insomnia can also be treated with benzodiazepines. Visual hallucinations and paranoid delusions are common due to visual impairments and disorientation in the setting of a relatively normal level of alertness. These symptoms can be treated with antipsychotics, with a preference towards quetiapine and clozapine due to the high prevalence of extrapyramidal symptoms in this patient population. Pyrexia, another end-stage symptom, can be managed with cold compresses and acetaminophen. Finally, hospice care is usually recommended, which includes palliative care as well as treating pain and agonal breathing with morphine or other opiates.

PRION DISEASES AND OTHER PROTEIN-MISFOLDING DISORDERS

Prion diseases posit a unique situation for studying protein-misfolding disorders, also known as proteinopathies. Proteinopathies are diseases caused by the formation of an abnormal isomer of a native protein. Through toxicity and/or loss of function mechanisms, proteinopathies cause neurodegenerative diseases including Alzheimer's disease (amyloid beta), frontotemporal dementia (tau), Parkinson's disease (alpha-synuclein) and Huntington's disease (huntingtin). Most of the above illnesses have familial forms caused by gene mutations (e.g. PS-1 and -2, APP, MAPT, TDP-43 and PGRN), but the majority of cases are of sporadic aetiology. Basic science research typically focuses on transgenic animal models, which may ignore the disease mechanisms that are responsible for the majority of these populations. Prion diseases are unique in that they are sporadic, familial and transmissible. Whereas transgenic mice can also be used to study prion diseases, PrP^{res} can be used to inoculate normal animals, causing them to become ill without any genetic modification. Hence, prion diseases are a unique proteinopathy because PrP^{res} is both necessary and sufficient to cause disease in a normal population. Prions also aggregate and form amyloid plaques, a process called nucleation. Other proteinopathies follow this pattern: amyloid-beta forms amyloid plaques in Alzheimer's disease, tau proteins aggregate into neurofibrillary tangles in frontotemporal dementia, and alpha-synuclein forms Lewy bodies in Parkinson's disease and dementia with Lewy bodies. Protein misfolding cyclic amplification (PMCA), as used in prion diseases, can also be used to study other protein misfolding disorders, which may share similar features such as abnormal chaperone activity. Although one of the rarest protein misfolding disorders, much more is known about prion diseases than most of the other proteinopathies. Prion diseases thus serve as an opportunity to study these diseases

from a much different, and perhaps easier, perspective. Additionally, the prion protein gene (*PRNP*) is routinely listed in the top 20 genes implicated in Alzheimer's disease and the native prion protein has recently been shown to inhibit beta site APP-cleaving enzyme (BACE-1), an enzyme associated with Alzheimer's disease.

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Alcoholic and Other Toxic Dementias

Eileen M. Joyce

Professor of Neuropsychiatry, UCL Institute of Neurology, Queen Square, London, UK

ALCOHOLIC DEMENTIA

The concept of a dementia consequent upon the neurotoxic effects of long-term alcohol abuse developed from clinical observations of a gradual deterioration in personality and intellect in many alcoholics. Subsequent research suggested that this is age related, is milder in degree than other forms of dementia and constitutes 11–24% of all demented patients^{1,2}. To put this in further perspective, of the estimated 18 million alcoholics in the USA, approximately 40% will have mild cognitive impairment which is potentially reversible with abstinence, but a further 10% will have persisting severe cognitive impairment requiring institutional care, comprising patients mainly with dementia and amnesia^{3,4}.

Amnesia in alcoholics is known as the Wernicke-Korsakoff syndrome. This is the result of thiamine malnutrition which causes subcortical periventricular vascular lesions in diencephalic structures, the mamillary body and thalamus, known to be critically involved in new memory formation⁵. Alcoholic dementia was originally thought to be distinct from the Wernicke-Korsakoff syndrome and due to the direct neurotoxic effect of alcohol on the cerebral cortex. Horvath⁶ prospectively examined 100 chronic alcoholics presenting clinically with a dementia syndrome and concluded that alcoholic dementia was different from the Wernicke-Korsakoff syndrome and that other non-amnesic organic syndromes exist in alcoholics characteristic of frontal, parietal or global cortical damage. Cutting⁷ performed a retrospective case-note analysis of alcoholic patients with cognitive impairment and found two forms of clinical presentation. One consisted of a rapidly developing illness in younger patients with preserved intellect, akin to the traditional Wernicke-Korsakoff syndrome, whereas the other was more characteristic of dementia, being a gradual and global cognitive deterioration in older patients.

Although these studies support the concept of alcoholic dementia as a distinct entity, other evidence suggests a more complex picture with there being several different neuropathological 'routes' to the development of brain damage sufficient to cause the diffuse cognitive impairment recognized clinically as dementia. Torvik and colleagues⁸ examined the clinical records of patients who at autopsy had diencephalic lesions characteristic of thiamine malnutrition; that is, Wernicke-type lesions. Seventy five percent of these were considered to be demented in life rather than amnesic and the majority had no additional neuropathological hallmarks of a neurodegenerative dementia. They concluded that the diencephalic lesions of thiamine deficiency can result in the clinical picture of both 'alcoholic dementia' and the Wernicke-Korsakoff syndrome. Victor and Adams⁹

then pointed out that 10% of their pathologically proven cases of the Wernicke-Korsakoff syndrome developed cognitive abnormalities insidiously rather than acutely⁵ and that cognitive impairment other than amnesia and behavioural abnormalities such as inertia and apathy can be demonstrated in these patients¹⁰. Thus they argued that, depending on the severity of the non-mnemonic deficits or the mode of presentation, cases of the Wernicke-Korsakoff syndrome may be misattributed as cases of alcoholic dementia. The neuropathological studies of Harper and colleagues^{11–13} are in agreement with this view. They found that two thirds of the alcoholics coming to post-mortem in their unit had lesions of thiamine deficiency; of these, only a third had received a clinical diagnosis of the Wernicke-Korsakoff syndrome in life and, in the remainder, the most common diagnosis was dementia.

This evidence points to the conclusion that subcortical lesions caused by thiamine malnutrition can be sufficient to explain both amnesia and dementia witnessed in alcoholics. However, Victor and Adams⁹ and Torvik and colleagues⁸ did not suggest that *all* cases of alcoholic dementia are unrecognized cases of the Wernicke-Korsakoff syndrome. Both considered that superadded cerebral lesions may explain the dementia-like presentation of a proportion of patients with the Wernicke-Korsakoff syndrome. Because these additional lesions can be attributed to a variety of pathological processes, including chronic hepatocerebral degeneration, communicating hydrocephalus, Alzheimer's disease and ischaemic infarction, they argued that there is no need to invoke a special process of alcohol neurotoxicity. Some studies have supported this hypothesis. For example, Kasahara and colleagues¹⁴ compared young and old alcoholics and found evidence of dementia only in the older group; most of these patients had additional medical diagnoses including hypertension, liver disease and cardiomyopathy and no case of dementia could be accounted for by the direct effect of alcohol alone.

Although these clinical studies suggest that dementia in alcoholics can be caused by factors other than the direct effect of alcohol on brain function, the neuropathological evidence is that alcohol is neurotoxic. The question therefore still remains as to whether this is sufficient to cause cortical damage and frank dementia. Carefully controlled neuropathological studies have frequently found whole brain atrophy involving grey and white matter in chronic alcoholics with and without evidence of thiamine depletion as indicated by the presence or absence of subcortical Wernicke-type lesions^{15–18}. This atrophy appears to reflect reductions of white matter volume, neuronal loss in the dorsal frontal association cortex and neuronal

shrinkage in other cortical areas such as the cingulate gyrus and the precentral motor cortex^{19–23}. The contribution of liver failure to this neuropathology has been assessed in several studies and the bulk of evidence suggests that cirrhosis alone does not account for the brain atrophy witnessed in alcoholics^{16,17,24}. Other findings suggest that thiamine depletion in the context of alcohol ingestion may contribute to this neuropathological picture even when this is insufficient to cause the subcortical lesions of the Wernicke-Korsakoff syndrome.

Thiamine is an essential co-enzyme for three enzyme complexes (pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase and transketolase) involved in mitochondrial oxidative phosphorylation and a number of cellular synthetic processes. Animal models have shown that lack of thiamine leads to mitochondrial dysfunction and cell death consequent upon oxidative stress, glutamatergic excitotoxicity and inflammatory responses; as these mechanisms are also active in other forms of neurodegenerative dementia, it is possible that thiamine depletion, as well as causing diencephalic vascular lesions, also directly causes cortical cell damage secondary to these actions²⁵. Animal models have also shown that alcohol alone can lead to cell damage via oxidative stress^{26–28} and that cortical cell death is greater in the presence of both alcohol and thiamine depletion than either factor alone²⁹.

Thiamine deficiency is common in alcoholics due to a combination of inadequate diet, poor absorption secondary to the effect of alcohol on the gastrointestinal tract and poor cellular utilization due to the direct action of alcohol on intracellular mechanisms^{30,31}. Thus it is likely that, even in alcoholics who have not developed Wernicke-Korsakoff syndrome, reduced thiamine availability will be present in a significant proportion and that this contributes to the development of dementia along with alcohol via a joint action on cortical neurones. Evidence that alcohol and thiamine deficiency are synergistic in man also comes from findings that the cortical pathological changes witnessed in alcoholics without evidence of thiamine depletion are similar to but less severe than those with co-existent subcortical Wernicke lesions^{16,18,21,24,32–34}.

In summary, it can be concluded from these studies that: (i) alcohol itself can cause neuronal damage including cell death; (ii) liver disease *per se* is not a major factor in the aetiology of the neuropathological cerebral changes seen in alcoholics; and (iii) thiamine malnutrition potentiates the neurotoxic effect of alcohol on the brain and it is likely that frank dementia in alcoholics is due to this combined action rather than the effect of alcohol alone.

What is the relationship between alcohol ingestion and the more common, milder cognitive impairment seen in alcoholics? The advent of *in vivo* neuroimaging has enabled clinicopathological correlational studies to clarify the consequences of alcohol consumption on brain function and cognition in alcoholics uncomplicated by liver disease or thiamine depletion. Well-controlled, prospective studies using both CT and MRI have reliably confirmed the presence of cerebral shrinkage in such alcoholics in life involving both cortical grey and subcortical white matter^{35–42}, which is more pronounced in older patients⁴³ and more apparent in the frontal lobe^{44,45}. One early imaging study highlighted the possibility that women are more vulnerable to the effects of alcohol in that brain atrophy was equivalent in age-matched men and women despite the women having shorter or less severe drinking histories⁴⁶. This remains controversial, however, as some later studies^{47,48} but not all^{49,50} have replicated this finding.

The development of the MRI modality of diffusion tensor imaging (DTI) has allowed a more detailed assessment of the white matter volume reductions found in postmortem and conventional MRI studies.

DTI depends on water diffusion being constrained by cell membranes or myelin sheaths and, when abnormal, may reflect pathology of myelin microstructure. Studies of alcoholics without complications of liver disease or a history of Wernicke's encephalopathy have found that white matter abnormalities are widespread in life, being present in areas not previously detected by conventional MRI^{51–53}. DTI data can also be used to examine specific fibre pathways using the technique of tractography. When applied to alcoholics, abnormalities in the frontal forceps, internal and external capsules, fornix, and superior cingulate and longitudinal fasciculi have been detected, and the severity of these abnormalities was found to correlate with lifetime alcohol consumption⁵⁴. In the same study, when matched for alcohol exposure, alcoholic women showed more DTI signs of white matter degradation than alcoholic men in several fibre bundles, suggesting that any sex differences in the vulnerability to alcohol may be neural tissue specific⁵⁴.

An important observation is that the percentage of alcoholics with evidence of cerebral damage on brain scans is far in excess of that noted in neuropathological studies¹⁵. This discrepancy is probably explained by the finding that brain changes are reversible with continuing abstinence^{37,41,42,46,55–63}, thus indicating that neuroimaging findings may not accurately reflect the permanent neuropathological changes previously described in postmortem studies. However, because some studies have found that neuroimaging changes worsen in patients who continue to drink, and may not be entirely reversible with abstinence in heavier drinkers^{56,64,65}, and others have found that greater total alcohol consumption is associated with greater decrease in cortical grey matter, particularly in the frontal^{62,66} and temporal lobes⁶², these neuroimaging abnormalities may represent neurotoxic processes which may ultimately lead to more permanent neuropathology if abstinence is not achieved.

Like dementia, the characteristic cognitive impairment witnessed in uncomplicated alcoholics is diffuse in nature but much milder. Parsons⁶⁷, following decades of his own research, concluded that both male and female sober adult alcoholics have deficits on tests of learning, memory, executive functions and speed of information processing which are equivalent to those found in other patients with known brain dysfunction of a mild to moderate nature. Similar findings have repeatedly been demonstrated by others (see⁶⁸). Like neuroimaging studies, controlled neuropsychological studies have shown that cognitive deficits are largely reversible following abstinence⁶⁹ although, again, these may not be reversible in those with severe and long-term alcohol abuse⁶⁷. Early studies attempting to relate cognitive and structural changes in alcoholics found weak and inconsistent correlations, the majority of which were explained mainly by age and premorbid IQ^{35,36,38,70–72}. However, the use of novel MRI techniques has produced stronger evidence for a link between cognitive impairment on the one hand and brain structural and functional abnormalities on the other. For example, studies have combined structural MRI and MR spectroscopy to demonstrate concomitant brain atrophy and metabolic abnormalities in the context of cognitive deficits, all of which improve together with abstinence^{60,61,73}. Precise volumetric analyses have also confirmed the neuropathological finding that the dorsal frontal association cortex is the area most vulnerable to alcohol, in that this undergoes the greatest reduction in volume, but that other areas such as the temporal cortex, insula and cerebellum are also affected, as well as widespread areas of white matter⁷⁴. In the same study, neuropsychological impairments correlated with the grey and white matter volume reductions even in detoxified patients with well-preserved social function⁷⁴.

These studies of uncomplicated alcoholics suggest that chronic alcohol ingestion can cause damage to widespread areas of the cerebral cortex and subcortical white matter sufficient to cause cognitive impairment even in people who otherwise appear to be functioning well. Such findings, although reversible with sustained abstinence if caught early enough, seem to herald more permanent brain damage and possibly dementia in those who continue to drink heavily, especially if there is co-existent thiamine depletion. Together with the recent findings of the combined action of alcohol and thiamine deficiency on cortical viability in animal studies^{25,29}, this underscores the need to suspect and treat thiamine malnutrition even in apparently healthy alcoholics.

OTHER TOXIC DEMENTIAS IN THE ELDERLY

The long-term neuropsychiatric effects of ingestion of drugs of abuse are unclear and probably differ depending on the compound; however, there is little evidence to suggest that these generally cause significant brain damage enough to produce dementia. For example, benzodiazepines, perhaps the most relevant substance in elderly populations, do not produce diffuse cognitive impairment or brain damage⁷⁵. As ageing populations will now include people with other forms of long-term drug abuse or dependence, it is also important to consider other substances. Although there is some evidence that opiate addiction can result in grey matter volume reductions, these studies have been contaminated by including subjects with co-morbid alcohol abuse, and at least one of these suggests that alcohol rather than opiates *per se* was responsible for their findings⁷⁶. There is one notable exception to the lack of strong evidence that substances of abuse cause dementia and that is the phenomenon of toxic leukoencephalopathy seen in heroin, cocaine and amphetamine abuse. This usually occurs in the context of an overdose via the intravenous route or by inhalation, and is thought to be due to a direct toxic effect causing impaired intracellular energy metabolism⁷⁷⁻⁷⁹.

The neuropsychiatric effects of long-term occupational solvent exposure are also relevant to the elderly. Although there is controversy concerning whether solvents *per se* produce long-lasting effects, most studies find evidence for lasting neuropsychological abnormalities⁸⁰⁻⁸². Of particular interest is that these studies also found that a combination of long-term solvent exposure and alcohol abuse is a particular risk factor for the development of dementia. Of final relevance to this age group is the identification of bismuth encephalopathy which results from the over-ingestion of bismuth-containing compounds commonly taken for gastric irritation and sold without prescription. Following an acute organic reaction characterized by delirium, seizures and neurological abnormalities, persistent sequelae of diffuse cognitive impairment and cerebral atrophy has been documented^{83,84}.

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Reversible Dementias

Michael Philpot

Mental Health of Older Adults, South London and Maudsley NHS Foundation Trust, Maudsley Hospital, London, UK

INTRODUCTION

The aim of this chapter is to review the causes of 'reversible' dementias, their prevalence, methods of investigation and response to treatment. Given the right circumstances, almost any illness can affect cognition, so the objective is to identify those treatable conditions that most commonly present in this way. The early literature on this subject included numerous case studies or series of 'dementia' that appeared to resolve completely following treatment of the associated physical or psychiatric condition. Undoubtedly many of the patients described were actually suffering from delirium or other organic brain syndromes¹. Also, the concept of 'reversible' dementia appears at odds with the term 'dementia', denoting an insidiously progressive disorder². This confusion extends to psychiatric disorders such as depression and schizophrenia that may present as 'pseudo-dementia'³. Lastly, many patients, indeed probably the majority, with 'real' dementias will have concomitant conditions that, while not being aetiologically related to the dementia, may reduce cognitive function.

AETIOLOGY

The timely investigation of patients presenting with symptoms of dementia is a keystone of many clinical protocols^{4–6}. Diagnosis of 'probable' Alzheimer's disease is largely by exclusion of other causes of dementia – including those reckoned to be reversible. A list of what are considered the classic potentially reversible causes of dementia (PRD) is given in Table 61.1. Table 61.2 lists PRD that have been described in the past 10 years – usually in either single cases or small case series. The identification of the latter can depend crucially on how intensively a case is investigated. They include conditions sometimes grouped together as the 'rapidly progressive' dementias⁷.

PREVALENCE

Despite the extensive lists in Tables 61.1 and 61.2, the frequency with which PRD occur in everyday clinical practice is an important factor in determining the rigour with which contributory physical disorders or other causes are pursued. The overall prevalence identified in case series or clinic surveys can vary depending on the setting (inpatient, outpatient or community), the medical specialty involved (geriatric psychiatry, geriatrics, neurology or neuropsychi-

atry) and the disease pattern of the country in which the study is carried out (e.g. neurological infections are more prevalent in developing countries). Early studies generally failed to provide follow-up data to confirm whether the identified PRD were actually reversible or not. Previous reviews^{24,25} concluded that approximately 11–12% of patients presenting to a variety of specialist services with symptoms of dementia during the 1970s and 1980s had PRD. Philpot and Burns²⁴ found that the rate was 18% in patients under the age of 65 years but only 5% in those over 65, an observation that has been supported^{26,27}. However, few of the early studies provided follow-up data to confirm recovery. Clarfield²⁸ has reviewed the literature for studies published between 1987 and 2000 and identified 39 that fulfilled meta-analysis criteria. He found that recent studies were more often community or outpatient based, but that only 9% of cases had PRD. These figures represented a fall in prevalence from a previous review examining studies published in the 1970s and early 1980s when 13% of dementias were potentially reversible²⁵.

Table 61.3 lists more recent studies of PRD since 2001. The frequency of each underlying cause is compared to Clarfield²⁸. Mental disorders (chiefly depression) comprise the most prevalent category, with alcohol-related disorders also being more prominent than in previous reviews. Space-occupying lesions, endocrine/metabolic disease and drug toxicity appear less frequently.

INVESTIGATION PROTOCOLS

A number of organizations have published guidelines for routine investigations used in the assessment of dementia, and the recommendations of three such are listed in Table 61.4^{4–6}. Chui and Zhang³⁹ examined the added value of using investigations routinely. After a thorough clinical assessment, blood tests and neuroimaging results changed management in only 13% and 15%, of cases respectively. Van Crevel *et al.*⁴⁰ found that the number of patients requiring investigation to find one case of PRD was approximately 100, and the financial saving on care costs was insignificant. Foster *et al.*⁴¹, in a detailed examination of the cost-effectiveness of brain computed tomography, concluded that scans should only be performed routinely if symptom duration was less than one year, symptoms were rapidly progressive, presentation was atypical or the patient was under 65 years. However, the hard facts of health economics need to be balanced against the imperative to do one's best for the patient, so consensus protocols tend not to specify limiting investigations to particular age groups.

Table 61.1 Classification of potentially reversible dementias (after Lishman²)

<i>Reversible dementias</i>	<i>Common clinical examples</i>
Degenerative	Normal pressure hydrocephalus, Wilson's disease
Space-occupying lesions	Cerebral tumour, subdural haematoma
Infection	Neurosyphilis, chronic meningitis and encephalitis, HIV-associated dementia
Collagen-vascular	Cerebral vasculitis systemic lupus erythematosus, sarcoidosis
Metabolic/endocrine	Liver disease, uraemia, remote effects of carcinoma, hypo- and hyperthyroidism, hypopituitarism, hypo- and hyperparathyroidism, hypoglycaemia, Cushing's disease, Addison's disease
Toxic	Primary alcoholic dementia, Wernicke-Korsakoff syndrome, chronic intoxication with sedative drugs, heavy metals
Anoxic	Chronic obstructive airways disease, sleep apnoea syndrome, chronic carbon monoxide poisoning, post-cardiac arrest, congestive cardiac failure
Nutritional	Anaemia, deficiencies of vitamin B12, folate, thiamine
Psychiatric	Depression, late-onset schizophrenia

Table 61.2 Recently reported reversible dementias

<i>Reversible dementias</i>	<i>Common clinical examples</i>
Autoimmune encephalopathies	Anti-NMDA receptor ⁸ , anti-neuronal antibodies (limbic and extralimbic paraneoplastic syndromes) ⁷ , potassium channel antibody-associated ⁹ , non-vasculitic meningoencephalitis ¹⁰ , Hashimoto's disease ^{11,12}
Space-occupying lesions	Dural arteriovenous fistulae ¹³
Infection	Neurocysticercosis ¹⁴ , cryptococcal meningitis ¹⁵ , enteroviral meningo-encephalitis ¹⁶ , Whipple's disease ¹⁷
Collagen-vascular	Cerebral amyloid inflammatory vasculopathy ¹⁸ , antiphospholipid syndrome ¹⁹ , other CNS vasculitides (multiple causes) ⁷
Metabolic/endocrine	Paget's disease ²⁰ , Cushing's syndrome ²¹
Toxic	Steroids ²²
Anoxic	Spontaneous intracranial hypotension ²³

RESPONSE TO TREATMENT IN ORGANIC DISORDERS

A minority of studies identifying the prevalence of PRD actually include follow-up data reporting the response to treatment. Individual retrospective studies from the 1980s (e.g. Byrne¹) found some improvement in two thirds of patients and complete recovery in 40%. However, Clarfield^{25,28} suggested a much less optimistic outcome: 15% of PRD showed some response to treatment, 8% with full recovery, the remainder only partial recovery. Overall, some degree of recovery was shown in only 0.6% of patients with dementia²⁸. In more recent studies listed in Table 61.3, treatment outcome was only reported in two studies. Takada *et al.*³³ found that 55% showed some degree of reversibility. Of the 10 patients with neurosyphilis, only one fully recovered: full recovery was also seen in a patient with normal pressure hydrocephalus (NPH) and partial recovery in a patient with a subdural haematoma (SDH). All the potentially reversible cases identified in Sheng *et al.*³⁸ showed some degree of recovery. However, 63% had functional psychiatric disorders, mainly depression. Clearly, the lack of reversibility revealed by these studies suggests that most of the potentially reversible disorders are actually *concomitant* with real dementia⁴². Treatment of concomitant disorders may have some clinical benefits, improving overall function while not eliminating the underlying cause. Some problems may also be secondary to the dementia itself, e.g. anaemia as a result of malnutrition. The response rates of a selection of disorders are now discussed in more detail.

Vitamin B12 Deficiency

Strachan and Henderson⁴³ first described dementia in association with B12 deficiency. Treatment with cobalamin brought about complete remission of cognitive impairment. However, there have been mixed results in prospective studies of replacement in patients with dementia and B12 deficiency, some showing improvement^{44,45} and others showing little benefit^{46–48}. Patients with mild cognitive impairment and B12 deficiency fare better^{44,47,48}.

Thyroid Dysfunction

The propensity for thyroid deficiency to lead to memory impairment and psychomotor slowing has been known since the nineteenth century⁴⁹ and hypo- and hyperthyroidism are among the traditionally accepted causes of PRD². However, a clear reversibility of cognitive impairment sufficient to be considered dementia is rare²⁸. Hypo- and hyperthyroidism are found in approximately 0.4% and 0.3% of older people, but subclinical thyroid dysfunction is found five or six times more often^{50,51}. There is a complex relationship between this condition and incident dementia. An increased risk of dementia has been associated with subclinical hyperthyroidism^{52,53} and hypothyroidism⁵⁴, while a U-shaped relationship with thyroid function has also been demonstrated⁵⁵. However, the association found between high free T4, T3 levels and atrophy in the hippocampus and amygdala in otherwise healthy elderly people might suggest a preclinical phase of cognitive impairment⁵⁶.

Table 61.3 Outcome of investigation in patients presenting with clinical symptoms of dementia: studies published since 2001

Source	Total with dementia	Cases of potentially reversible dementia, N (%)									
		Total	NPH	Brain tumour	SDH	CNS infection	Endocrine/metabolic	Alcohol	Mental disorder	Drugs	Misc
Van Hout <i>et al.</i> ²⁹	96	5	2					2		1	
Luce <i>et al.</i> ³⁰	132	38 ^a		1			2	5	28		2
Hejl <i>et al.</i> ³¹	432	18	15	3							
Vale and Miranda ³²	186	32	10			4		16	2		0
Takada <i>et al.</i> ³³	275	22	5		1	9		6			1
Stratford <i>et al.</i> ³⁴	369	51	NR	NR	NR	NR	NR	18	19	1	18
Knopman <i>et al.</i> ³⁵	560	32		7		1		7	11		6
Shelley and Al Khabouri ³⁶	100	10	2			1		1			6
Van der Flier <i>et al.</i> ³⁷	358	94	1	NR	NR	NR	NR		58		35
Sheng <i>et al.</i> ³⁸	385	24					2		15		7
Total	2893 (100)	326 (11.2)	35 (1.2)	11 (0.4)	1 (0.04)	15 (0.5)	4 (0.1)	55 (1.9)	133 (4.6)	2 (0.07)	75 (2.6)
Data from Clarfield ²⁸ ; 39 studies published between 1987 and 2000	3940 (100)	355 (9)	57 (1.4)	53 (1.3)	17 (0.4)	15 (0.4)	64 (1.6)	36 (0.9)	52 (1.3)	4 (0.1)	57 (1.4)

Source: Adapted from Clarfield²⁸.

NPH, normal pressure hydrocephalus; SDH, subdural haematoma; Misc, assorted conditions or studies not listing systemic physical disorders; NR, not reported.

^aIncludes patients with mild cognitive impairment.

Table 61.4 Physical investigations for the assessment of patients presenting with cognitive impairment

<i>Routine investigations (all cases)</i>	<i>Special investigations (atypical cases or clinically indicated)</i>
Full blood count ^{a,b,c}	Electroencephalogram ^b
Electrolytes ^{a,b,c}	Chest X-ray ^b
Renal function ^{a,b,c}	Electrocardiogram ^b
Liver function ^{b,c}	Lumber puncture ^{a,b}
Thyroid function ^{a,b,c}	Brain biopsy ^b
Calcium ^{b,c}	SPECT or PET ^b
Vitamin B12 ^{a,b,c}	Syphilis serology ^{a,b}
Folate ^{a,b,c,d}	
Glucose ^{a,b,c}	
Brain computed tomography or magnetic resonance imaging ^{a,b,c}	
Urine for culture ^{a,b}	

^aAmerican Academy of Neurology⁴.^bNICE (UK) guidance for dementia⁵.^cThird Canadian Consensus Conference⁶.^dTest is optional in Canada.

Brain Lesions

NPH is the single most common organic cause of PRD²⁸. Hakim and Adams⁵⁷ described two patients who presented with dementia, gait disturbance and incontinence in association with ventricular enlargement and normal cerebrospinal fluid (CSF) pressure. Most cases are idiopathic but NPH can follow meningitis, bleed or head injury. The treatment is shunt insertion diverting CSF from the lateral ventricles to the peritoneum. Good outcome in terms of an improvement in cognition can vary from 20% to 80%^{58–61}. Features associated with a good prognosis include younger age, shorter duration of symptoms, and whether temporary improvement occurs as a result of pre-operative CSF drainage^{59–61}.

SDH occur usually as a result of head injuries or anticoagulant drugs but can occur spontaneously. A chronic SDH may present solely with progressive cognitive impairment but this is usually accompanied by fluctuating confusion, drowsiness and headache. Bleeding occurs from the veins between the dura and arachnoid mater and the resulting fluid collection may exert localizing neurological signs⁶². Clots are removed via burr holes and a good prognosis is found in more than half the cases thought to have dementia preoperatively^{63,64}. Again, good prognosis is associated with younger age (under 74), milder cognitive impairment and less handicap⁶⁴.

The increasing prevalence and incidence of malignant brain tumours with age is well documented in surveillance studies^{65–67} and may relate to increasing population in the older age groups^{65,67}. Late-onset epilepsy, focal neurological signs or evidence of raised intracranial pressure raise the suspicion of a space-occupying lesion. Elderly patients may be less likely than younger ones to present with headache or seizures, but more likely to present with confusion, aphasia or memory impairment⁶⁶. Dementia is usually associated with slowly growing lesions that can develop without localizing signs, but may be accompanied by mood disorder, personality change, apathy or fatigue². In older patients, slowly growing meningiomas may indeed be largely asymptomatic and 'watchful waiting' with repeat neuroimaging annually may be the best approach⁶⁸.

With regard to malignant tumours, although the outcome of surgical and/or radiotherapy treatment can be less favourable than in young patients^{66,69}, aggressive approach to treatment is still advocated⁶⁹.

DEPRESSION AND DEMENTIA

The syndromes of depression and dementia interact in a complex way. Depression may be a risk factor for Alzheimer's disease⁷⁰, and is commonly found in association with established dementia⁷¹. Depression can be a reaction to the early symptoms of dementia⁷². Depression in late life is associated with impaired cognition^{73,74}. Impairment is in multiple areas – attention, working memory, visual and verbal memory, and executive function⁷³ – but slowed information processing might underline all difficulties⁷⁴. For the most part, cognitive dysfunction is relatively mild but in some patients it can be extreme. Although, in practice, it can be difficult distinguishing between these disorders, depressive 'pseudo-dementia' has traditionally been viewed as a treatable condition with a distinct clinical history and symptoms that distinguish it from 'true' dementia³. Patients have a relatively short clinical course and a clearly defined onset. They complain of a poor memory, poor concentration or difficulty thinking, emphasize their disability, and communicate distress and low mood. They may frequently answer 'don't know' to direct questions and be slow to respond. There is often a past or family history of depression. For the individual patient, physical investigations including brain imaging⁷⁵ and neurophysiological studies⁷⁶ are of little use in differentiating between pseudo-dementia and 'real' dementia.

Traditional teaching holds that treatment of the underlying depression with antidepressant therapy results in complete recovery in depressive pseudo-dementia^{1–3}. However, some degree of cognitive impairment may persist after treatment^{73,77}, and longitudinal studies tend to support the view that severe cognitive impairment in depression is a harbinger of true dementia in between 25% and 50% of patients^{78–80}. Indeed, elderly patients who develop cognitive impairment during depression are at four to five times increased risk of developing dementia within five years^{79,80}.

CONCLUSION

Reversible dementias are relatively uncommon but their identification is important from the individual patient's perspective. As investigative techniques improve and new treatments are developed, the range of potentially reversible conditions grows. However, the literature encompasses a polarization of views. Depression aside, the evidence-based view would suggest that given the rarity and poor response to treatment, extensive investigation is unnecessary. The more traditional, patient-centred view, perhaps coloured by the early literature and the fear of litigation, would demand the continued use of routine investigations in the hope of excluding treatable aetiologies, however rare. The introduction of care protocols reached by consensus should guide clinicians and ensure patients have equity of access to appropriate assessment.

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Cognitive Domains Affected by Conditions of Ageing and the Role of Neuropsychological Testing

Heather R. Romero, Scott M. Hayes and Kathleen A. Welsh-Bohmer

Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Department of Psychiatry (Div Medical Psychiatry), Department of Medicine (Div Neurology), Center of Cognitive Neurosciences, Department of Psychology, Duke University, Durham, NC, USA

INTRODUCTION

Memory loss and dementia are nearly universal concerns in the ageing sector of our population¹. In practice, differentiating the normal age changes from those of early Alzheimer's disease can be daunting. Advances in clinical diagnostics and laboratory imaging methodologies facilitate this process²; however, there remains no definitive diagnostic biological test for Alzheimer's disease or for other related neurodegenerative conditions. Ultimately, the diagnosis of a cognitive disorder rests on an informed clinical examination. A thorough neurobehavioural examination and more detailed neuropsychological assessment, when indicated, allow the clinician to determine the integrity of various mental processes. Using this information, diagnostic inferences can be made regarding the presence or absence of brain disease and the potential confounding influences of depression, anxiety and other medical factors. The purpose of this chapter is to provide an overview of the cognitive domains assessed by a standard neuropsychological evaluation with focused consideration of the domains specifically affected by normal brain ageing, mild cognitive impairment, Alzheimer's disease and geriatric depression.

PRINCIPAL COGNITIVE DOMAINS IN THE GERIATRIC EVALUATION

When patients present with memory or other cognitive complaints, objective verification of the nature and extent of these problems and the determination of their functional impact are goals of the neuropsychological evaluation. To ascertain this, the evaluation will assess eight major areas of cognitive function along with aspects of mood and personality. The basic areas assessed or 'cognitive domains' include: (i) general orientation and alertness, (ii) attention/concentration, (iii) intellect, (iv) memory, (v) language, (vi) executive functions, (vii) visuoperception/spatial judgement, and (viii) sensorimotor control. A brief discussion of each of these domains and the tests commonly used to measure each are described in the sections that follow. More detailed discussion of the range of instruments available to clinicians can be found in other sources³.

General Orientation

Orientation is a particularly important function that can be disrupted by a number of medical (e.g. delirium), psychiatric (e.g. depression) and neurological disorders⁴. In assessing general personal awareness, the neuropsychologist will establish the patient's ability to orient to time (e.g. year, date, time of day), place (e.g. current location), personal information (e.g. name, age) and situation (e.g. why they are having a doctor's appointment). Commonly, the examining clinician may use mental status tests in which orientation screening is included, such as the Mini-Mental State Examination (MMSE)⁵ or more detailed batteries, such as the Mattis Dementia Rating Scale⁶ and the comprehensive memory battery of the Wechsler Memory Scale⁷. Targeted, well-validated measures of orientation, such as the Temporal Orientation Test (TOT)⁸, are often selected and preferred by neuropsychologists over mental status screening tests, in order to streamline the evaluation and allow comprehensive evaluation of domains only cursorily measured in a screening metric.

Attentional Functions

The components of attention tapped within the neuropsychological examination include visual and auditory: (i) simple attention span, (ii) selective attention, (iii) vigilance or sustained attention, (iv) divided attention and (v) alternating attention⁹. There are a number of well-validated tests from which to choose when assessing attention and concentration, some of which are now computerized.

Simple attention span, the number of units held in immediate memory, is commonly assessed by tests such as the Digit Span subtest from the Wechsler Adult Intelligence Scale III (WAIS-III)¹⁰ or the Spatial Span test of the Wechsler Memory Scale III⁷. *Selective attention* requires the ability to respond to relevant stimuli while simultaneously inhibiting response to irrelevant, distracting stimuli, such as in speeded target identification tasks (e.g. Symbol Search of the WAIS-III) or the Ruff 2 and 7 Selective Attention Test^{10,11}). *Vigilance* requires that stimuli be attended to over a period of time, commonly assessed by computerized continuous performance tests (CPTs), such

as the Test of Variables of Attention (T.O.V.A.)¹². *Divided attention* requires response to multiple competing tasks that occur simultaneously, such as tasks involving the simultaneous performance of both verbal repetition and visual search tasks. *Alternating attention* requires an individual to shift between tasks, such as the Trails B task, which requires switching between number and letters. It should be noted that tests of attention are easily influenced by a number of factors.

Failure on any single attentional test, or any neuropsychological test for that matter, can occur for a myriad of reasons. Consequently, it is important to consider confounds (e.g. sensory or motor limitations) and factors that may modify performance (e.g. educational experience) before drawing conclusions regarding impairments. Typically a neuropsychologist will look for consistency of performance across at least two tests measuring the same cognitive function before drawing an inference of compromised function.

Intelligence

Intelligence is a multifaceted construct that examines capacities of reasoning, problem solving, creative thought and abstraction, measured both verbally and non-verbally. Significant impairments in this domain result in compromised function, a defining feature of dementia. The tests most commonly used for the purpose of assessing intelligence are those of the Wechsler Adult Intelligence Scale IV (WAIS-IV)¹³ (and its predecessors, WAIS-III and the WAIS-R), due to the well-established psychometric properties (reliability, validity and clinical utility) and extensive normative information for a broad age range (age 16–89). The WAIS tests also afford a comprehensive survey of a number of complex cognitive processes, including calculation, verbal and non-verbal abstraction, fund of knowledge, comprehension, reasoning and problem solving, spatial judgement, and sensorimotor integration. In situations where administration of an entire intelligence battery may be impractical, shorter versions are available (e.g. Wechsler Abbreviated Scale of Intelligence, WASI¹⁴). Alternatively, the neuropsychologist may sample specific areas of concern. Subtests of the WAIS, such as Block Design and Similarities, are sensitive indicators of brain

disease and are often selected to quickly assess non-verbal and verbal abstraction, respectively.

Learning and Memory

A considerable portion of the neuropsychological evaluation is generally devoted to the in-depth characterization of the different components involved in the learning and retention of new information as depicted in Figure 62.1. The pattern of deficit across these varying learning and memory processes can suggest one medical condition over another. In a standard neuropsychological evaluation of dementia there will be measures of *semantic memory*, the recall of well-learned facts and world knowledge, and *episodic memory*, the rich person-specific memory that records all new occurring daily events. Tests of semantic memory include category or semantic fluency tests, which require the patient to generate items to a category or group items that are related to one another along specific dimensions (living vs. non-living; instruments vs. tools). Other tests tap recall of world knowledge and are built into larger memory batteries⁷.

Episodic memory and its component processes of encoding, storing and retrieving new information are determined using tests aimed at verbal and visual learning and memory functions. Acquisition of new information over multiple trials examines the efficacy of encoding whereas assessment of memory retention over short intervals (less than 3 minutes) and extended delay periods (30+ minutes) allow inferences regarding consolidation. Recognition memory allows determinations of the integrity of retrieval when cueing is provided.

Tests commonly used to assess memory are summarized in Table 62.1 and include comprehensive batteries such as the Wechsler Memory Scale (WMS-III)⁷. Targeted verbal learning and memory measures include the California Verbal Learning Test II¹⁵, the Hopkins Verbal Learning Test-Revised¹⁶ and the Rey Auditory Verbal Learning Test (Rey AVLT)¹⁷. Complementary visual memory tests include the Brief Visuospatial Memory Test-Revised¹⁸ and the Benton Visual Retention Test¹⁹. An entire listing of all available memory tests is beyond the scope of this review. However, a summary of commonly used metrics in current practice is presented in Table 62.1, and the reader is referred to other comprehensive sources³.

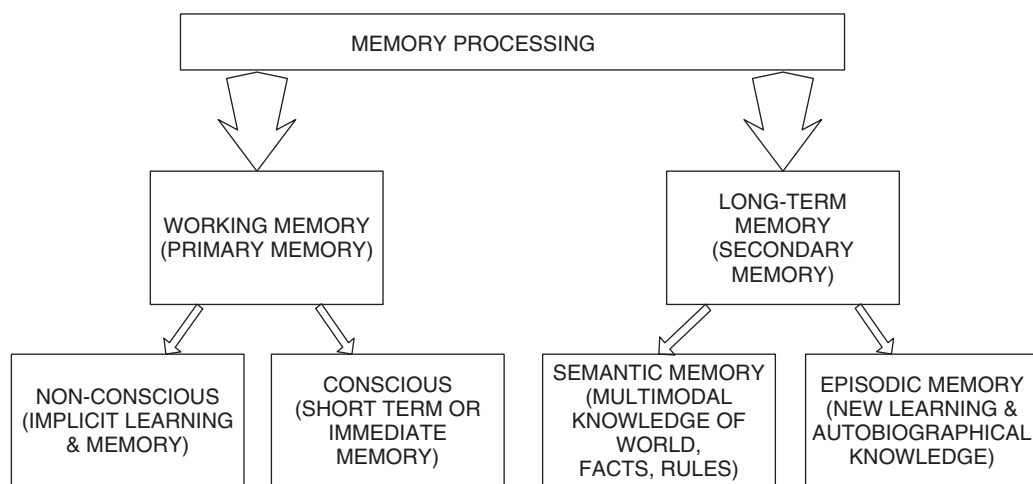


Figure 62.1 Neuropsychological conceptualization of learning and memory organization. Conscious aspects of working memory that require immediate, short-term processing of information and processes of semantic and episodic memory are typically assessed in the geriatric evaluation. Non-conscious learning and memory (e.g. motor memory, habits) are not typically assessed directly in the clinical neuropsychological examination

Table 62.1 Domains and common tests used to measure memory

<i>Domain</i>	<i>Common tests</i>
Orientation	Temporal Orientation Test ⁸ Mini-Mental State Examination ⁵ Mattis Dementia Rating Scale II ⁶ Wechsler Memory Scale III ⁷
Attention	Wechsler Adult Intelligence Scale III ¹⁰ Cancellation Tests (Ruff 2&7 test) ¹¹ Test of Variables of Attention (TOVA) ¹²
Intellect and premorbid function	Wechsler Adult Intelligence Scale (WAIS) WAIS-R, WAIS-III, WAIS-IV ^{10,13,31} Wechsler Abbreviated Scale of Intelligence (WASI) ¹⁴ Wechsler Test of Adult Reading (WTAR)
Memory	Wechsler Memory Scale (WMS): WMS-R, WMS III, WMS-IV ^{7,13,69} Rey Auditory Verbal Learning Test ¹⁷ California Verbal Learning Test-II ¹⁵ Hopkins Verbal Learning Test – Revised ¹⁶ Rey Osterrieth Complex Figure Test ³⁰ Brief Visuospatial Memory Test ¹⁸ Benton Visual Retention Test – 5th Edition ⁷⁰
Language	Multilingual Aphasia Examination (MAE) ²¹ Boston Naming Test 2 (BNT2) ²⁰ Boston Diagnostic Aphasia Examination – Third Ed (BDAA-3) ²⁰
Executive function	Wisconsin Card Sort Test (WCST) ⁷¹ Halstead Category Test ⁷² Stroop Color-Word Test ²³ Trail Making Test A and B Tests of Verbal and Design Fluency ^{21,73} Delis-Kaplan Executive Function System (D-KEFS) ²²
Visuospatial/perceptual	Judgment of Line Orientation Test ²⁸ Benton Facial Recognition Test ²⁸ Hooper Visual Organization Test ³² Clock Drawing Test ²⁰
Sensorimotor	Finger Tapping Test/Finger Oscillation Reitan Battery – Grip Strength Grooved Pegboard Purdue Pegboard Reitan Battery – Tactile Performance Test

Language

Verbal communication in day-to-day life relies on the individual's ability to express and comprehend oral and written speech. Formal neuropsychological evaluation focuses on spoken and written expressive language and on comprehension or 'receptive' language abilities. The Boston Diagnostic Aphasia Exam²⁰ and the Multilingual Aphasia Exam²¹ are two comprehensive batteries of language function commonly used. Administered in their entirety, each aphasia battery takes approximately 30–60 minutes to administer. Unless language disorder is the referral issue, more focused brief testing of specific functions is frequently a preferred approach. Expressive language will be assessed with fluency measures, such as the Controlled Oral Word Association Task (generating words beginning with a specified letter, e.g. 'R'), and with tests of 'semantic fluency' in which participants provide examples to a given category (e.g. sports). The Boston Naming Test, a visual naming procedure, is used to formally assess word-finding difficulty. Impairments in aural and written comprehension, if not detected during the interview, are often assessed with subtests of the Wechsler

Adult Intelligence Scale, including Comprehension, Vocabulary, Similarities or Information (see section on Intelligence).

Executive Functions

Executive functions, commonly referred to as higher order cognitive functions, comprise a number of supervisory processes that provide some control over many fundamental cognitive abilities and in the organization of general behaviour. The basic components of executive function include planning and organization abilities, monitoring and inhibition of responses, set shifting and cognitive flexibility, and verbal or non-verbal abstract reasoning. Attention and concentration processes, discussed previously, are also subsumed under the broad category of executive control; however, typically, these very specific functions are assessed separately.

There are a number of neuropsychological measures used to tap executive disorders. Comprehensive, all-in-one batteries of executive abilities include the Delis-Kaplan battery, which examines flexible behaviour, problem solving, judgement, personality and abstraction²². Targeted measures of decision making and flexible

behaviour include sorting tasks, such as the Wisconsin Card Sorting Test (WCST), or alternating letter–number sequencing procedures, such as the Trail Making Test. Measures commonly used to examine behavioural control and response inhibition include tests such as the Stroop Color Word test²³. Finally, assessment of abstract reasoning is commonly accomplished using subtests from the WAIS-III, such as the Similarities and Matrix Reasoning, or tests requiring the development of visual or verbal analogies, such as the Halstead Category Test.

Detection of executive deficits can be extraordinarily difficult, particularly in situations of subtle impairment and within the structured clinical setting, which is unlike the real world, where the patient must determine rules, contingencies and adjust behaviour accordingly. Consequently, in cases of suspected frontal lobe dementia, where executive disorders are prominent, and in neurodegenerative conditions (such as Alzheimer's disease and Parkinson's disease), where executive dysfunction emerges over the course of disease, the combined use of neuropsychological performance-based measures of executive function and informant-based measures of daily function, can be enormously helpful in determining the presence of problems in this domain and can help guide management approaches. Computerized tests of decision making and planning, such as the Cambridge Neuropsychological Tests Automated Battery (CANTAB), can augment the diagnostic process²⁴. Self-report and informant-report measures such as the Frontal System Behavioral Examination (FrSBe)²⁵ or the Behavioral Rating Inventory of Executive Function – Adult version (BRIEF-A)²⁶ are also useful for assessing personality change and patient insight.

Visuospatial Function

Neuropsychological assessment of visual–spatial function focuses on object perception, spatial appreciation, constructional praxis and complex visual integrative capacities²⁷. Object perception is often determined through tests such as the Facial Recognition Task²⁸, in which the patient is required to discriminate between faces presented from different views or under different lighting conditions. Spatial perception ability is determined via tests assessing judgement of angular relationships, locations of objects in space and detection of movement. Praxis will be assessed either through the copy of simple (e.g. CERAD battery²⁹) and visually complicated geometric figures (e.g. Rey-Osterich Complex Figure Test³⁰) or via three-dimensional constructional tasks (e.g. block design³¹). Integrating visual information into a meaningful whole is often determined with tests such as the Hooper Visual Organization test, which require visual processing and conceptualization³².

In clinical practice, visuo-spatial problems are often less obvious on screening evaluation than either memory or language disorders. Consequently, incorporation of simple visuo-spatial measures, such as the Clock Drawing test²⁰, to the neurobehaviour examination can augment the detection and tracking of these disorders and can improve the sensitivity of the Alzheimer's disease diagnosis³³. The information from a detailed neuropsychological evaluation of visuo-spatial function may be very useful for arriving at recommendations concerning daily activities, such as driving³⁴.

Sensorimotor Function

The neuropsychological examination of motor function will begin with the enumeration of any obvious motor signs, such as evident

hemiplegia, tremor, dyskinesia or chorea. Tests for subtle problems in fine motor control are then typically administered and can be highly instructive in pointing to potential lateralized central nervous system deficits³⁵. A number of standardized tests of manual strength and speed are available for quantifying and interpreting sensorimotor functions (Table 62.1). Typically, function with both the dominant and non-dominant hands is assessed using any of a number of metrics, permitting an evaluation of hand grip strength, rapid finger movement or fine motor dexterity (e.g. manipulation of small objects). Easy to administer, the measures are a sensitive indicator of general cognitive integrity and lateralized deficits in the nervous system, and can be useful in tracking disease progression and medication effects, particularly those treatments directly effecting extrapyramidal motor function³⁶.

Mood and Personality

The assessment of mood and personality begins with a psychological interview, allowing the neuropsychologist to assess the range of symptoms, level of functional impairment and relationship of the problems to the onset of cognitive dysfunction. This interview will then be augmented by objective metrics to determine changes from a pre-existing level and longstanding traits. Patient self-report measures of mood state include the Beck Depression Inventory II (BDI-II) or the Geriatric Depression Scale^{37,38}. More detailed measures, such as the Minnesota Multiphasic Personality Inventory 2 (MMPI-2), survey broad psychiatric symptoms and are used in situations where psychiatric or personality issues are considered primary to the complaint³⁹.

Informant report questionnaires are particularly helpful in dementia as patient insight into their own behavioural change may be impaired. The Neuropsychiatric Inventory (NPI) assesses eight different domains of behaviour affected in brain disease (depression, apathy, anxiety, disinhibition, hallucinations, paranoia, delusions, agitation) from an informed observer perspective⁴⁰. Changes in personality can also be assessed by questionnaires such as the FrSBe, discussed previously, which is an inventory that has both self and informant report forms and focuses on areas such of apathy, disinhibition and executive dysfunction²⁵.

COGNITIVE PROFILES ASSOCIATED WITH COMMON CONDITIONS OF AGEING

With performance across various cognitive domains established, consideration of the impairment profile and its relationship to underlying neural systems and brain disease is required for diagnosis. In the next section we review the typical neuropsychological profiles of normal ageing, Alzheimer's disease, mild cognitive impairment and geriatric depression.

Normal Cognitive Ageing

The profile of cognitive change due to normal brain ageing can be fairly easily distinguished from impairments due to neurodegenerative conditions, such as Alzheimer's disease, particularly in individuals who are 85 years of age or younger⁴¹. The neuropsychological findings of ageing reveal a spectrum of modest decline within a number of cognitive domains (Figure 62.2)⁴². Selective losses occur on tests of psychomotor speed and sensorimotor functions. Other functions affected include memory retrieval, attentional capacity, executive function and working memory⁴³. Semantic knowledge

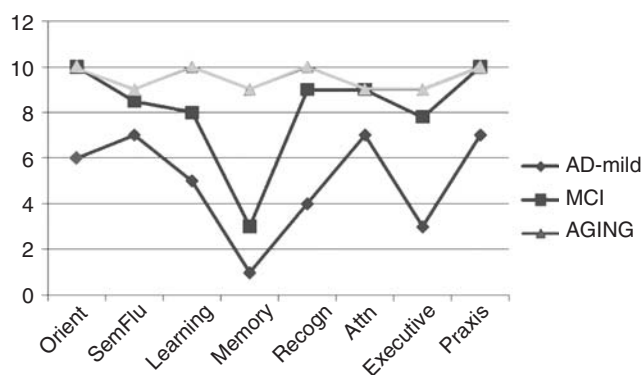


Figure 62.2 Neuropsychological performance in Alzheimer's disease, mild cognitive impairment and normal ageing. Presented are prototypical cognitive profiles of mild-staged Alzheimer's disease (AD), mild cognitive impairment (MCI) and normal ageing when considered relative to the performance of young adults on domains of Orientation, Expressive language (Semantic fluency), Learning, Delayed memory, Recognition memory, Praxis, and Executive function. Compared to young adults, normal older aged adults will demonstrate modest declines on tests of delayed free recall (Memory), word fluency (SemFlu), and higher order executive functions involving flexible behaviour (Executive). These rather modest changes in performance are exacerbated in MCI and AD. Delayed memory is particularly poor and there are also deficits in new learning and recognition memory. Verbal semantic fluency (SemFlu), simple attention, and praxis are also affected by the AD process, but become particularly problematic later in the course of the disease

and crystallized intelligence, which are acquired over the life span, are typically spared from age-related decline. Large cross-sectional comparisons across diverse cohorts aged 18–90 demonstrate monotonic declines across the broad domains noted, beginning as early as age 30; improved function is seen on tests of general knowledge and verbal comprehension⁴⁴. These findings are robust and are confirmed in longitudinal, within-person studies⁴⁵. In fact, within these within-subject comparisons there is evident test–retest improvement in test performance over time (i.e. practice effect)⁴⁶. It has been suggested that the absence of the practice effect on re-evaluation may be an important indicator of an early neurocognitive condition⁴⁷, an observation important to consider on repeated evaluation with mental status screens, such as the MMSE.

Alzheimer's disease

In contrast to normal ageing, the cognitive disorder of Alzheimer's disease is characterized, early and throughout the disorder, by a profound impairment in memory consolidation (i.e. effectively storing new information for recall later), making it exceptionally difficult to learn and retain new information. On neuropsychological evaluation this problem is manifest by rapid forgetting of new information, measured with delayed recall procedures administered 10–30 minutes after the individual has already effectively demonstrated ability to successfully encode new information on tests of immediate recall⁴⁸. Characteristically, the memory deficit is facilitated very little by structural support, such as recognition cuing. Recall becomes vague, and patients will commit errors on recognition tests, showing a tendency to over-endorse items as recognized targets (i.e. false positive errors⁴⁹). The failure to

benefit from cueing in Alzheimer's disease contrasts the memory disorders of normal brain ageing, depression, Lewy body dementia and vascular cognitive impairment. In each of the latter situations, retrieval cueing is beneficial and assists recall^{50–52}.

Although memory impairment is the prominent clinical sign of Alzheimer's disease, it is not the only deficit characterizing this neurodegenerative dementia. There are also highly characteristic problems in expressive language evident early in the illness. Later, problems in complex problem solving, executive control and abstraction are more clearly evident as well as disorders in visuo-spatial analysis and motor praxis (organization of skilled motor movements – such as writing, drawing, dressing, etc.). As each of these cognitive domains become more impaired, deficits in activities of daily function unfold²⁹.

On formal neuropsychological evaluation, the early language disorder of Alzheimer's disease is characterized by difficulties on tests of visual confrontation naming and on measures of semantic fluency, assessed by asking the patient to generate exemplars to a category (e.g. household tools, cars). Qualitatively, there may be a vacuous nature to speech output. With an absence of content words in their discourse, patients may resort to 'circumlocution' (i.e. description phrases) rather than easily accessing the precise word needed. Word substitutions and paraphasic errors also become common. Despite these difficulties in expression, comprehension of speech and repetition tend to be spared until later in the illness.

Praxis difficulties, impaired geographical orientation, and visuo-spatial errors may manifest as problems in spatial navigation, judgement of distances and difficulties locating and correctly identifying objects in the environment. On formal neuropsychological testing, these deficits are revealed using tests requiring visual integrative functions, judgement of spatial relationships between objects and form perception^{53,54}. Atypical presentations of pronounced and relatively isolated visuo-spatial deficits are noted on occasion in Alzheimer's disease and are common in the Lewy body variant of Alzheimer's disease^{53,55}. Similar presentations can also be seen in other progressive dementias, such as posterior cortical atrophy or 'Benson's Syndrome', multisystem atrophy, corticobasal dementia, forms of Creutzfeldt–Jakob disease⁵⁶. In making distinctions between aetiologies, consideration must be given to other salient clinical features including presence or absence of motor signs, history of symptom expression and disease course⁵².

Mild Cognitive Impairment

The concept of mild cognitive impairment (MCI) has emerged as a construct describing a transitional stage between normal ageing and the dementia syndrome common in Alzheimer's disease. The original MCI criteria specified: (i) a pronounced and rather isolated deficit in recent memory function, and (ii) preserved activities of daily living capabilities⁵⁷. MCI appears to be a risk factor for later dementia, with a 12% rate of conversion per year compared with 1–2% in normal ageing. The operationalization of this construct has greatly facilitated early Alzheimer's disease identification; however, it has been criticized as too restrictive and not capturing the broad range of sub-syndromal symptoms leading ultimately to Alzheimer's disease and to other closely aligned dementias. In addition, the construct has been found in many settings to be diagnostically unstable. Many individuals characterized as MCI in community settings and epidemiological surveys have been reported to revert back to normal function at later observation points, therefore, calling into question the validity of the diagnosis as a prodrome to neurodegenerative dementia⁵⁸.

Revised criteria now in use recognize that mild cognitive impairments may be a prelude to a number of different types of dementias, not only Alzheimer's disease⁵⁹. The new criteria have been broadened to include four subcategories of subsyndromal states, each of which share the core criteria of: (i) cognitive complaint, (ii) objective evidence of cognitive deficit beyond expectation for age (variably defined as either -1.0 SD or -1.5 SD below age, education mean), and (iii) activities of daily living are preserved and instrumental functions are either intact or are minimally impaired. With the new criteria, MCI can be dichotomized into an 'amnesic' and 'non-amnesic form', which is further dichotomized into 'single domain' affected vs. 'multiple cognitive domains' impaired. The four resulting subcategories are: 'amnesic MCI', corresponding to the original criteria; 'amnesic- multiple domain MCI', a situation where memory involvement is prominent but another domain (such as executive function or language) is also impaired; 'non-amnesic single-domain MCI', which captures conditions such as an early pronounced visuo-spatial, executive or language-based disorders; and 'non-amnesic multiple domain MCI', which captures multiple deficit disorders in which memory is by and large spared.

The predictive utility of the new subcategories of MCI for Alzheimer's disease and other dementias has yet to be fully demonstrated⁶⁰; however, initial information suggests that the amnesic forms of MCI are predictive of later Alzheimer's disease development⁶¹. Other non-amnesic forms may be more predictive of other forms of chronic, degenerative disorders, such as vascular dementia⁶². However, there is no universal information on the latter point, and some studies suggest that all categories are equally predictive of later dementia^{63,64}. This topic is an evolving area of clinical research, which will be facilitated as the pathobiology of the various chronic diseases and their interactions with one another are better understood.

Geriatric Depression

The neuropsychological profile in geriatric depression reveals highly specific cognitive disturbances in general cognitive efficiency. The entire profile of performance may be suppressed or there can be deficits confined to tests of executive processes of attention, working memory and processing speed^{65,66}. On detailed characterization, specific impairments are commonly detected in selective attention, sustained attention, organization, set shifting, initiation and response inhibition. Visuo-spatial deficits and deficient memory performance are also possible; however, unlike the disorder of Alzheimer's disease these impairments tend to result from executive and processing speed deficits, rather than being a problem in spatial ability or memory consolidation. Very poor acquisition of new information in the context of shifting attention leads to memory complaints and subsequent impairment on tests of delayed free recall. However, when memory tasks are more structured and less reliant on executive abilities, delayed recall improves in the depressed patient, sometimes to the normal level, underscoring the role of the initial processing deficits.

Treatment of depression can lead to some reversibility of cognitive deficits and improved function⁶⁷. Persisting cognitive impairment following adequate treatment may be due to underlying neuropathology, which is contributing to both depression symptoms and cognitive deficits, such as cerebrovascular disease or neurodegenerative conditions⁶⁸. Careful evaluation of mood is therefore essential both for differential diagnosis of memory disorder and also for optimizing patient outcomes.

SUMMARY AND CONCLUSIONS

By understanding the common profiles of neurocognitive dysfunction typical of the major disorders of ageing, such as Alzheimer's disease and geriatric depression, the examining physician is given valuable information that complements the more abbreviated mental status assessment. In enhancing the detection of dementia cases in everyday clinical practice, the application of targeted measures of episodic memory (recall after a delay) and executive function (flexible thought) can be quite useful while also providing adequate profile information for tracking the clinical progress of patients over time. To facilitate the recognition of subtle disorders such as MCI, the addition of a screen of functional ability may be necessary in order to establish the impact of a cognitive complaint on the patient's ability to carry out normal, routine activities of daily living. Although the current pharmacological treatments for Alzheimer's disease offer little hope in terms of disease reversal, early diagnosis allows the clinician to treat contributing conditions in an effort to optimize function and prevent excess disability. It also permits the anticipation of problems before they occur and allows inclusion of patients in care decisions, enhancing their sense of autonomy and self-determination in their illness.

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Memory Training for Older Adults

Karen Miller, Linda Ercoli, Jeanne Kim and Gary W. Small

*Semel Institute for Neuroscience and Human Behavior,
David Geffen School of Medicine at UCLA, Los Angeles, CA, USA*

Normal ageing is typically associated with a decline in select domains of cognitive functioning, including processing speed, memory and executive functioning^{1,2}. In addition, non-pharmacological interventions such as cognitive training and rehabilitation are being developed to enhance existing cognitive capacities, prolong independence in functional activities and promote healthy ageing. However, there is controversy as to whether cognitive stimulation enhances mental function³ or decreases risk for Alzheimer's disease⁴.

This chapter will present an overview of cognitive interventions that have been used with older adults, including healthy individuals with age-related memory changes, those with mild cognitive impairment (MCI), and persons with dementia, such as Alzheimer's disease (AD), and will include discussion of memory systems, metamemory, self-perceptions of memory, and interventions.

MEMORY SYSTEMS

Accumulated knowledge from studies in humans and animals has led to a widely accepted model of memory as being composed of multiple separate but parallel systems⁵. These multiple memory systems can be conceptualized as being either *declarative* or *non-declarative*⁵. Non-declarative memory is a general term for memory systems that do not involve conscious recollections but actions and performance-based tasks. Non-declarative memory is often targeted in rehabilitation interventions for skill maintenance, teaching skills, or functional abilities⁶. Declarative memory is the conscious recollection of information such as facts (*semantic memory*) and experienced single events linked to time and place (*episodic memory*)⁷. Individuals with progressive memory disorders, such as amnesic MCI and mild AD, present with deficits in declarative memory⁸, which is the target of most memory enhancement strategies for non-demented persons and persons with milder forms of cognitive impairment.

Another conceptualization of memory relevant to cognitive enhancement interventions is the *levels of processing* approach, which comes from learning theory⁹. Levels of processing is the concept that memory is a function of the degree to which a stimulus is analysed. The deeper and more meaningful the analysis, the better the stimulus is remembered. In memory training, forming associations, images or stories can be considered deep processing strategies. It renders the information more distinctive, and helps integrate new information with a framework of pre-existing knowledge that provides cues for later retrieval¹⁰.

METAMEMORY AND SELF-PERCEPTION OF MEMORY

A person's subjective understanding of their memory functioning is called *metamemory*. Most individuals have some understanding of their memory strengths, which might guide subsequent behaviours¹¹. In non-depressed individuals, memory self-perceptions have been found to be accurate indicators of memory difficulties on objective tests¹², and may be indicators of underlying brain processes¹³. Several studies indicate that memory training interventions improve self-perceptions of memory ability and reduce memory complaints^{14–16}. In healthy older adults, memory training may result in self-reported improvements in stability of memory functioning, and reduced anxiety and stress about memory functioning¹⁵. Effects of memory training on self-perceived memory are typically small, but nevertheless significant^{14,17}. However, self-perceived memory ability is not always accurate. Persons with developing dementia may lose awareness of memory dysfunction as memory impairment advances^{18,19}.

TYPES OF COGNITIVE INTERVENTIONS

There are three primary approaches to cognitive training intervention: *cognitive stimulation*, *cognitive rehabilitation* and *cognitive training*²⁰. The choice of approach depends on the degree and nature of deficits.

Cognitive stimulation typically involves participation in group activities and/or discussions aimed at general enhancement of cognitive and social functioning²¹. These types of interventions are non-specific to a cognitive domain, and include such activities as discussions of current events, supervised recreational activities, and group reminiscence therapies. Cognitive stimulation is typically used for demented patients and often as a control condition in studies investigating the effects of cognitive training.

Cognitive rehabilitation is an individualized intervention designed for patients with a specific brain injury or neurological disorder. Health-care providers work collaboratively with patients and their families or caregivers in order to identify personally relevant goals in day-to-day living and to develop strategies²⁰ that enhance functional tasks and activities of daily living, rather than increasing performance on a specific cognitive task²².

The focus of this chapter is *cognitive training*, which involves learning and practising strategies to improve specific cognitive

functions, such as memory, attention, or problem-solving. Cognitive training is often administered to people with mild forms of difficulties associated with normal ageing, and to clinical populations, including persons with MCI, dementia or schizophrenia. The goals of cognitive training are to maintain or improve cognitive function, and to learn to compensate for deficits. Cognitive training is based on the assumption that, with intensive training, people will apply the strategies they learn to real-life situations beyond the training session. Cognitive training typically involves teaching skills and strategies in a standardized and structured fashion to individuals or to small groups¹². Strategies vary in difficulty level and can be traditional paper–pencil tasks, classroom instruction or computerized activities²⁰.

MEMORY TRAINING APPROACHES

Many training techniques have been developed to specifically improve learning and recall. The techniques vary with respect to complexity, structure and application. One example is *errorless learning*, which is based on the premise that remembering new information will be more efficient if errors during learning are minimized and/or immediately corrected^{23–25}. *Spaced retrieval*²⁶, which is also known as expanded rehearsal²⁷, is another common technique and involves learning and retaining new information by recalling the information over increasingly longer periods of time^{28,29}.

Mnemonic strategies have been one of the primary memory interventions used within clinical settings. Generally, mnemonic strategies facilitate encoding and aid retrieval by enhancing the meaningfulness or personal relevance of information. Mnemonic strategies involve organizing information in meaningful ways, forming associations, or forming visual images. Examples include: (i) verbal organization (i.e. forming acronyms), (ii) semantic clustering and elaboration (i.e. categorizing lists of words into subgroups or clusters of items that share something in common; or creating a story linking all target words on a list), and (iii) visual imagery strategies (i.e. method of loci, face-name association, creating a mental picture of a target)¹¹.

One of the most popular and oldest mnemonic strategies is the *method of loci* technique, which was used by ancient orators to remember long speeches. The method of loci involves imagining a familiar path and identifying unique landmarks along the path. Visual imagery is used to associate items on a list with each landmark along the imagined path. To remember the list, simply take a mental ‘walk’ along the path, recalling each image at each landmark.

Another popular mnemonic strategy is *face-name association*³⁰. Individuals can use the face-name method for remembering someone they just met. The face-name strategy involves three steps: (i) looking at a person’s face and identifying a prominent facial feature, (ii) transforming the person’s name into something imaginative or that sounds concrete or meaningful, and (iii) developing a visual image integrating the prominent facial feature with the transformed name.

The efficacy of mnemonic or memory training strategies has been examined in a number of studies. Factors associated with memory improvement in one meta-analysis included younger age, higher cognitive functioning, group setting (versus individual training), shorter duration of sessions, education and ‘pretraining’¹⁷. Pretraining allows the participant to get comfortable with visualization and move beyond their comfort zone of thinking about ordinary or logical images. In addition, the number of sessions did not appear to limit the efficacy of memory training¹⁷. In fact, interventions as short as 4 weeks

can be just as effective as programmes that are 8 weeks, or even 6–12 months long^{31,32}. Most research demonstrating effectiveness of mnemonic techniques has focused on healthy adults, both young and old, but persons over 75 years of age show less improvement³³. The few studies of efficacy in MCI populations have yielded mixed results^{34,35}. A subset of subjects from the ACTIVE study (Advanced Cognitive Training for Independent and Vital Elderly) who were identified as ‘memory impaired’ (comparable to MCI) showed no significant benefit from memory training when compared to a no-contact control group, but had gains in speed of processing and inductive reasoning³⁶.

COMPUTER-ASSISTED COGNITIVE INTERVENTIONS

With the advancement of technology, researchers and clinicians are interested in computer-assisted training interventions for both healthy older adults and people with memory impairments. Initial studies have demonstrated that computer-based cognitive training has improved learning efficiency in healthy older adults³⁷, and supported cognitive and functional improvements in patients with AD³⁸. Computer-based software technology has also recently been introduced in rehabilitative and training settings for patients with AD and MCI. Results seemed to suggest that the individualized rehabilitative intervention could have different effects according to a patient’s diagnosis³⁹. Cognitively intact older adults who received computer-based training demonstrated improvements in information processing, working memory and verbal learning/memory, and these gains were maintained over a five-month follow-up⁴⁰. In mildly demented patients, computer-based training improved immediate recall of visual information and delayed retention of topographical information³⁸. Combining a cognitive seminar and computer-assisted training in demented patients resulted in short-term improvement on measures of global cognitive functioning and short-term memory, as well as behavioural and social improvements⁴¹.

Posit Science has developed a cognitive training program that contains increasingly difficult tasks of stimulus recognition, discrimination, sequencing and memory. Participants with mild cognitive changes associated with age demonstrated a significant increase on all computer tasks, with maintenance of improvements in attention over three months, when compared to active and no-contact controls⁴². In a subsequent larger trial, the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study⁴³, subjects demonstrated improvement in auditory memory and attention as compared to a general cognitive stimulation program that functioned as the active control condition.

Additionally, pilot studies have evaluated a computerized program, Brain Fitness by Dakim, which provides cognitive training and stimulation in language, visual processing, and memory domains. Results indicated improvement in memory functioning for those who could participate in the higher levels of the program, in addition to improved encoding and delayed recall for verbal pairs after just 10 sessions^{44,45}. Presently, a clinical trial is underway to investigate the short- and long-term impact of this computer program on memory functioning in a larger sample of older adults with mild memory complaints as compared to wait-list controls.

As people become more technologically aware, computer programs are likely to become an important conduit for simulating real-life environments and integrating goal-directed behaviours in order to increase ecological validity³⁸. These newer computer-based cognitive training interventions, however, have both advantages and

limitations. Many of the tasks included in these interventions are laboratory based and likely lack ecological validity for functional activities. Moreover, many older adults have not had regular exposure to modern technology and thus may be hesitant or cautious in using them. Some of the advantages to using computer-assisted cognitive training programs are their flexibility and ability to tailor interventions to specific aspects of cognitive impairments, as well as the ability of the computer to provide immediate and specific feedback regarding performance⁴⁰.

The effects of computer-based training on brain function have not been widely studied. To date, one study has shown that computer use (via internet searching) may involve more than a two-fold increase in brain activation (as measured by functional magnetic resonance imaging) for the areas of the brain that are associated with vision, complex reasoning and decision making⁴⁶.

COMPREHENSIVE PROGRAMMES

Comprehensive or 'multifactorial' memory training programmes address non-cognitive factors in addition to teaching cognitive enhancement strategies. Non-cognitive factors include: (i) self-efficacy, expectations, and beliefs about one's ability to improve cognition; (ii) anxiety; and (iii) general education about memory^{10,14,17,47,48}. Comprehensive training programmes may include interventions for stress or anxiety reduction, and cognitive restructuring to counter negative and self-deprecating thoughts about memory ability. Most programmes include pre-training because this facilitates learning more complex cognitive techniques. Overall, these integrative approaches take into account the multiple factors that impact an individual's receptiveness, or response to cognitive enhancement interventions.

There is recent evidence that the role of lifestyle and environmental factors can be neuroprotective and possibly lower the risk for developing AD⁴⁹; therefore, some researchers have developed comprehensive healthy lifestyle programmes that incorporate aspects of diet, physical exercise, relaxation strategies and mental exercise⁵⁰. Small and colleagues⁵¹ developed a 14-day lifestyle programme consisting of memory mnemonics, mental puzzles, cardiovascular exercises, diet and recipe suggestions and relaxation strategies. Subjects in the healthy lifestyle intervention group demonstrated significant improvement on objective measures of verbal fluency, and FDG-PET imaging revealed a 5% decrease in activity in the left dorsolateral pre-frontal cortex, an area associated with working memory, semantic organization skills, anxiety and verbal fluency. This decrease in activity was interpreted as greater cognitive efficiency. This 14-day programme was then expanded into a classroom-based Memory Fitness curriculum, which has recently been implemented and studied in retirement homes^{52,53}. Participants in the memory fitness programme had fewer memory concerns and better performance on immediate and delayed recall measures as compared to controls.

Researchers have developed similar programmes for individuals with amnesic MCI^{34,35}. These programmes are typically comprised of multifaceted group-training sessions that include relaxation techniques, education regarding memory and ageing, memory skills training, cognitive restructuring of memory-related beliefs, information regarding appropriate diet and recreational activities, and availability of community resources³⁵. Intervention programmes for those with MCI typically focus on improving memory for daily tasks and maintaining a level of functional independence⁵⁴. A four-week

multi-component rehabilitation programme resulted in improvement in activities of daily living, memory functioning and mood compared to a wait-list control group⁵⁵. An additional programme utilized occupational therapy and behavioural training with computerized cognitive training; results showed improvement in cognitive and affective status of patients with MCI and mild dementia⁵⁶.

Another area of research to consider is the combination of medication with a computer-based cognitive training programme, suggesting that a combination of pharmacological and non-pharmacological treatment in MCI might maximize the effects of acetylcholinesterase inhibitors and delay memory deterioration and conversion to AD^{32,57,58}. Gains may be maintained for approximately six months to one year, but individuals tend to experience a gradual deterioration by year two⁵⁷. Although the effects are time limited, these findings suggest a complementary relationship between cognitive interventions and drug therapy for both cognitive and psychosocial disturbances.

LONG-TERM OUTCOMES

Few studies have evaluated the long-term effects of cognitive interventions in healthy older adults. Overall, the effects of memory training interventions have been found to last from six months to five years^{59–62}, although the benefits tend to attenuate over time. The largest clinical trial to date is the ACTIVE study ($n = 2832$), which evaluated the effectiveness and durability of cognitive interventions on objective cognitive tests and on subjective and objective instrumental activities of daily living (e.g. financial management, driving)^{62,63}. This longitudinal study incorporated 3 cognitive training groups receiving a 10-session training programme for memory, reasoning, or speed of processing, and a wait-list control group. Subjects also received periodic refresher courses, called 'booster sessions', on the skills initially trained. Follow-up results from two⁶³ and five years⁶² revealed that the cognitive interventions in each group helped increase performance on objective measures of cognitive ability for which they were trained. According to self-report measures, this effect was significant only for the reasoning group, although the effect sizes for memory and processing speed were similar in magnitude to the reasoning effect sizes. Performance-based results demonstrated significant speed of processing benefits after additional booster sessions⁶². It is important to note that the lasting impact of cognitive interventions is still dependent on the individual's effort and motivation to maintain the use of the strategies. Future research in this area may consider factors such as motivation and maintenance in order to preserve treatment gains.

FUTURE DIRECTIONS

Overall, cognitive interventions are effective in improving cognition in subjects with mild age-related cognitive declines. However, there are important aspects of cognitive training that deserve more scrutiny. For instance, there is a need for more studies of persons with mild cognitive impairment and additional longitudinal studies in healthy older adults, in order to address whether cognitive training can delay dementia onset. Future studies should include functional outcome measures, to better address whether training can generalize beyond laboratory tests and improve practical, day-to-day functions^{34,35}. In addition, there are still unaddressed questions, such as how engaging in stimulating everyday activities (also called an engaged lifestyle) is as effective as specific cognitive training^{64,65}.

Another important area for study is non-compliance, which may partially account for the lack of generalization and maintenance of cognitive strategy use. The key to long-term benefit appears to be continued use of cognitive strategies after initial training ends⁶⁰. One solution to improve compliance is the implementation of periodic 'booster sessions', which may further help individuals use techniques with greater consistency and in more generalized situations (e.g. daily 'to-do' lists)^{62,63}.

Another limitation is the knowledge-base for the impact of 'brain games' and programmes targeted at stimulating cognition (e.g. cross-word puzzles, sudoku problems, hand-held computerized games) on facilitating memory improvement. Although epidemiological studies suggest an association between engaging in cognitively stimulating activities and lower dementia risk^{4,66}, these studies do not prove a cause and effect relationship.

Finally, the effect of cognitive training on brain function has received minimal attention. In the few studies available, cognitive training does affect brain activation or resting state brain activity, including areas associated with encoding and retrieval^{50,67,68}, and training may also result in changes in neurochemistry⁶⁹. Including brain function outcome measures will be important in addressing the more direct effects of cognitive training on neural circuitry and the mechanisms of action in cognitive enhancement interventions.

CONCLUSIONS

In sum, the research to date suggests that cognitive training is beneficial to individuals with memory complaints associated with normal ageing. The effectiveness in demented individuals is less consistent compared to persons with normal ageing. Even less is known about the effects of training on persons with MCI. There are a number of factors to consider before implementing a treatment trial, including the design of the training, the duration of the training, long-term compliance and the possible necessity of concurrent medication for those with cognitive impairment. Many options and designs are available to tailor programmes to the needs of individuals, or to develop programmes for small groups. Additional studies on the effectiveness of cognitive training in persons with MCI will help clarify the outcomes for this growing patient group.

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Complementary and Alternative Medicine Approaches to Memory Improvement in the Elderly

Helen Lavretsky

Department of Psychiatry and Biobehavioral Sciences, and Semel Institute for Neuroscience and Human Behavior,
David Geffen School of Medicine at UCLA, Los Angeles, USA

THE TRENDS IN USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE IN THE US

The use of complementary and alternative medicine (CAM) in the US is increasing rapidly, exceeding a prevalence of 60% in a nationally representative survey conducted by the National Center for Health Statistics in 2002. CAM therapies are defined by the National Center for Complementary and Alternative Medicine as a group of diverse medical and health systems, practices and products that are not currently considered to be part of conventional medicine. An alternative approach to mental health care is one that emphasizes the interrelationship between mind, body and spirit. A national US survey noted a 47% increase in total visits to CAM practitioners, from 427 million in 1990 to 629 million in 1997. These figures surpass total visits to primary care physicians¹. Estimated expenditures for CAM professional services were conservatively estimated at \$21.2 billion in 1997, with at least \$12.2 billion of out-of-pocket expenditures, exceeding out-of-pocket expenditures for all US hospitalizations. In a more recent nationwide survey, 36% of US adults aged 18 years and over were found to use some form of CAM¹, and ageing baby boomers are expected to accelerate the use of CAM in the coming years². Barnes and colleagues noted that nearly 33% of older adults used CAM in the preceding year (2004)². In a survey, 42% of the patients in a managed care organization reported using at least one CAM therapy, most commonly relaxation techniques (18%), massage (12%), herbal medicine (10%) or megavitamin therapy (9%). Perceived efficacy of CAM was very high, ranging from 98% (energy healing) to 76% (hypnosis)¹.

With the increasing public use of complementary and alternative medicine for preventive and therapeutic purposes, including a very active 'anti-ageing' movement, a significant effort is now devoted to the integration of alternative methods of treatment into mainstream health care practice and research³. The principal uses in older adults include anti-ageing effects of CAM for memory enhancement, and treatment of various neuropsychiatric symptoms, such as depression, anxiety, insomnia and pain. This chapter is devoted to the description of the existing CAM interventions applied to the care of older adults with late-life cognitive disorders.

DIET AND THE USE OF NUTRITIONAL AND HERBAL SUPPLEMENTS

Adjusting both diet and nutrition may help some people with mental illnesses manage their symptoms and promote recovery. For example, research suggests that eliminating milk and wheat products can reduce the severity of symptoms for some people who have schizophrenia and some children with autism. Similarly, some holistic/natural physicians use herbal treatments, B-complex vitamins, riboflavin, magnesium and thiamine to treat anxiety, depression, drug-induced psychoses and memory loss. A number of herbs and dietary supplements have demonstrable effects on memory, mood, and insomnia⁴. There is a significant amount of evidence supporting the use of *Ginkgo biloba* and omega-3 fatty acids for dementia, as reviewed below. Many users of CAM may take a variety of herbal products⁵.

Ginkgo Biloba

Ginkgo biloba leaf extract is among the most widely sold herbal dietary supplements in the United States. Its purported biological effects include scavenging free radicals, lowering oxidative stress, reducing neural damage, reducing platelet aggregation, and anti-inflammatory, anti-tumour and anti-ageing activities. Clinically, it has been prescribed to treat CNS disorders such as Alzheimer's disease and cognitive deficits. It elicits allergy and changes in bleeding time. Its components, quercetin, kaempferol and rutin, have been shown to be genotoxic⁶ but the mutagenicity or carcinogenicity of *Ginkgo biloba* itself has not been reported. There are no standards or guidelines regulating the constituent components of *Ginkgo biloba* leaf extract, nor are exposure limits imposed. Safety evaluation of *Ginkgo biloba* leaf extract is being conducted by the US National Toxicology Program.

Ginkgo biloba has been widely used for many years by people with symptoms attributed to 'cerebrovascular insufficiency,' despite the lack of evidence of a causal role. Many placebo-controlled trials of *Ginkgo biloba* in patients with various types of dementia have yielded contradictory results. Of the studies that revealed any

cognitive improvement, the effect was minor and did not last more than six months. Some studies reported haemorrhaging, indicating that it is necessary to use caution when prescribing *Ginkgo biloba* for cognitive deficits, especially in patients with increased risk of haemorrhage⁷. The recommended doses range widely, but in a trial of Alzheimer's disease prevention, 120 mg of *Ginkgo biloba* twice a day was not effective in reducing the overall incidence rate of dementia or Alzheimer's disease in elderly individuals with normal cognition or those with mild cognitive impairment⁸. Its short-term use is acceptable under some conditions, but the potential risk of bleeding must be seriously considered. *Ginkgo biloba* has been reported to reduce depression in dementia patients and counteract sexual side effects of antidepressants⁹.

The Use of Nutritional Supplements

In addition to herbal remedies, consumers use a variety of nutritional supplements (including vitamins, amino acids and fish oil) that may affect mood and functioning.

Elevated plasma homocysteine concentrations have been implicated with risk of cognitive impairment and dementia, but it is unclear whether low vitamin B12 or folate status is responsible for cognitive decline or can protect against it^{10,11}. Most studies reporting associations between cognitive function and homocysteine or B vitamins have used a cross-sectional or case-control design and have been unable to determine whether such associations are causal or merely a result of the disease. The homocysteine hypothesis of dementia has attracted considerable interest, as homocysteine can be easily lowered by folic acid and vitamin B12, raising the prospect that B-vitamin supplementation could lower the risk of dementia¹⁰. Incident dementia is more strongly associated with changes in folate, vitamin B12 and homocysteine, than with previous concentrations. These changes may be linked to other somatic manifestations of early dementia, such as weight loss¹². However, in a trial of high dose vitamin B in patients with Alzheimer's disease, the supplement did not slow cognitive decline in individuals with mild to moderate Alzheimer's disease¹³. Two other placebo-controlled trials of treatment with B12, folic acid and B6 showed no advantage of vitamins over placebo at reducing the severity of depressive symptoms or the incidence of clinically significant depression over a period of two years in older men¹⁴. Similarly, a recent Cochrane review found no evidence for short-term benefit from vitamin B6 in improving mood (depression, fatigue and tension symptoms) or cognitive functions. For the older people included in one of the two trials mentioned in the review, oral vitamin B6 supplements improved biochemical indices of vitamin B6 status, but potential effects on blood homocysteine levels were not assessed in either study. This review found evidence that there is scope for increasing some biochemical indices of vitamin B6 status among older people¹⁵. The limited available evidence suggests folate may have a potential role as a supplement to other treatments for depression. It is currently unclear if this is the case both for people with normal folate levels and for those with folate deficiency. More randomized controlled trials are needed to explore possible benefits from vitamin B6 supplementation for healthy older people and those with cognitive impairment or dementia.

Omega-3 Fatty Acids

Fish oil and omega-3 fatty acids are also commonly used supplements. Reductions in cardiovascular risk, depression and rheumatoid arthritis symptoms have been correlated with omega-3 fatty acid

intake, and there is increased interest in the use of omega-3 fatty acid supplementation for other psychiatric illnesses and prevention of Alzheimer's disease. Reported health benefits include improvements in cognition and mood in unipolar and bipolar mood disorders. Omega-3 fatty acids are found principally in fish and seafood although some can be derived from green vegetables. By contrast, omega-6 fatty acids are found in soft margarine, most vegetable oils and animal fat. Omega-6 is plentiful in most modern Western diets while omega-3 is often relatively lacking. A high dietary ratio of omega-6 to omega-3 has been linked to vulnerability to many physical and mental disorders¹. Most studies recommend omega-3 essential fatty acids with a ratio of eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) of 7:1. PUFA DHA 22:6(n - 3), a dietary essential, is important for maintaining normal nervous system function and cellular structure. A lack of DHA is associated with cognitive decline during ageing and neurodegenerative disease¹⁶. DHA-derived neuroprotectin D1 (NPD1) has recently been shown to provide homeostatic regulation of brain cell survival and repair involving neurotrophic, antiapoptotic and anti-inflammatory signalling¹⁶. Research suggests that growth factors and neurotrophins activate the synthesis of NPD1, which interacts with the molecular-genetic mechanisms affecting beta-amyloid precursor protein (betaAPP) and amyloid beta (Abeta) peptide neurobiology. Deficits in DHA or its peroxidation may play a role in inflammatory signalling, apoptosis and neuronal dysfunction in Alzheimer's disease^{17,18}.

In a well-designed trial of the effect of EPA and DHA on mental well-being using a double-blind, placebo-controlled design in the general older population, the study failed to find drug-placebo difference in improving cognition or well-being¹⁸. In a meta-analysis, the authors concluded that available data are insufficient to draw strong conclusions about the effects of omega-3 fatty acids on cognitive function in normal ageing or on the incidence or treatment of dementia¹⁹. However, limited evidence suggests a possible association between omega-3 fatty acids and reduced risk of dementia.

In summary, omega-3 fatty acids may have a role in the treatment of late-life dementia, cognitive impairment and neuropsychiatric disorders. Future studies should clarify the function and the optimal dose of omega-3 fatty acids or EPA in the treatment of cognitive decline and address lingering questions regarding the purity of marketed supplements.

S-ADENOSYL-L-METHIONINE (SAME)

S-adenosyl-L-methionine (SAME) is one of the CAM products that has been studied under rigorous controlled conditions. SAME is a methyl donor involved in the synthesis of monoaminergic neurotransmitters derived from the amino acid L-methionine through the one-carbon cycle. SAME has been investigated for its antidepressant properties in both open¹ and randomized controlled²⁰ trials. SAME dosages of 200–1600 mg/day (orally or parenterally) have been shown to be superior to placebo and as effective as tricyclic antidepressants in alleviating depression, although some individuals may require higher doses²⁰. At this time, the recommended doses range from SAME 200 mg bid up to 800 mg bid. Oral dosages of SAME up to 1600 mg/day appear to be significantly bioavailable and safe. SAME has been associated with minor adverse effects, e.g. gastrointestinal symptoms and headaches¹, and an occasional induced mania²¹.

SAME plays an essential role in maintaining neuronal health, and may prove to be an effective neuroprotective dietary supplement

in Alzheimer's disease. This disease is accompanied by reduced glutathione S-transferase (GST) activity, diminished SAME, and increased S-adenosyl homocysteine (SAH), the downstream metabolic product resulting from SAME-mediated transmethylation reactions. Panza *et al.* confirmed that SAME can exert a direct effect on GST activity, thereby making SAME an ideal neuroprotective candidate to slow the progression of Alzheimer's disease²². It remains unclear if such supplements can reduce the risk for cognitive decline in very mild Alzheimer's disease and mild cognitive impairment.

CULTURALLY BASED HEALING ARTS

Culturally based healing includes traditional Oriental medicine (such as acupuncture, shiatsu and reiki), Indian systems of health care (such as Ayurveda and yoga) and Native American healing practices (such as the sweat lodge and talking circles). All incorporate the beliefs that (i) wellness is a state of balance between the spiritual, physical and mental/emotional 'selves'; (ii) an imbalance of forces within the body is the cause of illness; and (iii) herbal/natural remedies, combined with sound nutrition, exercise and meditation/prayer will correct this imbalance.

Acupuncture

Acupuncture is the Chinese practice of inserting needles into the body at specific points to manipulate the body's flow of energy in order to balance the endocrine system. This manipulation regulates functions such as heart rate, body temperature and respiration, as well as sleep patterns and emotional changes. Acupuncture has been used in clinics to assist people with substance abuse disorders through detoxification; to relieve stress and anxiety; to treat attention deficit and hyperactivity disorder in children; to reduce symptoms of depression; and to help people with physical ailments. There have been only a few studies of acupuncture for dementia compared to studies of depression or stress. There is accumulating evidence from animal models of dementia that acupuncture can be useful for memory improvement. In a Chinese study, Zhou and Jin performed acupuncture on the scalp in areas corresponding to brain regions involved in Alzheimer's disease²³. Twenty-six patients with clinically diagnosed Alzheimer's disease underwent functional magnetic resonance imaging (fMRI) while undergoing acupuncture at four acupoints. Activation occurred in both the right main hemisphere and the left hemisphere in locations consistent with brain regions frequently impaired in Alzheimer's disease. These areas are closely correlated with cognitive function (memory, reason, language, executive etc.), providing evidence that acupuncture has a potential effect on Alzheimer's disease²³.

Despite promising results, there is insufficient evidence to determine the efficacy of acupuncture compared to medication, wait list control or sham acupuncture in the management of depression. Scientific study design is generally poor and the number of people studied is relatively small. One of the barriers to conducting appropriate studies of acupuncture is the difference between diagnostic systems in Western and Chinese medicine, precluding fair comparison.

In a vascular dementia model using rats, the effect of electro-acupuncture was tested on the formation system of free radicals in brain tissues. The researchers used the Morris's water labyrinth for testing learning ability and memory in rats receiving electro-acupuncture and rats assigned to the control group. The mean escape

latency in the electro-acupuncture group was much shorter in several cognitive tests compared with the control group. This research suggests that electro-acupuncture can improve learning and memory ability in vascular dementia rat models²⁴.

Ayurveda

Ayurveda is a natural health care approach that originated in India more than 5000 years ago. It is still widely used in India as a system of primary health care, and is growing in popularity worldwide. Ayur means 'life' or 'longevity' and Veda means 'knowledge or science.' Combined, Ayurveda means 'the science of life' and the practice of Ayurvedic medicine is described as 'knowledge of how to live'²⁵. As a form of complementary and alternative medicine, Ayurveda is commonly used as a method to enhance memory, combat ageing and as nerve tonic. It is also used as an anxiolytic, anti-inflammatory and immunopotentive remedy. Ayurveda incorporates an individualized treatment regimen, such as diet, yoga, meditation, herbal preparations or other techniques to facilitate lifestyle changes and to teach people how to release stress and tension. It is often used as a treatment for depression. There are some preliminary encouraging results for its effectiveness in treating various ailments, including chronic disorders associated with the ageing process. Pilot studies of depression, anxiety, sleep disorders, hypertension, diabetes mellitus, Parkinson's disease and Alzheimer's disease yielded positive results²⁶. However, no extensive controlled studies of Ayurveda in older adults are available to date.

There is an increasing number of publications on antioxidant, neuroprotective and memory enhancing properties of various herbal Ayurvedic preparations in rat and mice models of Alzheimer's disease²⁷. The part of the Ayurvedic system that provides an approach to prevention and treatment of degenerative diseases is known as Rasayana, and plants used for this purpose are classed as rejuvenators. Traditional medicinal plants in various countries, particularly in India, have been used for centuries for various ailments; however, there has been little scientific effort to validate these anecdotal uses mentioned in the literature.

A number of these traditionally used plant extracts and various 'Ayurvedic medicines' have been screened using the National Institute of Mental Health Synthetic Screening Program for scientific validation and the development of new leads of psychotherapeutic compounds²⁸. In young and ageing mice models, Anwala churna produced a dose-dependent improvement in memory scores. Furthermore, it reversed the amnesia induced by scopolamine and diazepam. Anwala churna may prove to be a useful remedy for the management of Alzheimer's disease because of its diverse beneficial effects, including its memory improving property, cholesterol lowering property and anticholinesterase activity²⁶. *Ocimum sanctum*, a plant widely used in Ayurveda, has been shown to possess anti-inflammatory, antioxidant and cognition-enhancing properties²⁹. In rats, the effect of methanolic extract from *Ocimum sanctum* leaves was studied in cerebral reperfusion injury as well as long-term hypoperfusion. Treatment significantly prevented long-term hypoperfusion-induced functional and structural disturbances. The results suggest that *Ocimum sanctum* may be useful in treatment of cerebral reperfusion injury and cerebrovascular insufficiency states²⁹.

Trasina is a herbal formulation of some Indian medicinal plants classified in Ayurveda as Medhyarasayanas, or drugs reputed to improve memory and intellect²¹. In a rodent model of Alzheimer's disease, subchronic administration of Trasina reversed deficits in

acetylcholine after 14 and 21 days of treatment. Thus the herbal formulation exerts a significant nontropic effect after subchronic treatment that may be due to reversal of perturbed cholinergic function³⁰.

Research that compares Ayurveda's comprehensive treatment approach, Western allopathic treatment and an integrated approach combining both the Ayurvedic and allopathic treatments would shed light on which treatment system is the most effective for the benefit of the patient.

YOGA AND MEDITATION

Practitioners of yoga, the ancient Indian system of health care, use breathing exercises, posture, stretch and meditation to balance the body's energy centres. Mindful physical exercise is a special kind of physical exercise with an additional element that focuses on one's state of mind. It has recently emerged as a therapeutic intervention for improving the psychosocial well-being of individuals. According to the IDEA Mind-body Fitness Committee (1997–2001), a mindful physical exercise is characterized by 'physical exercise executed with a profound inwardly directed contemplative focus.' A physical exercise is considered mindful if it: (i) has a meditative/contemplative component that is non-competitive and non-judgmental; (ii) has proprioceptive awareness that involves low to moderate level of muscular activity with mental focus on muscular movement; (iii) is breath centering; (iv) focuses on anatomic alignment, such as spine, trunk and pelvis, or proper physical form; and (v) concerns energy centric awareness of individuals' flow of intrinsic energy, vital life force, qi etc. With the above framework, yoga and qigong are two major streams of mindful physical exercise based on the literature. Yoga is used in combination with other treatments for depression, anxiety and stress-related disorders.

The principle of yoga is to achieve integration of mind, body and spirit. There are twenty-two types of yoga and many more modifications. The most popular in the US is Hatha yoga, a branch of yoga that requires a vast repertoire of physical postures during sitting, standing or lying on the floor, along with specific breathing patterns. Other than physical movement, participants are required to maintain a 'homeostasis' of mind and body, which refers to the relaxation of body tension with quieting of thoughts. The qigong exercise is a system of self-practising physical exercise, which includes healing posture, movement, self-massage, breath work and meditation. All forms of qigong are featured on balance, relaxation, breathing and good posture. The movements of qigong are executed at very low energy expenditure levels. A specific breathing pattern also applies to qigong. Similar to yoga, the breathing style of qigong is slow and deep in order to achieve body relaxation, clearing of mind and maintenance of health. Combining all of the above components, mindful physical exercise has been shown to provide an immediate source of relaxation and mental quiescence. Scientific evidence shows that medical conditions such as hypertension, cardiovascular disease, insulin resistance, depression and anxiety disorders respond favorably to mindful physical exercises³¹. Despite a growing body of evidence to show the effects of mindful physical exercises such as qigong, tai chi and yoga on depression, there is a dearth of review that examined mindful physical exercise as to its effects on memory enhancement. A review on complementary and alternative treatments on older adults shows that mind-body interventions were effective in treating depression, anxiety and insomnia in 10 out of 12 studies reviewed³². Some studies demonstrated improvement in functioning

on a spatial cognitive task while breathing through the left nostril. Performance improved in the cerebral hemisphere contralateral to the patent nostril³³. An integrated approach of yoga therapy in menopausal women improved cognitive functions such as remote memory, mental balance, attention and concentration, delayed and immediate recall, verbal retention and recognition tests³⁴.

RELAXATION AND STRESS REDUCTION TECHNIQUES, BIOFEEDBACK

Learning to control muscle tension and 'involuntary' body functioning, such as heart rate and skin temperature, can be a path to mastering one's fears. It is used in combination with, or as an alternative to, medication to treat disorders such as anxiety, panic and phobias. For example, a person can learn to 'retrain' his or her breathing habits in stressful situations to induce relaxation and decrease hyperventilation. Some preliminary research indicates it may offer an additional tool for treating depression.

Although there are no data in geriatric depression, an increasing number of publications describe the use of biofeedback for memory training and cognitive enhancement using neurofeedback. This is an electroencephalographic (EEG) technique for training individuals to alter their brain activity using operant conditioning. Research has shown that neurofeedback helps reduce symptoms of several neurological and psychiatric disorders. Ongoing research is currently investigating its application in the treatment of other disorders and for enhancing non-disordered cognition³⁵.

Angelakis *et al.* used EEG peak alpha frequency for neurofeedback because it has been shown to correlate positively with cognitive performance and to correlate negatively with age³⁵. In a pilot double-blind study of neurofeedback training in older individuals, they observed that peak alpha frequency neurofeedback improved cognitive processing speed and executive function, but had no clear effect on memory. Kotchoubey *et al.* reported the results of two groups of subjects, aged 20–28 and 50–64 years, matched for health status and verbal abilities³⁶. They described how subjects learned to control their slow cortical potentials in a feedback paradigm by producing, on command, shifts in these potentials in either the positive or negative direction. Both groups were able to differentiate significantly between the positivity task and the negativity task. Older subjects had only explicit, but not implicit, learning deficits. Elderly subjects showed consistently more negative slow cortical potential shifts, which may indicate their impaired cortical inhibition. This pattern is likely due to brain ageing. The question remains if biofeedback could be helpful in reducing cognitive deficits associated with ageing or dementia³⁶.

EXERCISE

Human and other animal studies demonstrate that exercise targets many aspects of brain function, providing broad effects on overall brain health. The benefits of exercise have been best defined for learning and memory, protection from neurodegeneration and alleviation of depression, particularly in elderly populations. Exercise increases synaptic plasticity by directly affecting synaptic structure and potentiating synaptic strength, and by strengthening the underlying systems that support plasticity including neurogenesis, metabolism and vascular function. In addition, exercise reduces peripheral risk factors such as diabetes, hypertension and cardiovascular disease, which converge

to cause brain dysfunction and neurodegeneration. Such exercise-induced structural and functional change has been documented in various brain regions but has been best studied in the hippocampus³⁷.

Randomized and crossover clinical trials demonstrate the efficacy of aerobic or resistance training exercise (2–4 months) as a treatment for depression in both young and older individuals that may have an effect on cognitive function³⁸. The benefits are similar to those achieved with anti-depressants³⁸. They are also dose dependent, and greater improvements are seen with higher levels of exercise^{38,39}.

In a study of exercise in early Alzheimer's disease, cardiorespiratory fitness was modestly reduced in subjects with Alzheimer's disease compared to subjects without dementia⁴⁰. The results were associated with whole brain volume and white matter volume reductions after controlling for age. In participants without dementia, there was no relationship between fitness and brain atrophy⁴⁰. Therefore, cardiovascular fitness may moderate brain atrophy related to Alzheimer's disease; however, further studies are needed to resolve inconsistent findings.

A key mechanism involved in the benefits of exercise on the brain is induction of central and peripheral growth factors and growth factor cascades. These growth factors instruct downstream structural and functional change. Inflammation, which can impair growth factor signalling both systemically and in the brain, is a common mechanism relating to the central and peripheral effects of exercise. Thus, through regulation of growth factors and reduction of peripheral and central risk factors, exercise ensures successful brain function³⁷.

In summary, cognitive ageing is one of the most common reasons for using complementary and alternative therapies in older adults. The amount of rigorous scientific data to support the efficacy of complementary therapies in the treatment of cognitive impairment is extremely limited. The areas with the most evidence for beneficial effects are exercise, herbal therapy (*Ginkgo biloba*), the use of fish oil, and, to a lesser extent, acupuncture and relaxation therapies (see Table 64.1). There is a need for further research involving randomized controlled trials to investigate the efficacy of complementary and alternative therapies in the treatment of dementia and cognitive impairment in late life. This research may lead to the development

Table 64.1 Complementary and alternative medicine interventions for the treatment of cognitive impairment and dementia⁴¹

<i>Mode of intervention</i>	<i>Postulated mechanism of action</i>	<i>Dementia, cognition</i>	<i>Main adverse effects and drug interactions</i>
Omega-3 fatty acids (fish oil)	Mood stabilization, memory enhancement, neuroprotection, reduction in amyloid production	Several RCTs are mixed or negative in the effect on cognition	Fishy aftertaste; gastrointestinal distress; increased effect of warfarin and NSAIDs
SAMe	Cofactor in neurotransmitter synthesis, methylation homocysteine to methionine	Animal studies are suggestive of potential use; no human studies available	Mania; gastrointestinal distress; headache interaction with SSRIs
Folate and B12	Cofactor in neurotransmitter synthesis, methylation homocysteine to methionine, precursor to SAMe	RCTs are suggestive of usefulness in prevention of cognitive decline and improved memory performance	Mania induction, interaction with SSRIs
<i>Ginkgo biloba</i>	Scavenging free radical; lowering oxidative stress; reducing neural damages; increased blood flow to the brain	Mixed and negative results in RCTs of dementia and other cognitive disorders	Increased bleeding time, allergic reactions
Ayurveda	Indian treatment system with the use of herbs, diet and lifestyle to achieve balance in cognition and well-being	Few RCTs; suggestive of positive effect; positive antiamyloid animal studies	Consistent with above side effect of herbals
Acupuncture	Balancing energy flow through the meridians in the body	In a few trials improved memory and other cognitive tests in Alzheimer's disease and vascular dementia	Needle phobia, bleeding
Yoga	Postures, breath, meditation; rebalancing the mind–body connections	A few uncontrolled studies showed improved attention and memory in nondemented adults	None
Biofeedback	Retraining of the autonomic nervous system or alpha brain waves	Alpha peak in brain waves is associated with enhanced cognitive performance	None
Spirituality	Lowers stress and enhances cognition via church attendance and prayer	Enhances cognitive performance in those who attend church	None
Exercise	Improved cardiovascular function, release of endorphins, increased energy, mental stimulation	Modest improvement in cognition in dementia and in ageing	None

SAMe, S-adenosyl-L-methionine; RCT, randomized controlled trial.

of effective treatment and preventive approaches for these serious conditions.

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Ethics of Dementia Care

Eran Klein¹ and Jason Karlawish²

¹*The Johns Hopkins Berman Institute of Bioethics, Baltimore, USA*

²*University of Pennsylvania Institute on Aging, Philadelphia, USA*

The stages of dementia, from presymptomatic concerns to diagnosis to death, present clinicians, patients and families with numerous ethical challenges. These challenges may stand out as acute problems or crises, while others simply form the background of living with chronic and progressive loss of cognition. Clinicians who aspire to provide the best care possible for their patients and patients' families need to recognize and respond appropriately to the ethical dimension of dementia. This chapter will present the major ethical challenges typical of each stage of dementia care – presymptomatic, symptomatic and end of life – and suggest ways to approach them.

AN OVERALL FRAMEWORK

The approach to the patient with dementia starts with identifying the goals of care. These vary with the stage of the disease. Early in the disease, the goal is to maximize autonomous decision making. The patient's own vision of what constitutes a life well lived should guide decisions. The clinician should help sustain this vision to the extent possible through pharmacotherapy, provision of patient and family education and support, treatment of co-morbid conditions, and an honest assessment of disease progression and what to expect in the future. As the patient's ability for autonomous decision making diminishes, the goals of care shift to those focused on what will maximize the patient's dignity and quality of life. Accurate assessment of quality of life relies on a complex interplay of expressed patient preferences as well as clinician and family observations and interpretations of patient moods and behaviours. To facilitate a commonsense discussion of quality of life, a clinician can ask both the patient and the family *what is a typical day?* The answers to this question will not only indicate the patient's abilities and disabilities but also the nature and character of the patient's social and emotional engagement in the world. The shift in goals of care tracks a shift in the role of the patient within the patient–caregiver–clinician relationship from being a co-participant in the decision making to a non-participant¹.

The patient, family and medical team all bring different perspectives and commitments that need to be taken into account. Sometimes these fit seamlessly together, such as when patients and families express a mutual preference for care that prioritizes comfort over longevity. At other times, disagreements may be evidence of deep differences in values, such as when a patient directs that care at a future stage of dementia be minimal out of a concern for

preserving dignity but the family is committed to sustaining life when at all possible. Various methodological tools are available for working through some of these deep disagreements^{2–5}. For instance, the appeal to – and balancing or specification of – the principles of respect for autonomy and beneficence is a common starting point for working through such cases⁶.

MANAGING UNCERTAINTY

As researchers uncover more about the genetic and biological markers of the common causes of dementia, such as Alzheimer's disease⁷, clinicians will have to address the ethical challenges of the presymptomatic stage of dementia. Can genes, biomarkers or imaging⁸ – or some combination of these – reliably predict a person's risk of developing dementia? Communicating such prediction models to patients presents clinicians with real challenges. For example, the use of the apolipoprotein E4 allele in predictive testing – which initially indicated a threefold increased chance of developing Alzheimer's disease if heterozygous for the allele but with quite poor specificity⁹ – already suggests that significant challenges face both the clinician in interpreting the meaning of predictive tests for patients and patients in applying probabilistic knowledge to future decisions. Similar questions and challenges apply to so-called biomarkers of common causes of neurodegenerative dementia such as tau protein in spinal fluid.

An approach to presymptomatic testing that addresses these issues is as follows. Patients are entitled to good quality predictive testing, if available, given the value that this information may have for some. In accordance with the Genetic Nondiscrimination Act of 2008 (GINA), this information has at least the same legal protections as other medical information¹⁰. The clinician (and the medical system) are only obligated to provide tests, however, that significantly improve upon current predictive information (e.g. family history, neuropsychiatric testing) and which the patient can understand and reasonably make use of (e.g. not make dramatic changes to future plans based on small differences in probability). The decision to provide a predictive test is an important clinical decision and, like the provision of other tests or treatments, requires clinical judgement. An essential clinical skill in exercise of this judgement is how to assess a patient's understanding and appreciation of such information. Below, we discuss techniques to do this.

DISCLOSING THE DIAGNOSIS

The first ethical issue that many clinicians face with regard to the detection of dementia is when, how and if to deliver a diagnosis of dementia¹¹. The question of 'if' is largely settled as a matter of policy. Patients are morally and legally entitled to their diagnosis. Although this approach has been widely endorsed by the Alzheimer's Association¹², the AMA¹³ and a consensus statement¹⁴, studies suggest that this policy has not fully filtered down to practice. Surveys of caregivers suggest that some physicians often do not disclose the diagnosis to the patient¹⁵. Instead, they disclose the diagnosis to the family¹⁶. And many generalists¹⁷ and dementia specialists^{18–20} choose not to disclose a diagnosis of dementia, particularly at a more advanced stage when comprehension is seriously compromised. This practice persists despite evidence that most cognitively intact adults say they would want to know if they were diagnosed with dementia²¹ (though the strength of this desire seems to wane with the increasing age at which this diagnosis would be made²²). This obviously paternalistic practice reflects the complexity of a disease with progressive cognitive decline that impairs a person's ability to adequately understand relevant information. The most compelling reason to disclose even at later stages of disease is that the patient with dementia is owed the chance, however small in some cases, of understanding (or gaining a glimpse of) why the things that are happening are happening and what this portends for the future. To deny the patient this, whether to make things easier for a caregiver or to prevent purported psychological harm to the patient ('therapeutic privilege'), is to deny an opportunity, perhaps the most important and last opportunity, for self-knowledge left to the patient with dementia.

A reasonable approach to guide whether to disclose a diagnosis to a patient is to converse with the patient about his or her awareness of cognitive problems, and, if the patient is aware of these problems, about the patient's desire to know what is their cause²³. Useful questions to elicit these symptoms include *Are you having problems with your memory?* and *Do your memory problems bother you?* If a patient endorses these symptoms, a follow-up question is *Would you like to know what is the cause of these problems?* In the case of a patient who has awareness of problems with memory and a desire to know the cause of these problems, a clinician has a clear warrant to disclose the diagnosis. Two useful techniques include asking the patient what he or she knows about Alzheimer's disease and clarifying any misunderstandings about the disease (*One of the most common causes of memory problems is Alzheimer's disease. Have you ever heard of that? Tell me what you know about it?*). This needs to be done in a way that balances truth with kindness. For example, after disclosing a diagnosis to a patient, it is sensible to ask how the patient feels about this diagnosis and whether any questions or concerns remain.

ASSESSING DECISIONAL CAPACITY AND MANAGING INCAPACITY

The central issue that is at the heart of many of the ethical concerns during the symptomatic stage of dementia care is the loss of decision-making capacity. Dementia progressively undermines the abilities necessary for competent medical decision making (e.g. understanding, appreciation, reasoning and expression of choice²⁴) and consequently undermines the capacity for giving informed consent or refusal for treatment or research. While the development of some clinical instruments has shown some promise for aiding the assessment of capacity^{25–27}, the determination of whether someone has sufficient capacity is still ultimately a clinical judgement.

When a clinician does judge that a patient has lost the capacity to make a decision, the appointment of a surrogate provides a way to protect and promote the patient's interests. In clinical practice, a surrogate tends to appear naturally as part of that person's other roles as knowledgeable informant and caregiver. Often this person is a spouse, partner, adult child or sibling. A surrogate can be designated preemptively by the patient (via an advance directive) or appointed through established (often state) standards for next of kin. The *raison d'être* of the surrogate is to make decisions on the patient's behalf.

Acceptable standards for how the surrogate makes decisions vary²⁸. Traditionally, ethics has posited a hierarchy of standards. The surrogate can try to decide *as the patient would have decided* given what is known of her previous beliefs, values, character and so on (called the *substituted judgement standard*). Absent the ability to fulfil this standard, the surrogate should decide based on what the surrogate believes is in the best interest of the patient (*best interest standard*). Studies suggest that most older adults do not want a surrogate to practice this hierarchy of standards, but instead to exercise a leeway that balances the two standards. In a study of 150 dialysis patients, two thirds preferred that their surrogate exercise at least 'a little leeway' in interpreting their advance directives to withdraw dialysis were they to develop advanced Alzheimer's disease²⁹. This has substantial implications for clinicians when they talk with surrogates. Specifically, it suggests a useful approach to guiding surrogates in decision making; consideration should be given both to what preferences, if any, their relative told them, and what they think will maximize their relative's dignity and quality of life. A surrogate decision should be challenged, in court if necessary, if clear evidence suggests that the surrogate is not acting with the patient's interests in mind. In the absence of such, the presumption lies in favour of the surrogate knowing how best to act on the patient's behalf.

Patients with dementia can formulate *instructional* advance directives. These advance directives spell out how a person wishes to be treated when, at some future time, a decision needs to be made but capacity for making that decision is no longer present. These have great intuitive appeal but variable practical usefulness. Where next of kin knows little of the patient or of the patient's end of life wishes, however, these can be helpful. And they can be useful when instruction is categorical (e.g. under no circumstances perform CPR). Where one would want instructional advance directives to be their most useful, however, they often cannot be. To anticipate and fully articulate the myriad variables that a particular decision will involve one year, five years or ten years into the future is unrealistic. If a decision is truly difficult and contested, it will be *because* there is disagreement about whether the particularities of a situation – some variable or variables – make it different than what is spelled out in the advance directive. This does not entail that instructional advance directives are useless, just that they need to be approached in a particular way. In designing them, one should help patients communicate how in general they want the end of life to go. Is more or less aggressive treatment preferable? Should pain relief or longevity be afforded priority? Where they can be categorical (e.g. do not attempt resuscitation; DNAR), they should be, but where they cannot be they should provide examples as guideposts for decision makers (e.g. 'no feeding tube unless likely to need for fewer than two weeks'). The ideal should not be to spell out decision rules in so detailed a manner that exercising judgement is unnecessary; this is impossible. The goal should be to provide decision makers a tool for knowing the spirit in which judgements should be made.

LIVING WITH DEMENTIA: THE CASE OF PARTICIPATING IN RESEARCH

Those with dementia constitute a vulnerable research population, like other vulnerable populations (e.g. children³⁰, pregnant women³¹, the mentally ill³², the incarcerated³³). The status of people with dementia as a vulnerable population has afforded needed protection from exploitation, but at some cost. It has exposed persons with dementia to the risks of medications for non-dementia ailments – risks that are largely unknown given the group's exclusion from most drug approval trials. And it has deprived a segment of the population that might be uniquely motivated to participate in research of the opportunity to do so and, in turn, closed off a way of giving expression to deeply held values. Though vigilance continues to be needed in protecting this vulnerable population in research, there is also a growing appreciation of the costs of excluding persons with dementia from research as well³⁴.

Surrogates face the decision of whether to enrol demented individuals in research. In the case of research procedures that involve the potential for therapeutic benefit to patients, the decision is made analogously to a surrogate treatment decision with a weighing of harms and benefits. In contrast, research procedures that do not involve direct therapeutic benefit present a challenge as exposure to these risks cannot be justified on the basis of benefits to the patient but rather on the value of the knowledge the research may realistically produce. In such a circumstance, a common set of proposals permit surrogate consent only if (i) the research presents minimal risk or some minor increment over minimal risk, (ii) the subject gives assent or lack of dissent, (iii) institutional review board (IRB) approval is obtained, and (iv) the surrogate gives consent on the subject's behalf consistent with the patient's previous preferences³⁵. Difficult issues remain as to how to define 'minimal risk', whether assent is necessary or even meaningful, and whether surrogates accurately reflect subjects' views on acceptable risk³⁶, but the current protections allow those with dementia to participate in limited forms of research while still acknowledging their status as a vulnerable population.

LIVING WITH DEMENTIA: THE CASE OF DRIVING

For many patients, the restriction of driving privileges marks a turning point in the disease process and often in the patient–clinician relationship as well. For many patients, driving is essential for their involvement in the larger social world. It allows freedom of movement and independence, and is central to a sense of self. When clinicians seek to restrict driving, confrontation can arise. Patients with dementia can lack the insight necessary to recognize their deficits and fail to appreciate that restrictions align their safety with the public's safety. And even when they do recognize some deficits, the value of driving may outweigh for them the added risks to self and others.

In the case of driving, clinicians are not only advocates for their patients, but stewards of the public health. They are obligated to step in and restrict driving even when this threatens individual patient–clinician relationships. Strategies can help minimize this threat. Frank, early discussion of driving and dementia can prepare patients for future restrictions, and timely neuropsychiatric and driving performance testing can help convince patients of unappreciated and evolving deficits. While the Mini-Mental State Examination (MMSE) only roughly predicts driving performance³⁷, substantial evidence correlates Clinical Disease Rating (CDR) scores

with driving performance. A CDR of 0.5 correlates with mildly impaired driving (akin to a 16- to 21-year-old) and a CDR of 1 with significant traffic safety risk³⁸. At a CDR of 0.5, patients should be encouraged not to drive or to restrict driving (e.g. shorter distance, time of day), and patients at a CDR of 1 should be advised not to drive. Where required by state law, a report should be made to the appropriate driving authority (with full disclosure to the patient), and where not required by law, one should clearly and without equivocation advise against driving, with mention, if appropriate, of possible financial or legal ramifications from driving against medical advice. Although not always acknowledged as such, driving is a privilege and responsibility, not a civil right.

A useful strategy to address driver safety issues is to ask the patient's family if they would be comfortable with the patient driving the grandchildren or someone else's grandchildren. If the answer is short of a resounding 'yes', then a driver's assessment is warranted.

LIVING WITH DEMENTIA: THE CASE OF VOTING

Voting is a civil right that is threatened both by dementia and by how those with dementia are treated. The elderly form a significant and growing proportion of the eligible (and active) voting population in many industrialized countries. Given the incidence of dementia in this population, the disease poses a significant challenge to those interested in protecting and promoting the right to vote. States determine voter qualifications and already restrict voting (e.g. based on criminal convictions)³⁹ and mandate certain kinds of assistance with voting (e.g. for the blind). Many states have been slow to provide voting assistance for those with dementia. This needs to change as methods of voting shift from traditional in-person polling stations to more private venues (e.g. absentee ballots mailed from private homes or nursing homes, home electronic voting). Studies suggest wide and worrisome variation in the access that people with dementia have to the vote and in systemic opportunities for voter fraud⁴⁰. At minimum, we owe to those with dementia an aggressive effort to extend the ease of voting (e.g. using mobile polling in nursing homes) and to all citizens simple safeguards against voter fraud (e.g. monitoring of absentee voting at large nursing homes).

DECIDING ON THERAPY

The decision to either pursue or to forgo therapy in dementia raises ethical concerns. Where potential therapies for dementia carry mild side effects and promise moderate benefits, such concerns may seem uncomplicated weighing of costs and benefits. However, as therapies are developed that promise significant improvement but at a cost of substantial inconvenience (e.g., intravenous medication infusion) or potentially seriously side effects (e.g. meningoencephalitis in an early beta amyloid vaccine trial⁴¹), the ethical importance of such decisions becomes more substantial. It is all the more important to clarify issues of capacity and surrogacy, and at an early stage, when potentially large risks and pay-offs are in the balance.

The need to clarify these issues arises as well for decisions about life-prolonging therapy (e.g. surgery, chemotherapy) for co-morbid conditions (e.g. oesophageal cancer). When capacity to make these decisions is lacking, a surrogate has to weigh the costs of potential side effects, including the cost of enduring side effects that the patient does not understand. In the case of incapacity, potentially life-prolonging therapy should be pursued if (i) the patient has previously

clearly expressed a prioritization for longevity over comfort and (ii) the therapy involves only mild to moderate time-limited discomfort in return for a substantially improved quality and quantity of life. Where these conditions are met, a complicated, expensive treatment should be regarded the same as a cheap, routine one (e.g. antibiotics). The aim of treatment in dementia should not be to prolong life for the sake of prolonging life; it should be to prolong life when the quality of that life falls within the range of that which someone could value.

The choice of whether to pursue enteral nutritional support in patients who have lost (or are soon to lose) the ability to swallow oral nutrition and hydration is one of the most difficult therapy decisions that surrogates face. Eating has deep symbolic and cultural meaning. The presumption has been that enteral nutritional support extends life, reduces respiratory infections by reducing aspiration, wards off other infections (e.g. skin ulcers) by improving nutritional status and provides a comfortable satiety. However, such presumptions, held by both physicians⁴² and surrogates⁴³, are not borne out by evidence⁴⁴. The emerging consensus is that since enteral nutritional support for the severely demented entails harms and provides little or no medical benefit, it can (and often should) be refused if requested by family or surrogates. Instead, the conversation should focus on what is good palliative care and how best to provide it for the patient.

PROMOTING SAFETY AND PRESERVING QUALITY OF LIFE

Personal safety can be an issue both for patients and for caregivers. Patients with impaired memory, insight, judgement and inhibition can wander out of beds, rooms and homes and exhibit other behaviour (e.g. aggression) that endangers themselves or others⁴⁵. Traditionally, the options for ensuring safety have been restraints such as bed rails, medications and locked wards. However, these interventions carry harms^{46,47} and may also mask the need to identify the underlying and potentially reversible causes of these behaviours (e.g. boredom, pain or thirst in the case of wandering and agitation). Recently, techniques of surveillance (such as video, electronic) have become increasingly popular. As valuable as these may be to limit concerns of safety, they must be balanced against other important harms (e.g. violations of privacy, infringements of liberty, indignity) that may result from their use.

Securing the physical safety of persons with dementia and those around them is a balance of freedom and control. Just as medical interventions (e.g. chemotherapy) have a cost in terms of suffering, so too do many safety measures. They should be judged in basically the same way. If these measures so distress the patient that it significantly diminishes whatever quality of life they are able to maintain, then one should seriously question their value. The goal in dementia care is not to prolong life by providing safety at all costs. It is to provide whatever safety is possible – balanced in terms of its costs – so that patients can enjoy the maximal quality of life of which they are able.

An appreciation of the ethical challenges in dementia care is important. It allows the clinician the opportunity for a more thoughtful and systematic approach to questions that are often the most vexing and meaningful for patients and families. There may be few easy answers in these areas but there are ways to approach problems that yield better results than others. Clinicians have an obligation to provide dementia patients with the best care possible and this includes attention to the ethical dimension of the care being provided.

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Successful Interventions for Family Caregivers

L. McKenzie Zeiss¹, Yookyung Kwon², Renee Marquett² and Dolores Gallagher-Thompson²

¹University of California, Irvine, CA, USA

²Stanford Geriatric Education Center, Palo Alto, CA, USA

INTRODUCTION

In the United States, an estimated 5.3 million people have Alzheimer's disease today¹; that number is projected to grow to 13.2 million by 2050². In the UK, approximately 700 000 people have some form of dementia, and that number is expected to top 1 million by 2025³. Most dementia patients will eventually need some form of care, and informal caregivers (usually family members) provide most of that care. It is estimated that there are about 9 million informal caregivers in the United States¹ and 4 million in England³. Family caregiving, although it allows dementia patients to stay in their homes with their loved ones longer and is less financially costly than nursing home care, places an immense strain on the caregivers.

Caregiving is difficult work, and dementia caregiving is particularly stressful⁴. Dementia family caregivers have higher rates of nearly every form of psychiatric and psychological distress, especially depression – several studies that used psychiatric interviews to evaluate caregivers found that rates of major depressive disorder were around 30% – considerably higher than anticipated in the general adult population⁵. Caregivers also report more physical health problems than non-caregivers, and numerous studies have found that compromised immune system function, changes in blood pressure and disrupted HPA axis function are common⁶. Although these indicators of stress are well documented, the development and careful evaluation of theoretically grounded interventions to address these problems and symptoms have been slow. Recent studies have begun to use better methodology and to show significant decreases in caregiver stress and depression. This chapter will describe assessment of caregiver distress, then review evidence-based treatments (EBTs) and other promising approaches emerging in the field today.

CAREGIVER STRESS

Dementia caregiving is stressful for many reasons. Caregivers are watching the inevitable decline of a loved one, often their significant other. They are often elderly themselves and face their own declining health. Family caregivers shoulder the intense burden of daily care activities, ranging from taking over the care recipient's finances to feeding and toileting. The constantly increasing level of care required over the course of a progressive illness like Alzheimer's disease deprives caregivers of time for their own activities and opportunities

for social support, and can even compromise their jobs and their ability to meet obligations to other family members. Yet many caregivers also feel there are positive aspects of caregiving that tremendously benefit their lives⁷.

The 'stress process' model has guided our understanding of caregiving for almost 20 years⁹. This model describes how caregivers use resources (both internal and external) to respond to the demands of their caregiving situation and other life circumstances (e.g. job, spouse, children). This process takes place within a sociocultural context. Perceived stress is a function of the extent to which demands exceed resources and the requisite coping skills to manage these demands are no longer adequate to the tasks at hand.

One must also take into account such 'individual difference' variables as age, gender, ethnicity, relationship and socioeconomic status, which interact with objective stressors and resources and play important roles in determining which caregivers develop physical and/or emotional problems in response to their situations. For example, spousal caregivers are particularly susceptible to depression and stress¹⁰. Being female and being married to the care recipient tend to be related to lower levels of both physical health and psychological well-being¹¹. A caregiver's age is also significant: younger caregivers and non-spouses are more likely to experience role strain, which is usually magnified by lack of resources and perceived intensity of caregiving-related stressors¹¹.

Cultural diversity is another important dimension that adds heuristic value to the stress process model. Many studies find that cultural differences affect multiple aspects of caregiving. Racial/ethnic groups vary greatly in how they perceive objective and subjective stressors, the knowledge they have and the use they make of resources, and the kinds of coping skills they prefer to employ to help them manage their situations^{11–14}. For example, Caucasian/white caregivers are

ⁱThere is great divergence in empirical findings on cultural differences, and to date there have been only a small number of studies on Asian-American and Hispanic caregivers. In order to give equal balance to each ethnic group and resolve heterogeneous or conflicting results, we rely here on available meta-analyses and reviews rather than individual studies. Note also that the terms 'Asian-American' and 'Hispanic' refer to very heterogeneous groups in terms of language, cultural heritage and socioeconomic status. These terms are used in this chapter because they are current designations used in the US Census; however, for clinical purposes, information about specific sub-groups is needed to work effectively – rather than relying on broad generalizations that may or may not be accurate or apply to the individual caregiver in your office.

more likely to be married to the care recipient and report higher levels of caregiver stress, burden and depression than African-American caregivers¹⁴. They tend to use more formal support, such as attending support groups and receiving help from professionals, than non-white caregivers. However, Caucasian/white caregivers also tend to report lower levels of confidence and mastery and less positive appraisal of caregiving compared to ethnic minority caregivers^{11,13,14}.

African-American caregivers often report more role strain, such as more cognitive and physical impairment of the care recipient and a higher number of caregiving tasks, than white caregivers¹¹. Their use of religious coping and their sharing of caregiving responsibilities with extended family and non-family members seem to buffer the impact of objective stressors. They express lower subjective burden, higher levels of mastery and greater satisfaction, and fewer depressive symptoms than white or Asian caregivers^{12,13}.

Asian-American and Hispanic/Latino caregivers may have language limitations, strong beliefs in filial obligation and low levels of both acculturation and health literacy. Combined, these factors make caregiving more stressful. Such caregivers are often reluctant to admit their distress openly, relying instead on more indirect means of expression. For example, Chinese-American caregivers tend to present with a high level of somatic complaints; Mexican-American caregivers often present with depression and guilt¹³. Those who have limited knowledge of English for both reading and writing also have less accurate information about dementia and less access to the health-care system in general and use fewer formal support services than do their Caucasian/white counterparts¹¹.

While cultural beliefs and practices, such as strong family ties and religiosity, can buffer and protect caregivers from negative health outcomes of caregiving, other cultural premises such as filial obligation, the priority of family needs over individual needs, and face saving carry special hazards. Many ethnic minority caregivers regard it as shameful or a 'loss of face' to admit caregiving-related distress. They are likely to under-report care recipients' behavioural and other problems, and to be reluctant to use formal services for elderly family members. Asian-Americans and Hispanics, in particular, may have low levels of acculturation, language barriers, and inadequate health literacy, which may lead to cultural isolation and inability to access services that are currently available in the US health-care system.

ASSESSMENT OF FAMILY CAREGIVERS

Current psychiatric practice emphasizes assessment and treatment of the patient with dementia¹⁵. We recommend a dyadic focus in which caregivers are also assessed and treated. Dementia family caregivers (across all racial and ethnic groups studied to date) are at risk of poor physical health and increased mortality, depression, anxiety, anger, frustration and feelings of grief and loss. A clinician should first assess a caregiver for serious difficulty in one or more areas; any diagnosable psychiatric disorders should be treated promptly with either pharmacotherapy or psychotherapy.

Existing guidelines suggest a variety of approaches for assessing the psychosocial and psychiatric status of the dementia family caregiver¹⁵. We suggest reviewing the Family Caregiver Alliance's recommendations on domains to assess^{16,17}. An easily downloaded 'kit' of these resources, including actual measures and the 'Caregivers Count Too!' toolkit for practitioners¹⁸, is available free from its website. These provide materials needed to follow up problem

areas with detailed assessment and begin directing caregivers towards treatment.

Key Domains to Assess

First: Assess the caregiver's knowledge of dementia. A crucial part of understanding the disease process is knowledge of what to expect as a caregiver. Practitioners should assess medical knowledge of the dementing illness and familiarity with problems caregivers commonly face. It is helpful to have brochures on hand to send home with caregivers, and to have a list of specific websites, such as the Family Caregiver Alliance (www.caregiver.org), Alzheimer's Disease Education and Referral Center (ADEAR, sponsored by the National Institute on Aging in the US) (www.nia.nih.gov/Alzheimers/), National Alliance for Caregiving (www.caregiving.org), and the national website of the Alzheimer's Association in the US (www.alz.org). Several of these groups provide free, downloadable materials about dementia, managing caregiver stress and handling common behaviour problems, in multiple languages besides English. Local chapters of many of these organizations also offer free support groups.

Second: Assess basic safety needs of both caregiver and care recipient. Driving, for instance, is a common safety concern, and caregivers are often grateful for physicians' insistence that care recipients give up their car keys permanently. Other environmental issues – can the care recipient be safely left alone and for how long? Does he/she smoke? – are also essential points to cover. Hints of abuse by either the caregiver or care recipient are also important targets that must be followed up with referrals to Adult Protective Services or similar agencies whose role is to investigate such claims and seek remedies for the situation.

Third: Assess caregivers' emotional and physical well-being. Several measures are available starting with the brief 'Caregiver Self-Assessment Questionnaire'¹⁹ developed by the American Medical Association as a screening tool for caregiver stress. It is free and downloadable from the AMA website.

The new 16-item Risk Appraisal Measure (RAM) was developed specifically for culturally diverse dementia caregivers and designed to provide a clear view of what treatments are indicated for a particular caregiver²⁰. Short enough to be administered to the caregiver in the waiting room, it addresses depression, burden, self-care and health, social support and patient problem behaviours. It also assesses safety, focusing on risks associated with both caregiver behaviours (those suggesting an abuse risk) and care recipient behaviours (e.g. continued driving). Caregivers' answers indicate areas for further assessment or treatment. The RAM is available free of charge and can be obtained in English or Spanish from the study authors.

Other common areas to assess are depressive symptoms and extent of perceived burden. Depressive symptoms can be evaluated quickly and reliably using the CES-D scale²¹ or the Geriatric Depression Scale²². The CES-D measures the frequency of occurrence of common symptoms of depression in the past week. The CES-D is not copyrighted and is available free of charge from numerous online sources.

The Geriatric Depression Scale is widely used in the US and other countries as a screen for depression. It was designed to tap psychological aspects of depression. Its simple 'yes/no' response format makes it easy to use with low-literacy caregivers. It is available free of charge and can be downloaded in many languages from the website: www.stanford.edu/~yesavage/GDS.html.

Perceived burden can be assessed using the Zarit Burden Inventory²³. Many other scales exist to assess this and other relevant domains, but due to space constraints we cannot describe them all; see citations 15 and 16 for details.

Fourth: Assess the care recipient's *cognitive status* and ability to perform activities of daily living. As dementia progresses and cognitive impairment increases, the care recipient's functional abilities will decline, resulting in increased hours of care and increasingly demanding tasks. Often caregivers of patients in the middle stage of dementia are the most stressed since behavioural problems are most common then. They need to learn flexibility and creative problem solving. They must be willing to accept the level of care the patient requires, and must have the personal, social and socioeconomic resources to provide that care. While advanced skills for dealing with problem behaviours are a common target of effective intervention programmes even for highly skilled caregivers, a caregiver who does not recognize that a patient can no longer be safely left alone, or who is not able to help with the patient's basic needs, is not able to provide adequate care.

Fifth: Assess the caregiver's perception of instrumental and emotional *social support*. Such support can substantially decrease stress and also improve the quality of care the care recipient receives. Often, caregivers are unaware of available community- or hospital-based support services or feel too overwhelmed to research them; however, day and respite care are invaluable adjuncts to treatment for distressed caregivers²⁴. Resources to assess include help from family and friends, transportation, legal and other professional services and financial assistance. The Administration on Aging's Eldercare Locator (www.eldercare.gov/eldercare.net/public/home.aspx) directs caregivers to the resources available to them locally. The Alzheimer's Association CareFinder service (www.alz.org/carefinder) is also an excellent guide.

Assessing Diverse Caregivers

Clinicians' cultural competence leads to more or less effective interactions with ethnically diverse patients and caregivers. 'Cultural competence' encompasses both clinicians' attitudes and knowledge about ethnic groups and their specific skills for interacting with them. The Stanford Geriatric Education Center (<http://sgec.stanford.edu>) provides online training in improving communication with ethnically diverse elderly; the *Diversity Toolbox* (Alzheimer's Association, www.alz.org) is likewise a useful resource. The book *Ethnicity and the Dementias*²⁵ is also a good source of information about working with ethnically diverse dementia patients and caregivers. A few points apply broadly to many minority groups: (i) health-care providers need to include the family unit. Ethnic elders generally prefer to be cared for by family, who often see caring for elderly parents and relatives as a family responsibility²⁶; (ii) assess ethnic minority caregivers' health literacy and cultural and linguistic competency. Low education levels, language barriers and low levels of acculturation are related to lower health literacy, which in turn affects ability to comply with treatment plans and access appropriate services. There are explicit assessment tools to measure health literacy²⁷ and implicit screening strategies such as asking caregivers to bring all medications and explain them, or handing caregivers a written document upside down to see if they turn it over to read; (iii) practitioners need to enhance the comprehensibility of health messages, use culturally appropriate examples and materials, and use a team

approach involving practitioners, family, culturally and linguistically competent counsellors and translators.

BEST PRACTICES FOR HELPING CAREGIVERS WITH STRESS

What are the Evidence-Based Treatments?

The most recent reviews^{28,29} of evidence-based psychological treatments (EBTs) note that three modalities show consistent effectiveness: psychoeducational small group programmes focused on teaching caregivers skills for coping with depression, frustration and common behavioural problems; cognitive behavioural psychotherapy (for those in need of more extensive treatment); and multi-component interventions combining several approaches. Other approaches, particularly respite care, show some promising results but have not yet met criteria for EBT. Support groups are important pieces to consider in multimodal approaches but are not empirically supported standalone treatments for caregiver distress. Gallagher-Thompson and Coon²⁸ found that evidence-based psychoeducational and psychotherapeutic treatments had the most empirical support, and in general produced large effect sizes. They further concluded that interventions combining support with skills building and targeting specific quality-of-life components were the most effective overall.

From our review of this literature, we propose that five key factors delineate the most effective treatments. They are:

1. **Treatment should be drawn from evidence-based practice.** Treating dementia caregivers is particularly difficult because of the intense stress they face in daily life. The most successful interventions for caregivers' distress are drawn from the same pool as those most successful with other patients. Well-supported modalities rooted in cognitive behavioural therapy and stress-management theory work well with caregivers. For example, individual cognitive behaviour therapy is an effective treatment for caregivers with a diagnosable disorder such as major depressive disorder. Psychoeducational programmes work well to teach behavioural management³⁰, depression management³¹, effective communication and relaxation and stress management³².
2. **Treatment should require active participation.** Some educational interventions consist of giving caregivers printed materials to complement a lecture delivered to the group. Others take a more 'Socratic' pedagogical approach, actively soliciting input from group members and encouraging them to discuss and question the materials. While both approaches might increase knowledge, neither does much to guide caregivers in the implementation of that knowledge – a feature that some researchers³³ suggest is far more important than what precise materials are covered or what pedagogical style a leader takes. 'Active participation' consists of participation in discussion of new skills and actively putting those skills into practice, with regular check-ins to ensure caregivers are using what they have learned. Using role-playing exercises and 'homework' assignments are ways to support this learning.
3. **Treatment should be tailored to meet individual needs.** Effective treatment begins with assessing a caregiver's areas of strength and weakness, setting specific goals and determining which avenues to pursue most vigorously. Imagine a caregiver who complains of depressed mood and low social support, and

has trouble getting her care recipient's physician to address her concerns, but who has no other pressing complaints. Skills training tailored to managing depression, increasing social support and communicating assertively (especially with medical professionals) is recommended. She would benefit less from a one-size-fits-all programme stressing relaxation exercises, for example, or from a programme that covers quality of life as a general domain without any specific targets. Some other specific guidelines suggested by the reviews and analyses include referring depressed caregivers for treatment. For those with sub-clinical distress, refer to a psychoeducational group; for those whose stress is very high, refer to a stress-management programme²⁸. Likewise, caregivers with more severe distress tend to require longer periods of treatment⁸. Finally, as Alzheimer's and other dementias are progressive illnesses, caregivers' specific profiles are likely to change over time as their caregiving situations change. Support groups are useful for learning about this process.

4. Treatment should be tailored to caregivers' individual differences. These include gender, age, family relationship, education, socioeconomic resources, ethnicity and language issues.

- Gender: Although female caregivers are generally more distressed and show greater levels of distress initially, male caregivers remain more distressed after treatment³⁴ and so may require more intensive treatment to achieve the same improvement. More research is needed with male caregivers since intervention studies are few.
- Age and family relationship: Spousal caregivers are usually older than adult child caregivers. Even when controlling for age, spousal caregivers show higher levels of depression³⁵ and are less responsive to treatment^{28,34}. There are, as yet, no studies showing a solid basis for preferring specific treatments for spousal caregivers as opposed to other caregivers, though preliminary research⁸ suggests that couples and family therapies may be of more help for them.
- Education and socioeconomic status: Numerous studies have found that caregivers who begin treatment with low education and resources improve more quickly and dramatically than their more-educated peers^{34,35}. Caregivers who have more knowledge about dementia and more access to support resources, but are still distressed, may not be helped much by extra information. They are therefore more likely to require psychotherapy or extended psychoeducational/skills-building programmes. At the same time, caregivers of lower socioeconomic status are less likely to avail themselves of services in the first place, so for these populations outreach is especially important.
- Ethnicity and cultural issues: Intervention with dementia caregivers is an active process that consists of conceptualizing individual caregiving contexts, identifying specific demands and vulnerabilities, and designing and implementing interventions for individuals of different cultural backgrounds. For example, REACH II, the largest randomized control trial on caregiver interventions to date and the only one meeting CONSORT standards, suggested different intervention targets for each race/ethnic group¹¹. Overall, the interventions produced statistically significant improvement on all short-term outcomes. Among African-American caregivers, however, only spousal caregivers benefited from the treatment. Furthermore, while all intervention groups except African-American non-spousal caregivers had lower depression scores, only white caregivers showed lower rates of clinical depression at

six months. Based on these outcomes, REACH researchers have suggested refining treatments further. White caregivers were more likely to experience intrapsychic strain, and to benefit most from interventions that target this (e.g., learning to regulate negative emotions). In contrast, Hispanic caregivers might benefit from psychoeducational interventions that increase knowledge of dementia processes, resources and services, and that train them to respond effectively to memory and behaviour problems. African-Americans tend to experience financial strain, and might benefit from interventions that provide financial support, e.g. respite-type services.

Finally, because minorities often place particular emphasis on familism and filial duty, family-based interventions may be particularly useful. They have been found to improve family communication and sharing of the caregiving role^{8,11,36,37}.

Further research is needed to support the usefulness of this approach with ethnically diverse caregivers.

5. Consider multi-component treatments. Although there is not a great deal of empirical data on multi-component treatments, it seems reasonable to expect a greater 'yield' from combining two or more approaches when possible. For examples, findings from Mittelman³⁸ and REACH I³⁷ suggest that multi-component treatments may be particularly effective at delaying nursing home placement and at reaching otherwise inaccessible groups.

One of the difficulties with this is that, precisely because they do combine multiple approaches, these interventions are a heterogeneous group and it can be challenging to figure out which component is really having the main effect. For example, a novel delivery system (such as the telephone-computer technology used in Miami during REACH I) counts as a 'component', even though a telephone or computer is not a means of treatment in and of itself. Yet because some caregivers face difficulties in attending appointments, telephone-based treatments may make interventions more accessible to them. New programmes along these lines that need more study include the Savvy Caregiver Program³⁹, which includes take-home information for use at home, and Powerful Tools for Caregivers, a web-based psychoeducational programme⁴⁰. New web-based programmes are currently in development and may be very useful at replacing at least some individual or small group meetings. Whether they should be viewed as 'supplements' or 'standalone' interventions requires additional research.

OTHER SUPPORT SERVICES FOR CAREGIVERS

Support groups are immensely popular, are usually free, have a long history and are readily available in most communities. However, support groups are not EBTs, as they simply do not have an empirical basis consistently demonstrating effectiveness.

Gallagher-Thompson and Coon²⁸ noted in their review that no methodologically sound study has shown support groups to be effective unless combined with another active therapy. Some studies have even shown worse outcomes for support-group participants⁴¹. Pinquart and Sorensen found in their meta-analyses^{34,35,42} that support group interventions generally underperformed on all measures of caregiver distress, concluding that they had fewer positive effects for dementia caregivers than they did for other types of caregivers studied. At the same time, support groups are recognized as a valuable adjunct to EBTs. When possible, clinicians should direct caregivers to other treatment options as well as support groups, and should clarify caregivers' expectations about what they may get out of a support

group. Many caregivers subjectively report that support groups are extremely valuable to them for the social support and 'normalization' they provide. Used in combination with EBTs, support groups can be very helpful as dementia progresses.

Many other services are available to caregivers, including pharmacotherapy, case management, respite care, environmental management/modification and technology-based programmes. At least two studies support case management for improving caregivers' quality of life^{43,44}. Respite care has been shown to be effective in reducing caregiver burden when used at least twice a week for at least three months. Its cost-effectiveness improves with increased use, suggesting that higher levels of funding for respite care to allow regular, long-term use might be a cost-effective public health policy^{45–47}. Respite care can delay nursing home placement⁴⁵, especially among minorities. Even in low doses, many find respite care extremely welcome as an occasional relief.

Programmes focused on modifying the home environment and teaching caregivers skills for engaging the care recipient in everyday pleasurable activities have also shown promise⁴⁸. This approach improves safety in the home and encourages positive interaction between caregiver and care recipient. It was especially helpful for elderly, poor, inner-city African-American families who would not otherwise have funds to make environmental modifications (e.g. installing grab bars in the bathroom, removing slippery rugs that could contribute to falls).

New technology-based programmes may be helpful for rural caregivers who are unable to travel to city centres for programmes. Although there are limitations to what these programmes can provide, they may meet the needs of some caregivers who otherwise would not have assistance^{49,50}. These and other programmes show promise, and it is likely that additional research will support their efficacy, at least to some extent.

WHERE IS THIS FIELD GOING IN THE NEXT DECADE?

While we are gaining in our knowledge of 'what works' to reduce depression, improve adaptive coping skills and reduce caregiving-related burden, there is still considerable room for improvement. For example, the patchwork of services that can be found in one state or region of the US may not be available in other states, there is little coordination of care, and there are still very few culturally appropriate services and programmes for caregivers (and care recipients) who are mono-lingual or whose primary language is not English. Given the fact that ethnic minority older adults are a rapidly increasing segment of the US population, their needs will only continue to grow. Programmes that meet their needs *and* are evidence-based are sorely lacking at this time.

A particular challenge facing this field is the lack of research to develop 'practice guidelines' for working with caregivers similar to those that now exist in other areas of medicine. There is also a lack of substantial data on how to match effectively the client/patient in your office with existing programmes and providers. The study of what level of care and what kinds of services are needed to adequately treat a given caregiver is just beginning – but it is being pushed forward at a rapid pace because of the expected onslaught of the baby boomers. From a public policy perspective, progress in this area is essential.

A final area for study is how long-term caregiving affects caregivers' physical health. Although we have some information, it is not extensive, due in part to the difficulty securing funding to conduct

long-term follow-up studies with caregivers at high risk for development of, say, type II diabetes or coronary artery disease. Since these conditions typically develop over a period of years, long-term follow-up is needed. New programmes that focus on modification of caregiver health habits are underway; it may be the combination of interventions focused on improving both physical *and* mental health that will have the greatest success with this population in the long run.

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The Role of Alzheimer Societies in the United States

Ruth O'Hara^{1,2} and Bevin Powers^{1,2}

¹*Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, USA*

²*VA Sierra-Pacific Mental Illness Research Education and Clinical Center, Palo Alto, USA*

Alzheimer's disease (AD) is listed by the Center for Disease Control and Prevention (CDC) as the sixth leading cause of death in the United States. Currently there are 5.3 million people diagnosed with AD¹, and it is estimated that one in eight people aged 65 or older will develop AD². As the baby-boomer generation approaches older age, the need for medical care and caregivers will be immense. Incidence rates are projected to double every 20 years with the aging of the baby boomers, therefore, it is predicted that 7.7 million people will be diagnosed with AD by 2030, and by 2050, AD is estimated to reach between 11 million and 16 million people¹. The psychological, social and financial costs of this illness are substantial, with approximately \$148 billion per year in medical expenses¹.

Alzheimer's disease societies can be traced back to the 1950s with the forming of the National Counsel of Aging whose aim was to improve the lives of aging Americans³. From that point forward additional AD societies in the United States were created for multiple reasons, however largely humanitarian. Table 67.1 lists AD societies in the United States. As the prevalence of AD increases, the need for caregivers and services will be astronomical.

Approximately 54% of the US population has been touched in some way by AD, either having a family member diagnosed with AD, or knowing someone who has been diagnosed with AD¹. In 2009 alone, AD contributed to the death of 660 000 Americans which continues to climb each year. AD produces more deaths compared to AIDS (16 316), prostate cancer (27 350), Parkinson's disease (17 898) and hepatitis C (12 000)⁴. Yet, the disparity of funds allotted to AD research compared to other diseases is striking. In 2007, the National Institute of Health (NIH) awarded AIDS research \$2.9 billion, while AD research received \$644 million⁴. As the frequency of AD diagnosis continues to climb with the growing aging population, the lack of caregivers, health-care professionals and burden on family and services will generate a national crisis.

Over the decades, AD societies have been developed in many ways to address these issues and gaps in service. These societies are dedicated to implementing and disseminating more effective treatments, assessment and supportive interdisciplinary services. The majority of AD societies particularly focus on the community need for resources, family needs and early detection and diagnosis. Some are more clinical and research oriented exploring prevention, the pathophysiological mechanisms and disease process, and ultimately, a cure. However, all provide levels of hope and support for victims of AD, their families and caregivers.

Alzheimer's disease societies have been shown to result in stress reduction in those diagnosed with AD or a caregiver for an individual with AD⁵. The burden of the disease and the quality of life are of great relevance to those who suffer from an illness or disease, and warrant careful consideration and comprehensive care. A number of AD societies aim to target care planning and other support needs required by the patient and their caregivers. However, it is estimated that those diagnosed with AD and caregivers do not seek support from AD societies for three years after diagnosis, and the support is often sought out only in a time of crisis¹. Frequently, by the time support is obtained, patients with AD may be at a disadvantage; missing an opportunity to explore research options or other available treatments, advanced care planning, taking advantage of caregiver and family education and training, and establishing support before stress and burden have taxed the family and caregiver.

FEDERAL AGENCIES

As a federal agency of the United States Department of Health and Human Services agency, the Administration on Aging (AoA) has supported the Older Americans Act (OAA) of 1965 mandated programmes⁶. Also, the AoA awards research grants that support the needs of an aging population. Centers for Medicare and Medicaid Services also receive support from the AoA.

The AoA's primary interest is the aging population and caregiving, and it aims to invest in research, aging programmes and policy, including improvement of health care, aging in place, optimal aging and protecting the rights of older people. Some programmes are focused to provide home and community-based services such as home-delivered meals or nutrition services in congregate settings, or transportation, adult day care, legal assistance, health promotion programmes and local ombudsman⁶. In addition, AoA provides funding for a range of support services for family caregivers.

The US National Institutes of Health National Institute on Aging (NIA) is the aging and health scientific based agency of the NIH. By an act of Congress in 1974, the NIA was authorized to lead aged-focused research, training and health information distribution⁷. The NIA is the leading federal agency supporting research on Alzheimer's disease and other neurodegenerative disorders.

Through research, the NIA supports the well-being of older Americans with a primary focus on the aging processes, age-related diseases and distinct needs of the aged. The NIA train, develop and

Table 67.1 Alzheimer's disease societies in the US

<i>Agency</i>	<i>Funding source</i>	<i>Description</i>
Administration on Aging (AoA)	Federal	Awards research grants, provides home and community-based services including nutrition services, transportation, adult day care, legal assistance, health promotion programmes, ombudsman and support services for family caregivers
National Institute on Aging (NIA)	Federal	Health- and science-based agency focused on research, training and health information distribution
Alzheimer's Disease Cooperative Study (ADCS)	Federal	Primary aim is to conduct clinical trials on cognitive and behavioural treatments and interventions for AD
Alzheimer's Disease Neuroimaging Initiative (ADNI)	Federal	Primary aim is a worldwide clinical trial on MCI and AD, and to establish a database to improve future treatment trials
Alzheimer's Disease Centers (ADC)	Federal	Research focused on the mechanisms of AD, prevention, management and improvement of patient care. Also provides clinical and community programmes and services
National Alzheimer's Coordinating Center (NACC)	Federal	Provides collaborative research data collection, database, analysis, methodological and technical support.
The National Cell Repository for Alzheimer's disease (NCRAD)	Federal	National resource for clinical and genetic research, specifically housing a genetic databank
Alzheimer's Disease Education and Referral Center (ADEAR)	Federal	National archive centre for publications, audiovisual material. Responsible for dissemination for AD treatment and diagnostic information
The Geriatric Research, Education, Clinical Center (GRECC)	Federal	Primarily focused on research, education and clinical advancements for the care programmes and advancements in the quality of life of the aging veteran.
The Stanford Geriatric Education Center (SGEC)	Federal	Through academic and community educational dissemination the SGEC offers ethnogeriatric multidisciplinary education and didactics including health literacy, caregiving for dementia patients and other chronic disease, hospice and spirituality, ethics in geriatric care and emergency preparedness.
The National Association of Area Agencies on Aging (n4a)	Federal	Supports Agencies on Aging (AAA) to address support initiatives to assist older Americans through community-based and home services.
Stanford/VA/NIA Aging Clinical Research Center (ACRC)	Federal	Investigates normal cognitive aging and AD through medical and neuroscience disciplines to improve the lives of patients with memory loss
Memory and Aging Center	Federal/Private	Coordinating site for ADRC, conducts research, provides clinical services, education and outreach
Alzheimer's Disease Research Center (ADRC)	Federal	Focuses on laboratory and clinical studies in dementia and aging, improvements in diagnosis and treatments, and community education
Alzheimer's Caregiver Support Online (Alzonline)	Federal/Private	Provides online support for caregivers through education, information and support networks
Alzheimer's Association (AA)	Non-profit	Funds advance research, provides community support for AD or other dementias
Alzheimer's Foundation of America (AFA)	Non-profit	Several collaborating agencies dedicated to providing AD patients and families educational, social and emotional support
Association for Frontotemporal Dementias (AFTD)	Non-profit	Promotes and funds research and education for frontotemporal dementias
Alzheimer's Research & Prevention Foundation (ARPF)	Non-profit	Through the 4 Pillars of Alzheimer's Prevention programme, the agency provides training and educational opportunities for professionals and communities
Family Caregiver Alliance (FCA)	Non-profit	Supports caregivers with caring for those with AD or other chronic illnesses with local services tailored to each individual
The National Family Caregivers Association (NFCA)	Non-profit	Provides caregiver education, support and empowerment
The Lewy Body Dementia Association (LBDA)	Non-profit	Community support for family and caregivers, and research focused on scientific advances

Table 67.1 (continued)

<i>Agency</i>	<i>Funding source</i>	<i>Description</i>
National Council on Aging (NCOA)	Non-profit	Implements and disseminates programmes into communities to improve lives of older adults. Dedicates effort to raising awareness and lobbying for funding and programmes for the aging population
International Longevity Center	Non-profit	Research, education and policy driven to advance healthy aging, promotes productive engagement and to eliminate ageism
Institute on Aging (IOA)	Non-profit	Improves the quality of live for aging Americans in diverse community settings. Promotes independent living for older and disabled adults
National Alliance for Caregiving	Non-profit	Conducts research, analyses policy and produces programmes devoted to improving the quality of live for care recipients
Dementia Advocacy and Support Network (DASN)	Non-profit	Internet-based support group for individuals with dementia
American Federation for Aging Research (AFAR)	Non-profit	Research aimed at exploring the aging process and age-related diseases

support researchers in the field of aging, and place a funding priority on those research endeavours that will likely help illuminate the mechanisms underlying the pathological features of AD.

In 1991, the Alzheimer's Disease Cooperative Study (ADCS) was established by the National Institute on Aging's (NIA) Neuroscience and Neuropsychology of Aging Program, and the University of California San Diego⁸. Funded by the Federal Alzheimer's Disease Prevention Initiative, the ADCS clinical trials focus on cognitive and behavioural treatments for AD in response to an increased need to development of drugs that might be useful for treating patients with AD. The ADCS employs a multi-site approach to conduct pharmaceuticals clinical trials to test new treatments that may improve cognition, decrease decline and delay the onset or progression of AD. The ADCS offers over 30 research studies nationally which are disseminated through the media and journal publications. A strength of this approach is that the investigators across the different sites comply a core set of identical assessment tools in order to achieve the maximum leverage for ongoing research projects.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) was built upon the resources of the ADCS. ADNI is funded through NIH, National Institute of Bioimaging and Bioengineering, the pharmaceutical industry and several foundations. The ADNI's aim was to produce, conduct and report the results of a worldwide study designed to 'define the rate of progress of mild cognitive impairment (MCI) and Alzheimer's disease, to develop improved methods for clinical trials in this area, and to provide a database which will improve design of treatment trials'⁹. Using a national network of centers engaged in AD research, ADNI employs a common protocol to assess cognition, function, biomarkers and brain structure in the elderly with mild cognitive impairment, and AD across the multiple sites. This allows investigators to have sufficient numbers of subjects enrolled to be able to get a better scientific picture of the pathology, course and symptoms of this disorder.

The NIA funds the Alzheimer's Disease Centers (ADCs) at major medical institutions across the United States^{10,11}. Research at ADCs focus on the basic mechanisms of AD, prevention, management of symptoms and improvement in patient care^{10,11}. Each ADC has a unique focus within a common goal shared by all centres, to enhance research on AD. ADC programmes offer collaborative clinical, research and community programmes, such as, diagnosis and medical management, information about the disease, services

and resources, opportunities to participate in drug trials and clinical research projects. Additionally ADCs offer diagnostic and treatment services and research opportunities in underserved, rural and minority communities.

Created by NIA, the National Alzheimer's Coordinating Center (NACC) was founded in 1999 to promote collaborative research and offer technical support throughout the 29 nationwide NIA-funded ADCs¹². The NACC encourages ADC collaborative research and data collection, and maintains a primary database of clinical and neuropathological research data collected from each ADC. From the NACC-maintained database, data analysis is conducted to generate descriptive and hypothesis within specific areas, and develop methodological areas of study.

The National Cell Repository for Alzheimer's Disease (NCRAD) was also founded and funded by the NIA in 1989¹³. The Repository serves as a national resource for clinical and genetic research. The Repository's mission is to help identify the genes that lead to the development AD which can lead to more effective treatment and eventually prevention¹³. Programmes offered by the Repository are primarily research based and focused on families with a history of AD. This databank is instrumental in storing genetic data from Alzheimer's patients and their families for future use and current scientific exploration.

The Alzheimer's Disease Education and Referral Center (ADEAR) is the information centre and library on AD and is also operated under the NIA umbrella. It provides access to publications and audiovisual materials that can be retrieved online or through mail. ADEAR was created in 1990 to 'compile, archive, and disseminate information concerning Alzheimer's disease' for health professionals and the community^{10,11}. This federally funded agency has the most updated, comprehensive information about the cause, treatment and diagnostic advancements of AD. As a community resource for information, the ADEAR services include free publications, referrals for services and AD specialized centres, literature and educational materials.

Within the Veteran Health Administration (VHA) system are 20 Geriatric Research, Education, and Clinical Centers (GRECC)¹⁴. In the mid-1970s, the VHA focused awareness on the aging veterans and their care¹⁴. The GRECCs were designed to advance and integrate research, education and clinical achievement in geriatrics and gerontology into the VHA health-care system. GRECCs have

developed and expanded clinical models such as Geriatric Evaluation and Management (GEM) programmes, Palliative Care Programs for Late-Stage Dementia patients, education and training products¹⁴.

The National Association of Area Agencies on Aging (n4a) supports the 629 Area Agencies on Aging (AAA) and 244 Title VI programmes. AAA was created in 1973 by the Older Americans Act (OAA) to address the needs of aging Americans¹⁵. The n4a oversees programmes to support initiatives that help older adults age in place through community-based and home services. The n4a advocates in large for services and resources for older adults and persons living with disabilities.

Beyond federal-supported enterprises, there are several state-supported centres dedicated to AD. For example, in 2000, Alzheimer's Caregiver Support Online (Alzonline) was established to support the caregiver community through daily challenges and provide expanded caregiver education, information and support¹⁶. Alzonline continues to receive funding through the State of Florida Department of Elder Affairs and the University of Florida (UF) Center for Telehealth¹⁶. Alzonline provides caregivers of Alzheimer's patients support, education and up-to-date information on caregiving.

NON-PROFIT AGENCIES

The Alzheimer's Association (AA) was started in 1980 by Jerome Stone in Chicago, IL, as it merged with the Alzheimer's Disease and Related Disorders Association¹. Beginning with only seven chapters, the Alzheimer's Association has developed into one of the most prominent non-profit health associations focused on Alzheimer's care, support and research. Appropriately, Alzheimer's Association's vision is a 'world without Alzheimer's disease'¹. Its purpose is to promote prevention and elimination of AD through advances in research, and to provide and improve care and support for all those affected by AD, or other dementias¹. The programmes offer vast community outreach, support and education through local chapters, including telephone hotlines, support groups for caregivers and those in the early stages of the disease, personal consultations, referrals to local health-care services and facilities, online services and caregiver workshops.

The Alzheimer's Foundation of America (AFA) is a non-profit organization consisting of a number of agencies across the nation. These collaborating agencies are committed to providing AD patients and their families, educational, social and emotional support. The AFA promotes community awareness about the disease and contributes expertise and grants to health-care professionals and other organizations to enhance services¹⁷. The AFA was established in 1999 to oversee quality of care and services nationally that are provided to individuals with AD, their caregivers and families. They strive to improve the quality of life and public awareness of AD for those affected by the debilitating disease¹⁷.

The AFA offers educational, social, emotional and practical needs of individuals with AD and related illnesses, and their caregivers and families with 950 member organizations untied under the AFA's umbrella¹⁷. Some of the AFA's member organizations include Dementia Care Professionals of America, Teens for Alzheimer's Awareness, AFA Quilt to Remember and National Memory Screening Day for early diagnosis¹⁷. The National Memory Screening Day for early diagnosis and detection of AD and other dementia began in 2003, and is dedicated to early recognition of AD to provide patients and families the opportunity to explore treatment and care-planning options. Frequently early symptoms of AD

are mistaken for cognitive decline associated with normal aging. Failure to recognize early symptoms of dementia may lead to possible harmful and unsafe behaviours displayed by the patient as the disease progresses. Moreover, early detection can help lessen the burden on the family and/or caregiver(s) and can provide opportunities for research and other medical interventions to help slow the progression of the disease.

The community services accessible are social work case managers, resource and referral centres, educational conferences and workshops, Early-stage and middle-stage programmes, adult day services, family services, respite and telephone support, and memory assessments.

The Association for Frontotemporal Dementias (AFTD) was created in 2002 by a caregiver who lost her husband to Pick's disease and saw the need to address the requirements of all those with frontotemporal dementias with treatment and cure promotion and education¹⁸. The AFTD is a national non-profit organization that promotes and funds research and education for the cure of frontotemporal dementias¹⁸. AFTD provides information, education and support to those afflicted with frontotemporal dementias (FTD), their families and caregivers.

The academic research based Alzheimer's Research & Prevention Foundation (ARPF) was founded as a first of its kind in implementing a prevention programme for memory loss and AD through the 4 Pillars of Alzheimer's Prevention¹⁹. The 4 Pillars of Alzheimer's Prevention combines training conferences on preventing memory loss and AD for medical professionals, educational opportunities for communities and medical professionals, and conducts research for the possible prevention of AD¹⁹.

PATIENT AND CAREGIVER SUPPORT ORGANIZATIONS

Although all of the organizations previously mentioned provide excellent support and education, several organizations were founded to specifically provide ongoing services and resources for AD patients and their caregivers. Founded in 2000, Dementia Advocacy and Support Network (DASN) has formed an internet-based support network for people with dementia. DASN establishes a forum for autonomy, respect and support for persons with dementia²⁰. Through educational services, counselling, advocacy and local service connection, DASN promotes quality of life for those diagnosed with dementia.

In 1977, the Family Caregiver Alliance (FCA), a non-profit organization, was founded to assist and support caregivers of those with AD and other chronic conditions²¹. The FCA is a national community-based programme funded through corporate and foundation grants, the State of California, Area Agencies on Aging, and program participants and donations, which promotes services for caregivers and families providing care for those with chronic illnesses²¹.

The FCA established the National Center on Caregiving (NCC) to develop national programmes and policies for caregivers²¹. The FCA acts as a concierge for services and programmes, helping caregivers locate support services in their communities. It offers a broad array of services from caregiver service and programmes, publications, education and training programmes, direct services, online information and support programmes, research and policy development. The National Family Caregivers Association (NFCA) was founded in 2003 to educate, support and empower caregivers of those who are living with a chronic illness or disability²². The community-based NFCA raises awareness about the caregiver's role and helps empower caregivers with education and support to lead full, productive and healthy lives.

The National Alliance for Caregiving was established in 1996 as a non-profit association in collaboration with other national organizations dedicated to caregiving²³. In union with grassroots organizations, professional associations, service organizations, disease-specific organizations, a government agency and corporations, the National Alliance for Caregiving conducts research, analyses policy, pioneers national programmes and continues public awareness of family caregiving challenges²³. Moreover, the Alliance remains devoted to improving the quality of life for families and care recipients. The Alliance has implemented the National Caregiver Survey, the Family Care Resource Connection, a National Caregiving Agenda and international conferences on family caregiving.

OTHER ORGANIZATIONS PROVIDING SUPPORT FOR AD

There are several other programmes and centres, that do not specifically focus on AD, but who still consider it under the boarder umbrella of their mandates. In 1950, the National Council on Aging (NCOA), a non-profit organization, was formed to develop, implement and disseminate innovative programmes to improve the lives of older adults³. NCOA collaborates with organizations nationally to provide older adults affordable and independent living, employments and activities. Although the NCOA does not have a primary focus on AD, it does consider the impact of AD. This is important as this organization has been instrumental in shaping public policy. The NCOA has had a congressional hand in Medicare, the Age Discrimination in Employment Act (ADEA), and the Older Americans Act (OAA)³. Furthermore, the NCOA is dedicated to raising awareness of the challenges older Americans with limited income and resources face.

Other such organizations include the International Longevity Center, a research and educational organization, devoted to the development of science-based policies²⁴, the Institute on Aging (IOA) a community-based, non-profit organization, which embraces diverse aging communities' need for health, social service, creative arts, spiritual support and education programmes, as well as continuous research. Today the IOA is one of the largest providers for community-based services for the aging population²⁵.

The American Federation for Aging Research (AFAR), established in the 1980s, has been a leader in a 'revolutionary approach to the science of healthier aging'²⁶. AFAR explores aging and the aging processes in understanding age-related diseases. By studying the components of disease that are related to aging and the underlying mechanisms of aging and how they regulate the processes in our bodies, AFAR has contributed to the understanding of aging and mechanisms of age-related disease. AFAR funds 2500 early-career scientists from prominent institutions each year, and together explores the fundamental mechanisms of aging and aging with age-related diseases²⁶.

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Psychiatric Manifestations of Nervous System Infections

Jeffrey T. Guptill and E. Wayne Massey

Duke University School of Medicine, Duke University Medical Center, Durham, USA

This chapter highlights nervous system infections that may masquerade as psychiatric disease or may be coincident in the geriatric patient with psychiatric disorders. This is not meant to be an exhaustive discussion, but rather emphasizes a few conditions that may enter into the differential diagnosis of patients presenting with psychiatric symptoms.

A thorough history and clinical examination are paramount to recognizing the neurological origin for patients presenting with psychiatric symptoms. Rapidly progressive symptoms, alteration in the patient's level of consciousness, seizures, focal weakness or numbness, slurred speech, tremor, vision change or diplopia, difficulty walking or falls, and headache are symptoms that should raise the suspicion for neurological disease and should be investigated further. The reader is encouraged to refer to the provided references for in-depth reviews of each topic.

Subacute and chronic infections are more likely to have manifestations confused with primary psychiatric disease. We have limited our discussion to the neurological manifestations, diagnosis, and treatment of tuberculosis, Lyme disease, syphilis, cryptococcosis, and herpes virus.

MYCOBACTERIUM TUBERCULOSIS

Although relatively uncommon in the United States, the incidence of tuberculosis has been increasing since the mid-1980s related, in part, to the increased prevalence of HIV infection. Other than patients with HIV, tuberculosis infection in the USA is mostly seen in substance abusers, immigrants from underdeveloped countries (35% of new cases in the USA), and the elderly (25%)¹. In Europe 80% of infected individuals are over the age of 50 and similar figures have been reported in Asia². The incidence in the USA is estimated at 4.4 per 100 000³, but it is more common in developing nations, particularly Africa and Asia. Approximately one third of the world population, about 2 billion people, is infected with *Mycobacterium tuberculosis*. One in ten will develop active disease⁴.

Three important, and occasionally overlapping, presentations occur with central nervous system (CNS) tuberculosis infection. A myeloradiculitis may result in pathologic hyperreflexia, spasticity, paraplegia, sensory level, and/or radicular weakness and numbness with depressed reflexes. Next, tuberculomas of the brain parenchyma are composed of inflammatory cells and granulation tissue and often

behave like tumours due to mass effect. Tuberculomas are often multiple but can be single and large. Symptoms and signs are usually related to location and size. If located in a periventricular location, hydrocephalus may develop. Tuberculomas are more likely to be confused with psychiatric disease, particularly with involvement of the frontal lobes or with the gradual development of hydrocephalus⁵. Finally, tuberculous meningitis may present with slowly progressive headache, confusion, lethargy and meningeal signs or as an acute meningoencephalitis. Multiple cranial neuropathies are not infrequent due to basilar leptomeningeal involvement⁶. Hydrocephalus with increased intracranial pressure, develops later in the course and results in progressive lethargy and confusion. Importantly, meningitis may occur in patients with inactive lung nodules, no other evidence of infection, and a negative purified protein derivative (PPD) test⁷. As expected, the patient with HIV co-infection tends to have a more fulminant presentation. Rapid clinical deterioration may also be associated to HIV/AIDS.

Although 75% of geriatric patients present with pulmonary tuberculosis, extrapulmonary presentations increase with age¹. Atypical presentations of tuberculosis, including meningitis, are well described in the elderly. However, the prevalence is not well known. Geriatric patients may present with non-specific symptoms such as fatigue, cognitive impairment, encephalopathy, and impaired activities of daily living². As a result of co-morbid conditions, tuberculosis is often not initially considered in the elderly, resulting in delayed diagnosis, more advanced disease and lower cure rates with higher mortality.

When the diagnosis of tuberculous meningitis is suspected a lumbar puncture should be performed following computed tomography (CT) scan of the brain evaluating for impending herniation. The cerebrospinal fluid (CSF) profile typically shows an elevated opening pressure, high protein content, lymphocytic pleocytosis and a mildly low glucose. Rarely, acid-fast bacilli are identified. Early in the disease process polymorphonuclear (PMN) cells may be the predominant immune cell type, but if the lumbar puncture is repeated several days later, the typical lymphocytic pleocytosis will usually be observed⁵. Paradoxically, the lymphocytic pleocytosis may shift towards a PMN predominance following initiation of treatment. This shift is felt by some experts as nearly pathognomonic of tuberculous meningitis and has been utilized in developing countries to direct therapy⁶. Methods of identifying the organism include

standard culture, rapid culture techniques and polymerase chain reaction (PCR) with DNA amplification. The diagnostic yield of culture is highly dependent on the amount of fluid sent for analysis (10 cc recommended). Growth with standard culture techniques would not be expected before about four weeks and rapid culture techniques may yield results in a week or slightly less. Treatment is often begun without isolating the organism when there is a high clinical suspicion and a compatible CSF profile. Brain CT or magnetic resonance imaging (MRI) may show evidence of hydrocephalus or infarct. Imaging obtained with contrast often shows strong enhancement of the basilar meninges and cranial nerves. Tuberculomas have imaging characteristics suggestive of primary brain tumours such as peripheral enhancement and vasogenic oedema.

Therapy of CNS tuberculosis typically consists of a three- or four-drug regimen, usually rifampin (10 mg/kg/d, maximum 600 mg daily), isoniazid (5 mg/kg/d), ethambutol (15 mg/kg/d), $\pm$ pyrazinamide (20–35 mg/kg/d) or ethionamide (15–25 mg/kg/d in divided doses). Streptomycin (10 mg/kg, maximum 750 mg daily) may be considered with isoniazid, rifampin and pyrazinamide in multidrug-resistant strains. Antimicrobial therapy typically lasts 12–18 months, but may extend up to two years and should be tailored to the presence/absence of drug-resistant mycobacterium⁵. Pyridoxine (50 mg daily) is typically added to prevent the neuropathy associated with isoniazid. Corticosteroids may be used to reduce inflammation and are recommended in cases of hydrocephalus, spinal block or impending herniation. Rifampin, streptomycin and ethambutol penetrate the CSF better in the presence of meningeal inflammation, whereas isoniazid and pyrazinamide are unaffected. Mortality may be reduced with dexamethasone treatment, but morbidity appears unaffected⁶. Large tuberculomas exerting significant mass effect or spinal osteomyelitis/granulomas resulting in cord compression may require surgical intervention. In the immunocompetent population mortality is about 10% and is greatest in children and the elderly. In the HIV-infected population mortality is higher, at 20%. Residual neurological deficits are seen in a quarter to one third of patients⁵.

BORRELIA BURGDORFERI: LYME DISEASE

In the USA, Lyme disease is contracted from *Ixodes* ticks harbouring the spirochete *Borrelia burgdorferi*. *Borrelia garinii* and *Borrelia afzelii* account for the overwhelming majority of organisms isolated in Europe in cases of neuroborreliosis. Lyme neuroborreliosis is felt to occur in Asia and has been documented in Russia. Currently, there is no evidence of the disease in South America or Africa⁸. The majority of cases in the USA occur in northeastern, mid-Atlantic and north-central states. The number of cases reported to the Centers for Disease Control (CDC) in Atlanta, Georgia has climbed steadily since it became a reportable disease in 1991⁹. In 1992 approximately 10 000 cases were reported, while 2007 produced more than 27 000 cases with an incidence of 9.1/100 000. In the 10 states reporting the most cases, the incidence was significantly higher at 34.7/100 000¹⁰. Mandatory reporting does not exist in Europe, so obtaining accurate epidemiological data is more difficult. The eastern central region of Europe probably has the highest incidence of neuroborreliosis⁸.

Early manifestations of *Borrelia burgdorferi* infection include an expanding 'bullseye' rash, also known as erythema migrans, as well as headache, fever, myalgia or arthralgia, and fatigue¹¹. CDC review of cases from 2003 to 2005 demonstrated that erythema migrans was present historically in about 70% of cases⁹, while other sources

cite 90% of cases with rash, about 40% of which have central clearing¹². The rash typically appears within 30 days of *Ixodes* tick exposure. In the European form, rash is much less common. Other early presentations include facial palsy, radiculopathy, meningitis/encephalitis and heart block. European Lyme neuroborreliosis most commonly presents with a painful radiculitis (86%), which is called Bannwarth's syndrome⁸. Onset of symptoms in the USA is typically during the months of June, July or August, and less than 8% of cases occurred from December to March⁹. Rickettsial infections, including Rocky Mountain spotted fever, can also present with acute encephalitis and patients may have cranial neuropathies, focal neurological signs and seizures.

Patients with untreated *Borrelia burgdorferi* infections often develop a subacute to chronic disease with musculoskeletal, cardiovascular or neurological symptoms. Arthritis is typically oligoarticular and most commonly involves the knee joint (60%). Cardiovascular involvement occurs in about 8% of patients and is typically a pericarditis or myocarditis producing conduction abnormalities⁵. Chronic skin manifestations are more common in European Lyme neuroborreliosis and take the form of acrodermatitis chronica atrophicans and lymphocytoma. Neurologic symptoms and signs develop in about 15% of patients and include cranial neuropathy, painful radiculopathy, peripheral neuropathy and meningoencephalitis. The most common cranial nerve affected in Lyme neuroborreliosis is the facial nerve, causing a 'Bell's palsy'. Between 25% and 50% of patients developing meningitis will have multiple radiculopathies or peripheral nerve lesions. The peripheral neuropathy is typically axonal and not severe⁸. Myelitis, cerebellar ataxia, seizures and chorea are rare⁵.

Manifestations of chronic infection may overlap with its subacute features and include fatigue, dermatitis, arthritis and neuropsychiatric symptoms such as depression and cognitive dysfunction. Patients with chronic Lyme disease may report poor concentration and attention, irritability and memory complaints. Other considerations in the differential diagnosis typically include fibromyalgia and chronic fatigue syndrome. Importantly, symptoms and signs suggestive of early disseminated disease should have been present at an earlier point¹³. Other reported psychiatric symptoms include mania, delirium, dementia, psychosis, panic attacks, personality change, obsessions/compulsions and catatonia^{14,15}. There is no clear evidence that Lyme disease causes the majority of these reported symptoms.

Cerebrospinal fluid examination in patients with Lyme disease typically shows a mild lymphocytic pleocytosis with a mildly elevated protein and normal glucose. In patients with a history of tick exposure, erythema migrans and suggestive symptoms and signs, the enzyme linked immunosorbent assay (ELISA) is a helpful screening test. A positive test with a rise in IgM occurs in about 90% of patients who have acute and chronic serum samples tested⁵. The presence of elevated IgG without IgM suggests a chronic exposure. A positive ELISA test must be confirmed with Western blot due to the possibility of false positive screening tests. In Europe where multiple strains cause neuroborreliosis, an antibody index comparing CSF and serum antibody levels is typically used for diagnosis⁸. CSF culture has a yield of about 5% and is not useful, while CSF PCR is positive in about 30–40% of cases, usually early in the disease. CT and MRI are usually most helpful in ruling out other neurological diseases, but may rarely demonstrate multifocal periventricular white matter lesions in advanced cases⁵. These lesions are not specific for Lyme disease and are seen in several other neurological diseases, including demyelinating disease, migraine and cerebrovascular disease.

Treatment of acute disease is typically with oral doxycycline (100–200 mg bid) or amoxicillin (500 mg tid) for 2–4 weeks. Options for neuroborreliosis include intravenous ceftriaxone (2 g daily) for 2–4 weeks, high-dose penicillin (20 million units daily) for 2–4 weeks or tetracycline (500 mg qid) for 30 days¹⁶. A recent European trial demonstrated similar efficacy when comparing two weeks of therapy with intravenous ceftriaxone 2 g daily versus oral doxycycline 200 mg daily¹⁷. Following treatment, patients may report continued fatigue, difficulty concentrating and memory difficulty. This is the so-called ‘post-Lyme syndrome.’ These patients have often been given extended courses of treatment with oral or intravenous antibiotics in an attempt to clear their ‘chronic infection’. Typically, there are alternative explanations for their symptoms, and there is a little data to support prolonged antimicrobial treatment in individuals who have received adequate treatment^{8,16,18}.

TREPONEMA PALLIDUM: NEUROSYPHILIS

Close to 37 000 cases of syphilis were reported in the continental United States in 2006 and the majority occurred in the southeastern region. Late and latent syphilis accounted for over 17 000 of the total cases¹⁹. During that same year, it was noted that 64% of cases occurred in men who have sex with men. Cases occur predominantly in young adults, and there has been a steady increase in syphilis cases in patients with HIV. Syphilitic chancres increase the risk of acquiring HIV when exposed to the virus between two and five times²⁰.

Neurosyphilis may occur at any point after exposure to *Treponema pallidum* and is most commonly an asymptomatic meningitis. The meningitis occurs in about 25% of syphilis cases and may remain asymptomatic for years before becoming symptomatic or regressing. Early nervous system involvement with *Treponema pallidum* typically affects the meninges, blood vessels and cranial nerves. Late CNS infection typically involves the parenchyma of the brain and spinal cord⁵. The classical late presentations of ‘tabes dorsalis’ and ‘general paresis of the insane’ (dementia paralytica) have become exceptionally rare following the widespread availability and general use of antibiotics^{21,22}. General paresis is a progressive dementia with prominent neuropsychiatric features, including psychosis. Tabes dorsalis affects the dorsal columns of the spinal cord and sensory nerve roots and manifests with sensory ataxia, urinary incontinence, lancinating pain and lower extremity hyporeflexia²³. Recent reviews and case series emphasize the atypical presentations of neurosyphilis and its preponderance in the HIV-positive population. The remainder of this discussion focuses on ‘modern neurosyphilis’ in the antibiotic era. The reader is encouraged to refer to Ropper and Brown⁵ for further information on parietic and tabetic neurosyphilis.

Meningovascular neurosyphilis may present with stroke symptoms such as hemiparesis, aphasia, sensory disturbance or visual loss. The symptoms are commonly referable to medium and small branch arteries of the anterior and middle cerebral arteries. Confusion, psychosis, delirium and dementia have been increasingly reported. About 50% (82 of 161) of neurosyphilis cases in a recent South African retrospective review had neuropsychiatric presentations defined as psychosis, delirium or dementia. 15% presented with stroke, 12% with ocular symptoms, with myelopathy, 9% with seizure, about 9% with seizure and 5% with cranial neuropathy or other brainstem symptoms. Overlapping presentations occurred predominantly with seizure, neuropsychiatric features and stroke²¹. Other series from

Europe and the USA have emphasized neuropsychiatric presentations of neurosyphilis, including psychosis, atypical depression and memory loss^{24,25}.

Ocular and otologic infections are often included in discussions of neurosyphilis. Ocular syphilis may involve any eye structure and can occur at any time during the course of infection. Overall, however, ocular involvement tends to occur early and uveitis is the most common clinical diagnosis. Though otologic syphilis with sensorineural hearing loss has traditionally been associated with chronic *Treponema* infection, more recent studies have reported early otologic involvement with sensorineural hearing loss and occasionally tinnitus and vertigo. Treatment of ocular and otologic syphilis is the same as neurosyphilis, though the addition of steroids is recommended by many experts for ocular syphilis²².

CSF examination typically shows a lymphocytic pleocytosis and elevated protein with a normal glucose. An elevated IgG index and oligoclonal bands are often present²³. According to the CDC, the diagnosis of neurosyphilis is confirmed with a reactive CSF Venereal Disease Research Laboratory (VDRL) test and syphilis of any stage. Probable neurosyphilis is defined as syphilis of any stage, a non-reactive VDRL, symptoms and signs consistent with neurosyphilis and no other known cause, and an elevated CSF protein or WBC count without another explanation²⁶. The CSF-VDRL test is very specific but not sensitive and, therefore, may be negative in cases of neurosyphilis. The fluorescent treponemal antibody (FTA-ABS) is a direct treponemal test with very high sensitivity and less specificity. Many experts advocate using the FTA-ABS to essentially exclude the diagnosis of neurosyphilis with a negative test due to its high sensitivity. All patients with syphilis should be tested for HIV²². Neuroimaging may be normal or show meningeal, nerve root or cranial nerve enhancement, cerebral atrophy or stroke.

Traditionally, treatment is with aqueous penicillin G (3–4 million units every 4 hours or 24 million units daily) for 10–14 days. Procaine penicillin (2.4 million units IM daily) with probenecid (500 mg orally qid) is an alternative²⁷. Patients with penicillin allergy may be desensitized, but ceftriaxone (2 g daily) is more convenient and appears effective. Lumbar puncture should be repeated every six months after treatment until a normal CSF profile is demonstrated. The CDC recommends re-treatment if the WBC count has not normalized six months after adequate treatment or other CSF abnormalities persist after two years. Other experts recommend re-treatment with an increase in CSF WBC count or a four-fold rise in the CSF-VDRL titre²².

CRYPTOCOCCOSIS

Cryptococcal infection was once rare, but it is now one of the most common fungal infections of the nervous system due to the HIV epidemic and more widespread availability of organ transplantation. Although it is most prevalent in immunocompromised patients with solid organ transplant or HIV/AIDs, it may also occur in immunocompetent individuals²⁸. In the HIV-positive population, cryptococcal infection typically occurs with a CD4+ count less than 50, and approximately 10% of AIDS patients will develop cryptococcal CNS infection. Worldwide, 80% of patients infected with *Cryptococcus* are HIV positive, and cryptococcal meningitis may be the presenting illness in patients with undiagnosed HIV infection. The highest incidence of cryptococcal meningitis occurs in Africa and Asia where HIV is most common, and 20–30% of

HIV patients in Africa die from cryptococcal meningitis²⁹. In the USA, the incidence is about 4.9/100 000.

Cryptococcosis is usually acquired through the respiratory tract or occasionally through mucus membranes or wounds. Two species cause disease in humans, *Cryptococcus neoformans* and *C. gattii*. The nearly ubiquitous *C. neoformans* is present in soil and is associated with bird nesting sites. *C. gattii* is unique in that it is more geographically limited, typically affects immunocompetent patients, presents more insidiously, and is associated with a delayed response to treatment. *Cryptococcus* can infect any organ, though the central nervous and respiratory systems and skin are common sites of clinical involvement²⁸.

Cryptococcal CNS infection commonly presents as a chronic granulomatous meningitis or meningoencephalitis developing over days to weeks or months. Headache, encephalopathy, dementia, nausea and vomiting, and cranial neuropathy are common⁵. Importantly, headache may be the only symptom and cryptococcal meningitis should be considered in the adult patient without a prior headache history developing a chronic, unremitting headache²⁸. Patients may also have gait difficulty, and case reports have described new-onset psychosis and mania^{30,31}. Fever is documented on presentation in less than 50% of immunocompetent patients. In a recent French prospective study French of 230 patients with cryptococcosis, neurological abnormalities were present in 46% of patients diagnosed with meningoencephalitis at the time of initial evaluation, independent of HIV status; 77% of the patients were HIV positive. Mental status changes (33%), seizures (10%) and cranial neuropathy (15%) were the most common abnormalities³². Another series of 43 adult patients with neoplastic disease (predominantly leukaemia and lymphoma) reported 90% had altered consciousness on presentation, which varied from mild behavioural change to psychosis or coma³³. More rarely, cryptococcomas, consisting of small cortical gelatinous cystic nodules or large predominantly subcortical granulomas, may occur and cause focal neurological symptoms. Due to meningovascular infiltration, strokes may rarely occur⁵.

Lumbar puncture in cryptococcal CNS infection may show an elevated opening pressure, lymphocytic pleocytosis and elevated protein. The CSF glucose level is low in about 75% of cases. However, the glucose and cell count may be normal in AIDS patients. India ink preparation often shows the thickly encapsulated organism and cultures often become positive, but take days to yield results. Microscopy and culture are labour and time intensive and have a sensitivity of 50–80%. Furthermore, large volumes of CSF may need to be analysed and cultured if the burden of the organism is relatively low. A capsular polysaccharide antigen forms the basis of the widely available latex agglutination test. It is a rapid test and has a sensitivity of 93–100% and a specificity of 93–98%, though false positives are well described in the literature²⁸. A titre of >1:8 should be considered a positive test. Finally, enzyme immunoassay tests have been compared to the polysaccharide antigen agglutination test with promising results³⁴. This test is not widely available, however. Neuroimaging is usually normal but may show parenchymal lesions, hydrocephalus, meningeal enhancement, dilated Virchow–Robin spaces and cystic lesions (see Figure 68.1). Abnormal brain imaging generally confers a poorer prognosis.

Treatment is with amphotericin B (0.5–0.7 mg/kg/d), typically with flucytosine (150 mg/kg/d) for 2 weeks, followed by fluconazole for at least 10 weeks. In the AIDS patient, maintenance fluconazole therapy is generally continued for life unless the CD4+ count rises above 100–200 cells/μl for 3–6 months at which time the asymptomatic

patient with sterile spinal fluid may be discontinued. Historically, a lumbar puncture has been performed after the first two weeks of therapy to confirm therapeutic response, although some authorities now forgo the second lumbar puncture if the patient is clinically responding and has a normal neurological examination. If the initial lumbar puncture showed an elevated opening pressure and the patient has symptoms of increased intracranial pressure, a lumbar puncture should be repeated daily until the patient becomes asymptomatic or the pressure normalizes for a minimum of two days. HIV patients with low CD4+ counts who are started on highly active antiretroviral therapy at the time of diagnosis of a cryptococcal CNS infection are at risk for immune reconstitution inflammatory syndrome (IRIS)³⁵. Independent risk factors for treatment failure regardless of HIV status include high serum antigen titres, widespread dissemination at the time of diagnosis, and the absence of flucytosine during the induction phase of treatment. Three-month survival is reduced in patients with an abnormal neurological exam or brain imaging at baseline and haematological malignancy^{32,33}. The three-month mortality rate of CNS cryptococcal infection is at least 20%, and 40% of survivors have lasting neurological impairment.

HERPES SIMPLEX ENCEPHALITIS

Herpes simplex virus type 1 (HSV-1) is the most common sporadic viral encephalitis in the USA and accounts for about 10% of all encephalitis cases. Over 2000 cases occur annually in the USA and the worldwide incidence is estimated at 2–4 cases per million per year³⁶. HSV-2, associated with genital infection, also causes neurological disease, which is most commonly aseptic meningitis and occasionally acute encephalitis. The remainder of the discussion will focus on HSV-1 CNS infection due to its prevalence (HSV-1 accounts for 90% of herpes encephalitis cases)³⁷ and significant morbidity and mortality. Herpes simplex encephalitis (HSE) occurs more commonly in individuals with recurrent HSV infection. It has been hypothesized that propagation of the virus from the trigeminal ganglion, where it lies dormant, along the ophthalmic division of the trigeminal nerve results in its tropism for the orbital frontal lobes, insular cortex and medial temporal lobes³⁸.

HSE usually presents acutely with fever and seizures, behavioural changes, altered mentation, aphasia or other focal neurological deficits. Olfactory hallucinations may occur. Without treatment the patient usually progresses to obtundation and coma³⁹. Although HSE typically has a fulminant course, cases progressing over several weeks to months occur, and merit mention due to the potential diagnosis of psychiatric disease. In a series of 24 adult patients with HSE, 4 (17%) reportedly had atypical presentations, consisting of slowly progressive encephalitis often with a non-focal clinical exam⁴⁰. Patients with several months of memory impairment, confusion, lethargy and progressive headache have been reported in the literature⁴¹; these patients may or may not have focal signs.

Examination of the CSF shows a lymphocytic pleocytosis with normal glucose and elevated protein. The opening pressure may be elevated. Although HSE causes haemorrhagic pathology in the brain, xanthochromia and red blood cells are only occasionally present on CSF examination. HSV PCR, which is sensitive and specific, should be sent. Imaging classically shows temporal lobe hypointensities on CT (see Figure 68.2) and areas of T2 prolongation on MRI. Abnormalities may extend contiguously to the insular cortex and orbitofrontal lobes, as well as into the rostral midbrain. Enhancement usually occurs following administration of contrast (indicating disruption of the blood–brain barrier)⁵. Electroencephalography may

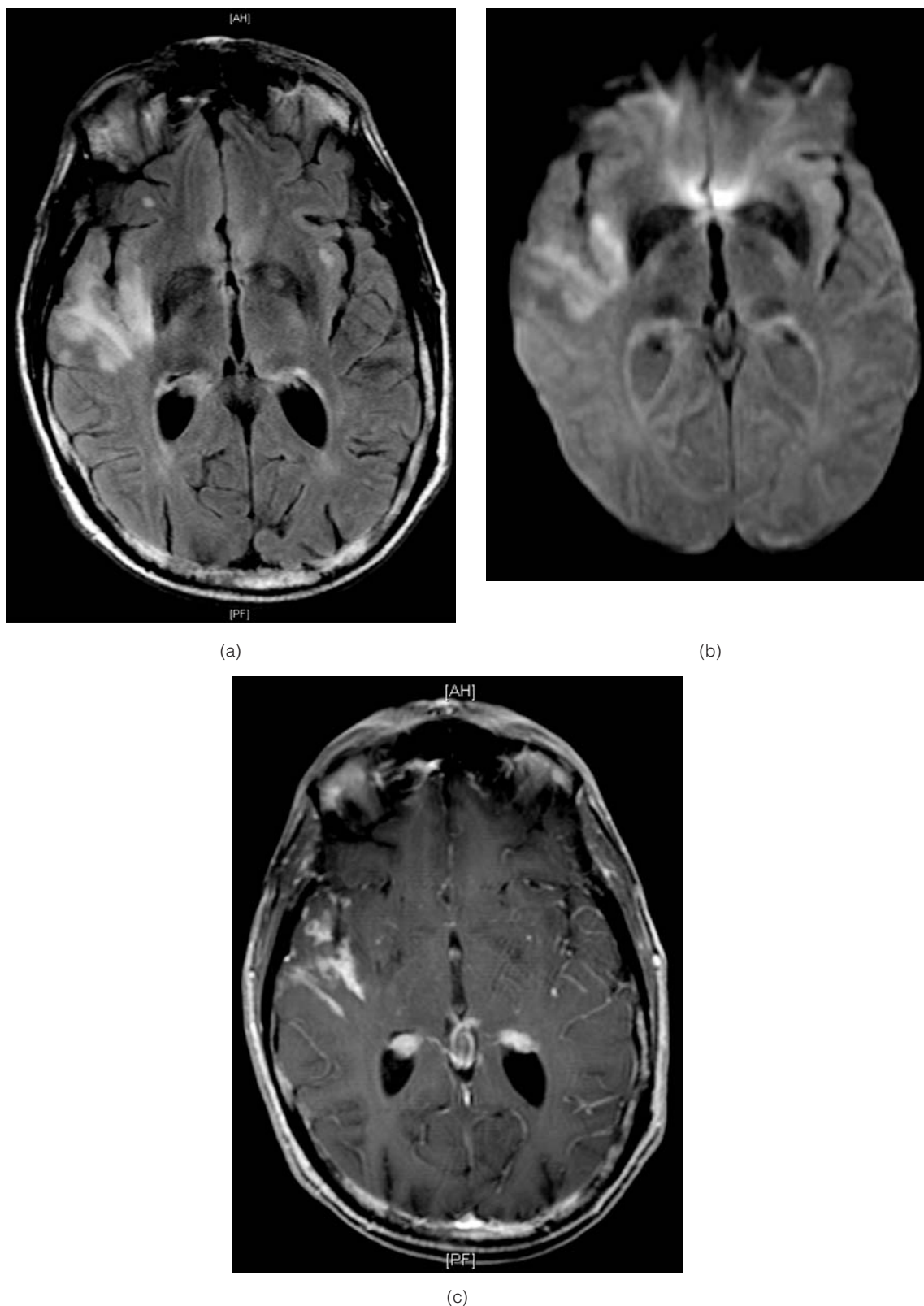


Figure 68.1 A 60-year-old male with hepatic cirrhosis from alcoholism presented with eight months of progressive headache, several months of intermittent left arm numbness and new onset gait difficulty. Neurological exam revealed encephalopathy and gait ataxia. MRI of the brain showed A) prominent T2/FLAIR signal prolongation in the right temporal lobe with B) restricted diffusion. C) Contrast enhancement was present in the right temporal lobe and diffuse leptomeningeal enhancement was also seen. Lumbar puncture showed 83 nucleated cells, glucose <20, 3 red blood cells, protein 584. Opening pressure was normal. Cryptococcal antigen was positive (1:16) in the CSF and serum. HIV testing was negative.

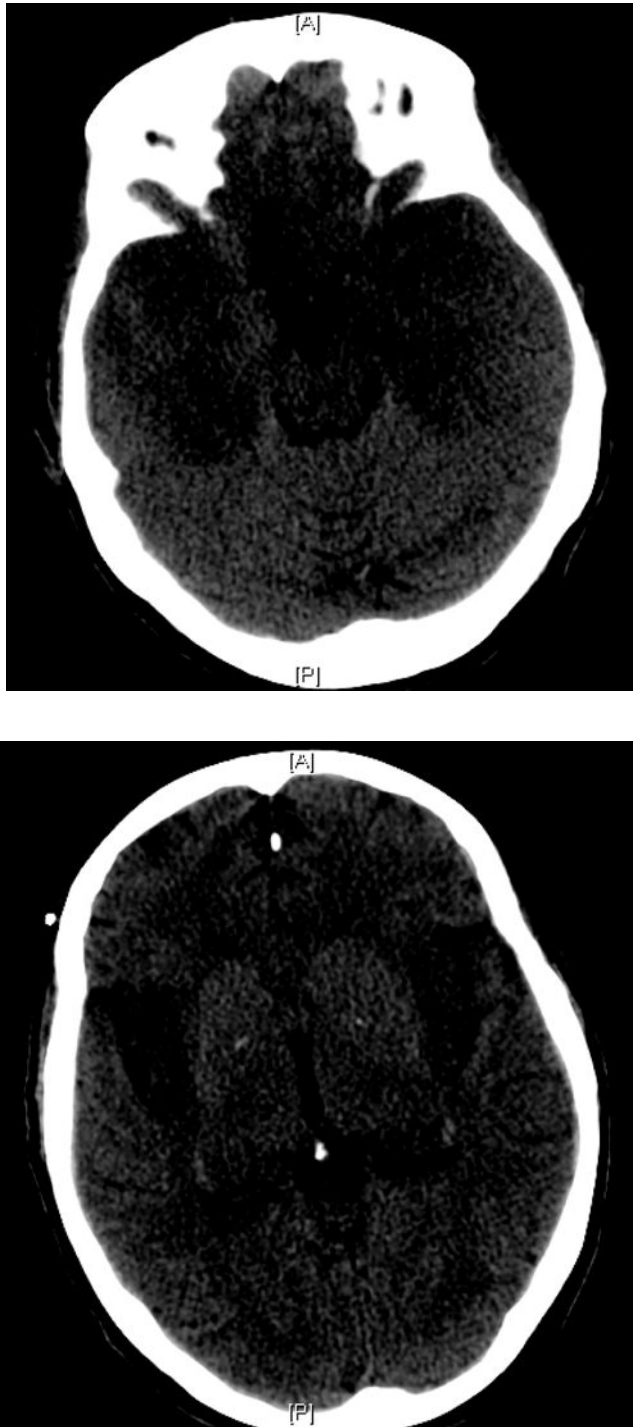


Figure 68.2 A 70-year-old female presented with four days of progressive confusion, lethargy and fatigue. Sodium on presentation was 110, and neurologic exam was non-focal. Non-contrasted head CT on presentation was read as normal. Repeat head CT 10 days after onset of symptoms (shown above) shows bilateral temporal, insular and inferior frontal lobe hypodensities. Lumbar puncture showed 69 nucleated cells (94% lymphocytes), protein 78, and glucose 53. HSV PCR was positive. EEG showed slowing in the theta and delta range with interspersed GPED activity.

show focal temporal slowing or more generalized slowing. These findings often evolve into periodic lateralized epileptiform discharges (PLEDS) at two to three per second intervals or generalized periodic epileptiform discharges (GPEDS)³⁸.

Treatment with acyclovir (30 mg/kg per day divided three times daily) should be started as soon as possible in suspected cases and should not be delayed for PCR results. Treatment is continued for 10–14 days⁵, and some experts emphasize 14 days of treatment to reduce the risk of relapse³⁹. Other management includes medical treatment of seizures, supportive ventilation and possibly corticosteroids to control cerebral oedema. There is scant evidence to support worsening of infection with administration of steroids. The mortality from untreated HSE is 60–70%. Treatment reduces mortality to about 20–30% in some series³⁸. Practically, the patient's age and level of consciousness at the time of treatment initiation strongly predict outcome⁵.

Neuropsychiatric and cognitive sequelae of HSV-1 encephalitis occur in up to 80% of patients³⁸. In one series of 34 patients, the most common long-term effects included memory impairment (69%), behavioural and personality change (45%) and epilepsy (24%). Clinical examination following HSE infection revealed short-term memory loss (70%), anosmia (65%) and aphasia (41%)⁴². The memory impairment following HSE is typically anterograde, resulting from damage to medial temporal structures. Other reported sequelae include visuo-spatial, executive function and retrograde memory deficits, as well as aggression, disinhibition, catatonia and Klüver–Bucy syndrome (behavioural and cognitive deficit, placidity, apathy, hypersexuality, hyperorality and visual/auditory agnosia)³⁸. Although imaging typically reveals evidence of infection in both hemispheres, residual deficits may be relatively lateralized, and right hemispheric infection tends to produce less severe functional impairments. Hokkanen and Launes³⁶ recently published a comprehensive review of the neuropsychological sequelae of acute viral encephalitis. Typical and atypical antipsychotics, antidepressants, benzodiazepines, stimulants and anticonvulsants have been used to manage the behavioural and cognitive sequelae. Treatment, however, remains empirical due to a paucity of data³⁸.

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Magnetic Resonance Imaging and Computed Tomography

Howard Aizenstein and Vijay Venkatraman

University of Pittsburgh School of Medicine, Pittsburgh, USA

COMPUTED TOMOGRAPHY

Computed tomography (CT) is a general term for several radiographic techniques that result in a series of images showing slices of an organ or body region, such as the brain. The CT systems measure the attenuation of X-ray beams passing through target tissue; this is done using a small X-ray device that rotates around the body region of interest in a fixed plane. Various absorption and scattering processes are utilized in CT: coherent scattering, photoelectric absorption and Compton scattering. The X-ray tubes provide incident X-rays yielding a spectrum of X-rays with a transmission of the signals. The signals are sent to a computer that produces the corresponding cross-sectional slice for that plane. The image is composed of a set of individual pixels, which represent the attenuation of the X-ray at the corresponding point. These attenuation values are referred to as the CT number or Hounsfield units. The computer can create sections in axial, coronal and sagittal alignments using an image reconstruction process. The three major paradigms of image reconstruction are (i) simple back-projection, (ii) filtered back-projection, and (iii) iterative reconstruction.

In a single CT scan across one section in a patient, thousands of X-ray transmission measurements are obtained along many different angular projections. From these measurements, utilizing a variety of mathematical paradigms, a matrix of CT numbers can be computed for the cross-sectional plane through the patient and then displayed as a grey-scale image. There are a number of artefacts that affect the performance of CT scanning and the quality of the acquired data. These artefacts lead to streak patterns on the image display or appear in the form of CT number inaccuracies. Some of the artefacts are caused during the X-ray transmission phase (e.g. patient motion, polychromatic effects), X-ray detection and measurement (e.g. detector imbalance, scatter collimation), data acquisition (e.g. slice geometry, profile sampling) and data processing (e.g. algorithm effects). CT scans require the use of a limited amount of radiation, which presents a potential health risk for those undergoing CT scans. The estimated radiation exposure varies by the particular type of CT scan performed. It is estimated that a head CT is associated with 1.5 millisieverts, which is equivalent to the radiation exposure from 75 chest X-rays. This amount of radiation exposure is considered an acceptable risk when the CT is medically indicated. CT studies should follow the radiation recommendation, including the special cases for multiple exposures and overlapping scanning techniques.

With advances in scanning, software and display systems, the quality of CT images improved (i.e. better resolution) and has led to many useful clinical applications, including virtual CT colonoscopy or angiography. Neuroimaging with CT is used for studying various psychiatric populations including schizophrenia and depression, as well as aging and dementia.

CT imaging is used to examine brain structure; it allows for the ready identification of many structures, although it does have limitations. By measuring differences in density, it can distinguish among CSF, blood, bone, grey matter and white matter. CT is particularly useful for demonstrating injuries such as skull fractures (bone abnormalities), subdural haematoma (haemorrhage regions) and different lesions (mass effect). CT is also used to study variation in atrophy or ventricular enlargement. However, CT studies are restricted by location of the structures like the brain stem because of surrounding bone. CT has been used to measure cerebral atrophy and grey matter (secondary loss of neurons) since 1974¹. CT has been widely used in the identification of dementia². Many studies were performed to study age variation in geriatric populations^{3–6}, normal ageing⁷ and the effect of presence of dementia^{8,9}.

With improvement in resolution of CT, it was used to distinguish some pathological processes, which primarily affect white matter (i.e. demyelination)^{10,11}. A large number of CT studies of white-matter diseases in the geriatric population were published^{12–16}. CT measurements of the cerebrospinal fluid (CSF) spaces from patients with geriatric depression, normal control subjects and patients with primary degenerative dementia have been compared and studied also¹⁷.

CT is widely available and well understood, but is nowadays supplemented with magnetic resonance imaging (MRI) to use the advantages of both techniques.

MAGNETIC RESONANCE IMAGING

In 2003, Paul C. Lauterbur and Peter Mansfield were awarded the Nobel Prize in Medicine for their discovery of MRI. MRI revolutionized *in vivo* human brain imaging, allowing for remarkably clear high-resolution images of the brain. MRI is based on the concept of nuclear magnetic resonance (NMR), where the measurement of the signals comes from the nuclei in response to radio waves that have the same frequency as the nuclei themselves^{18,19}. For a comprehensive review, please refer to^{18,19}.

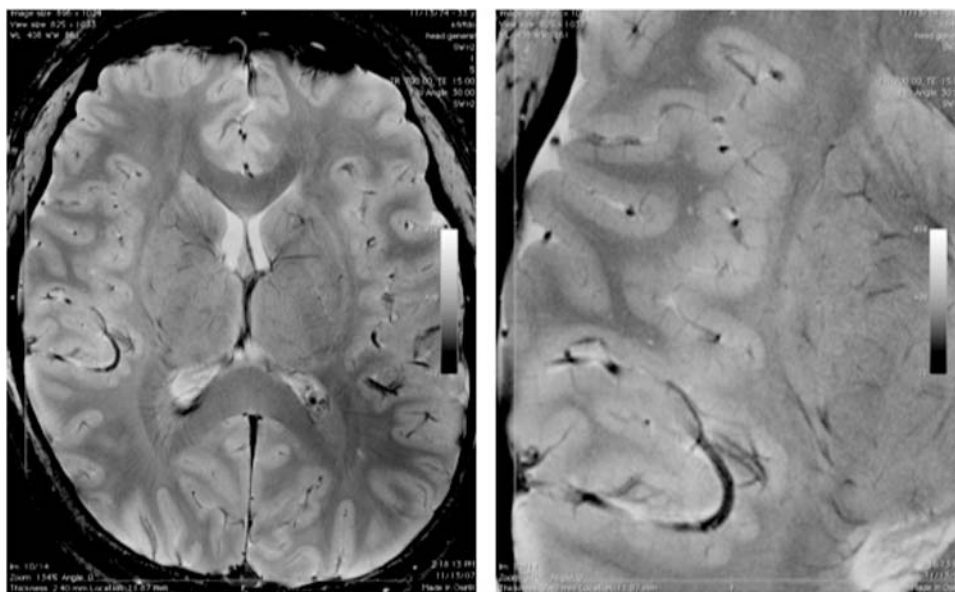


Figure 69.1 SWI image using 7 T Siemens scanner

The relaxation time (T1) is a property of a tissue at a given magnetic field strength. With each excitation pulse, the longitudinal magnetization begins to recover and reduces to steady state after several pulses. The time between repetitions of the excitation pulse is called the repetition time (TR). The repetition time and flip angle are the two major parameters varied to control the T1 weighting of an image. The transverse magnetization decays at the rate of T2 relaxation time. The delay between the creation of the transverse magnetization and the measurement of the resulting echo is called the echo time (TE). The images where signal intensity is largely dependent on T2 differences (or TE values) are called T2-weighted images. The various pulse sequences are designed based on TR, TE and other parameters to obtain the necessary contrast variation in the magnetic resonance image. The magnetic resonance image can have different artefacts, such as motion-induced artefacts, susceptibility, wrap around, edge artefacts (partial volume, chemical shift edge, truncation, relaxation), ghost artefacts, altered signal intensity, stripes and image distortion. The different pulse sequences used in imaging sequences, such as T2*, echo planar imaging used in BOLD fMRI, fluid-attenuated inversion-recovery imaging (FLAIR), diffusion weighted imaging, magnetization transfer imaging and others, are novel variations obtained from optimization of the various parameters.

Difference between 1.5 T, 3 T vs. 7 T Images

Typically the MRI scanner is built around a permanent magnet, which is the most expensive and important component of the scanner^{18,19}. The strength of the main magnet and its precision (homogeneity of the field strength) is important. Magnetic field strength is an important factor in determining image quality. Higher magnetic fields increase signal-to-noise ratio, permitting higher resolution or faster scanning. The higher field strengths have drawbacks such as more costly magnets, higher maintenance costs, increased safety concerns and increases in certain artefacts compared to lower field strengths. The 1.0–1.5 T field strengths are a good option for general medical use. Field strengths up to 3.0 T may be desirable for research

(such as brain imaging) and the latest research studies use 7 T field strengths. Figure 69.1 provides the susceptibility-weighted imaging (SWI) using a 7 T Siemens imaging scanner.

Structural MRI

Structural MRI methods can be used to identify and quantify patterns of changes in volumetric neuroimaging studies. The various structural MRI sequences enable the identification of structural alterations such as (i) volume in grey matter, white matter and cerebrospinal fluid from high resolution T1-weighted images^{20–22}, (ii) white matter hyperintensities (WMH) from FLAIR images^{23,24}, (iii) white matter integrity from diffusion weighted imaging^{25,26}, and (iv) myelination from magnetization transfer imaging²⁷ (Figure 69.2). Advanced neuroimaging sequences such as diffusion spectrum imaging (DSI) and Q-ball imaging are currently been used for studying the white matter tracts²⁸.

Structural MRI is useful for studying the patterns of neuroanatomical changes in geriatric research. Structural MRI is important for studies in normal ageing, late-life depression, dementia, Alzheimer's disease and other cognitive disorders to examine how age-associated changes in neuroanatomy are associated with specific age-related changes, such as the changes in cognition.

Functional MRI

In the 1960s and 1970s a number of investigators showed that not only could MRI be used to visualize neuroanatomy and structural

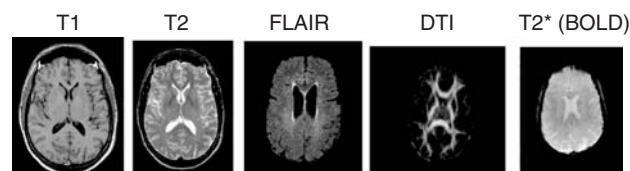


Figure 69.2 T1, T2, FLAIR, DTI and T2* images from 3 T scanner

pathology, but by tuning the MRI contrast appropriately, MRI could be used to visualize the dynamic changes in blood oxygenation across the brain; this was the beginning of functional MRI (fMRI). Over the subsequent years, a number of studies have shown that this blood oxygenation level dependent (BOLD) signal could be used to map brain activity on a variety of cognitive and affective tasks.

Functional MRI has been a major advance for the fields of cognitive and affective neuroscience by allowing investigators to test theories of the underlying neural pathways controlling cognitive and emotional processes. This approach is often referred to as 'human brain mapping'. In addition to studying 'normal' human brain function, fMRI can also be used to characterize the functional activation patterns in patient groups. This area of clinical fMRI research has recently led to a number of new insights into the nature of psychopathology and treatment – including recognition of a dorsal versus ventral processing imbalance in depression²⁹, overlap in response patterns with placebo as with medication³⁰, and paradoxical non-linear activation patterns in mild cognitive impairment³¹, suggesting a compensatory stage prior to the onset of dementia.

The functional circuit involved in a particular task can be identified by contrasting the MRI images acquired while someone is doing the task versus when they are doing a control task. There are two main ways this can be done: (i) blocked design, where the subject performs several minutes of task and then several minutes of control, and the images during these blocks are compared; and (ii) event-related design, where the subject performs discrete events during the scanning session, and the images during discrete events are compared. The task could also be a mixed design of block and event designs. Several studies have examined the statistical advantages between block design and event-related fMRI, and the general view is that for the same amount of time spent scanning (on the same task), the observed effect size is larger for a block design study as compared to an event-related study³².

Perfusion MRI: An Alternative to BOLD

A significant limitation in BOLD fMRI is concern that the BOLD haemodynamic response is inherently relative. That is, the raw BOLD signal does not provide a reliable estimate of regional blood flow in a region. Rather, it is contrast of the BOLD signal on alternating experimental versus control tasks that provides the meaningful signal. In contrast to this limitation, PET imaging with an O15 radioligand is capable of providing quantitative blood flow measures. In MRI, a technique analogous to O15 PET is also available, and is referred to as arterial spin label (ASL) imaging, or perfusion imaging^{33,34}. In perfusion MRI the MRI excitation signal is inverted to provide a 'tagged' signal, which is alternated with an 'untagged' image. Comparing the tagged and untagged images provides a quantitative measure of the perfusion of the region. Full-brain voxel-wise perfusion images acquired can provide a quantitative image of the perfusion across the brain. Investigators have recently used perfusion imaging to demonstrate similar findings as with PET blood flow studies, e.g. decreased parietal-temporal resting perfusion with Alzheimer's disease³⁵. In addition to providing quantitative resting perfusion, ASL has also recently been used for investigating the blood flow changes associated with tasks. For instance, Fernandez-Seara *et al.*³⁶ have used ASL to show medial temporal lobe activity on an encoding task. The two primary methods for perfusion imaging are referred to as continuous arterial spin labelling (CASL) and pulsed arterial spin labelling (PASL). CASL is believed to provide

better signal quality, but generally requires special hardware for providing the continuous tagging pulse.

Methodological Challenges of fMRI in Geriatric Psychiatry

In order to appropriately interpret fMRI results in geriatric psychiatry, it is important to consider whether differences in brain structure may impact the resulting fMRI signal, and similarly it is important to consider whether changes in brain physiology may influence assumptions about the BOLD fMRI signal. These concerns about brain morphometric changes in the elderly and age-related changes in the BOLD signal are the two primary methodological challenges of fMRI in geriatric psychiatry.

The change in brain volume with age and with the diseases of ageing presents a particular challenge for fMRI studies in these populations: how should these structural changes be accounted for when comparing the functional signal? In a standard fMRI analysis plan, the functional signals from all the subjects in a study are lined up with each other (referred to as normalization). If the brains have significantly different shapes and sizes then this brain alignment may bias the results by contributing more CSF (due to the larger sulci and ventricles) of the more atrophic brains as compared to more grey matter from the less atrophic brains. The standard alignment algorithms vary in their ability to account for the variability in brain structure³⁷. Some investigators have addressed this problem by using a larger smoothing kernel in studies of ageing subjects (e.g. 10 mm instead of standard smoothness of 6 mm or 8 mm full-width half-maximum Gaussian). An alternative approach that other investigators have used involves avoiding the registration problems altogether, by focusing on a region-of-interest (ROI)-based analysis³⁸.

SUMMARY

There has been tremendous increase in the use of CT and MRI (functional and structural) in studying the brain. The neuroimaging studies have provided insight into normal ageing and the neuropsychiatric diseases of ageing. In this chapter we reviewed the basis of CT and MRI (structural and functional).

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Functional MRI Studies in Ageing and Early Alzheimer's Disease

Ottavio V. Vitolo^{1,2,5,7} and Reisa A. Sperling^{1,2,3,4,5,6,7}

¹*Memory Disorders Unit, Harvard Medical School, USA*

²*Brigham and Women's Hospital, Harvard Medical School, USA*

³*Alzheimer's Disease Research Center, Harvard Medical School, USA*

⁴*Gerontology Research Unit, Harvard Medical School, USA*

⁵*Massachusetts General Hospital, Harvard Medical School, USA*

⁶*Department of Neurology, Harvard Medical School, USA*

⁷*Psychiatry, Harvard Medical School, USA*

INTRODUCTION

The last few years have seen a rapid upsurge in the number of functional magnetic resonance imaging (fMRI) studies of Alzheimer's disease (AD). The increasing popularity of fMRI is likely due to the tremendous need to find early markers for this devastating illness, prior to the point of irreversible neuronal loss. The clinical course of AD is typically insidious, characterized by episodic memory impairment beginning years prior to the time a clinical diagnosis is established. Evidence from postmortem and antemortem molecular imaging studies of subjects at risk for AD suggests that underlying pathology of AD may begin more than a decade prior to onset of dementia¹. The link between the pathophysiological process of AD and the earliest clinical manifestations remains to be fully elucidated. Animal studies indicate that amyloid-related synaptic dysfunction precedes the onset of neuron loss and may account for early memory deficits^{2,3}; however, autopsy studies suggest that tangle pathology and neuronal loss may correlate better with clinical dementia severity at later stages of the disease^{4,5}.

The lack of reliable diagnostic biomarkers, which can detect AD early in its course, continues to limit our ability to effectively develop and initiate disease-modifying therapies. In this respect, fMRI has the potential to elucidate the pathophysiological process that ultimately leads to AD and could prove to be an invaluable tool for early detection of the disease and to assist in monitoring the effectiveness of new therapies.

This chapter will focus on recent findings from fMRI research on ageing and early AD, focusing on potential applications of fMRI for the diagnosis of AD and development of therapeutic agents.

POTENTIAL APPLICATIONS OF FUNCTIONAL IMAGING

Functional imaging techniques, in particular those that study brain activity during cognitive processes, have the potential to detect

the earliest impact of pathophysiological changes on the functional integrity of neural networks. Although volumetric magnetic resonance imaging is presumably quite sensitive to loss of neurons and surrounding neuropil, it may not be able to detect changes until there is significant neuronal loss in specific medial temporal lobe (MTL) structures⁶, at a point too late to intervene with disease-modifying therapies. Functional imaging techniques that observe the brain at rest, such as fludeoxyglucose (¹⁸F) (18-fluorodeoxyglucose; FDG) positron emission tomography (PET), perfusion MRI^{7,8} and resting-state fMRI^{9,10}, have shown evidence of regional abnormalities in early AD and may prove valuable in predicting subsequent decline in at-risk subjects. In order to detect brain dysfunction in individuals with very subtle cognitive impairment, and even asymptomatic individuals with early pathology of AD, we may need to employ more sensitive measures that probe the brain during exactly the types of cognitive processes that will become clinically impaired as the disease progresses. Task-related functional MRI may be able to detect alterations in the brain's functional capacity prior to neuronal loss, or even evidence of dysfunction at rest.

PHYSIOLOGICAL BASIS OF fMRI

The fMRI technique most widely used to investigate neural activity is based on imaging of the blood-oxygen-level-dependent (BOLD) contrast¹¹. This depends on the magnetic properties of haemoglobin, which differ depending on whether or not it is bound to oxygen. The ratio between oxygenated haemoglobin, which is a diamagnetic substance with zero magnetic moment, and deoxyhaemoglobin, which instead is a natural paramagnetic substance, in capillary beds and larger blood vessels subserving neural tissue creates an image contrast detected by the MRI machine. Neuronal activity affects the ratio by increasing oxygen consumption and blood supply. Since the blood supply exceeds the oxygen demand, this results in an increase of the amount of deoxyhaemoglobin and therefore of the MR signal¹². Thus, BOLD fMRI is an indirect measure of neuronal activity but

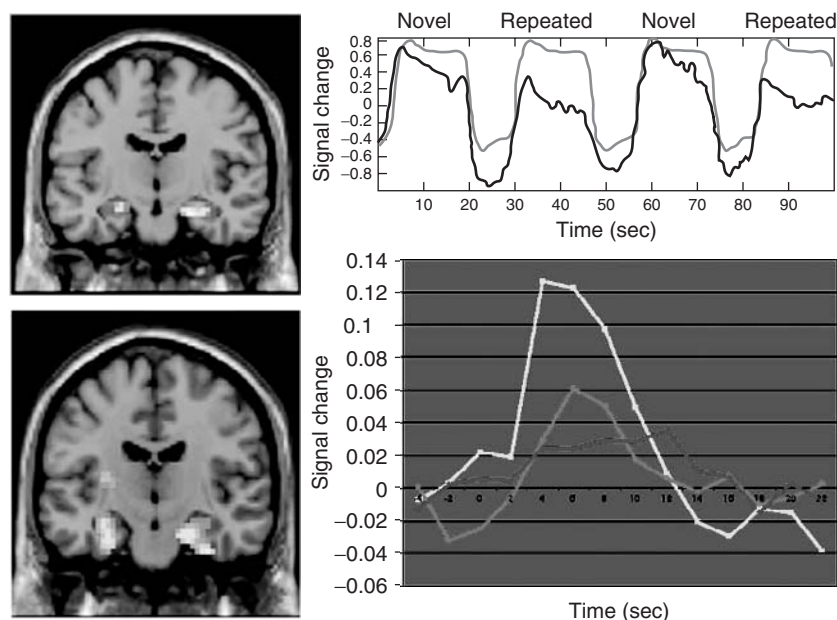


Figure 70.1 Functional MRI data during a face-name encoding paradigm. The top left figure demonstrates a statistical parametric map (SPM) of the hippocampus showing greater MR signal response to novel (N) face-name pairs compared to repeated (R) face-name pairs in a block-design fMRI paradigm. The top right shows a representative time course of the MR signal in the block-design paradigm, with marked increase in signal during novel blocks compared to blocks of visual fixation (+) or repeated blocks. The bottom left demonstrates significant hippocampal activation for an event-related face-name paradigm comparing successful vs. failed encoding. The bottom right graph shows the MR signal change in the right hippocampus for those face-name pairs correctly remembered with high confidence (yellow line), low confidence (pink line) or forgotten (blue line). *A full colour version of this figure appears in the colour plate section*

can provide an important 'window' into the neural underpinnings of complex cognitive processes.

Typically BOLD fMRI is almost always reported as a 'relative measure', comparing the MR signal during one task (e.g. memory encoding) to a control task (e.g. viewing familiar stimulus) or a 'baseline condition' (e.g. visual fixation). Stimuli of each cognitive condition can be either grouped together in blocks lasting 20–40 s, as in a 'block-design' paradigm (see Figure 70.1), or can be interspersed with single stimuli of different conditions as in 'event-related' paradigms. The peak haemodynamic response is typically observed 4–6 s after the stimulus onset. Comparisons between conditions are performed using statistical packages that analyse the raw data of each voxel according to a general linear model (Statistical Parametric Mapping (SPM) and Brain Voyager are some commonly used analysis toolboxes). This type of analysis considers all the variables that can affect signal within each voxel and ultimately translates in either increased BOLD signal, referred to as 'fMRI activation', or decreased BOLD signal, referred to as 'fMRI deactivation' in one condition compared to another. Deactivations or negative BOLD responses have been shown to reflect task-related decreases in neuronal activity below levels detected during spontaneous activity¹³, but it remains unclear whether this phenomenon is due to specific inhibitory influences.

At the present there is no way to determine an absolute measure of fMRI signal at 'baseline', and even resting fMRI scans investigate the correlations between regional MR signal over time to measure resting activity. Arterial spin labelling (ASL) perfusion fMRI techniques may provide a more robust baseline measurement of perfusion, but most task-related fMRI studies utilizing ASL techniques still rely on the 'subtraction' of MR signal in one condition versus another.

Intrinsic or resting connectivity studies examine the inter-regional correlations in the MR signal time course¹⁴.

In the future, information from multiple imaging modalities, particularly perfusion MR, FDG-PET, and task-related BOLD fMRI, may be useful in determining whether the observed functional changes in patient populations relate primarily to alterations in 'baseline' function vs. the neural requirements of the cognitive task, or perhaps to a combination of both factors.

A few studies have demonstrated fMRI alterations in sensorimotor areas in both cognitively normal older and AD patients^{15–17}. These findings have invited caution in the interpretation of fMRI study results in ageing and AD, and raised concerns that changes in BOLD response could be due to a global decoupling of the haemodynamic response related to ageing and pathological processes of the vascular system.

Multiple studies have now demonstrated that the fMRI alterations in subjects with mild and moderate AD reflect regional changes specific to the memory task and that the BOLD response in unaffected brain regions is quite similar in magnitude and extent to that seen in age-matched normal older control subjects^{18,19}.

NEUROIMAGING IN NORMAL AGEING

In recent years, fMRI studies have provided important insights into the neural underpinnings of the cognitive changes associated with ageing. Neuroimaging studies of non-demented older subjects compared to normal young adults have demonstrated group differences in the activation of brain regions responsible for the cognitive task in study. These findings have led to the formulation of the functional compensation theory and the dedifferentiation

theory to explain the observed changes. The first theory postulates that decreased activation of brain regions in older compared to younger adults may represent less efficient processing. Instead, increased activity reflects compensatory mechanisms recruited to maintain efficient performance. Both PET and fMRI studies of memory performance have found loss of hemispheric asymmetry activation in older adults who have performances similar to those of young adults. Cabeza renamed this phenomenon 'hemispheric asymmetry reduction in older adults' (HAROLD). In one fMRI study of a word recognition task controlled for performance²⁰, older participants showed increased activation of bilateral regions. In addition to increased bilateral activation to maintain performance, additional evidence points to age-related increased activation of the prefrontal cortex (PFC) associated with successful performance. This mechanism has been called 'posterior–anterior shift in ageing' (PASA)²¹ and is thought to compensate for deficient perceptual processing in the sensory areas seen in ageing. According to the dedifferentiation theory, the more widespread engagement of brain areas, not found to be involved in the execution of the same task in younger individuals, represents loss of efficiency of networks activated in younger subjects. To further support this view, some authors propose that various cognitive processes possess a higher degree of interdependence in older individuals²². These changes can be thought of as lying on a continuum that moves from lack of differentiation in childhood, to differentiation in adulthood, then to dedifferentiation in older adults.

The adaptive nature of the changes described above is at the core of what Park and Reuter-Lorenz have termed the 'scaffolding theory of ageing and cognition' (STAC). They define scaffolding as 'a process that results in changes of brain function through strengthening of existing connections, formation of new connections, and disuse of connections that have become weak or faulty'. In their view, both HAROLD and PASA can be conceptualized as part of the same compensatory process that reallocates tasks to preserved circuitries unaffected by ageing and possibly pathology to meet the task demands²³.

NEURAL NETWORKS SUPPORTING MEMORY FUNCTION

The use of fMRI can be extended to investigate the brain networks involved in memory formation and how they are affected in AD. In particular, those studies using a 'subsequent memory' paradigm have demonstrated that greater fMRI activity in the MTL, as well as the left inferior prefrontal cortex, during encoding is associated with the likelihood of subsequent successful retrieval of the information^{24–28}. This is further supported by the observation that compounds with known amnesic effects, such as benzodiazepines and anticholinergics, induce decreased activation in the hippocampus and prefrontal regions^{29,30}.

Our own fMRI work has focused primarily on associative memory processes and, in particular, face-name associations. One primary role of the hippocampal formation in episodic encoding is to form new associations between previously unrelated items of information^{31,32}. Learning the relationship between a name and a face is a particularly difficult cross-modal, non-contextual, paired associate memory task, and difficulty remembering proper names is the most common memory complaint of older individuals visiting memory clinics^{33,34}. Tasks that tap into this cognitive process may be particularly useful in detecting the earliest memory impairment in AD^{1,35,36}. Several fMRI

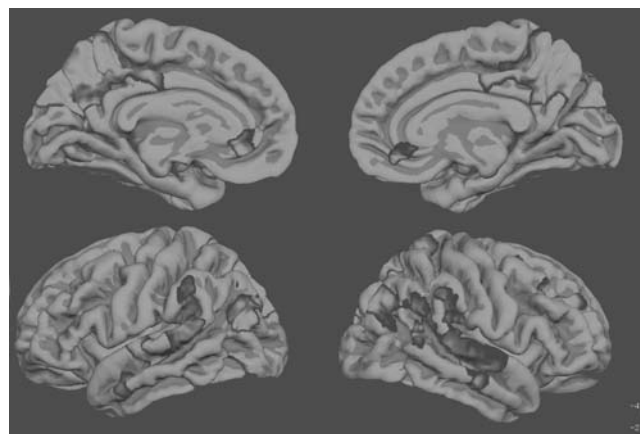


Figure 70.2 The default network, a set of regions that demonstrate higher fMRI activity during rest compared to challenging cognitive tasks. In this group fMRI data map, regions in blue demonstrate greater MR signal during rest (visual fixation) compared to novel face-name encoding. *A full colour version of this figure appears in the colour plate section*

studies, including our own in young subjects using a face-name associative encoding task^{27,29,37} show that associative memory paradigms produce robust activation of the anterior hippocampal formation^{38–40}.

While activation in the anterior hippocampal formation is required for successful memory formation, a similar task-induced decrease in MR signal (i.e. deactivation), particularly in medial and lateral parietal regions, is also associated with successful encoding^{41,42}. These lateral and medial parietal regions, including the precuneus and posterior cingulate, are central components of the 'default-mode network' (see Figure 70.2), characterized by Raichle and colleagues in a series of both PET and fMRI studies^{43,44}. These regions typically exhibit increased activity at rest and decreased activity during externally focused task performance⁴⁴. These parietal regions also appear to have significant connectivity with the hippocampus in resting-state network analyses^{14,45}, and overlap with a 'retrosplenial memory system' that typically activates during memory retrieval tasks^{46,47}. Our own work in cognitively normal young and older adults suggests that the MTL system and the default-network system can be conceptualized as the 'yin–yang' of a distributed memory network. Successful encoding appears to require coordinated activity between these components, such that the lateral and medial parietal regions need to deactivate, while the MTL regions are activated^{42,48} (Figure 70.3).

fMRI STUDIES IN PATIENTS WITH CLINICALLY DIAGNOSED ALZHEIMER'S DISEASE

Since episodic memory impairment is an early finding of AD, the majority of fMRI studies to date have focused on episodic memory tasks^{18,19,49–57}. These studies have employed a variety of unfamiliar visual stimuli, including faces^{17,49}, face-name pairs^{19,55}, scenes⁵⁴, line-drawings^{50,57}, geometric shapes⁵¹ and verbal stimuli⁵⁶, and have consistently reported decreased hippocampal and parahippocampal activity in AD patients compared to healthy older controls during the encoding of novel stimuli. In our own studies using the block-design face-name paradigm, we found evidence that AD patients demonstrate significantly less hippocampal activation in the novel vs. repeated comparison than normal older controls^{19,53}. Instead,

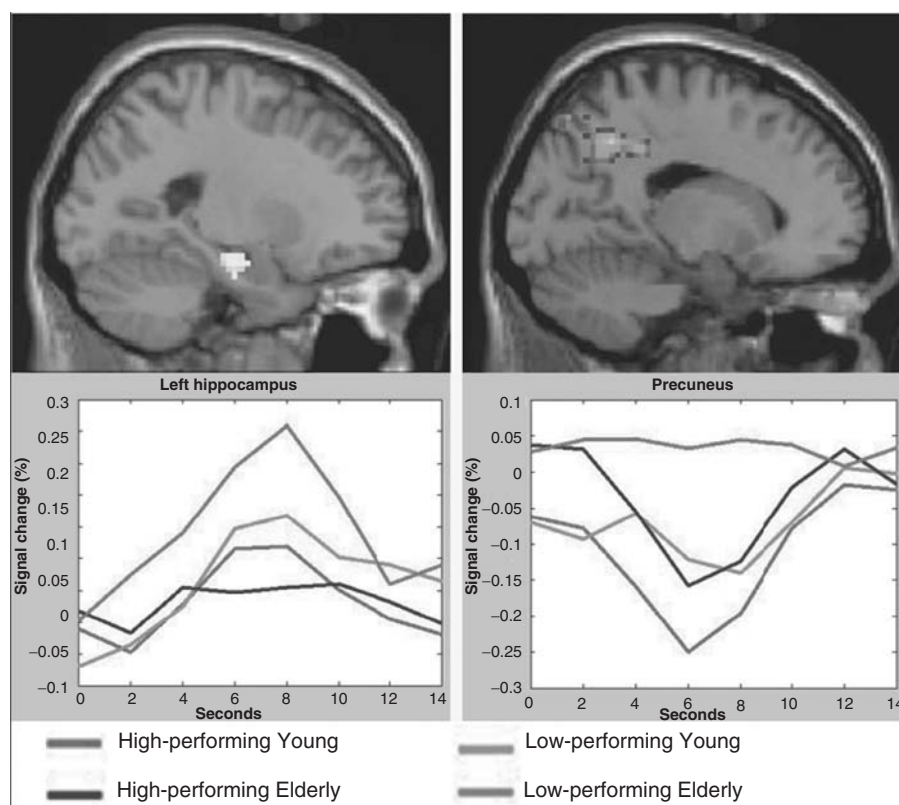


Figure 70.3 Group fMRI data maps (top) with MR signal time courses (bottom) for Young and Elderly controls show hippocampal activation (left) and precuneus deactivation (right) during the successful encoding of face-name pairs. Low-performing Elderly failed to deactivate the precuneus and demonstrated increased hippocampal and prefrontal activation for successful but not failed encoding trials, perhaps as a compensatory response to failure of default network activity. A full colour version of this figure appears in the colour plate section

during repeated stimuli exposure, AD patients continue to demonstrate increased MTL activation to stimuli that are highly familiarized to normal older controls⁵⁸, and the degree of hyperactivation relates to poor post-scan memory performance. These findings indicate that intact MTL response suppression is an integral part of successful memory encoding and consolidation process and that failure of repetition suppression may be a sensitive marker of hippocampal dysfunction early in the course of AD⁵⁹. Interestingly, in addition to MTL hyperactivation, several fMRI studies have also found evidence of increased activation in frontal and parietal regions in AD patients compared to controls, which, as described before, may represent a compensatory process in the setting of hippocampal failure^{19,55,56,60}.

Abnormal patterns of fMRI activity have also been found in the default-mode network regions of AD patients^{17,47,61,62}. Buckner *et al.*⁴⁷ were the first to note that these regions are strikingly similar to those regions that typically demonstrate evidence of fibrillar amyloid deposition binding with Pittsburgh compound B (PiB) in PET studies in AD⁶³, as well as to the pattern of hypometabolism found on FDG-PET studies of AD patients^{64–66} and subjects at-risk for AD^{67–69}; and of hypoperfusion on resting MR perfusion studies in AD^{7,8}. More recently, we have also noted that the pattern of intrinsic connectivity, or ‘hubs’ also overlaps the pattern of amyloid deposition⁷⁰, supporting the hypothesis that amyloid-beta deposition is dependent on neuronal activity⁷¹.

The alterations in hippocampal activation and parietal deactivation over the course of mild cognitive impairment (MCI) and AD appear to be strongly correlated⁷². Similarly, resting-state fMRI data has

demonstrated alterations in parietal and hippocampal connectivity in MCI and AD⁹. Thus, converging evidence suggests that a distributed memory network is disrupted by the pathophysiological process of AD, which includes both medial temporal lobe systems and medial and lateral parietal regions involved in default-mode activity. Future studies to probe alterations in connectivity between these systems, which combine fMRI with other techniques such as diffusion tensor imaging, may prove particularly valuable in elucidating the early functional alterations in AD⁷³. Of particular interest is a recent study by Seeley *et al.*⁷⁴, combining functional and structural network mapping in patients with AD and other neurodegenerative disorders. This study evidences how each neurodegenerative disorder affects a specific intrinsic connectivity network. The regions showing the greatest atrophy and functional connectivity disruption in AD corresponded to the ‘default-mode network’ involved in episodic memory, thus further confirming the previous findings of the fMRI studies described above.

fMRI ALTERATIONS IN MEDIAL TEMPORAL LOBE ACTIVITY IN MILD COGNITIVE IMPAIRMENT

We began this chapter by describing the realm of possibilities available through the use of fMRI as a diagnostic tool for early diagnosis of AD and for establishing the effectiveness of disease-modifying treatments. Unfortunately, the use of fMRI to characterize the cognitive changes of mild cognitive impairment is still in its infancy. This is due to several limitations including: (i) the heterogeneity of MCI

as a diagnostic category, and (ii) the lack of standardized criteria until very recently developed and implemented in large-scale clinical trials and imaging studies⁷⁵. Although we conceptualize MCI as a transitional state between normal ageing and mild AD⁷⁶, in reality MCI includes a diverse group of subjects, some of whom will never develop clinical AD. Most studies suggest that 15–18% of individuals with MCI convert to clinical AD within one year of follow-up. Interestingly, both autopsy and amyloid imaging studies have not demonstrated evidence of AD pathology in a large proportion of MCI patients, suggesting that the mechanisms for cognitive impairment in those who do not convert to AD may be different^{77,78}.

It is not surprising, then, that the few fMRI studies in MCI which have been published to date have shown heterogeneous findings, with some studies reporting hyperactivation and others hypoactivation of MTL. In part this apparent discrepancy could be ascribed to the broad definition of MCI, the wide range of cognitive impairment allowed in these studies and the type of cognitive tasks employed. In addition, we hypothesize that the MCI subjects' ability to perform the specific cognitive tasks has contributed to the variability in the published literature.

Studies Showing MTL Hypoactivation

Several studies^{18,49,62,79} have reported hypoactivation in the MTL of MCI subjects similar to that seen in AD subjects during novel pictures encoding¹⁸, face-encoding paradigm⁴⁹ and forced-choice recognition (retrieval) condition⁶². In addition, the study by Small *et al.* also found a group of impaired subjects with entorhinal and hippocampal activation similar to controls, and decreased activation in the subiculum. In the study by Petrella *et al.*⁶², hypoactivation disappeared when memory performance was included as a covariate in the analysis. One of our own studies also found evidence of decreased MTL activation during face-name encoding in subjects who were thought to be at late stages of MCI with significant functional impairment as assessed by a high Clinical Dementia Rating Sum of Box score (CDR-SB)^{72,80}. Other examples of hypoactivation findings include two studies by Johnson *et al.*^{59,79}. In the first one, using a paradigm involving face repetition, MCI patients failed to show the same slope of decreasing hippocampal activation with stimulus repetition seen in control subjects, suggesting disruption of the habituating response to familiar stimuli in MCI⁵⁹. The second study instead found right hippocampal hypoactivation in MCI patients compared to controls during a recognition paradigm for novel compared to previously learned items⁷⁹.

Studies Showing MTL Hyperactivation

In contrast, several studies have reported increased MTL activation in MCI subjects^{53,57,81–83}. Using a visual object encoding paradigm, Hämäläinen *et al.* found greater activation in the caudal hippocampal formation, parahippocampal gyrus and fusiform cortex. Based on MMSE (mini-mental state examination) and neuropsychological data, this group had intermediate impairment between AD and mild MCI. Our own group has showed evidence of increased MTL activation in MCI subjects, using an associative face-name encoding paradigm. One study compared subjects across a range of clinical impairment assessed with CDR-SB and controls, using a scene encoding fMRI paradigm⁸³. The results indicated a positive correlation between the degree of clinical impairment and the extent of activation in the posterior hippocampus and parahippocampal regions, such that subjects

with more impairment had a greater extent of MTL activation. A multivariate analysis showed that increasing impairment (CDR-SB) was related to older age, *decreased* volume of the left hippocampus, and *increased* extent of activation in the right parahippocampal gyrus. Greater MTL activation and larger MTL volume correlated with better performance on the post-scan recognition memory test. Importantly, two years later, those subjects with greater MTL activation were more likely to demonstrate clinical decline. We recently published a longer follow-up study, which further suggested that greater hippocampal activation at baseline predicted faster rate of clinical decline up to four years later⁸⁴. The phenomenon of hippocampal hyperactivation in MCI subjects compared to controls was further confirmed by one of our studies which used the face-name encoding paradigm to compare MTL activation in subjects with very mild MCI (vMCI), AD and controls⁵³. Compared with controls, the vMCI subjects showed a greater extent of hippocampal activation, and only minimal atrophy of the hippocampus. These very mild MCI subjects also performed in the same range as controls on post-scan memory test. The AD patients had smaller MTL volumes, decreased activation in these regions, and performed below controls on the post-scan memory test. Post-scan memory task performance of each group correlated with extent of activation in the hippocampus. Another one of our studies confirmed evidence of greater activation in the vMCI subjects compared to controls, particularly in the MTL (Figure 70.4) using the same face-name paradigm. A subset of subjects from the first study was analysed, applying independent component analyses to explore the alterations in larger memory networks in older controls, two groups of MCI subjects, one on the milder end and one on the more impaired end, and a group of mild AD patients⁷². In line with the previous findings, the significantly impaired MCI (sMCI) group showed significantly decreased activation down to levels similar to those found in AD. The MTL hypoactivation paralleled changes in medial and lateral parietal regions of the default network so that performance on the post-scan memory task was directly related to activation in the MTL and deactivation in the default network.

Further confirmation of the validity of the finding of MTL hyperactivation in MCI comes from fMRI studies that have applied an event-related design. This type of design allows the division of stimuli on the basis of successful vs. failed memory processes and can better control for the effects of memory performance. In one study, Kircher *et al.*⁸² found that while performing similarly to controls, MCI subjects activated the left hippocampus and surrounding cortical regions to a greater degree than controls. This result was echoed by the evidence from an event-related verbal memory retrieval task, in which Heun *et al.* also found evidence of increased activation in MCI subjects compared to normal older controls when specifically examining successful retrieval trials⁸⁵.

How to Reconcile Hyperactivation and Hypoactivation?

Despite variability related to demographic, clinical and neuropsychological data, there is evidence that less-impaired MCI subjects, who perform better on the fMRI memory tasks, show greater MTL activation, whereas subjects who have more cognitive impairment perform worse and display less MTL activation. Thus, these differences may lie on a continuum, with MTL hyperactivation at one end happening early in the course of MCI, representing a compensatory mechanism to counteract the network dysfunction early in its course and to maintain an efficient memory performance. On the other hand, subjects with more severe MCI, whose pathology

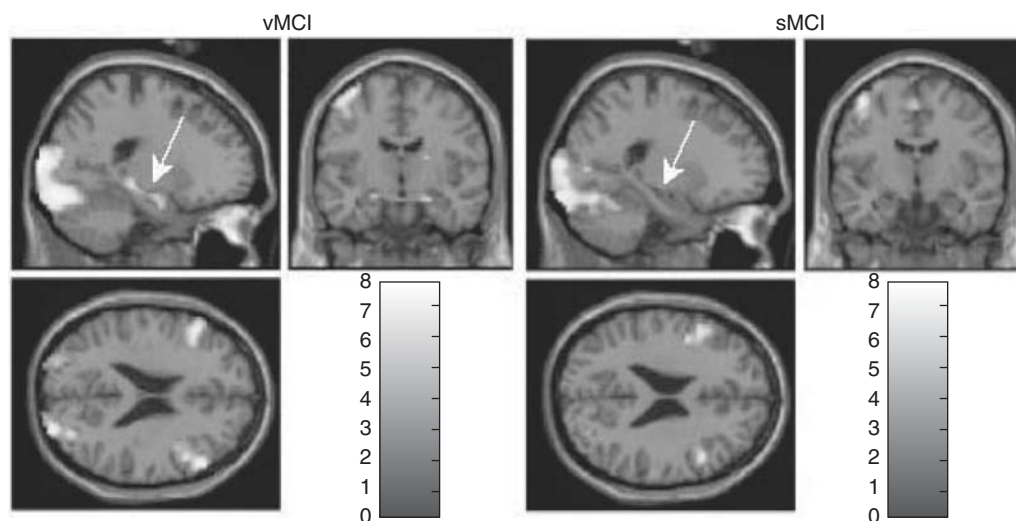


Figure 70.4 Group fMRI data from 15 very mildly impaired MCI (vMCI) and 12 significantly impaired MCI (sMCI) subjects on a face-name encoding task. The vMCI subjects showed evidence of hippocampal ‘hyperactivation’ compared to controls. The sMCI subjects showed significantly decreased hippocampal activation at levels similar to those seen in mild AD patients. *A full colour version of this figure appears in the colour plate section*

is closer to that found in AD, fail to perform well on the memory task and have MTL hypoactivation. This may represent an inability to compensate for the overwhelming pathological changes that have irreparably damaged the memory network with extensive synaptic and neuronal loss. We can assimilate the course of these changes to an ‘inverse U-shaped curve’ which goes progressively from normal to hyper to hypoactivation, paralleling changes in behavioural and neuropsychological performance.

PHARMACOLOGICAL fMRI IN MCI AND AD

A relatively new but promising area of application for fMRI is that of clinical trials of pharmacological agents. fMRI may provide a faster and more sensitive approach to assess efficacy of new therapies without the need to await for the completion of large and long trials. As of today, there have been few published studies that use fMRI to assess pharmacological effects of the available cholinesterase inhibitors for the treatment of AD, but their number is expected to grow as soon as other ongoing trials are completed.

One of these studies⁸⁶ looked at the effects of donepezil in patients with amnesic MCI compared to matched controls using working memory tasks. The results showed improvement of activation in the frontoparietal regions, which were found to be hypoactive before initiation of treatment. The changes occurred in the presence of preserved hippocampal integrity and were visible after only an average of six weeks of treatment. Another study⁸⁷ investigated the effects of acute rivastigmine treatment in patients with mild AD using fMRI with both a face encoding and a working memory task. The results indicated that rivastigmine increased bilateral activation in the fusiform gyrus during the face encoding task and in the prefrontal cortex in the working memory task. When working memory load was further increased, not only was increased activation seen, but in certain areas there was also decreased activation.

In a following study, Goekoop *et al.*⁸⁸ compared patients with AD to subjects with MCI using a face recognition task before and after a single dose of, or five-day treatment with, the cholinesterase inhibitor

galantamine. Acute exposure to the drug produced strong activation in both groups. In particular, MCI subjects showed increased activation in the posterior cingulate, left inferior parietal and anterior temporal lobe. Prolonged exposure decreased activation in similar posterior cingulate areas and in bilateral prefrontal areas. In AD, acute exposure increased bilateral hippocampal activation, while prolonged treatment led to decreased activation in the same areas. The authors argued that differential response to cholinergic stimulation in MCI and AD could suggest differences in the functional status and integrity of the cholinergic system and provide a useful biomarker to monitor disease progression and treatment response.

More recently, Petrella *et al.*⁸⁹ published the first double-blind placebo-controlled fMRI study of the effect of a cholinesterase inhibitor, donepezil, on brain function in subjects with MCI. The subjects were assessed at baseline and following 12 or 24 weeks of therapy with an event-related delayed-response visual memory task for novel faces. The imaging findings were correlated with ADAS-Cog score, a commonly used clinical outcome measure in trials of therapies for dementia and MCI. The results indicated that donepezil increases activation in the ventrolateral prefrontal cortex, compared with baseline, and in both the bilateral dorsal and ventrolateral prefrontal cortices, compared with the placebo group post-treatment. The authors conclude that donepezil, when administered during a three to six month period to subjects with MCI, may potentially induce brain activation in the left inferior frontal gyrus during memory processing, thus improving performance.

CONCLUSIONS

Functional MRI has begun to establish itself as an important tool to probe the neural underpinnings of cognitive functions in the living brain. Although the use of fMRI in the study of MCI and AD is relatively new, it holds great potential for illuminating the black box between the pathophysiological process of AD and the early clinical symptomatology. A lot of questions remain to be answered, particularly regarding the early phases of MCI and how to identify

subjects who will ultimately develop dementia. This can be done only with a rigorous methodological approach that reduces intergroup variability⁹⁰. Integrating different imaging modalities including volumetric MRI, FDG-PET and PiB-PET with neuropathological analysis, will expand our knowledge of the temporal and spatial course of the pathophysiological changes involving the affected brain networks. Ultimately, fMRI may prove particularly valuable in early 'proof of concept' studies for novel pharmacological approaches to treating AD, predicting long-term response to potential disease-modifying therapies for this devastating illness.

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Magnetic Resonance Spectroscopy

Olusola Ajilore¹, Brent Forester², Matthew R. Woodward² and Anand Kumar¹

¹Department of Psychiatry, University of Illinois-Chicago, IL, USA

²Geriatric Psychiatry Research Program, McLean Hospital, Belmont, MA, USA

BASIC PRINCIPLES OF MAGNETIC RESONANCE SPECTROSCOPY

In vivo magnetic resonance spectroscopy (MRS) is a non-invasive technique that allows for the measurement of brain biochemicals in particular regions of the brain. In magnetic resonance imaging, the image is generated from the signal derived from water hydrogen nuclei. MRS suppresses the water signal to measure metabolites in the tissue fluid. It takes advantage of the chemical shift effect, a property that describes the notion that the same nuclei in different molecules respond differently to a magnetic field. Magnetic field strengths usually range from 1.5 Tesla (T) to 4 T in human studies. The chemical shift is typically measured in parts per million relative to the nuclear frequency and plotted on the horizontal axis of a spectrum with the vertical axis displaying the amplitude or intensity of a peak (Figure 71.1). Each peak represents a metabolite of interest for a given nucleus, with the area under the peak reflecting the concentration of that metabolite in the measured region.

There are several signal detection parameters that determine the shape of a spectrum. One is the voxel size which determines the region of tissue being studied and the concentration of metabolites measured. Another important parameter is relaxation time represented by T1 and T2. T1 is the time necessary for hydrogen nuclei to emit 63% of the energy from the stimulating pulse, while T2 is the time for 63% of the transverse energy pulse to be lost due to dephasing. These parameters affect signal strength since long T1s and short T2s are typically found in intracellular molecules with high molecular weights and thus can lead to weak signals. As a result, MRS is particularly useful for measuring low molecular weight molecules that are highly concentrated. Typical concentrations of metabolites detected by MRS are in the range of 4–10 mM. It is difficult to detect metabolites under 1 mM. These concentrations can be reported in absolute measures or as ratios to creatine concentrations, using creatine as an internal control.

NUCLEAR ISOTOPES USED IN MRS

Phosphorous

³¹P-MRS (Figure 71.2) can be used to measure the following metabolites: adenosine triphosphate (ATP), phosphomonoesters (phosphoryl choline, phosphoryl ethanolamine and glycerophos-

Table 71.1 Summary of metabolites detected using proton MRS

Metabolite	Measure
<i>N</i> -acetylaspartate	Neuronal density and viability, mitochondrial function
Choline and choline-containing metabolites	Neuronal membrane integrity
Myo-inositol	Glial function
Glutamate/glutamine	Excitatory neurotransmitter
GABA	Inhibitory neurotransmitter

phate), phosphodiester (glyceryl phosphoryl ethanolamine, glyceryl phosphoryl serine and glyceryl phosphoryl inositol), phosphocreatine and inorganic phosphate. This is a useful isotope to measure the bioenergetics of neuronal processes.

Proton

Hydrogen or proton MRS is used to probe for the following neurochemicals: choline (Cho), creatine (Cr), *N*-acetylaspartate (NAA), myo-inositol (mI), glutamate/glutamine and gamma amino butyrate (GABA) (Table 71.1). NAA is generally viewed as a marker of neuronal viability and may represent a measure of neuronal volume, number and/or function. However, some evidence suggests that it may more specifically reflect mitochondrial function^{1,2}. The choline signal represents a composite of choline-containing metabolites such as phosphocholine, glycerophosphocholine and phosphatidylcholine. These metabolites are involved in cell membrane integrity. Myo-inositol is seen as a marker of gliosis and is the storage form of the inositol phosphate second messenger system. Glutamate/glutamine and GABA are the most ubiquitous excitatory and inhibitory neurotransmitters, respectively.

Other less commonly used nuclei include carbon, lithium, fluorine and sodium. Often, studies utilizing these nuclei involve measuring the impact of pharmaceutical agents containing these metabolites.

NORMAL AGEING

Several studies have used MRS to study neurochemical changes associated with normal, healthy ageing. Perhaps due to methodological

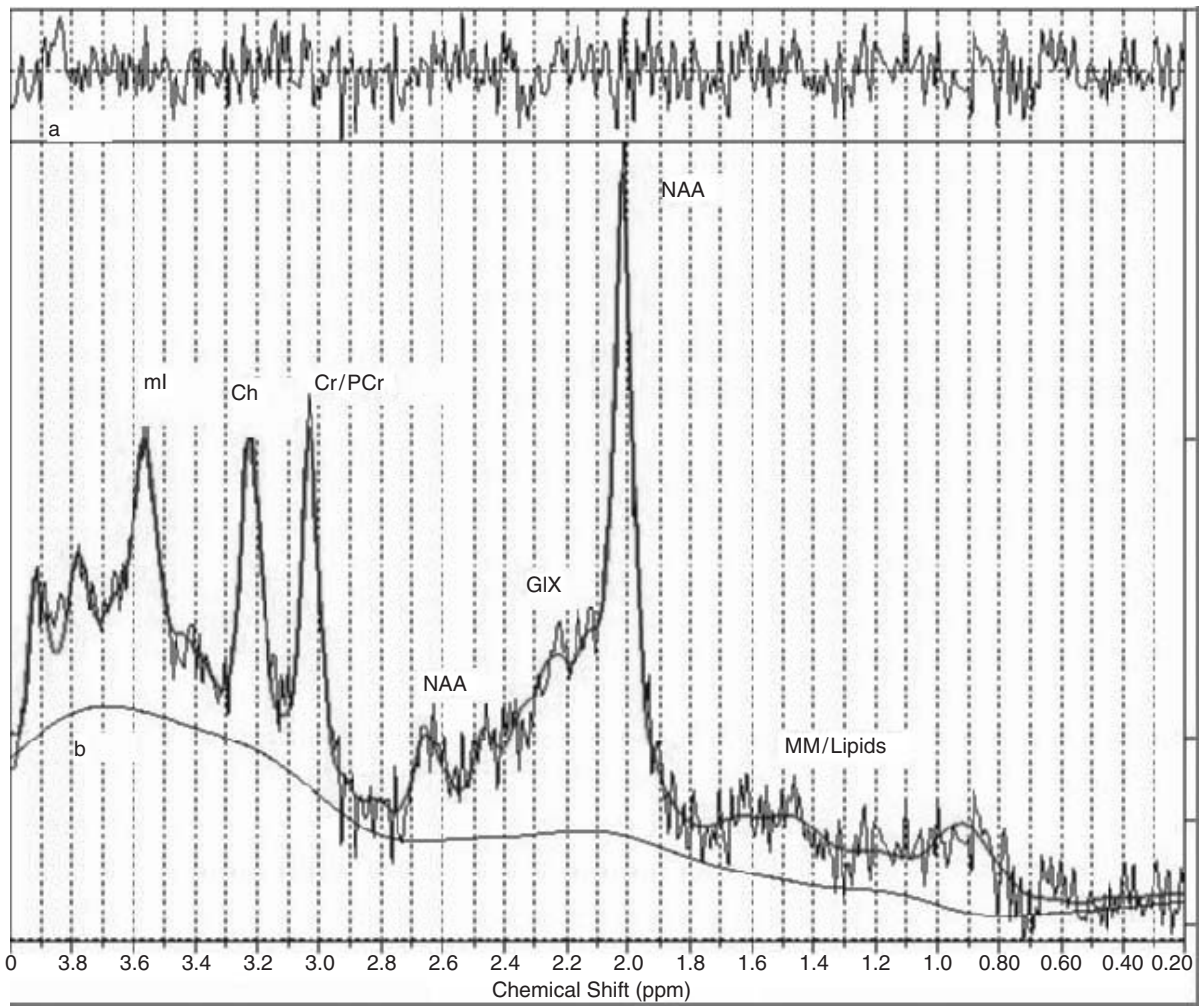


Figure 71.1 Sample proton MRS spectrum. Each peak represents a different metabolite with the area under the peak equivalent to the concentration of the metabolite

limitations, early studies using MRS to examine brain alterations associated with normal ageing failed to find significant changes over time^{3,4}. However in a study by Cohen and colleagues comparing brain uptake of choline using proton MRS in younger subjects (mean age 32) and older subjects (mean age 73), it was shown that older subjects had decreased choline uptake⁵. In a 2001 study, Brooks *et al.* showed a significant decline in frontal lobe NAA comparing subjects from age 20 to 70 with an overall decrease of 12%⁶. This decline was interpreted as a decrease in neuronal volume, number or function as NAA is thought to be a marker of neuronal viability. In addition to decreases in NAA, increases in myo-inositol have also been seen in white matter associated with normal ageing. Kaiser *et al.* found a significant increase in both absolute levels and myo-inositol ratios in older subjects (mean age 56 years) compared with younger subjects (mean age 26 years)⁷.

The impact of these neurochemical changes associated with ageing in frontal white matter have been explored in correlational studies examining the relationship between metabolite levels and cognitive function. For example, in a study by Valenzuela *et al.*, frontal white matter NAA/Cr ratios were significantly correlated with cognitive tasks of executive function⁸. In a study by Elderkin-Thompson *et al.*, choline, myo-inositol and phosphocholine ratios were correlated with performance on learning and recognition tasks⁹.

The neurochemical changes described above are not limited to frontal white matter as demonstrated in a study that showed age-related decreases in NAA, NAA/Cho and NAA/Cr ratios across 30 different voxels¹⁰. In a longitudinal study examining similar measures over a three-year period, Ross *et al.* demonstrated that there were no significant changes in brain metabolites (with the exception of myo-inositol) or cognitive function over the time period studied¹¹. In a comprehensive review and meta-analysis of MRS studies in normal ageing, while the majority of studies showed no significant change in metabolites with age, the authors did note a trend towards an increase in frontal and parietal choline with increasing age and a trend towards increases in parietal and occipital creatine with increasing age¹².

The studies above describe whole brain or cortical measurements of metabolites associated with normal ageing. However, age-related neurochemical changes in subcortical regions have also been demonstrated. For example, significant decreases in NAA/Cr and increases in choline/Cr in the genu of the corpus callosum have been shown when older subjects have been compared with younger subjects¹³. In the pons, decreases in NAA and increases in choline and creatine were noted in subjects over 50 years of age compared with subjects under 50¹⁴. In a study of the hippocampus, age-related decreases in NAA were measured by Szentkuti *et al.*¹⁵. These changes appear

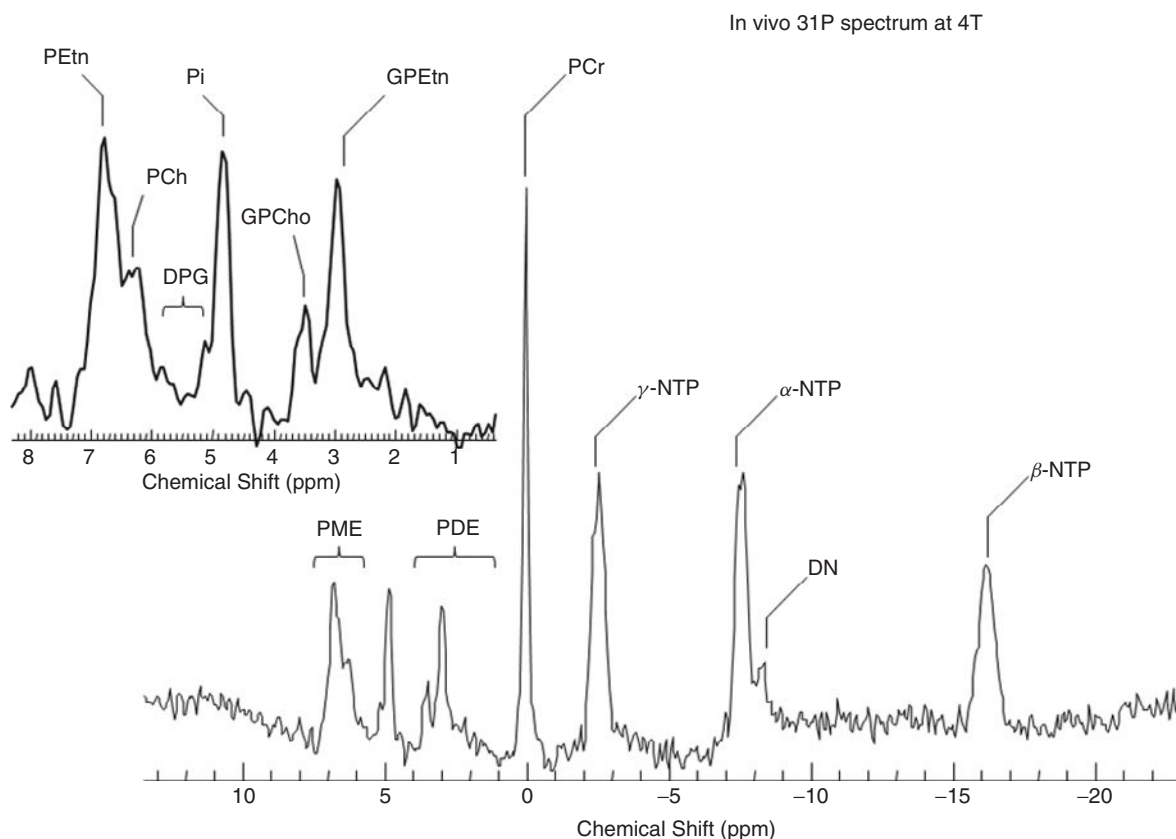


Figure 71.2 ^{31}P sample spectra. PEGn, phosphoryl ethanolamine; PCh, phosphoryl choline; DPG, diphosphatidylglycerol; GPEtn, glyceryl phosphoryl ethanolamine; PME, phosphomonoesters; PDE, phosphodiester; PCr, phosphocreatine; NTP, nucleoside triphosphate; Pi, inorganic phosphate; DN, dinucleotides. Reprinted courtesy of Dr Eric Jensen

to have a functional impact as well, noted by a correlational study showing that hippocampal NAA/Cr was a significant predictor of performance on a verbal memory task¹⁶.

GERIATRIC DEPRESSION AND BIPOLAR DISORDER

MRS has been used increasingly to study mood disorders in geriatric populations (Table 71.2). Comparing older adults with depression or bipolar disorder with healthy control subjects may offer insight into the pathophysiology of geriatric depression and predictors of treatment response and aid the development of more specific therapeutic interventions.

Most of the studies of geriatric depression utilize proton MRS. Changes in myo-inositol, choline and NAA have been observed in association with major depression. In the prefrontal region, increased myo-inositol and decreased NAA have been observed^{17–19}. These findings are hypothesized to be associated with changes in myelination and/or neuronal loss. However, there have been differing findings for choline in which Venkatraman *et al.*¹⁷ found a significant decrease and Kumar *et al.*¹⁸ a significant increase. Two proposed reasons for these differences include differing severity of depression and region of interest. The subjects in the Venkatraman study were depressed older adults who were responsive to treatment and had only residual symptoms, whereas Kumar and colleagues studied acutely depressed older adults. Additionally, Venkatraman *et al.* focused on the anterior cingulate while Kumar's findings were located in the dorsolateral prefrontal cortex. An additional novel finding for Venkatraman and

colleagues was increased NAA in the left medial temporal lobe, which may result in increased amygdala activity via diminished frontal lobe inhibition. Furthermore, changes in metabolite concentrations were found in the basal ganglia, where NAA was decreased in the caudate and choline was increased in the putamen²⁰.

A negative correlation was found between magnetization transfer ratio (MTR) and NAA+NAAG/Cr (*N*-acetylaspartylglutamate) and between myo-inositol/Cr and MTR²¹ in white matter. MTR is associated with structural tissue integrity and it is hypothesized that changes in myo-inositol and NAA pools may result in the observed changes in macromolecular protein pools. Decreases in NAA were also found to be positively correlated with increased severity of white matter hyperintensities²².

Changes in glutamate and glutamine have also been observed in geriatric depressed subjects. In comparing older adults with major depression, diabetes mellitus and healthy controls, subcortical nuclei glutamate and glutamine levels were significantly decreased in subjects with diabetes mellitus and depression compared with diabetic subjects and healthy controls. It is hypothesized that reduced glutamate and glutamine may be a result of glial dysfunction as well as impaired glucose metabolism. Also of note, myo-inositol was significantly increased in both depressed patients and depressed patients with diabetes mellitus versus controls²³. In another study examining myo-inositol levels and visuo-spatial functioning, it was found that increased frontal white matter myo-inositol levels, present in both depressed and non-depressed diabetes mellitus subjects, were correlated with visuo-spatial dysfunction²⁴. Patients with diabetes are

Table 71.2 Brain MRS findings in geriatric depression and bipolar disorder

<i>Author</i>	<i>MRS type</i>	<i>Findings</i>
Venkatraman ¹⁷	¹ H	NAA decreased in prefrontal cortex NAA increased in left medial temporal lobe Cho decreased in prefrontal cortex Cre decreased in prefrontal cortex mI increased in left medial temporal lobe
Binesh ¹⁹	¹ H	mI increased in dorsolateral prefrontal region PE increased in dorsolateral prefrontal region Glx increased in dorsolateral prefrontal region
Kumar ¹⁸	¹ H	mI/Cr increased in frontal white matter Cho/Cr increased in frontal white matter
Vythilingam ²⁰	¹ H	NAA decreased in caudate Cho increased in putamen
Wyckoff ²¹	¹ H, MT and MRS	Inverse relationship between MTR and mI/Cr in left dorsolateral white matter Inverse relationship between MTR and (NAA+NAAG)/Cr in left dorsolateral white matter
Murata ²²	¹ H	Correlation b/t increased WMH severity and decreased NAA/Cr in frontal white matter
Ajilore ²³	¹ H	Significantly decreased Glu and Gln for DM+MDD and DM vs. HC in subcortical nuclei
Haroon ²⁴	¹ H	Increased mI in DM and DM+MDD correlated with visuo-spatial dysfunction in frontal white matter
Moore ²⁹	³¹ P	Beta NTP decreased in basal ganglia Total NTP decreased in basal ganglia
Volz ³⁰	³¹ P	Beta NTP decreased in frontal lobes Total NTP decreased in frontal lobes
Renshaw ³¹	¹ H and ³¹ P	Average purine levels were not different between depressed and comparison groups in basal ganglia; however, female responders to fluoxetine treatment had 30% lower purine levels than non-responders Beta NTP 21% lower in beta NTP of responders to fluoxetine than non-responders, correlated with purine levels
Iosifescu ³²	³¹ P	Mg ²⁺ decreased at baseline in frontal and parietal slice superior to corpus callosum of depressed subjects Total NTP increased in frontal and parietal slice superior to corpus callosum of T3 responders PCr decreased in frontal and parietal slice superior to corpus callosum of T3 responders
Pettegrew ³³	³¹ P	Prefrontal phosphomonoester levels increased at baseline; decreased with ALCAR treatment, trend between HDRS and phosphomonoester ALCAR increased PCr in prefrontal region, PCr levels correlated with HDRS
Forester ³⁴	³¹ P	Whole brain total NTP decreased in geriatric depressed, difference in WM, not GM, total NTP decreased with treatment Whole brain beta NTP decreased in MDD Whole brain pH increased in GM for pretreatment depressed; pH decreased following treatment
Forester ³⁵	⁷ Li	Increased brain Li in the superior edge of the corpus callosum associated with increased HDRS scores and frontal lobe dysfunction
Forester ³⁶	⁷ Li	Brain Li levels in the anterior cingulate gyrus associated with increased NAA in BP Brain Li levels in the anterior cingulate gyrus associated with increased mI in BP

ALCAR, acetyl-L-carnitine; BP, bipolar disorder; Cho, choline; Cre, creatine; DM, diabetes mellitus; Gln, glutamine; Glu, glutamate; Glx, glutamate + glutamine; GM, grey matter; H, hydrogen; HDRS, Hamilton Depression Rating Scale; Li, lithium; MDD, major depressive disorder; Mg²⁺, magnesium ion; mI, myo-inositol; MT, magnetization transfer; MTR, magnetization transfer ratio; NAA, *N*-acetylaspartate; NAAG, *N*-acetylaspartylglutamic acid; NTP, nucleoside triphosphate; P, phosphorous; PCr, phosphocreatine; T3, triiodothyronine.

at increased risk of suffering from depression and increased medical burden may be a risk factor for poor response to antidepressant treatment²⁵.

These metabolic changes associated with major depression seem to be clinically relevant as demonstrated by treatment effect studies. For example, an increase in amygdala region NAA was seen in depressed patients who exhibited a positive response to electroconvulsive therapy²⁶. In addition, Glx concentrations (a composite of

glutamate and glutamine) in left dorsal lateral prefrontal cortex were negatively correlated with severity of depression and increased significantly after electroconvulsive treatment²⁷. In a report examining the effect of antidepressant treatment, it was shown that decreased NAA levels in the anterior cingulate cortex in depressed patients were reversed with venlafaxine treatment²⁸.

In addition to using proton MRS in depression, ³¹P-MRS allows for examination of membrane phospholipids and high-energy

phosphorous-containing molecules, such as ATP and phosphocreatine (PCr). Previous ^{31}P -MRS studies have demonstrated lower levels of beta and total NTP in the basal ganglia²⁹ and the frontal lobes³⁰ of depressed adults. Bioenergetic changes have also been demonstrated to correlate with response to pharmacological treatment^{31,32}. Earlier studies have been inconclusive regarding whether differences in bioenergetic metabolism reflect a trait condition for those individuals at risk for depression or a state condition related to depression severity³².

Studies examining changes in high-energy phosphate metabolites with treatment in geriatric depression are limited. In prefrontal tissue, phosphomonoester concentration was increased in two male older depressed subjects compared with six male controls of similar age. In the depressed group, prefrontal phosphomonoester levels decreased with acetyl-L-carnitine (ALCAR) treatment³³. In addition, following ALCAR treatment there was a significant increase in PCr levels. In this study a trend level correlation was also found between phosphomonoester levels and Hamilton Depression Rating Scale (HDRS) scores³³. A recent ^{31}P -MRS study of 13 older depressed adults and 10 healthy older controls at 4T demonstrated that both total NTP (nucleoside triphosphate) and β -NTP (which primarily reflects levels of ATP) were decreased in the geriatric depressed subjects. More specifically, total NTP among depressed subjects was significantly decreased in white matter, but there was no significant difference in grey matter vs. controls. Following sertraline treatment, there was a significant decrease (2%) in total NTP. In addition, intracellular pH in grey matter, which was significantly greater in depressed subjects vs. controls pretreatment, was decreased to levels similar to that of healthy controls following treatment³⁴. The authors propose that further study of high-energy phosphate alterations in geriatric depression is warranted and this may lead to bioenergetically based treatment approaches in late life major depression.

MRS studies in late-life bipolar disorder are more limited, though recent findings using ^7Li -MRS hold promise for a clinical application of this method to help regulate lithium dosing more accurately in older bipolar adults. Examining the superior edge of the corpus callosum in a 4T MRS study of older adults with bipolar disorder treated with lithium, increased brain but not serum Li levels were associated with increased depression symptoms (measured by the HDRS) as well as frontal executive dysfunction (measured by the Stroop Interference Tests, Trails B and Wisconsin Card Sort)³⁵. In addition, brain Li levels were associated with increased myo-inositol and NAA levels³⁶. Increased NAA suggests potential neuroprotective and neurotropic effects of lithium treatment while increased myo-inositol levels were thought to reflect increased inositol monophosphatase activity in the setting of chronic lithium treatment.

Studies utilizing proton (^1H) MRS have identified changes in cerebral concentrations of NAA, Glx, choline-containing compounds, myo-inositol and lactate in adult bipolar subjects compared with normal controls³⁷. Other studies using ^{31}P -MRS have examined additional alterations in levels of PCr, phosphomonoesters and intracellular pH (pH_i)³⁷. Based on these findings, some have hypothesized that the majority of MRS findings in bipolar disorder can be fit into a cohesive bioenergetic and neurochemical model that is focused on central nervous system (CNS) energy metabolism¹⁹. Treatment studies examining bioenergetic changes in geriatric bipolar depressed individuals utilizing both ^1H - and ^{31}P -MRS at 4T are currently underway and may provide further insight into the pathophysiology of late-life bipolar disorder.

DEMENTIA AND COGNITIVE DISORDERS

Mild Cognitive Impairment/Cognitively Impaired Non-Demented

MRS studies in mild cognitive impairment (MCI) have been used to distinguish MCI from normal ageing, as well as more advanced forms of cognitive dysfunction. An early study by Kantarci *et al.* examined regional metabolic changes associated with MCI. They found that increases in myo-inositol/Cr ratios in the posterior cingulate were the metabolic change unique to patients with MCI and Alzheimer's disease, while decreases in NAA/Cr and Cho/Cr only seemed present in the patients with more progressive disease³⁸. Subsequent studies have shown a similar pattern of changes associated with MCI compared with control subjects³⁹. Other regions have been shown to demonstrate metabolic perturbations restricted to MCI. For example in a study by Ackl *et al.*, hippocampal decreases in NAA occurred in MCI and Alzheimer's patients, but NAA changes in the parietal region seemed to only occur in more advanced patients⁴⁰. MRS has been studied as a predictor of developing dementia in a number of studies. For example, cognitively impaired non-demented (CIND) patients have been shown to have reduced NAA in the medial temporal lobe, hippocampus and neocortical grey matter compared with controls. There was also a difference between stable CIND patients and CIND patients who developed dementia over 3.6 years of follow-up⁴¹. In another study, changes in occipital NAA/Cr ratios predicted conversion to dementia with 100% sensitivity and 75% specificity⁴². Thus, MRS has been a useful tool in determining the early metabolic profiles that distinguish MCI from more advanced dementia and the changes that predict the development of more advanced dementia.

Alzheimer's Disease

The majority of studies using MRS to measure brain metabolites associated with dementia have been in Alzheimer's disease. The most consistent finding is reduced NAA, a marker of neuronal viability, and increased myo-inositol. This has been demonstrated in a number of cross-sectional studies⁴³⁻⁴⁶. These patterns also occur longitudinally as demonstrated in a brief report from Adalsteinsson *et al.* They showed that grey matter NAA levels (on average) declined 12.26% over the course of year in Alzheimer's disease patients, whereas controls had no significant change over the same time period⁴⁷. Metabolic alterations associated with AD have associated with cognitive function as well. For example, NAA reductions in the left medial temporal lobe were associated with impairment in verbal memory, while myo-inositol increases in the right parietotemporal cortex were associated with impairment in visuoconstructional performance⁴⁸.

There have been several studies looking at the effects of treatment of Alzheimer's disease on brain metabolic profiles. In a study on donepezil, the authors found that patients receiving treatment demonstrated higher NAA concentrations compared to patients receiving placebo over a 24-week period⁴⁹. In a subsequent study, these types of changes were shown to be significantly correlated with cognitive improvement associated with donepezil treatment⁵⁰. Rivastigmine has also been shown to positively affect the metabolic profile associated with Alzheimer's disease. Patients treated with rivastigmine over a four-month period exhibited significant increases in frontal cortex NAA/Cr ratio⁵¹.

The newest pharmaceutical agent in the treatment of Alzheimer's disease, memantine, is thought to exert an anti-excitotoxic effect by the inhibition of the glutamate-receptor agonist, *n*-methyl D-aspartate

(NMDA). In keeping with this mechanism, a recent proton MRS study has shown that memantine decreases hippocampal glutamate in Alzheimer's disease⁵². Thus, with the evidence from these treatment effect studies, it appears the metabolic alterations seen in Alzheimer's disease appear to be related to the underlying pathophysiology of the disease and in the case of memantine may reflect pharmaceutical mechanisms.

Vascular Dementia

While a number of studies have attempted to use MRS to distinguish Alzheimer's disease from vascular dementia^{53,54}, there are more similarities in the patterns of change than differences. The main distinguishing feature of vascular dementia is the subcortical predominance of metabolic alterations versus more cortical changes in Alzheimer's disease. However, as with Alzheimer's disease, patients with vascular dementia have been shown to have decreased NAA as well as increased myo-inositol⁵⁴.

Frontotemporal Dementia

As to be expected with frontotemporal dementia, metabolic changes in this disorder are associated with more frontal structures, as evidenced by a study showing decreased NAA in frontal areas compared with more posterior regional changes in Alzheimer's disease patients⁵⁵. In a study comparing patients with frontotemporal dementia patients with those with Alzheimer's disease and controls, frontal lobe NAA and Glx concentrations were decreased in conjunction with increases in myo-inositol⁵⁶. The NAA results have been replicated in a later study examining metabolites in the posterior cingulate cortex of frontotemporal dementia patients⁵⁷.

Lewy Body Dementia

A few studies have used MRS to examine brain changes associated with Lewy body dementia. One report including 20 patients with Lewy body dementia showed Cho/Cr ratios were significantly elevated compared with healthy controls⁵⁸. In another study, white matter changes were detected with significantly lower mean NAA/Cr, Glx/Cr and Cho/Cr ratios in patients with Lewy body dementia compared with controls⁵⁹.

SUMMARY

Overall, the studies outlined above demonstrate a general pattern that applies to most of the neurodegenerative diseases. Dementia subtypes appear to differ only in terms of the neuroanatomical regions affected. In a number of areas, including grey and white matter and cortical and subcortical regions, NAA tends to be decreased compared to controls, while increases in myo-inositol and choline have been detected. This is thought to reflect the loss of neurons (with NAA), membrane breakdown (choline) and reactive gliosis (detected by myo-inositol) associated with these diseases.

STRENGTHS AND LIMITATIONS OF MRS

The major strength of MRS is that it allows for the measurement of specific metabolites in a particular region of the brain. Thus, the selection of crucial brain regions plays a vital role in the

understanding of the pathophysiology underlying late-life mental illness. This is also a potential limitation as many studies choose different brain regions to study the same illness, thus generalizability and broad interpretation across studies are difficult to achieve.

Another limitation is poor resolution of specific peaks. Often, GABA, glutamate and glutamine peaks overlap, making it difficult to determine exact concentrations of these metabolites. One technique designed to surmount this limitation is two-dimensional magnetic resonance spectroscopy (2D-MRS).

TWO-DIMENSIONAL MAGNETIC RESONANCE SPECTROSCOPY

Two-dimensional (2D) spectroscopy is a technique that allows for greater resolution. The advantage of 2D spectroscopy is that it allows for the detection of GABA which is typically masked by the spectral peaks of other metabolites such as *N*-acetylaspartate and glutamate/glutamine. One of the first papers to apply 2D-MRS techniques to brain chemistry was done by Thomas and colleagues showing the feasibility of the 2D J-coupled point-resolved spectroscopy (JPRESS) technique in human subjects⁶⁰. They were able to detect peaks representing NAA, glutamate/glutamine and lactate in occipital cortex.

Two-dimensional J-resolved spectroscopy has been successfully applied to measure previously hard-to-detect levels of GABA⁶¹. This technique has also been used to measure grey matter/white matter differences. In a study by Jensen *et al.*, it was shown that GABA levels are significantly higher in grey matter than in white matter⁶².

Localized two-dimensional chemical shift correlated magnetic resonance spectroscopy (2D-COSY) is a method that presents certain advantages over the JPRESS and J-resolved techniques. This method was successfully used in human brain in a study by Thomas *et al.* where peaks for *N*-acetylaspartate (NAA), glutamate/glutamine (Glx), myo-inositol (mI), creatine (Cr), choline, aspartate, GABA, taurine, glutathione, threonine and macromolecules were identified⁶³. The authors demonstrated that 2D-COSY generates spectra with better resolution and less overlap of peaks. 2D-COSY has also shown to be highly reliable and reproducible⁶⁴.

The advantage of this technique is that it allows for the detection of important metabolites that are difficult to measure by traditional MRS methods. In particular, it allows for better resolution of aspartate and GABA, important neurotransmitters that have been implicated in mood disorders.

CONCLUSION

MRS is an important tool for the localized measurement of brain metabolites that has been successfully applied to the understanding of geriatric mental illness. Despite its limitations, the method continues to evolve more sophisticated techniques for the improved measurement of clinically important neurochemicals to better understand pathophysiology, functional impact and treatment effects.

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Affective Disorders

Nosology and Classification of Mood Disorders

Dan Blazer

Duke University School of Medicine, Duke University Medical Center, Durham, USA

The mood or affective disorders are a group of disorders characterized by disturbance of mood and accompanied by a partial or complete change in mood or affect that is either manic (or hypomanic) or depressed (or mildly dysphoric). These disorders are classified in both the ICD¹ and the DSM² diagnostic systems in the three-digit rubric (296.xx in DSM-IV and F30.x–F39.x in ICD-10). With some exceptions noted below, the nosology of mood disorders in ICD-10 and DSM-IV is appropriate for the classification of mood disturbances in older adults. The classification of the disorders will therefore be described below, with specific comments related to older adults.

It should be noted at the outset of this chapter that DSM-IV is unchanged since the second edition of this text. A new version, DSM-V, is due for publication in 2012. ICD-10 has been instituted since the second edition, yet many changes in ICD-10 and the desire to bring the classification systems into closer concert were anticipated in the chapter from the second edition. It should also be noted that, despite the many advances in the pathophysiological investigation of late life mood disorders and new studies of therapies (pharmacological, psychological and social), DSM-IV and ICD-10 classifications have been accepted by investigators and clinicians alike. Some suggestions of new syndromes, such as 'depression in Alzheimer's Disease', have emerged and will be discussed briefly though none of these are widely employed.

MANIC EPISODE (F30, 296.4–7)

A manic episode is characterized by an elevated mood that is unrelated to the patient's circumstances. This elevated mood usually varies from an expansive or irritable syndrome to an almost uncontrollable excitement and psychotic agitation. Changes in mood are accompanied by increased energy, a decreased need for sleep, a decline in normal social inhibitions, as well as inflated and grandiose ideas, which frequently become delusional. Older persons can experience a typical episode of mania as well as hypomania (a less severe elevation of mood) but are more likely to suffer a so-called 'irritable' or 'angry' manic episode. Joviality and elation are replaced by irritability and agitation (as described elsewhere in this text). Nevertheless, older persons who suffer manic episodes usually meet both ICD-10 and DSM-IV criteria, even when the predominant symptoms are irritability and anger, as other diagnostic criteria are met.

ICD-10 defines a hypomanic episode as a disorder characterized by a persistent mild elevation of mood, increased energy and activity, and usually marked feelings of well-being and both

physical and mental efficiency. Increased sociability, talkativeness, over-familiarity, increased sexual energy and a decreased need for sleep are often present but not to the extent that they lead to severe disruption of work or result in social rejection. Older adults, however, often experience irritability and anger as with a full episode. A parallel diagnosis is bipolar II disorder in DSM-IV.

DEPRESSIVE (F32) OR MAJOR DEPRESSIVE (296.2, 3) EPISODE

A major depressive episode is characterized by a depressed, disinterested or irritable mood, associated with the loss of interest or pleasure in all or almost all activities, accompanied by a number of other symptoms. These additional symptoms include a reduced capacity for enjoyment, reduced interest in surroundings, difficulty concentrating, lethargy, sleep disturbances, appetite disturbances, decreased self-esteem and self-confidence, and frequent ideas of guilt or worthlessness. Although older persons are somewhat less likely to report a specific decrease in their mood, they almost always describe a loss of interest in usual activities (anhedonia) in the midst of a major depressive episode. The categories of severe depressive episode in ICD-10 and major depressive episode in DSM-IV are very similar. DSM-IV and ICD-10 permit the diagnosis of a minor depressive episode (in the appendix of DSM-IV and categorized as mild in ICD-10); that is, a depressive episode which fulfils some of the symptom criteria for a major depressive episode and/or dysthymia and which lasts two weeks or longer. The more severe consequences of a depressive episode, such as a successful suicide or a retardation that progresses to stupor, would be characteristic of a severe but not a mild depressive episode in ICD-10.

Older persons who suffer a complicated, severe depression are easily diagnosed according to both ICD-10 and DSM-IV criteria. Problems do arise, however, when the episode experienced by older persons is accompanied by a severe medical illness or significant cognitive impairment. The frequency of psychobiologic symptoms in more severe depressions renders the distinction between symptoms of depression and symptoms of physical illness/functional impairment difficult in the midst of a depressed mood associated with medical illness. The current nosology is not helpful in disaggregating mood disorders from either the symptoms of physical illness or normal psychological reactions to physical illness. Some have suggested that a unique criterion for older persons with depression and cognitive impairment should be instituted (but this is yet to be included in

any extant diagnostic system). The co-morbidity of depressive symptoms in cognitive disorders such as dementia, Parkinson's disease and small strokes renders such an approach potentially useful in improving the current nosology. Two examples are presented below.

'Vascular depression' has been proposed as the diagnostic entity secondary to vascular lesions in the brain and appears to increase in frequency with age³. The clinical presentation may differ from major depression, even if only in subtle ways. Elders with vascular depression exhibit impairment in set shifting, verbal fluency, psychomotor speed, recognition memory and planning (executive cognitive function), a 'depression-executive dysfunction syndrome' characterized by psychomotor retardation, and reduced interest in activities. Vascular depression is associated with an absence of psychotic features, less likelihood of a family history, more anhedonia and greater functional disability when compared with nonvascular depression.

Others have proposed a depression of Alzheimer's disease⁴. The criteria are as follows. In persons who meet criteria for dementia of the Alzheimer's type, three of a series of symptoms that includes depressed mood, anhedonia, social isolation, poor appetite, poor sleep, psychomotor changes, irritability, fatigue or loss of energy, feelings of worthlessness and suicidal thoughts must be present for the diagnosis to be made.

BIPOLAR (F31, 296.4–7) AND UNIPOLAR DISORDER (F32, 296.2, 3)

In both ICD-10 and DSM-IV, individuals who present with a history of recurrent mood disorder (at least two), in which mood and activity were profoundly disturbed and at least one of the episodes was manic, are classified as suffering from bipolar mood disorder. Bipolar disorder usually has an early age of onset, although it can have its onset later in life, and the categorization is useful in older as well as younger persons. Bipolar disorders are classified as manic (the individual is currently in a manic episode), depressed (the individual is currently in a depressed episode and has at least one well-authenticated manic episode in the past) or mixed (the individual's current episode involves a full symptomatic picture of both manic and depressed episode, except for the duration requirement of two weeks of depressed episodes). Symptoms are often intermixed or rapidly alternating within hours or days in the latter category.

Bipolar II disorder (F31.8 and 296.89) is characterized by at least one hypomanic episode and at least one episode of major depression. These disorders are probably more common among older persons than the more classic bipolar disorder described above. Older persons frequently experience depression and occasionally mania secondary to medical illness or medications, categories that are specified in DSM-IV as mood disorder due to a general medical disorder and substance-induced mood disorder. Common examples of causes of these secondary mood disorders in the elderly include hypothyroidism, Parkinson's disease, chronic obstructive pulmonary disease, various forms of cancer, alcohol, β -adrenergic blockers and L-dopa. Mood disorders with a seasonal pattern are less frequent in the elderly⁵.

Individuals who never experience an episode of mania or hypomania but nevertheless suffer episodes of major depression are generally classified as 'single-episode' or 'recurrent'. Most depressive disorders are recurrent; that is, distinct episodes of major depression followed by distinct episodes of normal functioning may be the exception rather than the rule. For this reason, additional diagnostic categories have been instituted in the nosology to disaggregate the

classification of the natural history of depressive episodes. In ICD-10, a category of 'recurrent severe depressive disorder' (F33.3) is analogous to the DSM-IV category of 'major depression recurrent' (296.3). Recurrent mild depressive disorder (F33.0) is categorized in ICD-10 by repeated episodes of depression, the majority of which fulfil the description given for mild depressive episode above. These recurrent mild episodes may or may not be associated with environmental stress and may be either acute or insidious in onset. Recovery is usual, although not always complete.

Cyclothymia is included in both DSM-IV (301.13) and ICD-10 (F34.0). According to ICD-10, cyclothymia is a persistent instability of mood involving numerous periods of mild depression and mild elation. The instability usually develops early in adult life and pursues a chronic course, although at times mood may be normal and stable for months. Cyclothymia is difficult to establish without a prolonged period of observation or an unusually good account of the subject's past behaviour. In DSM-IV, cyclothymia must persist for at least two years to be diagnosed and involve numerous hypomanic episodes.

Yet another phenomenon has emerged in the study of the natural history of depression – rapid cycling^{6,7}. Rapid cycling is the occurrence of four or more episodes of depression or mania per year, with either two weeks of normal mood between episodes, or a shift directly from mania to depression, or vice versa. Others have classified rapid cycling as involving either mixed mood states, or frequent mood fluctuation without discrete intermorbid periods, or involving 24- or 48-hour cycles of mood disturbance. Rapid cycling occurs in persons regardless of age, although there may be some tendency for individuals to decrease their propensity to rapid cycling with increased age. Rapid cycling appears to be more common in individuals with bipolar disorder than unipolar disorder, but it is not limited to individuals with bipolar disorder. Rapid cycling is a specific type of bipolar mood disorder in DSM-IV (296.8) and major depression (311). Research criteria are proposed in the appendix of DSM-IV-TR.

DYSTHYMIA (F34.1, 300.4)

Dysthymia is a category included in both ICD-10 and DSM-IV. Dysthymia is a chronic depression of mood that does not fulfil the description and guidelines of mild recurrent depressive disorders (in ICD-10) and is characterized by periods of days or weeks at a time when patients feel tired and depressed, where everything is an effort and where nothing is enjoyed. They 'brood and complain', sleep badly and feel inadequate, but are usually able to cope with the basic demands of everyday life. This description is similar to the description of dysthymia in DSM-IV, where the essential feature is a chronic disturbance of mood, involving a depressed mood for most of the day and more days than not for at least two years (the two-year minimum duration is not a criterion in ICD-10 but rather is to last at least several years). In addition, individuals suffering dysthymia suffer many of the symptoms of the more severe depression but with less severity, such as poor appetite, insomnia, low energy and low self-esteem. Older persons often meet criteria for a dysthymic disorder (in terms of duration of symptoms) when diagnosed with major depression. It is difficult to determine, however, whether the dysthymic disorder is a separate entity or whether it is part of the same syndrome which 'waxes and wanes' in severity. Recent studies have suggested that dysthymic disorder may exist most often in the elderly as an entity not associated with major depression. Dysthymic disorder has usually been equated with depressive neuroses, as described in earlier versions of both the ICD and DSM diagnostic systems,

which assumes that the depressed mood results from psychoneurotic and stress-related difficulties.

Yet another category that has been suggested is minor or mild depression. Criteria for minor depression can be found in the appendix of DSM-IV and variants can be found in the Research Diagnostic Criteria and in ICD-10 (F32.0). There is virtually no data to substantiate a specific entity for minor depressions, except that persons who experience minor depression (that is, symptoms less severe than major depression for at least two weeks, according to DSM-IV) exhibit a similar risk factor profile and are at much greater risk for developing major depression over time. There have been a number of studies of minor depression among the elderly. The renewed interest in minor depression once again brings the categorical vs. continuum controversy to the forefront in the phenomenology of depression.

ADJUSTMENT DISORDER WITH DEPRESSED MOOD (F43.2, 309.0)

In the DSM-IV system of classification, an adjustment disorder is a reaction to an identifiable psychosocial stressor that leads to maladaptive reactions, including impairment in occupational functioning and symptoms that are in excess of normal and expected reaction to this stressor. The maladaptive reaction may take many forms and an exaggerated depressed mood is one of the forms.

Symptoms of adjustment disorder with depressed mood include tearfulness and feelings of hopelessness. By definition, the maladaptive reaction can persist no longer than six months, does not meet criteria for other disorders and does not represent uncomplicated bereavement.

ICD-10 includes the category of adjustment disorder (but depressed type is not specifically coded) and the clinical form may take the characteristic of a 'prolonged depressive reaction'; that is, a mild depressive state occurring in response to prolonged exposure to a stressful situation but of a duration not lasting six months. The categories of adjustment disorder are therefore very similar for both diagnostic systems. In theory, the stressor may include physical illness and therefore this category is most relevant to depressive episodes in later life. A lack of acceptable longitudinal data on the association of depressive symptoms with physical illness renders it difficult to determine whether older persons do recover from the depressive episode, which often accompanies a physical illness, within the six months required by the diagnostic category of adjustment disorder.

CONCLUSION

In general, the current classificatory systems of both DSM-IV and ICD-10 work relatively well for classifying older persons suffering from mood disorders. A number of distinct exceptions must be

recognized, however. Categories such as dysthymic disorder, adjustment disorder and minor depression in DSM-IV do not appear to be adequate, and therefore more exploration of the ICD-10 construct of mild depression (but possibly not utilizing the specific diagnostic criteria of ICD-10) would appear in order. A major problem with the current classification systems is the inability to take into account co-morbidity, especially co-morbid depression and physical illness. Co-morbid depression and physical illness is a grossly unstudied area, compared to the clinical relevance of the condition. To what extent do our current classification systems accommodate individuals suffering mild or even severe depressive symptoms in the midst of physical illness? In addition, depression is often co-morbid with other psychiatric symptoms, especially anxiety disorders and somatic complaints. Neither ICD-10 nor DSM-IV adequately accommodates the co-morbid psychiatric syndromes that are frequently seen in older adults.

Finally, when classifying mood disorders many individuals suffer a depressed mood in late life that is not disordered. Uncomplicated bereavement is an expected accompaniment of older persons who experience a significant loss in old age. In addition, other older persons may become demoralized, given the current circumstances in their lives. Such persons should not be classified in a disease-oriented classification system. Nevertheless, these human experiences are not to be ignored by the clinician working with the older adult suffering a mood disorder.

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Genetics of Affective Disorders

Carolina Aponte Urdaneta and John L. Beyer

Duke University Medical Center, Durham, NC, USA

INTRODUCTION

With the completion of the Human Genome Project, the field of genetics has vastly changed. Even our current definitions of disorders and treatment of diseases are anticipated to evolve pending the interpretation of our new genetic data¹. However, rather than just narrowly looking at genetic associations in persons with affective disorders, the contributions obtained from the wider body of research examining the genetic basis of psychiatric disorders need to be interpreted in the context of environmental influences and the heterogeneous nature of these disorders^{2,3}. This is especially true for late-life disorders, in which simple Mendelian genetics do not apply, and multiple genes each likely play a small role, together with co-morbid illnesses, earlier life insults and environmental factors^{4,5}.

Genetic studies can be classified into linkage studies, gene–disease association studies (looking at specific single nucleotide polymorphisms (SNPs)), and the more recent genome-wide association studies (GWAs). Other more classic forms of genetic studies include familial aggregation studies, twin studies, adoption studies, and linkage studies of an illness with a genetic marker. Finally, an area of recent intense research that may soon show significance in late-life psychiatric disorders is that of copy-number variations (CNVs). Findings have suggested that CNVs may cause disease due to genomic rearrangements that result in altered number of copies. These disorders have primarily been associated with neurodevelopmental and neurodegenerative disease processes^{6,7}, a classification in which late-life affective disorders could well be included.

In this chapter, we will review the current understanding of genetic influences in late-life affective disorders. However, before looking at specifics, it is important to highlight the intricacies of examining the associations of genetic variations with complex diseases such as late-life affective disorders; researchers have had difficulty replicating associations⁸. Therefore, many of the findings reviewed here may be considered suggestive, but not fully verified. It will be up to future research to clarify and reveal the developing story of genetic influences in late-life mood disorders.

LATE-LIFE AFFECTIVE DISORDERS

As with affective disorders in the early and mid-life ages, late-life mood disorders are quite heterogeneous. Age of onset appears to be an important clinical variable in the genetic study of affective illness. Therefore, two groups of affectively ill elderly patients are usually

differentiated: those who had an early onset of illness with continued symptoms or episodes in their later life, and those who had a late onset of illness (usually defined as a first onset after the age of 60 years)⁹. When differentiated by age of onset, late-onset depressive disorders have qualities suggesting that they may be genetically different from early onset forms, including clinical differences in expression and non-conformity to expected genetic models¹⁰.

For example, basic genetic models propose that diseases with strong genetic influences are most often found in earlier onset and/or more severe forms of an illness. However, late-onset affective syndromes are typically among the most severe and most refractory to treatment^{11,12}. Further, many studies have consistently found that patients with late-onset depression and bipolar disorders have less familial aggregation of mood disorders than those with the early onset affective disorders^{13–18}. Also, late-onset mood disorders are also less likely to display the gender disparity present in early onset mood disorders¹³. These considerations challenge our models of genetic influence for late-life affective disorders.

Two explanations have been proposed for the age-related variation in genetic influence for affective illnesses: multifactorial inheritance and increased phenocopy expression with age. Multifactorial inheritance (also called polygenic inheritance) suggests that inheritance patterns are a result of a combination between multiple interacting genes and environmental factors. Examples of traits that have multifactorial inheritance include stature, intelligence or blood pressure¹⁰. According to the multifactorial theory, the onset of an affective disorder results from the additive effects of several genetic and environment factors. One could also assume that early onset illnesses probably result from greater genetic loading, while late-onset illnesses may have less genetic loading but increased occurrence of environmental events with age.

The second explanation, increased phenocopies, may explain the limited specificity of the affective disorders diagnosis. Both bipolar disorder and major depressive disorder are syndrome diagnoses; that is, the diagnosis is based on the presence of a collection of observed symptoms (phenotypes) rather than an etiological cause. In this theory, late-onset affective illness is a collection of phenocopies. Phenocopies are illnesses with a characteristic phenotype but different underlying causes.

It has long been known that depressive syndromes are very common in neurological disorders such as Parkinson's disease, Alzheimer's disease and stroke; more recently added to this list would be the proposed subtype of depression called 'vascular

depression'^{19,20}. Taking these into account, the age-related variation in late-life affective disorders may be explained by increasing phenocopies in older adults who have late-onset affective disorders. Patients with early onset affective disorders (which would include elderly patients with previous diagnosis of affective disorders) may be, therefore, more likely to have a genetic cause. As research sharpens our understanding of these diseases, the 'heterogeneous' group of affective disorders will be differentiated into various subtypes, each with a more specifically defined course, prognosis and treatment. Each new subtype will also suggest new ways that genes and the environment may contribute to the expression of the illness.

There is one further consideration in studying genetic contributions to late-life affective disorders. This is the fact that not all subjects with higher or lower genetic susceptibility may reach the developmental age of expression. Competing causes of death must be taken into account (i.e. individuals at high risk of developing a disorder may not express the disease symptoms during their lifetime). This in turn means that the actual risk of developing a disease is decreased when other causes of mortality are in play²¹.

GENETICS OF LATE-LIFE DEPRESSION

First-degree relatives (parents, siblings, offspring) of depressed adult patients are twice as likely to develop depression as those in the general population^{22–26}. In two twin studies of adult populations, the relative risk for monozygotic twins to develop depression was 1.9, while the risk for dizygotic twins was 1.2^{27,28}. Adoption studies have suggested that certain environmental influences, especially parental loss and parental alcoholism, may be predictors of depression²⁹. Heritability, therefore, is estimated at around 40% in the adult population³⁰; however, it has also been estimated to be lower in the elderly^{31,32}. Evidence of only limited heritability (16%) was found in a sample of elderly reared-apart and reared-together Swedish twins studied for characteristics of depression⁴. In contrast, a sample of Danish twins 75 years of age and older revealed that depression symptomatology is moderately heritable in late life (approximately 35%)⁵. Moreover, both studies consistently implicated environmental factors as the major source of variance in depression symptoms among the elderly.

Large-scale family linkage studies of major depression to chromosomal loci have been conducted focusing predominantly on early onset major depression, with some consistency of findings³³. In the area of candidate genes mainly drawn from monoamine theory of depression, study findings have suggested that 44 base pair deletions or insertions in the serotonin transporter (*SLC6A4*) may result in dysfunction or reduced expression of the transporter and, possibly, depressive symptoms or major depression^{34,35}. In the same area, the gene *SLC6A4* has been associated in several studies with increase risk for depression induced by life stresses^{35,36}. However, caution is still warranted about these associations because, as in repeated cases of genetic association findings in psychiatric disorders, several studies have failed to replicate the findings on *SLC6A4* and stress reactivity^{37,38}. Still, *SLC6A4* variations may be implicated in functional effects³⁹. As with most findings, further research is required.

Other candidate genes that have been proposed and received attention in the field of late-life depression are the genes associated with brain-derived neurotrophic factor (*BDNF*), tryptophan hydroxylase 2 (*TPH2*), and *APOE* (apolipoprotein E). Studies in *BDNF* and *TPH2* genetic associations have reported mixed results^{35,40,41}. Since one of the major complications of Alzheimer's disease is the development of

a major depressive disorder, researchers have been especially interested in the *APOE* genes. Research has suggested that the presence of one of the *APOE* alleles may predispose patients to the development of major depression⁴². Other researchers have not supported this finding^{43–45}.

GENETICS OF LATE-LIFE BIPOLAR DISORDER

Bipolar disorder has been widely recognized as having a strong genetic component⁴⁶. Heritability has been estimated at over 80%⁴⁷. Depending on which particular study is cited, first-degree relatives of adult bipolar patients may have a 3.7 to 17.5% risk for developing bipolar disorder^{22–26}. The risk of bipolar disorder diminishes in second-degree relatives (grandparents, grandchildren, aunts, uncles) of bipolar patients, though still elevated over the general population. The average concordance rate for bipolar disorders in monozygotic twins is 60%, while the concordance rate in dizygotic twins is 12%. This five-fold greater rate of concordance strongly indicates the importance of genetic factors in the familial aggregation⁴⁸.

Large samples for genetic analyses have been obtained by combining family data sets. These studies have found consistent evidence of a linkage region on chromosome 6q. Other regions that seem to be implicated include chromosomes 4q and 8q^{46,49–51}. Associations with the schizophrenia risk genes D-amino acid oxidase activator (*DAOA*), disrupted in schizophrenia 1 (*DISC1*), neuregulin 1 (*NRG1*) and catechol-O-methyltransferase (*COMT*) have been reported^{46,47,52,53}. Meta-analyses of bipolar disorder genetic association studies have also identified small effect sizes for *BDNF*, *MTHFR*, and *SLC6A4*⁵⁴. However, even these candidate genes appear to explain a small proportion of bipolar disorder's heritability since the odds ratios for individual susceptibility variants typically are less than 1.5. Specific associations for genetics in late-life bipolar disorder are unknown.

CONCLUSIONS

Late-life affective disorders are genetic complex diseases, resulting from the interplay of multiple genes, environmental factors, comorbid illnesses and life stressors. This complexity makes the results obtained from the various studies difficult to interpret and replicate. Furthermore, translating the findings into clinically useful data that results in advancements in treatment is at this point still elusive. This is especially true given that these diagnoses are syndromal, not necessarily clearly and cleanly elucidated, and therefore likely to represent a conglomerate of diseases (each with its own genetic make-up). Moreover, most of the research to date, including that discussed in this chapter, is not specific to late-life affective disorders but also to early onset affective disorders. Despite the biases and difficulties mentioned above, genetic research in late-life affective disorders remains a very exciting field of study, where new advances and breakthroughs are paving the way for future research in this area. With the advent of GWAs, there is increased hope that susceptibility loci will be identified, and that the ultimate identification and characterization of affective disorder susceptibility genes will clarify the biological mechanism of the disorders and lead to new treatment strategies.

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Environmental Factors, Life Events and Coping Abilities

Toni C. Antonucci and James S. Jackson

Institute for Social Research, University of Michigan, Ann Arbor, USA

Understanding physical and social environmental factors, life events and coping abilities in the lives of older people is best accomplished by applying both a life-span and a life-course perspective. The life-span framework allows one to incorporate information about individual experiences over the life course, the successes and failures that individuals have coping with these experiences, the tangible and human resources that have or have not been helpful, as well as the organizational or societal events that have influenced their development¹. Thus, understanding how the elderly cope with environmental factors and life events must also be considered within a dynamic family and friendship context that is multigenerational, influenced by ageing, cohort differences and historical events^{1,2}.

These intersecting contexts are characterized by exchanges which are perceived as either reciprocal or non-reciprocal over time. These transactions have been described as being of three types: those earmarked by the anticipation of linear downward transfers, i.e. from older to younger generations; those characterized by curvilinear exchanges, from the middle to younger and older generations; and resource-based exchange networks, which assume that resources will be exchanged based on availability rather than generational lineage membership. Akiyama *et al.*³ have argued that cultural and resource differences affect how generations exchange goods and services. But this argument can also be extended to expectations based on lifetime affective relationships and competencies. These resource exchanges also contribute to the individual's experience of the physical and social environments, life events they encounter and their coping capacities and abilities. Each model predicts a certain expectation or resource availability. The degree to which individuals have positively experienced these exchanges will directly affect their successful adaptation to old age.

It is clear that individuals vary in their ability to cope with the stresses and strains of life. As individuals age, it has been assumed that they are faced with more negative experiences, that the environment in terms of both physical and psychological characteristics becomes more difficult. One therefore seeks to understand the mechanisms individuals use to cope with these events.

Education has been linked to health, a well-documented finding indicating that those with higher levels of education enjoy better health. However, Antonucci *et al.*⁴ showed that this relationship can be attenuated for specific groups and levels of support; less-educated

men enjoyed the same good health as men with higher levels of education if they had key social supports. Less-educated men with larger networks, emotional, financial and sick care support from a child have better health than less-educated men without these supports. Interestingly, these findings were not found for women. The findings can be interpreted as illustrating the protective potential of social relations, though the gender differences highlight the complexity of the relationships.

Another important question is whether as people age they become better able to cope with relationships over time. Research thus far, although cross-sectional, suggests this is the case at least for most relationships⁵. Social relations with parents, children and friends do tend to decrease in negativity over time. Spousal negativity, however, remained stable over time, well into old age. It appears that part of the successful coping strategy seemed to be reduced contact with the 'difficult' party. This is less easily accomplished with a spouse living in the same household. Strained spousal relationships can be devastating, since they tend to be one of the most significant long-term relationships of adulthood, understanding what factors allow an individual to cope with stressful spousal relationships is important. Birditt and Antonucci⁶ examined relationship profiles of married people. They were able to demonstrate that married individuals with two high-quality relationships had higher well-being, if one of these was a best friend, regardless of whether they reported a positive relationship with their spouse. However, if the married individual did not have a best friend, quality of spousal relationship was singularly and significantly related to well-being. Thus, as previous research has shown, while spousal relationship is an important predictor of well-being, the potentially negative influence of a poor spousal relationship can be offset by other significant and high-quality relationships.

Coyne and Downey⁷ argue that people evidencing depressive symptoms generate a negative exchange loop for their support network. The life-span perspective is useful because individuals do not suffer isolated single depressive episodes, but rather a series of depressive episodes over time. Network members may come to recognize the negative aspects of these episodes and as Coyne and Downey argue, subsequently distance themselves from the individual in crisis. It is speculated that knowledgeable network members recognize this crisis as one of many that have negative consequences. In an effort to protect themselves from the unsuccessful

and frustrating experience of attempting to be helpful, network members may ignore, isolate or abandon the individual in crisis. This is most likely to happen, unfortunately, when the individual has a history of being maladaptive. Thus, in the case of the individual in need, but with a history of depressive episodes or other series of crises events, it may be difficult to activate a support network. On the other hand, for individuals who have a more successful history of coping with crises, their support networks are likely to respond to a crisis with both affective and instrumental support.

Recent work suggests that it is vital to consider the realistic viability of various coping behaviours^{8,9,10}. Socioeconomic status (SES) and the challenging nature of physical and social environments, especially in large urban areas, simultaneously help to afford greater opportunities for engaging in what we have termed 'negative' coping behaviours (e.g. smoking, drinking alcohol and drug use) and fewer opportunities for relying on positive coping alternatives, a traditional focus of the coping literature. Studies report that lower SES individuals have a more limited set of coping resources at their disposal compared to those with more income or education¹⁰; these findings suggest that some coping choices may not be readily available to poor populations, particularly those living in urban centres. Limited access to exercise and public recreation facilities and perceived poor neighbourhood safety have been linked to reduced physical activity levels and increased obesity in lower income neighbourhoods^{11,12}. Lower levels of education, unskilled and semi-skilled versus professional occupations and lower levels of income, have all been associated with lower levels of emotional support, less contact with friends and lower frequency of disclosing problems¹³.

At the same time, people of low SES and traditionally disadvantaged ethnic minority populations are more likely to smoke, use alcohol and be obese^{14,15}. They are more likely to live in close proximity to liquor stores¹⁶. They are also more likely to have limited access to healthy foods, putting them at greater risk for obesity and obesity-related diseases^{15,17}. This suggests that the physical and social environments characterizing the urban poor may facilitate certain negative coping mechanisms that are effective at relieving psychological symptoms of stress over more positive behaviours that may be less accessible to these populations, especially in middle and older ages^{8,9}.

Comprehending the effectiveness of potential stress-reducing strategies has important implications for understanding the epidemiology of chronic diseases that are more prevalent among low SES and certain race and ethnic groups. A variety of coping strategies may help reduce the body's response to chronic stressors; some linked to those having negative health consequences and others linked to more neutral or positive health outcomes. It is clear that more research needs to be conducted to understand the role of positive coping behaviours in alleviating the physiological responses to stressful events among different social and economic groups and at different ages and at different points in the life course².

Although it is clearly true that some people experience more crises than others, it is not always the case that those who experience a great many crises are the ones overwhelmed by them. The same environmental conditions or life events which might devastate one person may have much fewer negative effects on another. As noted above we have some information about risk factors or vulnerabilities, but we actually know very little about what makes some people capable of coping with stress and others incapable of coping with the same events. Among the explanatory hypotheses which have been offered are personality characteristics, supportive interactive exchanges, self-concept and self-efficacy. We are not at a point where there is clear

evidence in support of one explanatory concept over another and it may, of course, be some combination of these influences. Nevertheless, a series of studies by Taylor and his colleagues¹⁸ offers interesting insights about the interactive basis of coping strategies. In their studies of men recovering from uncomplicated myocardial infarction (MI), they found that wives who believed in their husbands' ability to recover were more likely to have husbands who did recover. It is especially interesting that these husbands were no less disabled by their MI than others in the study. The researchers were able to experimentally augment the wife's view of her husband's potential for recovery, which in turn directly affected the husband's actual recovery. This series of studies, replicating the impressions of many clinicians, dramatically demonstrate that individuals can be fundamentally influenced in how they face life conditions and events which confront them. The mechanisms through which these influences occur are not well understood. Bandura¹⁹ has argued that the relevant characteristic is self-efficacy. Whether self-efficacy is the critical variable or not, it is clearly evident that 'objective' facts or events are influenced by very 'subjective' factors.

Social support is not always or solely considered a coping ability or strategy. In fact, it may be best considered as a resource that individuals may call upon if needed to cope with particular environmental stressors. Moreover, successful coping is the ability to activate the kinds of support needed to meet the needs of a specific situation and to help the individual achieve a positive affective disposition. We know that people vary in their ability to develop a supportive entourage or network; in their ability to mobilize or activate this network once established; and in their ability to benefit from this support. We can best understand these differences as indications of how older people differentially experience their environments and life events; and how they cope with these experiences.

Once again it is critical to recognize the life-span and life-course contexts because the individual old person confronts a specific event with a history of either positive or negative coping experiences. A related issue is the question of how frequently the individual experiences crises and at what points in their lifetime. The now classic work of Brown and Harris²⁰ established both the lifetime vulnerability of people who experience the loss of significant intimate others early in their lives and their frequent lack of healthy, positive adult intimate relationships. Others have also established the influence on depression and overall affective well-being of negative relationships with close supportive others.

The life-course and life-span perspectives^{1,21} emphasize that people evolve throughout their lifetime and become more heterogeneous with age. As people grow older the separate experiences of their lifetime combine uniquely to shape the individual. There is every reason to believe that this is especially important to the question of how individuals cope with the challenges of old age. Although major theoretical and empirical questions have not been resolved, research concerning social support as a coping strategy does provide insights into how people manage the stresses and strains that they face in late life. It has been suggested that an individual's ability to cope with specific environmental conditions and life events is best understood through a consideration of the resources and experiences available to that person. One simplistic way to consider this is that successfully coping with stresses and strains in early life is the best predictor of the individual's ability to cope with stressful situations in later life. This is likely to be true, even if the exact nature of the stressful event varies. There is also reason to believe that individuals develop coping styles over their lifetime which can be seen to be generally successful and adaptive while others develop coping styles which are generally

unsuccessful or maladaptive. These coping strategies, at their best, match the environmental conditions and life events that the individual experiences. It is probable that, although the specific nature of these experiences will change with age, an individual's ability to cope with these events is likely to show fairly stable life-span continuity. As research clearly demonstrates, however, individual coping and adaptation competency can be improved through informal and professional intervention at all points in the individual life course.

It is also important to consider the influence of non-psychiatric factors on the experience of events in old age and how one copes with stressors and stress. Jackson *et al.*²² have noted that different racial, cultural and other socio-demographic factors fundamentally affect how a situation is experienced. If an individual is one of many suffering the same negative experience(s), the aetiology of that experience may not be devastatingly personalized. On the other hand, if everyone else in one's reference group is significantly more successful, the relative comparison can be devastating, even if 'objectively' the situation is quite positive. Similarly empirical evidence indicates that different national groups appear to vary considerably in the degree to which they respond negatively to environmental factors and life events. Recent profile analysis of social relations and relationships among different groups has suggested interesting similarities, but also differences. Using almost identical measures in the US, Germany and Japan, three sets of profile analyses were conducted. Interesting similarities and differences emerged. Cross-cultural work²³ examined social relations and mental health among older men and women in the US, Japan, France and Germany. Findings indicate that women experience more resource deficits, i.e. widowhood, illness, financial strain, than men in all these countries. In addition, the social relations of women in France and Japan were shown to offset the effects of these deficits on depressive symptoms and well-being, but this was not the case for women in the US and Germany or for men in any of the four countries. Apparently not only gender, but also the unique cultural environment, influences how well an individual copes with even the same life events.

One additional approach to understanding environmental factors, life events and coping is through the study of relationship profiles among individuals of different cultures. Studies in the US²⁴ and Israel²⁵ indicate that common network types could be conceptualized as diverse (including both family and friends), predominantly family, predominantly friends and restricted (very limited). While all four existed in both cultures there were actually two types of restricted networks in the US, those restricted to only family and those restricted to only friends. Diverse networks were associated with the highest levels of well-being, whereas restricted networks were associated with the lowest levels. Interestingly, in the US, sample individuals who might be seen as vulnerable because of the limited number of family members in their networks were shown to be less so if there were friends in the network. Among those with limited friends in their networks, however, their vulnerability was not mediated by the presence of family members. In keeping with the increased awareness of the importance of the quality of relationships, the US study also demonstrated that quality of relationship, not just the existence of the relationship, influenced mental health and depressive symptoms. Additional profile studies^{26,27} in the US, Japan and Germany reinforce these findings. The same four types of clusters were found, although each country also had additional unique clusters. The frequencies of these clusters and their associations with well-being varied by country: in the US the diverse network was the most prevalent, but this was less true in Japan and Germany.

Nevertheless, only in the US and Germany was there an association between clusters and well-being. In the US and Germany, the diverse networks were associated with better mental health and the restricted networks were associated with poorer mental health. The unique, country-specific clusters and associations with well-being are interesting and informative. For example, in Germany people with friend-focused supportive networks had relatively high levels of depressive symptoms, perhaps suggesting that the lack of family support cannot be compensated for among this post World War II cohort of elders. The lack of association between network type and well-being in Japan and the poor well-being among those with high levels of friend support in Germany suggests that there may be deep-seated cultural differences that require explanation.

Further work is needed to better elucidate which aspects of social support are more important as strategies to cope with chronic stressors (e.g. a large social network, or higher quality support received regardless of quantity) in specific environments. In addition, more research is needed to develop a better understanding of the physiological mechanisms through which social support may exert its mental and physical health benefits^{8,9}.

Finally, several researchers have shown that the size of social networks and the frequency of contact with network members change over the life course. In general, older adults tend to have smaller social networks and have less frequent contact with members than younger adults, though this depends on how social networks are assessed. It is possible that these smaller networks represent a voluntary diminution because of perceived growing time constraints, as well as an increasing awareness of their own pending mortality among elders. Research suggests that this awareness may lead older adults to build deeper relationships with a small group of friends with whom they feel emotionally close rather than maintaining a large network. These changes in the nature of social support in later life may influence its utilization and effectiveness as a coping resource over the life course among different socioeconomic and ethnic groups, but more work among diverse groups at different points in the life course is needed^{4,22}.

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Vascular Disease and Late-Life Depressive Disorder

Robert Baldwin

Manchester Mental Health & Social Care Trust, Manchester Royal Infirmary, Manchester, UK

DEPRESSION COMPLICATING VASCULAR DISEASE

Stroke and Mood Disorder

Stroke is associated with a high risk of depression as well as pathological laughing or crying and emotionalism. These are covered in Chapter 82.

Heart Disease

Soon after a coronary event about 15–20% of patients develop depressive symptoms¹. By two months, out of 804 patients with stable coronary heart disease (CHD), 7.1% met criteria for major depression and 5.3% for generalized anxiety disorder². These rates are at least double that expected in the general population.

Diabetes

The frequency of type 2 diabetes increases with age. In a cohort of patients aged 70–79 years followed for about six years those with diabetes had an increased rate of depression which attenuated after adjustment for diabetes-related co-morbidities, although this still represented a significantly increased risk compared to controls³. In this study HbA1c was a predictor of recurrent depression.

Blood Pressure and Depression

Whether the prevalence of depression increases as blood pressure rises is controversial. Rabkin *et al.*⁴ found a three-fold higher frequency of major depression in 452 patients treated for hypertension whereas Jones-Webb *et al.*⁵ found no association between resting blood pressure and self-rated depression in 4352 young subjects. Scalco *et al.*⁶ suggest that a link between depression and hypertension may be mediated by hyperreactivity of the sympathetic nervous system. There is also a potential link between low blood pressure and depression. An inverse relationship between low diastolic blood pressure (below 75 mmHg) and depressive symptoms (such as fatigue, pessimism and sadness) was shown in a study of 846 elderly men without a psychiatric diagnosis⁷.

Vascular Depression

Central to the notion of vascular depression is that vascular brain disease may predispose to depression, precipitate it or perpetuate it⁸. Features include reduced depressive ideation, more psychomotor retardation, poor insight, executive dysfunction (see below), greater disability and often an age of onset over 60. Magnetic resonance imaging (MRI) has shown higher rates of hyperintensities in the deep white matter and basal ganglia compared with control subjects, an effect seen most in late-onset cases⁹. Epidemiological studies confirm that the severity and location (especially in the basal ganglia) of white matter lesions (WMLs) seem to be causally related to late-life depression^{10,11}. Pathological data show that WMLs in the brains of depressed patients are more likely to be ischaemic compared to those seen in the brains of non-depressed subjects¹.

A clear-cut association between the symptoms of vascular depression and common cerebrovascular risk factors (such as hypertension, smoking, hyperlipidaemia and diabetes) has not been shown and the vascular depression hypothesis has its critics. McDougall and Brayne¹² analysed 13 studies comparing depressive symptoms in subjects with and without co-morbid vascular conditions and concluded there was insufficient evidence to agree an operational definition of vascular depression. However, Sneed *et al.*¹³ applied the statistical technique of latent class analysis to two naturalistic clinical trials of treatment in late-life depression. WML burden was the most accurate indicator of vascular vs. non-vascular depression. This internal consistency is important for confirming vascular depression as a distinct entity.

Chronic hypoperfusion (rather than small vessel infarction) may be another cause of vascular depression. Hypoperfusion might be secondary to hypotension (as discussed above), damage to blood pressure regulating mechanisms or arterial stiffness and/or failed compensation by the brain¹⁴. Brain hypoperfusion is not readily detectable by 'bedside' measures of cerebrovascular function other than perhaps by assessing postural hypotension.

The 'Depression–executive dysfunction syndrome' is an important feature of vascular depression¹⁵. Deficits involve executive tasks (planning, initiation and task persistence) and speed of information processing¹⁶. Clinically, these patients present with slow inefficient thinking, patchy memory impairment and are often apathetic.

DEPRESSION AS A RISK FACTOR FOR VASCULAR DISEASE

A number of studies have demonstrated that depression is a risk factor for cardiovascular and cerebrovascular events. However, the quality of evidence has been variable, for example fully accounting for factors which might explain such an association (such as severity of cardiac disease and vascular risk factors) markedly attenuates the association.

Stroke

Whether depression is a risk factor for stroke is controversial. In the Framingham study¹⁷ participants aged 65 or below with raised depression scores on a rating scale were four times more likely to experience a stroke or transient ischemic attack compared with those of the same age without depression, after controlling for smoking status and education. The effect was not seen among those who were 65 or older. A positive association between the presence of depression and the risk of stroke across the entire adult age range was, however, found in another study¹⁸.

Wouts *et al.*¹⁹ reported that patients with baseline cardiac disease and depression were most at risk of later stroke and that there was a dose–response relationship: greater severity and chronicity of depression increased the risk. This may reflect the synergistic effect of depression and vascular disease or it may be that depressive symptomatology merely reflects the severity of underlying vascular disease (reverse causality).

Heart Disease

A meta-analysis concluded that depressed mood moderately increases the risk of myocardial infarction, coronary heart disease and cerebrovascular diseases by about the same amount (odds ratio between 1.43 and 1.63)²⁰ and adversely affects the prognosis of CHD to about the same degree²¹. The evidence for depression as an *independent* risk factor for vascular events has been sufficiently robust for the American Heart Association to recommend screening for depression in cardiac patients²². As a risk factor for cardiovascular disease, depression may rank somewhere between active and passive smoking²³. However; adjustment for baseline factors, especially left ventricular function, substantially attenuates this association.

A Dutch epidemiological study of older adults showed that cardiac patients with minor (subthreshold) depression had a relative risk of subsequent cardiac mortality of 1.6 rising to 3.0 for those with major depression, after adjustment for confounding factors²⁴, an effect replicated by Ariyo and colleagues²⁵. Negative effects on cardiac outcome are seen whether or not subjects are healthy at baseline and can last for many years²⁶ but generally manifest themselves within the first year after an acute myocardial infarct²².

Diabetes

For diabetes, again there is some evidence that depression is a risk factor for diabetes but this may apply mainly to the non-insulin dependant type²⁷, the commonest form in older adults. The risk though is only modest once other factors (for example lifestyle) are accounted for. The occurrence of diabetic complications and poorer glycaemic control are more likely in depressed subjects because depression undermines motivation (Figure 75.1). Painful neuropathy

Figure depression & vascular disease

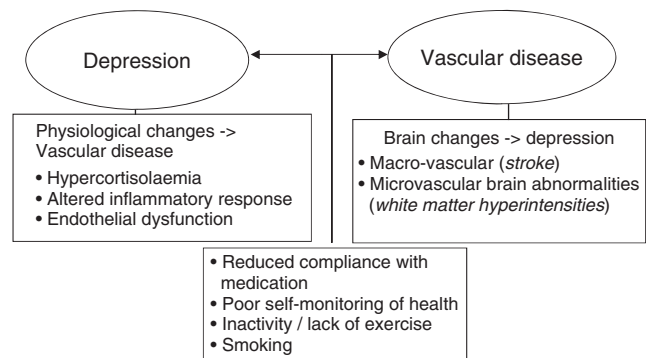


Figure 75.1 Depression and vascular disease

may be another factor in triggering depression. Diabetes can cause small vessel pathology in the brain that leads to subcortical encephalopathy, not unlike that seen in vascular depression. This may lead to both cognitive impairment and depressed mood.

Hypertension

Some evidence suggests that depressed people have higher resting blood pressure than non-depressed people⁶. This may be because depression reduces medication compliance, but one study of normotensive, non-elderly subjects followed over several years showed that high levels of depressive symptoms doubled the risk of hypertension²⁸.

Cholesterol

Low cholesterol may reduce serotonin available to the brain, although there is no convincing evidence which links cholesterol and depression via vascular disease. One study of statins did not demonstrate that lowering cholesterol increased depression²⁹.

POSSIBLE MECHANISMS OF CAUSATION

The relationship between depression and vascular disease is two-way (Figure 75.1) and there are aetiological factors which may be shared, such as genetic risk and lifestyle factors.

Genetic Mechanisms

In a study of older, middle-aged patients with late-onset depression a higher prevalence of the homozygous or heterozygous forms of the C677T mutation of the methylenetetrahydrofolate reductase enzyme (MTHFR) was found compared to those with early-onset depression³⁰. This enzyme system is relevant to homocysteine, B₁₂ and folate metabolism. A high level of homocysteine has been implicated in depression and in vascular disease³¹. No convincing role has been identified for the apolipoprotein E (APOE) gene in late-life depression.

Autonomic Dysfunction

Autonomic imbalance is associated with major depression and leads to sympathetic over-activity and/or parasympathetic under-activity,

with decreased heart rate variability, downregulated beta-adrenergic receptor function and decreased baroreflex sensitivity, making the diseased heart more susceptible to arrhythmia. Autonomic imbalance contributes to hypertension and atherosclerosis and is an independent risk factor for early cardiovascular mortality³².

Platelet Dysfunction

A number of studies have found subtle changes in one or more platelet markers such as increased plasma platelet factor 4, beta-thromboglobulin and fibrinogen suggesting enhanced platelet activation. Platelets seem to be more activated in depressed patients with heart disease than in depressed patients without. The current evidence that antidepressants improve platelet function in depression is inconclusive, but it is known that selective serotonin re-uptake inhibitors (SSRIs) can normalize platelet hyperactivity³³.

Neuroendocrine Abnormality

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and hypercortisolism are two well-known factors seen in major depression and associated with hippocampal damage and insulin resistance. The latter is a feature of the metabolic syndrome (abdominal obesity, hypertension and triglyceride abnormality) which is associated with increased cardio- and cerebrovascular disease as well as hypercoagulation, enhanced inflammatory responses and possibly endothelial damage (see below). The metabolic syndrome may be an intermediary linking depression to vascular disease.

Endothelial Dysfunction and Subclinical Atheroma

The vascular endothelium produces local vasoactive agents including nitric oxide, a vasodilator, and the peptide endothelin, a vasoconstrictor. Endothelial dysfunction is thought to precede and predict atheroma. In non-elderly subjects endothelial function was impaired irrespective of the presence of vascular risk factors³⁴. Using carbon dioxide inhalation to assess vasomotor reactivity in the middle cerebral artery, depressive symptoms were associated with lower reactivity, which is a risk factor for cerebrovascular disease³⁵. Tiemeier *et al.*³⁶ also found that carotid artery distensibility and pulse wave velocity (measures of arterial stiffness) were significantly associated with late-life depression. Lastly, the same group assessed coronary calcification and found that for every standard deviation increase in extracoronary atherosclerosis there was a 30% increase in depression³⁷.

These studies do not prove that depression causes vascular damage as causality could be in either direction. In a study of 324 adults, mean age 60.6 years³⁸, measures of carotid intima media thickness (IMT) to detect subclinical atheroma showed that baseline depressive symptoms were associated with a significantly greater three-year worsening in carotid IMT, even after adjusting for potential confounding factors. Similar conclusions were reached in a study of participants aged over 65³⁹, while another study of women showed that it was those with recurrent depression who were most at risk of subclinical atheroma⁴⁰. Again this is not proof but it is strong evidence that depressive disorder is bad for a person's arteries.

Inflammatory Responses

Inflammatory markers include C-reactive protein (CRP), interleukin-6, tumour necrosis factor (TNF) and fibrinogen. In a two-year study,

Frasure-Smith *et al.*⁴¹ investigated the relationship between depression and inflammatory markers. Elevated depressive symptoms and raised CRP two months after an acute event were overlapping risk factors for later cardiac events in men. Carney *et al.*³² demonstrated that fibrinogen was most associated with altered heart rate variability in depressed CHD patients and proposed that this could be attributable to deficits in parasympathetic modulation of immunity and coagulation. In contrast, another study found that major depression was associated with lower levels of CRP, fibrinogen and interleukin-6⁴². Nevertheless, pro-inflammatory cytokines are known to be expressed in the brains of those with late-life depression⁴³.

Behavioural and Psychological Factors

Lifestyle factors in depression include a reduced likelihood of taking medication such as antihypertensives and antidepressants, inactivity, lack of exercise, smoking and excessive alcohol intake. Clearly these can act as intermediaries between depression and vascular disease (Figure 75.1). It is also possible that patients with vascular disease subtly recognize that something is wrong before it becomes clinically apparent, thereby triggering depression.

Treatment

The presence of WMLs, especially when numerous, severe in extent or strategically located (as in the basal ganglia) is of relevance to poorer outcomes for depression in later life⁴⁴. One study has shown that in patients with late-life depression nimodipine (a drug with vasoprotective properties) when combined with antidepressant medication led to a reduction in time to remission and a longer time before recurrence compared to placebo augmentation⁴⁵. This needs to be replicated before vasoactive drugs can be recommended. Likewise, statins can improve vascular function⁴⁶ but it is not known whether they benefit depression. Omega 3 fatty acid is a promising treatment for vascular disorder but a study of two dosages in patients with late-life depressive symptoms did not show benefit to depression over placebo⁴⁷.

There is no evidence that antidepressants have adverse effects on the vasculature; possibly they are protective as SSRIs reduce platelet aggregation⁴⁸. However some SSRIs can interfere with the metabolism of some cardiac drugs. Treatment of vascular depression with electroconvulsive treatment is effective but there is an increased risk of post-treatment confusion; a recent trial showing that repetitive transcranial magnetic stimulation (rTMS) was moderately effective in older patients with clinically defined vascular depression is of interest⁴⁹.

Apathy is common in both depression and vascular disease and amphetamines have been used to treat it. There are data showing that augmentation of an SSRI with methylphenidate can improve response rates in late-life depression⁵⁰ and that problem-solving treatment for the dysexecutive syndrome associated with depression is effective⁵¹.

Metyrapone reduces adrenal cortisol synthesis. Broadley *et al.*⁵² gave this drug to 30 depressed subjects (mean age 40) and 36 control subjects, showing that cortisol levels reduced in the depressed group and endothelial function improved. More innovative studies like this are needed.

CONCLUSION

The relationship between depression and vascular disease is two-way; that is, depression may lead to vascular disease and vascular

disease may trigger depression. The overall burden of vascular disease seems to be the best predictor of subsequent depression⁵³. Clinical trials are needed to study whether drugs with vasoprotective properties can improve outcomes in depressive disorder. These will not be easy to conduct but in the meantime the management of depression should encompass the optimum treatment of both affective disorder and vascular disease.

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Mood Disorders in Parkinson's Disease

John V. Hindle

*Senior Clinical Lecturer in Neurodegenerative Diseases, School of Medical Sciences, University of Bangor, North Wales, UK,
Consultant Physician Care of the Elderly, Llandudno Hospital, Llandudno, Conwy, UK*

INTRODUCTION

Parkinson's disease is the second commonest cause of chronic neurological disability after stroke. The prevalence of Parkinson's disease increases with increasing age and in the United Kingdom is ~150 per 100 000 population with an incidence of 10.8 cases per 100 000 population. The mean age of onset of Parkinson's disease is in the seventies. The diagnosis is based on the presence of bradykinesia, rest tremor, rigidity and loss of postural reflexes, all of which are likely to be asymmetrical. It is now recognized that Parkinson's disease is much more than a motor disorder, having a spectrum of non-motor symptoms, which may occur prior to the onset of the motor signs. The non-motor symptoms of Parkinson's disease may have more impact on long-term quality of life than the motor symptoms¹. Non-motor symptoms include autonomic impairment (e.g. constipation, sweating, urinary problems, dribbling and dysphagia), psychiatric problems (e.g. depression, dementia, psychosis), sleep disturbances (e.g. sleep behaviour disorder), sensory disturbances, nutritional problems and problems of balance and falls.

This chapter will focus on depression in Parkinson's disease, which is the most common psychiatric non-motor symptom of Parkinson's disease. Depression in Parkinson's disease is associated with a poor quality of life, excess disability and carer stress, and treatment of depression can reduce functional disability².

DIAGNOSIS

Depressive symptoms are common in Parkinson's disease, especially in elderly patients. Recognition of depression in Parkinson's disease can be confounded by the symptoms of Parkinson's disease itself. It is not clear whether the symptoms of depression in Parkinson's disease differ from those of depression in persons without Parkinson's disease. Some have suggested that patients with depression in Parkinson's disease have less guilt and sadness, whereas others have shown no difference when compared with patients with major depression. Anhedonia, or the lack of ability to enjoy, may be a clinical feature of Parkinson's disease and a key symptom of depression in Parkinson's disease. Tearfulness and emotionalism can occur in Parkinson's disease in a similar manner to stroke and must not be confused with depression. Clinicians should be aware of the difficulties in diagnosing mild depression and should have a low threshold for the diagnosis in Parkinson's disease.

Depression in Parkinson's disease probably represents a spectrum of mood disturbances from mood changes before Parkinson's disease motor symptoms through to depression associated with dementia. DSM-IV criteria may not adequately capture the spectrum of mood disorders seen in Parkinson's disease. A broader definition of mood phenotype to include greater levels of psychological distress and particularly anxiety may be more appropriate in Parkinson's disease. DSM-IV criteria for depression have been modified for depression in Parkinson's disease by a consensus group to be more inclusive of symptoms, to include subsyndromal depression, to specify the timing of assessment and to use informants in those who are cognitively impaired³. These modified criteria have been validated prospectively⁴.

In a prospective cohort study of mood states in Parkinson's disease it has been shown mood disturbance can be divided into depression plus anxiety, depression alone, excessive worry and normal mood⁵.

A variety of rating scales have been used to assess depression in Parkinson's disease although they may reflect the presence of depressive symptomatology rather than depressive illness. For screening, the Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Montgomery and Asberg Depression Rating Scale (MADRS) and the Geriatric Depression Scale (GDS) have been shown to be valid. For measurement of severity of depressive symptoms, the HDRS, MADRS, BDI and Zung Self-Rating Depression Scale (SDS) are recommended. The HADS and the GDS include limited motor symptom assessment and may, therefore, be most useful in rating depression severity across a range of Parkinson's disease severity⁶. The HDRS is based on a structured interview whereas the self-rated GDS takes 5 minutes to complete, has been validated against the HDRS and is used commonly in United Kingdom practice in older patients.

EPIDEMIOLOGY

People who are prescribed anti-parkinsonian drugs are more likely than controls or diabetics to be prescribed antidepressant drugs. Recent prescription of antidepressants is associated with an increased risk of developing Parkinson's disease since depression can be a premorbid sign of early Parkinson's disease⁷. A prevalence meta-analysis showed the weighted prevalence of major depressive disorder was 17%, and that of minor depression 22% and dysthymia 13%. Clinically significant depressive symptoms were present in

35%⁸. In a study of mood disorders in Parkinson's disease in the United Kingdom the prevalence of major depression was 2.8% and minor depression was 7.7% although there was a high prevalence of up to 80% of worry and tension⁵. Depression is often unrecognized. In a survey of 1000 patients, 50% reported depressive symptoms but only 1% identified themselves as depressed⁹. This may be because people do not believe themselves to be depressed unless they feel sad. Similarly doctors can miss depression, in the majority of cases.

Age, psychosis and depression in Parkinson's disease increase mortality, with a relative risk of 2.7 in patients with depression in Parkinson's disease compared with those without depression, with the increased risk not due to suicide. The prevalence of depression is not related to disease duration. The five-year cumulative risk of depression onset is around 10%. Depression in Parkinson's disease has a chronic course, and in one study, 56% of patients with major depression at baseline still had major depression at follow-up, while by combining major and minor forms, depression was chronic in 89% of cases¹⁰. Minor depression can lead to major depression in 11% of cases over a year and major depression will lead on to minor depression in 33% of cases and will remain chronic in the majority of cases¹¹.

DEPRESSION IN PARKINSON'S DISEASE AND COGNITION

It is unclear whether cognitive impairment in Parkinson's disease is a risk factor for depression or vice versa, or whether the two sets of symptoms represent a depressive–executive syndrome. Depression in Parkinson's disease may be similar in nature to depression associated with the depression–executive dysfunction syndrome of later life, which is associated with a slow or poor response to antidepressants. Depression and dementia combined may represent a subtype of Parkinson's disease¹². Studies comparing depression in Parkinson's disease with depression without Parkinson's disease have shown similar cognitive deficits in both conditions, with reduced verbal fluency and attention deficits in depression and problems of abstract reasoning and set shifting in depression in Parkinson's disease. Patients with depressive pseudodementia respond to cueing in a similar manner to Parkinson's disease patients with subcortical dementia, which suggests that similar neural pathways are involved. Defining and diagnosing depression in Parkinson's disease in the presence of dementia are problematic since most rating scales are unsuitable. The Cornell Scale for Depression in Dementia has been used in research but takes 30 minutes to administer and may not be practical for screening in clinical practice¹³.

AETIOLOGY

It is still unclear how much the depression in Parkinson's disease is due to the biology of the disease or is the result of psychosocial effects of chronic disease. An organic basis for depression is supported by a number of factors. Depression has been shown to be common in early disease, impairing activities of daily living and increasing the need for symptomatic therapy for Parkinson's disease¹⁴. One case–control study has shown that initiation of any antidepressant therapy may be associated with a higher risk of Parkinson's disease in the two years after the start of treatment, which suggests that depressive symptoms could be an early manifestation of Parkinson's disease, preceding motor dysfunction⁷. The early pathological stages of Parkinson's disease (Braak stage 1 and 2) with

pathology in the brainstem linking to the limbic system before the onset of motor symptoms may be associated with depression and anxiety. Depressed patients are more likely to develop Parkinson's disease than they are to develop osteoarthritis or diabetes, suggesting some common underlying aetiological factors. At diagnosis, 9.2% of Parkinson's disease patients have a background history of depression compared with 4% of controls, again suggesting a link between depression and Parkinson's disease¹⁵.

There is a possible familial aggregation of unipolar depression and Parkinson's disease. Female gender, young onset, akinesia, postural and gait problems and right hemi-Parkinson's disease have a significantly higher risk of depression in Parkinson's disease. Depression is more pronounced in 'off' periods, possibly due to the deregulation of the locus caeruleus similar to that found in rapid cycling bipolar affective disorder. Positron emission tomography (PET) studies of depression in Parkinson's disease have shown reduced cortical serotonin (5HT) binding and reduced limbic noradrenaline and dopamine but no correlation with basal ganglia dopamine levels¹⁶. Abnormalities of the mesencephalon on MRI and transcranial ultrasound, frontal cortical under-activity on PET scans, and reduced caudate metabolism all suggest an organic basis for depression in Parkinson's disease.

Cerebrovascular disease is an important determinant in the aetiology of depression, especially in the elderly, and may also be an important contributory factor to the development of depression in the elderly Parkinson's disease patient.

There is no good evidence for a direct correlation between disease severity and depression. There is, however, considerable disadvantage and handicap associated with a chronic neurological disorder. Some workers have gone so far as to suggest a mainly psychosocial model for depression in Parkinson's disease. A particular pattern of negative beliefs and worries described as metacognitive style may increase the risk of depression in Parkinson's disease¹⁷. It is difficult to attribute functions of the human mind to purely neurochemical and structural changes, and intuitively it seems most likely that depression in Parkinson's disease has a major organic predisposition interacting with psychosocial factors influencing its presentation.

MANAGEMENT

The general principles of management of depression in chronic physical health problems are outlined in the guideline *Depression with a Chronic Physical Health Problem* published by NICE¹⁸.

Psychological Therapies

Provision of support, advice and counselling to both patients and carers may be all that is needed in sub-syndromal and mild cases. A clear explanation that depression is a common intrinsic part of Parkinson's disease is needed in order for patients and carers to accept appropriate help and treatment. Support groups can provide an informal form of group therapy. Counselling and support can be provided for patients and carers by social workers and counsellors with a special interest in Parkinson's disease. In the United Kingdom the Parkinson's disease nurse specialists have a key role in the provision and coordination of these support services in the management of depression. Cognitive behavioural therapy (CBT) can benefit mild or moderate depression in the elderly but there have only been small open studies of CBT in patients with depression in Parkinson's disease¹⁹. Group-based cognitive therapy or computerized cognitive

therapy has not been studied in depression in Parkinson's disease. Bright light therapy has been shown to have a positive effect on mood and motor function in a small study²⁰. Exercise interventions may help function in Parkinson's disease but the effects on mood have not been well studied²¹.

Drug Treatments

There is insufficient evidence from randomized controlled trials of the safety or efficacy of any antidepressant in depression in Parkinson's disease²². In a meta-analysis of the treatment of patients with depression in Parkinson's disease compared with elderly depressed patients without Parkinson's disease, the newer antidepressants were well tolerated in depression in Parkinson's disease. Patients with depression in Parkinson's disease may benefit less from antidepressant treatment, particularly SSRIs, than do elderly patients without Parkinson's disease. The meta-analysis showed a positive effect for depression treatment in patients with depression in Parkinson's disease whether with active drug or placebo²³. A large placebo effect because of the expectation of reward may be found in Parkinson's disease and this may be caused by placebo-induced dopamine or serotonin release in depression. This placebo effect may be an important consideration in future strategies for the management of depression in Parkinson's disease and emphasizes the need for placebo-controlled trials. In a veterans' study of the impact of a diagnosis of Parkinson's disease on depression treatment the presence of a Parkinson's disease diagnosis had little impact on the frequency and type of antidepressant treatment.

Efforts to improve the care of depressed Parkinson's disease patients should focus on improving recognition, ensuring adequacy of treatment and evaluating the efficacy of existing antidepressants²⁴.

Dopaminergic Treatment

The first option in the drug treatment of depression in Parkinson's disease is to ensure optimal dopaminergic treatment. Mood elevation and anxiety reduction can be demonstrated using levodopa infusions, and therefore smoothing out fluctuations may be important in the control of depression in Parkinson's disease. Optimization of dopaminergic therapy could include the addition of a non-ergot dopamine agonist. Direct-acting dopamine agonists acting on the D3 receptors (e.g. pramipexole) in the limbic system may have an antidepressant effect, and this may be due partly to an effect on psychomotor retardation. Pramipexole has compared favourably with sertraline²⁵. Catechol-*O*-methyltransferase (COMT) inhibitors may have a similar effect through enhancement of dopaminergic transmission and reduction in motor fluctuation, but this has not been studied in trials. Older reviews suggested that selegiline may be effective; however, later evidence-based reviews have not confirmed this.

Serotonin Re-Uptake Inhibitors

A favourable side effect profile possibly makes selective serotonin re-uptake inhibitor (SSRI) antidepressants the first-line treatment in depression in Parkinson's disease, although trial evidence for efficacy is limited²³. There is a theoretical risk of increased parkinsonism with SSRI antidepressants, and some case reports exist of akathisia, tardive dyskinesia and dystonia, but there is no clinical evidence that these effects are significant. Possible increased suicide risk need to be considered, especially when treating younger patients. The pattern

of liver enzyme induction varies from one SSRI to another, and this may influence the choice of drug. There is no trial evidence that the SSRI antidepressants help symptoms of low mood outside a depressive illness in Parkinson's disease. A generic SSRI such as sertraline may be the best choice for efficacy and tolerability since it has low propensity for interactions¹⁸.

Combined Re-Uptake Inhibitors

The noradrenaline and serotonin combined re-uptake inhibitors may have a role in depression in Parkinson's disease but have yet to show advantages over SSRI drugs. Venlafaxine, a serotonin and noradrenaline re-uptake inhibitor (SNRI) has an anxiolytic effect with a rapid onset of action in the elderly at 1–2 weeks although these effects have not been demonstrated in depression in Parkinson's disease. Mirtazepine, a derivative of mianserin, is a noradrenaline and specific serotonin antidepressant (NaSSA) which may have a rapid onset of action. Theoretically this profile of neurotransmitter action may be useful in depression in Parkinson's disease. Mirtazepine may produce weight gain which can sometimes be used to good effect in depression in Parkinson's disease. There are only a few uncontrolled reports using reboxetine or nafazodone and no studies of duloxetine in patients with depression in Parkinson's disease¹⁸.

Tricyclics

An evidenced-based review suggested that amitriptyline should be considered in the non-demented patient with depression in Parkinson's disease²⁶. A trial comparing the short-term efficacy of the predominantly noradrenergic tricyclic desimipramine with citalopram showed a significant improvement in depression at 30 days with a more rapid onset of effect at 14 days with desimipramine. This effect was outweighed by the side effects of desimipramine which can include increased tremor in Parkinson's disease²⁷. Other studies show that imipramine is most effective in patients with rigidity and nor-triptyline may improve Parkinson's disease. In elderly patients, the anticholinergic side effects of these drugs, including confusion, hallucinosis, urinary retention, blurred vision, faecal impaction and dry mouth, reduce their tolerability. Since anticholinergic drugs are now avoided by most experts in the treatment of Parkinson's disease²², tricyclic antidepressants are usually reserved for situations where other antidepressants have failed.

Other Drug Treatments

Moclobamide, a reversible monoamine-oxidase A (MAOA) inhibitor is used rarely in depression in Parkinson's disease. Some have combined MAOA inhibition with MAOB inhibition, showing enhanced antidepressant activity with no hypertensive effect. High-dose SSRI regimes have not been studied in depression in Parkinson's disease and are only weakly supported by trial evidence outside Parkinson's disease. From experience the combination of an SSRI in the day and mirtazepine at night may be useful in resistant depression in Parkinson's disease.

Other High-Intensity Therapy of Depression in Parkinson's Disease

Electroconvulsive therapy (ECT) has been shown to be effective in the treatment of depression, motor fluctuations and drug-induced

mania. Motor symptoms, especially rigidity, have been shown to respond and relapse more quickly than depression, the response being greater in the elderly. In a randomized controlled trial, repetitive transcranial magnetic stimulation (rTMS) has been shown to improve depression in Parkinson's disease to the same extent as fluoxetine²⁸. The effects on depression may last only two weeks, and concurrent antidepressants are needed. In future rTMS may be a useful alternative to ECT since it has a more focal effect, reducing adverse cognitive symptoms and avoiding the need for a general anaesthetic, in addition to improving motor function. Stimulation over the motor cortex can reduce motor slowing and improve cognition in elderly Parkinson's disease patients. rTMS requires further evaluation, but

has a promising future role in the treatment of depression in Parkinson's disease.

Summary of Management of Depression in Parkinson's Disease (Figure 76.1)

Treatment should take into account a patient's needs and preferences. People with depression in Parkinson's disease should have the opportunity to make informed decisions, including advance decisions and advance statements, about their care and treatment, in partnership with their practitioners¹⁸. It is important to consider both Parkinson's disease-related and non-Parkinson's disease-related

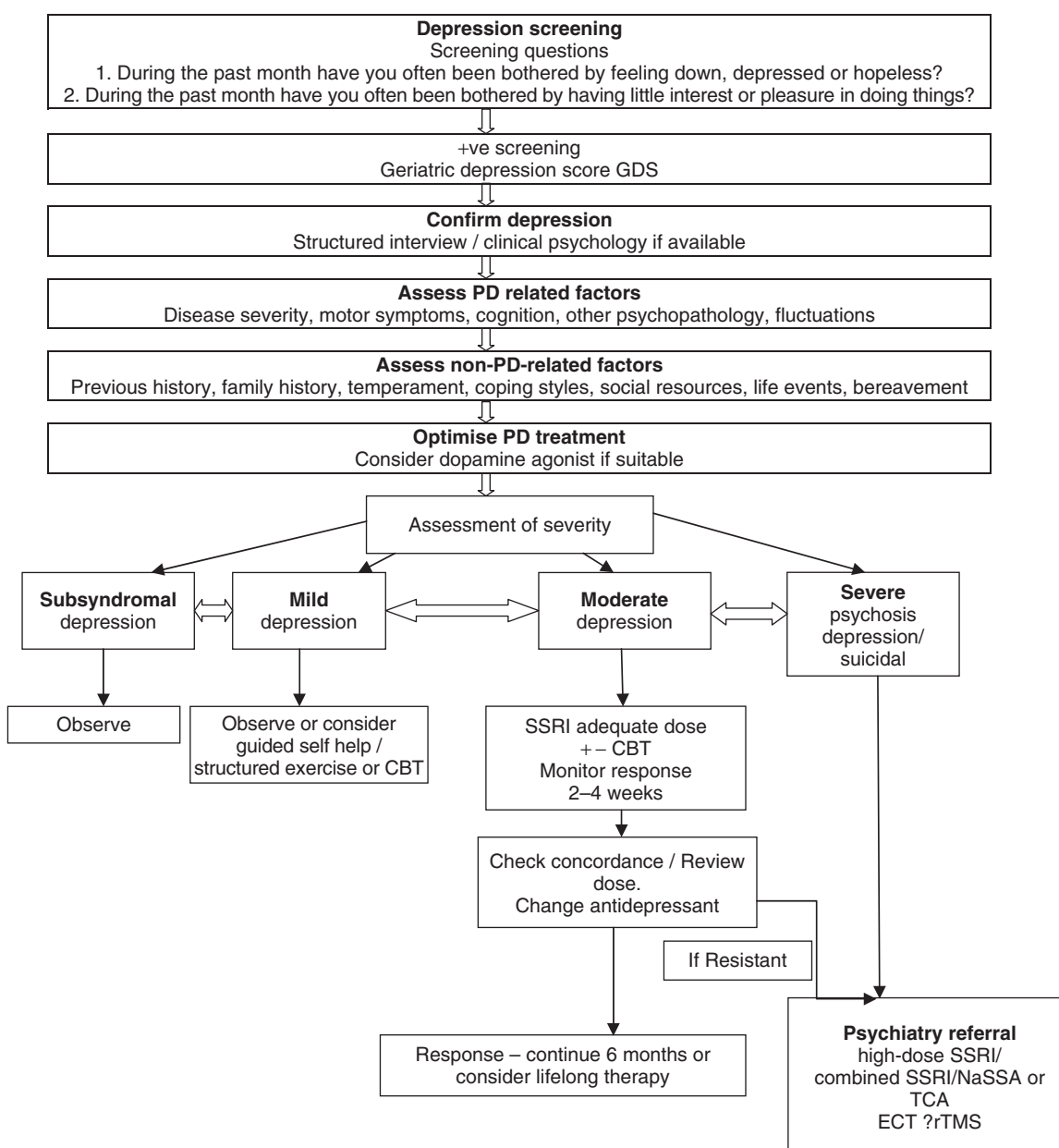


Figure 76.1 Depression screening. PD, Parkinson's disease; CBT, cognitive behavioural therapy; SSRI, selective serotonin re-uptake inhibitor; NaSSA, noradrenaline and specific serotonin antidepressant; TCA, tricyclic antidepressant; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation

factors. Parkinson's disease-related factors include reviewing and managing disease severity, motor symptoms, cognitive impairments, other disease-related psychopathology, and reviewing psychiatric side effects and fluctuating response to medications²⁹.

Non-Parkinson's disease-related factors include obtaining insights into previous psychiatric history, family history, temperament, coping styles, social resources and life events which all contribute to the aetiology of depression and may also significantly affect its management²⁹.

Two screening questions could be used and then if the person responds positively to these a rating such as the GDS completed. Once depression is identified a stepwise collaborative approach to management is based on an assessment of severity and response to interventions¹⁸. Both the number and severity of symptoms, as well as degree of impairment determine the severity of depression. A clinical assessment of severity of depression, into subsyndromal, mild, moderate and severe based on DSM categories as per the NICE guidelines may help with management decisions¹⁸. Stepped care encompasses intervention ranging from support, low intensity psychosocial interventions, and medication through to ECT and inpatient management.

In subsyndromal and mild cases a watch and wait approach may be appropriate. Counselling or CBT may be considered in mild cases. In moderate depression, the first step is to optimize dopaminergic therapy and to consider the use of a dopamine agonist if the patient is suitable. If there is no improvement, a trial of an adequate dose of a SSRI antidepressant should be considered with careful monitoring of the patient's mood and motor function. The presence of anxiety may influence the choice of a more sedative antidepressant such as mirtazepine. There is a small risk of producing a serotonin syndrome (hyperpyrexia, agitation, confusion) when selegiline is combined with tricyclics or SSRI antidepressants. The response to an antidepressant is best reviewed after 2–4 weeks of a therapeutic dose¹⁸. If there is no response after this period, a change of antidepressant can be considered. Patients should be seen on a regular basis at intervals of 2–4 weeks in the first three months and at longer intervals thereafter, if response is good. Antidepressants are usually continued for six months after remission. Two or more episodes of depression have been considered an indication for long-term treatment, but the chronic nature of depression in Parkinson's disease suggests that lifelong therapy may be needed in most cases. Referral to a psychiatrist should be considered if there is a severe depression with psychosis – especially if insight is lost, if there is medication failure in chronic depression or if there are suicidal ideas. The development of suicidal ideas or life-threatening complications, such as refusal to eat, should be taken seriously, and ECT may be considered.

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Epidemiology of Depression: Prevalence and Incidence

Ruoling Chen¹ and John Copeland^{1,2}

¹*Centre for Health and Social Care Improvement, School of Health and Wellbeing, University of Wolverhampton, UK*

²*Division of Psychiatry, University of Liverpool, UK*

INTRODUCTION

The most common geriatric psychiatric disorder is depression. Depression in older people has become a serious health-care issue worldwide. But it is often ignored, and thus opportunities are lost for prevention and early treatment. Blazer in his introduction to this section in the second edition of this book states, 'Many symptom checklists have been used to estimate the burden of depressive symptoms in community populations. The results of these studies are remarkably consistent, with the range of significant depressive symptoms estimated to be 10–25%'. He quotes from 10 studies. In order to update information on prevalence and incidence of depression, we have now been able to review 38 studies of prevalence and 10 of incidence appearing in the English language during the last 10 years. Blazer continues, 'Lower prevalences of major depression have been found in more rural samples with an estimate of less than 1% in a North Carolina rural sample, whereas urban studies have typically estimated higher prevalence. The prevalence of dysthymic disorder is generally higher than that for major depression, approximately 2–8%, depending on the instrument used in the survey'.

The problem that Blazer highlights including the diverse case-finding methods causing difficulties in drawing comparisons has substantially increased since the second edition. Most of the studies reviewed used at least one of the following instruments to diagnose depression, including those clinically based, replicating a psychiatrist's diagnosis using ICD-10, DSM-III, -R DSM-IV criteria, CSNMD (clinically significant non-major depression) applied to the results of case-finding instruments, others to the results of psychiatrists' clinical examination, CIDI and GMS-AGECAT (Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy), and those based on scale cut points such as GDS-30, 15-item GDS (score >5), EURO-D scale, CES-D (Center for Epidemiological Studies Depression Scale). Although there is some correspondence between these methods, precise comparisons are difficult to make. There is also the problem of the type of selection of samples, whether or not they were purely community based, that is to say people living in their own homes or also in residential accommodation, or included hospital admissions, especially in those

countries where hospitals still accommodate large proportions of patients. Are the samples randomly selected and what were the dropout rates? Was a one-stage method of identification used or a two-stage method with loss due to death, illness or refusal between stages (a particular problem in the calculation of incidence rates). Studies report their samples, grouping the data in different ways. Most do not state the kind of case they are trying to identify. The majority are likely to be interested in cases suitable for intervention but use DSM or ICD criteria aimed specifically at improving reliability between psychiatrists, and therefore likely to lead to a narrower more sharply defined concept of a case than would be acceptable to most clinicians who, as a consequence, are tempted to invent their own 'subsyndromal' cases for treatment. Nevertheless, in spite of these difficulties it may be possible to draw broad conclusions.

Blazer warns: 'One of the major tasks facing psychiatric epidemiologists studying depression cross-nationally in the elderly is to explain the residual depressive symptoms in community samples not easily captured by the usual diagnostic categories' and goes on to quote the 34 studies of the prevalence of late-life depression where the prevalence varied from 0.4% to 35%¹. Arranged according to diagnostic category, major depression was relatively rare (weighted average prevalence of 1.8%), minor depression more common (weighted average prevalence of 9.8%) while all depressive syndromes deemed clinically relevant yield an average prevalence of 13.5%. Depression was more common among women and among older people living under adverse socioeconomic circumstances.

Below, we review 38 studies of the prevalence of depression and 10 of incidence across the world, published over the last 10 years, divided by continent and whether clinically-based diagnosis was used or scale cut scores.

PREVALENCE OF DEPRESSION IN EUROPE (TABLE 77.1)

The EURODEP study² (1999) reported the prevalence of depression in nine countries in Europe, which had all used the GMS-AGECAT assessment and computerized differential diagnosis. This instrument was designed to facilitate large epidemiological studies in older people where psychiatrists could not be employed for screening every

case. A case was defined as one requiring some form of intervention. This package was prepared before DSM-III and ICD-10 revisions but AGE-CAT cases of depression have been shown in a number of studies to equate with major depression, dysthymia and 'depression not otherwise specified'.

In the EURODEP study² all subjects were aged 65 or over, randomly selected or total samples in the community except for the Dublin centre which sampled a general practice, to yield a total of 13 803 individuals. Substantial differences in the prevalence of depression were found, with Iceland having the lowest level at 8.8%, followed by Liverpool 10.0%, Zaragoza 10.7%, Dublin 11.9%, Amsterdam 12.0%, Berlin 16.5%, London 17.3%, Verona 18.3% and Munich 23.6%. There was no constant association between prevalence and age. A meta-analysis of the pooled data on the nine European centres yielded an overall prevalence of 12.3% (95% CI, 11.8–12.9%); for women 14.1% (95% CI, 13.5–14.8%) and for men 8.6% (95% CI, 7.9–9.3%).

Using Clinically Based Diagnosis

DSM-IV criteria. Prevalence of major depression in France. Ritchie *et al.*³ randomly recruited 1873 non-institutionalized persons aged 65 and over from the Montpellier district electoral rolls to assess current and lifetime depression symptoms using the Mini-International Neuropsychiatric Interview. Cases identified were re-examined by a clinical panel. Major depression was found to be 3% and lifetime prevalence 26.5%. A level consistent with many other studies.

GMS-AGECAT. Como (personal communication) reported the findings of the random community study of participants aged 65 and over in Tirana, Albania, which formed part of the EURODEP study but entered at a later date. Prevalence levels of depression were 19.3%. This is the first EURODEP study from a Muslim state in Europe. de Jonge and colleagues found levels of depression in the second Zaragoza study of persons aged 55 and over of 11.2%⁴. McDougall *et al.*⁵ reported the prevalence of depression in the Medical Research Council Cognitive Function and Ageing Study (MRC-CFAS), and the prevalence of depression and depressive symptoms in those living in institutions⁶. The MRC-CFAS is a population-based cohort comprising 13 004 individuals aged 65 and above from five sites across England and Wales. A stratified random sub-sample of 2640 participants were interviewed by GMS-AGECAT, showing that the prevalence of depression in those living at home was 9.3% (similar to the 9.2% in an earlier Liverpool study ($n = 5222$)² and for those living in institutions was 27.1%. The prevalence increased if subjects with concurrent dementia were included. This is of interest because such cases of dementia are often excluded in surveys of depression but may require treatment for depression. Also, such exclusion may give a spurious impression of a fall in the proportion of people with depression with increasing age as the prevalence of dementia escalates. Depression was more common in women (10.4%) than men (6.5%) and was associated with functional disability, co-morbid medical disorder and social deprivation.

Using Scale Scores

EURO-D based prevalence in 10 European countries. Castro-Costa *et al.*⁷ administered the EURO-D with score ≥ 4 to cross-sectional nationally representative samples of non-institutionalized persons aged 50 years and over ($n = 22 777$) across 10 European

countries – Denmark, Sweden, the Netherlands, Germany, Austria, Switzerland, France, Spain, Italy and Greece – as part of the SHARE study. The distribution of gender and age did not differ between countries. Educational levels were lowest in the Latin countries (France, Italy and Spain) and in Greece. The highest country-specific depression prevalence rates were found in France (33.7%), Italy (33.7%) and Spain (36.8%), with a 9% difference between the lowest of these (33% in France) and the next lowest (24% in Greece). Prevalence in the remaining countries was 18–19%. Heterogeneity between countries was statistically significant ($p < 0.001$). The pattern and extent of between-country differences were not affected by direct standardization for gender, age, education, verbal fluency or memory. But the SHARE data are limited by the relatively low proportion of households and individuals responding. This may, unfortunately, represent a secular trend in more developed countries. The net effect may be an underestimation of the true prevalence of depression^{8,9}.

The EURO-D scale was developed in order to include more centres in the EURODEP study. It was shown to have strong conceptual validity and high internal consistency when applied to data from 21 724 subjects. EURO-D scores tended to increase with increasing age, unlike the levels of prevalence of depression. Women had generally higher scores than men, and widowed and separated subjects were higher than those who were currently or never married.

GDS in the Netherlands. Stek *et al.*¹⁰ assessed the prevalence of depression and correlates from a representative sample of 599 community-based 85-year-old subjects with a MMSE > 18 . The prevalence of depression, as measured with a GDS-S score of 5 points or more, was 15.4%, not very different from the EURODEP level for Amsterdam of 12.0%.

CES-D in the Netherlands. Van't *et al.*¹¹ assessed the prevalence of depressive symptomatology and risk indicators in 2850 participants aged 75 years or more in the PIKO study. The prevalence of depressive symptoms was 31.1% across all participants.

PREVALENCE IN THE AMERICAS (TABLE 77.2)

Using Clinically Based Diagnosis

DSM-IV. One study¹⁵ in the United States examined the current and lifetime prevalence of depressive disorders in 4559 non-demented individuals aged 65 to 100 years. This sample represented 90% of the elderly population of Cache County, Utah. The researchers employed DSM-IV criteria for major depression, dysthymia and sub-clinical depressive disorders using a modified version of the Diagnostic Interview Schedule. The point prevalence of major depression was 4.4% in women and 2.7% in men ($p = 0.003$), similar to the level (3%) found by Ritchie *et al.*³ in France using similar criteria. Other depressive syndromes were surprisingly uncommon (combined point prevalence, 1.6%), and the current prevalence of major depression did not change appreciably with age. They also estimated that lifetime prevalence of major depression was 20.4% in women and 9.6% in men ($p < 0.001$) (Ritchie 26.5%), decreasing with age.

In Quebec, Preville *et al.*¹⁶ used the 'Enquete sur la sante des aines' study, conducted in 2005–6, to obtain a representative sample ($n = 2798$) of community-dwelling older adults. Of this sample, 12.7% met the criteria for depression, mania, anxiety disorders or benzodiazepine dependency. The 12-month prevalence rate of major depression was 1.1% (again demonstrating the low levels found with these criteria) and the prevalence of minor depression was 5.7%.

Table 77.1 Prevalence of depressive symptoms in community samples of older adults in Europe

<i>Author</i>	<i>Sample</i>	<i>n</i>	<i>Screening method</i>	<i>Findings</i>
<i>Clinically based diagnosis</i>				
Como (personal communication)	Random community sample in Tirana, Albania (65 years and over) part of the EURODEP Consortium	1239	GMS-AGECAT	19.3% depression
de Jonge <i>et al.</i> ⁴	Second random community sample in Zaragoza, Spain (55 years and over)	4803 (M2771, F2032)	GMS-AGECAT	11.2% depression, 2.7% men, 9.3% of women
Ritchie <i>et al.</i> ³	Community sample in France (65 years and over)	1873	Mini-International Neuropsychiatric Interview DSM-IV criteria	3% for major depression (26.5% with major depression lifetime prevalence)
Intorre <i>et al.</i> ¹²	Community sample in Rome, Italy (70–85 years)	359 (M167, F192)	Mental health assessment	9% men, 19% women with possible depression
McDougall <i>et al.</i> ⁵	Five centre community samples MRC CFAS (England and Wales) (65 years and over)	2640	GMS-AGECAT	9.3% depression (95% CI, 7.8–10.9%) living at home
<i>Score cut point</i>				
Stek <i>et al.</i> ¹⁰	Community sample in the Netherlands (85+) MMSE > 18	500	GDS-S (score 5 or more)	15.4% depression (no age, gender or racial difference in prevalence) 25% of participants who were seen by their GP with depressive symptoms
Jansson <i>et al.</i> ¹³	Twin pairs in Sweden (50+, mean 72) female monozygotic (MZ), Male MZs, Female DZs, Male DZs, opposite-sex DZs)	959 (123, 90, 207, 109, 430)	CES-D	16% men, 24% women (clinically significant depressive symptoms)
Wilson <i>et al.</i> ¹⁴	Community sample living alone in their own home in UK (80–90)	376	GDS (score 5 or more)	21% depression
Castro-Costa <i>et al.</i> ⁷	Community sample in 10 European countries (50+)	22 777	EURO-D (score 4 or more)	The prevalence of symptoms higher in the Latin ethno-lingual group 33.7% France; 33.7% Italy; 36.8% Spain other countries in between these and 24.0% Greece
van't <i>et al.</i> ¹¹	Community sample in the Netherlands (75+) the PIKO study	2850	CES-D (score 16 or more)	31.1% depression

ICD-10, SCAN. Two studies were conducted in Brazil, and one study in Peru, Mexico and Venezuela. Costa *et al.*¹⁷ investigated the prevalence and correlates of common mental disorders with semi-structured interviews administered by a psychiatrist. During the study, a two-phase population survey of 392 persons aged 75 years and over were screened for depression and mental disorders using the General Health Questionnaire (GHQ-12) and Geriatric Depression Scale (GDS). In the second phase, 20% were evaluated using the SCAN to generate ICD-10 diagnoses. The prevalence of depressive episode was 19.2% with no effect of gender or age. Lay-administered interviews were thought to underestimate the prevalence of mental disorders in older people and they recommended one-month prevalence as more appropriate for the oldest-old given patchy recall of distant experiences.

DSM-IV. Xavier *et al.*¹⁸ described the prevalence of minor depression as 12% of the oldest-old in a random representative sample ($n = 77$ subjects) aged 80 years and over from the Brazilian rural southern region using DSM-IV criteria. A small but interesting study which was found to be consistent with others quoted here concerning younger age groups.

DSM-IV and ICD-10 GMS-AGECAT. Investigating the prevalence in five locations in Latin America, Guerra *et al.*¹⁹ conducted a one-phase cross-sectional survey of 5886 people aged 65 and over from urban and rural locations in Peru and Mexico and an urban site in Venezuela. Depression was identified according to diagnostic criteria, and scale scores with EURO-D cut-off point. DSM-IV major depression prevalence varied between 1.3% and 2.8% by site (consistent with other sites in Europe and North America), ICD-10 depressive episode between 4.5% and 5.1%, GMS-AGECAT all forms of clinical depression between 30.0% and 35.9% (high, because of the low level of education stage one of the algorithm was used, i.e. level of depression in all participants regardless of other diagnoses such as dementia), and for EURO-D depression between 26.1% and 31.2%. The prevalence of EURO-D depression was in a similar range of 24–36.8% in Latin countries in Europe. The prevalence of DSM-IV major depression was lower than that in men in the United States (4.4% in women and 2.7% in men). The authors of this important study (part of 10/66 Dementia Research Group) from low and middle income countries draw several conclusions, ‘the population attributable prevalence fractions suggest that 13.6% of the prevalence of severe disability in Peru, 32.4% in Mexico and 31.7% in Venezuela could be independently attributed to depression’; ‘a strong and independent association between subsyndromal depression and an established criteria of relative severe disability, 15 or more disability days in the past month, would appear to indicate that DSM-IV and ICD-10 diagnostic criteria might indeed be missing a substantial proportion of clinically significant cases. We have also demonstrated... that the true population burden of depression is significantly under estimated by these very narrow diagnostic definitions’; ‘late-life depression in Peru, Mexico and Venezuela is similar to that seen in Europe’.

Using Scale Scores

Alvarado and colleagues²⁰ in the SABE (Salud Bienestar y Envejecimiento) study interviewed a sample of 10 661 persons aged 60 and over in seven Latin American and Caribbean countries using the GDS. They found the prevalence of depression varied from 0.4–5.2% in men and 0.3–9.5% in women. They concluded that current socioeconomic conditions and health status as well as functional disabilities mainly accounted for gender differences in prevalence.

PREVALENCE IN ASIA – CHINA AND TAIWAN (TABLE 77.3)

Using Clinically Based Diagnosis

GMS-AGECAT studies in mainland China. In urban communities, the prevalence of depression was 2.2% – about five times lower than that of older people in Liverpool including older people of Chinese origin²² – but in poorer rural communities depression was higher at 6.0%²³. Could these low levels be due to failure to recognize cultural ways of expressing depression? This would seem unlikely because the GMS-AGECAT diagnosis, as in other studies, was formally validated by local psychiatrists using a translated version and comparing their diagnosis with one provided by computer. Chong *et al.*²⁴ and Chen *et al.*²⁵ investigated the one-month prevalence of clinically significant depression in 1500 subjects aged 65 years and older, randomly selected from three communities of urban and rural elderly in southern Taiwan. One-month prevalence of depressive neurosis and major depression were 15.3% and 5.9%, respectively. These results reflect similar differences in prevalence rates from Europe and North America found in surveys of younger adults.

CIDI. In a Beijing study²⁶ involving urban and rural regions, the overall 12-month prevalence of depression was 4.33% (2.65% in men, 5.83% in women). The overall lifetime prevalence was 7.83% (4.65% in men and 10.66% in women).

Using Scale Scores

CES-D. The prevalence of depression was 9.5% (6.7% men and 11.7% women) in a two-centre study by Pan *et al.*²⁷: north China (Beijing) 14.9% rather different from south China (Shanghai) 4.1% ($p < 0.001$). These also appeared to be low rates for a CES-D study.

GDS (≥ 8). In Hong Kong, three urban random community samples were undertaken by Li *et al.*²⁸ examining obesity and depression among 18 750 men and 37 417 women aged 65 or over in health centres using the 15-item Chinese GDS (CGDS; ≥ 8) found 4.9% depression in men and 7.9% for women ($p < 0.001$). Since attendance at the health centre was voluntary severe depressive symptoms may have been under-represented. Chi *et al.*²⁹ using the same instrument with a random community sample of 917 people aged 60 and over found depression levels of 11.0% men and 14.5% women, a prevalence rate not dissimilar to that in the United States, England and Finland. The same scale was used by Chou *et al.*³⁰ in a representative community sample of 1903 Chinese aged 60 and above, finding prevalence rates for the oldest-old of 31.1%; for those aged 70–79, 22.4% and for those 60–69, 19.1%. Chiu *et al.*³¹ compared depression in urban and rural elders finding that 20.1% of urban elders and 12.8% of rural samples were classified with depressive symptoms. Tsai *et al.*³² using stratified random sampling of 1200 elderly participants from northern, middle, southern and eastern regions of Taiwan found the prevalence of depression to be 13%, within the range of previous findings 4.9–20.1%^{28,31}. Overall, the prevalence of depression based on this scale and cut-off point in Taiwan and Hong Kong lay between 4.9–31.1% – an apparently large geographical disparity.

The GMS-AGECAT prevalence of depression was higher in rural than that in urban mainland China, while in Taiwan the urban sample had a relatively higher prevalence of depressive symptoms than that found in rural elders³¹.

Table 77.2 Prevalence of depressive symptoms in community samples of older adults in North, South and Central America

<i>Author</i>	<i>Sample</i>	<i>n</i>	<i>Screening method</i>	<i>Findings</i>
<i>North America – Clinically based diagnosis</i>				
Steffens <i>et al.</i> ¹⁵	Community sample in Cache County, Utah (non-demented; 65–100 years)	4559	Diagnostic Interview Schedule	2.7% men, 4.4% women (major depression), prevalence did not change with age. 1.6% with other depressive syndromes 9.6% men, 20.4% women (lifetime depression, decreasing with age)
Heo <i>et al.</i> ²¹	Community sample – nationally representative survey data from 2006 BRFSS in US (18+ years)	188 292	Doctor diagnosed	15.7% depression; 11% men, 20.6% women (117% increase from year 2005–50 in older people)
Preville <i>et al.</i> ¹⁶	Community sample in Quebec	2798	DSM-IV	12.7% depression (12-month prevalence: 1.1% major depression, 5.7% minor depression)
<i>South and Central America – Clinically based diagnosis</i>				
Xavier <i>et al.</i> ¹⁸	Community sample of Italian descent in rural Southern Brazil (80+)	77	DSM-IV	12% minor depression (frequency greater in women)
Guerra <i>et al.</i> ¹⁹	Urban and rural community sample in Peru and Mexico and an urban in Venezuela (65+)	5886	DSM-IV GMS- AGECAT EURO-D	1.3–2.8% DSM-IV major depression 4.5–5.1% ICD-10 depressive episode 30.0–35.9% GMS-AGECAT 30.0–35.9% GMS AGECAT depression 26.1–1.2% EURO-D depression
Costa <i>et al.</i> ¹⁷	Community sample in Brazil (75+)	392	SCAN/ICD10 GHQ-12 GDS	19.2% depressive episode No age, gender or racial difference in prevalence
<i>South and Central America – Score cut point</i>				
Alvarado <i>et al.</i> ²⁰	Urban community sample in Latin America and the Caribbean region		GDS	Overall 0.4–5.2% men depression, 0.3–9.5% women depression Buenos Aires 2.1% men 3.2% women Barbados 0.4% men 0.3% women Havana 1.9% men 6.7% women Mexico City 1.6% men 6.2% women Montevideo 3.4% men 5% women Santiago 5.2% men 9.5% women São Paulo 2.2% men 4.9% women

PREVALENCE IN OTHER ASIAN COUNTRIES (TABLE 77.3)

Using clinically Based Diagnosis

GMS-AGECAT with ICD-10, DSM-IV. Rajkumar *et al.*³³ investigating 1000 participants aged over 65 years from a rural south Indian community using the Geriatric Mental State, ICD-10 and DSM-IV diagnoses of major depression within the previous one month found 12.7%.

GMS AGECAT with DSM IV. Suh³⁴ with a community sample of 1241 persons in Korea aged 65 and over found 10.5% depression.

GMS AGECAT. With the community sample of 1156 people aged 65 and over in Nakayama, Japan, Ikeda *et al.*³⁵ found a level of depression of 5.8% (AGECAT) and 4.3% (DSM IV) (personal communication).

GMS AGECAT (Arabic version). Ghubash *et al.*³⁶ investigated the prevalence of depression within a random sample of households representing the United Arab Emirates national population. They screened 610 UAE nationals aged 60 years and over, irrespective of the age of other individuals in each household. The researchers found 20.2% with depression at syndrome case level. An important study and the only one so far from Arabic countries. More studies are required from the Islamic world as a whole.

Using Scale Scores

GDS-15 cut-point 5/6. Wada *et al.*³⁷ used this scale to assess depression in a 2695 community sample aged 60 and over living in five rural Asian towns. They found 29.0% of depression overall. Indonesia was 33.8%, (sample size 411), Vietnam 17.2% (379) and Japan 30.3% (1905). Malhotra *et al.*³⁸ using the same scale and cut-off point with an 1181 community sample of Sri Lankans (aged 60 years and over) found a prevalence of depression of 27.8% overall (24.0%

men, 30.8% women), lower than in Indonesia and Japan and higher than in Vietnam. In Japan, Niu *et al.*³⁹ assessed depression in 1058 community-dwelling Japanese individuals aged 70 years and over using the 30-item Geriatric Depression Scale with two cut-off points: 11 (to include most clinical depressions) and 14 (severe depressions) yielding 34.1% and 20.2%, respectively.

GDS (Korean). The majority of studies have rarely examined both urban and rural populations simultaneously. Kim *et al.*⁴⁰

Table 77.3 Prevalence of depressive symptoms in community samples of older adults in Asia

Author	Sample	n	Screening method	Findings
<i>Clinically based diagnosis</i>				
2. Chong <i>et al.</i> ²⁴	Community sample in Taiwan (65+)	1500	GMS-AGECA	5.9% major depression (one month) 15.3% depressive neurosis high
Ghubash <i>et al.</i> ³⁶	Community sample in United Arab Emirates (60+, 68.6 ± 8.3)	610 (M347, F263)	GMS- AGECAT	20.2% depression
Chen <i>et al.</i> ²²	Urban community sample in Hefei City, central-east China (65+)	1736	GMS-AGECAT	2.2% (95% CI, 1.5–2.9%) depression (five times lower than that of older people in Liverpool, UK)
Chen <i>et al.</i> ²³	Rural community sample in China, low income (60+)	M754 F 846	GMS-AGECAT	6.0% (4.8–7.3%) with depression (85.9% living with family members)
Ma <i>et al.</i> ²⁶	Urban and rural community sample in Beijing, China (60)	1601	CIDI 1.0	4.33% 12-month prevalence 2.65% men, 5.83% women (7.83% lifetime prevalence, 4.65% men, 10.66% women)
Rajkumar <i>et al.</i> ³³	Rural community sample in south Indian (65+)	1000	GMS ICD-10	12.7% One month prevalence (95% CI 10.64–14.76%)
Chen <i>et al.</i> ²⁵	Community sample in Taiwan (65+)	1500	Assessment by psychiatrists (CSNMD)	8.8% prevalence of 1 month
Suh <i>et al.</i> ³⁴	Community sample in Korea (65+)	1241	GMS AGECA/DSM IV	10.5% depression
Ikeda <i>et al.</i> ³⁵	Community sample in Nakayama, Japan (65+)	1156	GMS-AGECAT	5.8% depression
<i>Score cut point</i>				
Thongtang <i>et al.</i> ⁴¹	Community sample in Thailand	1713	Thai GDS TMSE	12.78% depression 8.23% only depression (5.43% men, 9.63% women) 4.55% both depression and cognitive impairment (male 2.8%, female 5.54%)
Kim <i>et al.</i> ⁴⁰	Urban and rural community sample in South Korea (65+)	485(U) 649(R)	Korea form of the GDS (KGDS)	No difference between urban and rural in prevalence
Li <i>et al.</i> ²⁸	Urban community sample in Hong Kong (65+)	56167 M18750 F37417	GDS	4.9% depression men (4.6–5.2%) 7.9% depression women (7.6–8.1%)
Chou <i>et al.</i> ³⁰	Community sample in Hong Kong (60+)	1903	GDS-15 (score 8 or more)	(31.1% ± 9.7%) depression for 80+ 22.4% ± 4.2% for 70–79 19.1% ± 2.8% for 60–69

Table 77.3 (continued)

Author	Sample	n	Screening method	Findings
Wada <i>et al.</i> ³⁷	Rural community sample in three Asian countries (60+)	411 (Ind) 379 (Viet) 1905 (Japan) total 2695	GDS-15 (score 5 or 6)	33.8% Indonesia 17.2% Vietnam 30.3% Japan 29.0% depression overall
Chi <i>et al.</i> ²⁹	Urban random community sample in Hong Kong (60+)	917	GDS-15 (score 8 or more)	11.0% depression men 14.5% depression women
Chiu <i>et al.</i> ³¹	Urban and rural community sample in South Taiwan	678 (urban) 327 (rural)	The Chinese GDS	20.1% depression urban 12.8% depression rural
Tsai <i>et al.</i> ³²	Community sample in northern, middle, southern and eastern regions of Taiwan	1200	GDS-S	27.5% depression
Pan <i>et al.</i> ²⁷	Community sample in northern and southern China (Beijing and Shanghai) (50–70)	3289	CES-D	14.9% Beijing 4.1% Shanghai 9.5% depression overall 6.7% men 11.7% women
Niu <i>et al.</i> ³⁹	Community sample in Japan (70+)	1058	GDS (score ≥ 11 mild and severe, 14 severe)	34.1% mild and severe depression 20.2% severe
Malhotra <i>et al.</i> ³⁸	Community sample in Singapore (60+) of elderly Sri Lankans	1181	GDS-15 (score ≥ 6)	27.8% depression 24.0% men 30.8% women

investigated 485 urban-dwelling and 649 rural-dwelling participants within Kwangju, South Korea for depression. No differences rural/urban were found, findings being consistent with other studies in China.

GDS Thai (TGDS). Thongtang *et al.*⁴¹ using in addition the Thai Mini Mental State Examination (TMSE), screened 1713 elderly people in 35 communities from four districts finding a prevalence of depression of 12.7% (8.2% depression alone (5.4% men, 9.6% women) and 4.5% depression with cognitive impairment (2.8% men, 5.5% women).

PREVALENCE IN AFRICA (TABLE 77.4)

Using Clinically Based Diagnosis

CIDI DSM IV. Gureje *et al.*⁴² estimated major depressive disorder in a representative sample of 2152 people aged 65 years and older by sampling households in the Yoruba-speaking areas of Nigeria. Twelve-month and lifetime prevalence estimates of major depressive disorder were 7.1% and 26.2%, respectively. The 12-month prevalence estimate of major depressive disorder was higher than the rate of 1.1% in the study in Quebec¹⁶.

Using Scale Scores

GDS. Baiyewu *et al.*⁴³ undertook a two-stage study. The community-based samples aged 69 years and over were first screened for

dementia, 2627 individuals in Indianapolis of whom 17.2% underwent clinical assessment including GDS and 2806 in Ibadan with 21.6% having clinical assessment. Prevalence of depression was estimated using weights indicated by the sampling stratification. The prevalence of mild and severe depression was similar for the two sites: 12.3% and 2.2%, respectively in Indianapolis and 19.8% and 1.6% in Ibadan. However, Ibadan men had significantly higher prevalence of mild depression than Indianapolis men. Poor cognitive performance was associated with significantly higher rates of depression in Ibadan.

PREVALENCE IN AUSTRALIA

Using Clinically Based Diagnosis

DSM. Snowden and Lane⁴⁴ re-examined the data from a 1985 survey of 146 elderly people living at home. Depression and cognitive impairment were also assessed in a local hostel ($n = 42$) and nursing home ($n = 74$). DSM diagnoses were made by an old-age psychiatrist. In the nursing home, 23 residents could not respond to interview questions and were considered to have severe dementia. Subjects in all three settings were followed up after four years. They found that seven community subjects (4.5%, 95% CI 1.3–8.3%) and three in residential care fulfilled criteria for major depression. The estimated total prevalence of depressive disorders among older people in Botany was between 13.0% and 13.6% (4.6% major depression, 3.6% dementia with depression, 5.4% other depressive disorders).

Table 77.4 Prevalence of depressive symptoms in community samples of older adults in Africa

Author	Sample	n	Screening method	Findings
<i>Clinically based diagnosis</i>				
Gureje <i>et al.</i> ⁴²	Community sample in Ibadan, Nigeria (65+)	2152	CIDI DSM-IV	7.1% (5.9–8.3) major depressive disorder (12-month prevalence) 26.2% (lifetime prevalence) (95% CI 24.3–28.2%)
<i>Score cut point</i>				
Baiyewu <i>et al.</i> ⁴³	Community sample in Indianapolis and Ibadan, Nigeria of African Americans and Yoruba (69+)	2627 (451) 2806 (605) total 5433	Screening GDS for sub-sample	19.8% Ibadan (mild depression) and 1.6% (severe depression) 12.3 Indianapolis% (mild depression) and 2.2% (severe depression)

INCIDENCE OF DEPRESSION IN OLDER PEOPLE

In the original chapter for the second edition of this book Blazer wrote, incidence studies of depression in the elderly are extremely rare in the literature. Two studies provide some estimate of incidence, however, Rorsman *et al.*⁴⁵ estimated incident depression from the Lundby cohort in Sweden among 2612 individuals evaluated in 1957 and later in 1972 (i.e. 15-year incidence) until the age of 70. The cumulative probability of suffering a first episode of depression was 27% for men and 45% for women, a very high incidence figure in this cohort (especially compared to lifetime prevalence figures, reported in other studies, of less than 15%). The annual age-standardized first incidence for depression, all degrees of impairment included, was 0.43 for men and 0.76 for women. Incidence appears to decrease in the studies as individuals aged, especially for men. Eaton *et al.* (1997)⁴⁶ estimated the incidence of major depression over 10 years for the ECA cohort from Baltimore. They found an overall estimated annual incidence of 3.0 per 1000 per year, with a peak while subjects were in their 30s, a smaller peak when subjects were in their 50s and a definite lower incidence in the elderly. Prodromal symptoms were present many years before the full criteria for major depression were met, further linking the minor and major depression. Foster *et al.* (1991) estimated the incidence of depression in long-term care facilities. In a cohort of 104 new admissions followed for a year, they found an incidence of 14%. One-third of these new cases were diagnosed as major depression, two thirds as minor depression.

In the last 10 years, nine important studies on the incidence of depression in older people have been conducted in the Netherlands, UK, London, USA, Austria, Thailand and Republic of Korea. Depression was diagnosed in these studies by using the 15-item GDS?score >4 or 5)? the 10-item CES-D (score >8)? the Geriatric Mental State, SDS (Zung self-rating depression scale) and the Thai Geriatric Depression Scale (TGDS). Participants were generally community-dwelling older people or patients registered with primary care practices participating in community-based cohort studies.

Incidence Rate

After one-year follow-up: Thongtang *et al.*⁴⁷ assessed 1713 elderly people in 35 communities from four districts in Bangkok using the Thai Geriatric Depression Scale (TGDS) and the Thai Mini Mental State Examination (TMSE). The point incidence (one year) of depression was 1.58% in men and 5.68% in women⁴⁷.

After two-year follow-up^{46,47}: out of 521 people aged 65 years and over from an East Asian population, incident depression was found in 63 (12% or 6% per year). In Austria, 331 non-demented and never-depressed individuals were followed up for 30 months, by which time 31.4% had developed a subsyndromal, minor, or major depressive episode. In a prospective cohort study with index assessment and two-year follow-up of patients initially aged 65 years and over registered with two south London practices ($n = 1164$), the incidence of depression was 8.4% (4.2% per year)⁵⁰.

An eight-year follow-up⁵¹: A study of a cohort of 5653 community-dwelling elderly free of dementia was conducted in the Netherlands. For depressive syndromes, the incidence rate was 7.0 (95%CI 6.0–8.3) per 1000 person-years which was more than doubled when episodes of depressive symptoms were included. The rate was almost twice as high for women compared with men. The incidence did not appear to change with age.

During a follow-up period of 15 years, depressive symptoms in 464 men aged 64 to 84 years were assessed by the Zung self-rating depression scale (SDS). The cumulative incidence for depressive symptoms was 44%⁵².

Among the oldest old, depression is frequent^{13,14}. In a population-based prospective study, depressive symptoms were annually assessed in 500 people aged 85 years or above with the 15-item GDS, using a cut-off of 4. During a mean follow-up of 3.9 years, the annual risk for the emergence of depression was 6.8%.

Of 376 participants aged between 80 and 90 years, who lived alone and followed-up for one year, the annual incidence of depression was 12.4%, with the depression identified by GDS of 5 or more.

RISK FACTORS

Risk factors for incidence of depression 'Dispositional optimism' predicted a lower cumulative incidence of depressive symptoms with an odds ratio of 0.23⁵². Poor daily functioning and institutionalization predicted depression¹³. Subsequent development of clinically significant depressive symptoms was associated with baseline increased scores in depression (OR 1.68, 95% CI 1.21–2.34)¹⁴.

Family factors

Risk factors associated with prevalence depression include not living close to family and friends (OR 2.54, 1.44–4.47)¹⁴. Having severe

troubles with relatives and pre-existing cognitive impairments may enhance the probability of developing a late-onset depression⁴⁹.

Vascular depression hypothesis

The vascular depression hypothesis suggests that age-related vascular diseases and risk factors contribute to late-life depression. A study of 1796 elders ages 70–79 without depression at baseline were followed-up to assess two-year incidence of elevated depressive symptoms, defined as a score >8 on the 10-item Center for Epidemiologic Studies Depression (CES-D) scale. After adjustment for demographic data and physical and cognitive functioning, increased risk of depressive symptomatology remained associated with several vascular conditions, including metabolic syndrome and its components, coronary heart disease, a positive questionnaire for angina, and high haemoglobin level. Cumulative vascular risk based upon a composite of 10 vascular diseases and risk factors was independently associated with incident elevated depression at two-year follow-up after controlling for demographic data, physical and cognitive functioning, and selected co-morbid medical conditions. These results provide support for the vascular depression hypothesis in demonstrating an association between vascular conditions and risk factors and subsequent risk of depressive symptomatology. The authors suggest older adults with vascular conditions and risk factors require close monitoring of depressive symptoms⁵³.

CONCLUSIONS

From all this data there emerge certain conclusions. There are major differences between classification schemes. There is a difference between clinically based diagnosis, whether by humans or computers, and those derived from scale scores. The latter tend to be higher if only because they usually include all participants regardless of diagnosis. They give an estimate of morbidity and co-morbidity, and point to a level of suffering in a community. There is a major difference between diagnostic classifications ostensibly aimed at improving reliability between psychiatrists, so necessary in the 1960s and 1970s in the USA and now elsewhere, and diagnostic classifications such as GMS-AGECAT, which aim to identify cases for intervention. Clearly the evidence is now strong that these are quite different types of cases⁵⁴. Those persons concerned with relieving suffering rather than cutting back on health resources need to take up this cause and those responsible for international classification systems may need to reassess their aims. Has the time come to move from improving reliability between doctors to acknowledge that in vast areas of the globe doctors are not particularly active or apparent and that guidance on suitability for intervention must have a higher priority? That after all is what it is about. No longer is it sensible to hide under the shield of 'they may have symptoms, but do they have disability'? Many excluded from the classifications do have serious disability.

The increase in the number of studies in Asia and South America is gratifying but we need more studies in Africa to persuade governments that mental illness, the hidden illness, is behind much human disability and is treatable.

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Neuroimaging in Geriatric Depression

Faith M. Gunning

Institute of Geriatric Psychiatry, Department of Psychiatry, Weill Cornell Medical College, USA

OVERVIEW

Geriatric depression is a complex and heterogeneous syndrome that likely has multiple environmental and biological determinants. Among these, structural and functional abnormalities in specific cerebral networks likely confer vulnerability that increases the likelihood of developing geriatric depression. The aetiology of such brain abnormalities may be diverse and likely results from processes commonly occurring in older adults including cerebral ageing, vascular, inflammatory, autoimmune and endocrine processes¹.

Significant effort has been devoted to characterizing alterations that occur in the brains of elderly depressed patients. In this chapter, we discuss work using a number of different neuroimaging modalities to advance our understanding of the neurobiology of late-life depression. In addition, when data exist, we will examine the question of how these neuroimaging correlates of late-life depression relate to specific features of the illness, including the presence of cognitive deficits and the course of the illness.

VOLUMETRIC STUDIES

Volume reductions are often present on T1-weighted magnetic resonance imaging (MRI) in the brains of elderly depressed patients in select frontal, limbic and subcortical regions. These regions include the anterior cingulate cortex, the orbitofrontal cortex, the neostriatum, the hippocampus and the amygdala^{2–11}. The anterior cingulate cortex and orbitofrontal regions demonstrate the most consistent alterations. MRI-based parcellation of prefrontal regions in elderly depressed patients confirms that relative to elderly control subjects, there are significant attenuations of grey and white matter in the anterior cingulate cortex and the gyrus rectus, as well as reductions of grey matter in the orbitofrontal cortex¹².

In addition to the presence of volumetric differences between elderly depressed patients and non-depressed individuals, there is evidence that specific clinical characteristics of the illness may be related to volumes of select regions^{2,7,13–15}. For example, reduced amygdala volumes have been reported in recurrent depression¹⁵. In addition, one of the early studies to use voxel-based morphometry (VBM), revealed that smaller hippocampal volumes in elderly depressed patients were associated with greater number of years since first depressive episode¹³. Furthermore, apathy has been associated with smaller volume of the right anterior cingulate

cortex in elderly subjects, although this may not be specific to depressed patients¹⁶. Finally, antidepressant medication itself may impact regional brain volumes. Lavretsky and colleagues⁷ observed that orbitofrontal grey-matter volumes were larger in patients with geriatric depression who had been treated with antidepressant medication relative to drug-naïve patients, although these volumes were smaller than those of age-matched controls.

Although most of the volumetric studies in late-life depression have focused on specific regions of interest (ROIs), a study by Andreescu and colleagues² applied an automatic labelling pathway technique to 24 ROIs to examine the relationship of volumes of grey-matter regions in elderly depressed patients to age of onset and duration of illness. Relative to non-depressed subjects, elderly depressed patients had smaller volumes in 17 of the ROIs examined. Both shorter duration of illness and later age of onset were correlated with smaller volumes of parahippocampal and inferior parietal ROIs. However, a later age of onset was also correlated with smaller volumes of several frontal and temporal ROIs, the cingulum and the putamen. These findings were interpreted to support the hypothesis that small volumes in late-life depression may be more related to neurodegenerative changes than the result of a toxic stress response².

In cross-sectional studies of geriatric depression, poor performance on tasks of episodic memory and executive functions have been associated with reduced volume of the hippocampus and select prefrontal regions^{8,17}. In one study of late-life depression, volumes from specific ROIs within the prefrontal cortex were calculated and related to performance on a battery of executive measures¹⁷. Poorer performance on tests of response inhibition was associated with smaller anterior cingulate volumes, whereas poorer performance in nonverbal inductive reasoning tasks were associated with smaller gyrus rectus volumes¹⁷. Longitudinal studies of the hippocampus, indicate that smaller hippocampal volumes predict MCI and subsequent dementia^{8,9}.

There is little published data about the relationship of MRI volumes to response of late-life depression to treatment. However, in one study of elderly non-demented depressed patients, the relationship of remission status following treatment with escitalopram and volume of subregions of the anterior cingulate cortex was evaluated. Regional anterior cingulate volumes were manually outlined (dorsal, rostral, anterior subgenual and posterior subgenual) on high-resolution T1-weighted images. Analyses revealed that patients who failed to remit following escitalopram treatment had smaller dorsal

and rostral anterior cingulate grey-matter volumes than patients who remitted, whereas subgenual cortical volumes did not differ between the groups¹⁸.

Volumetric differences in elderly depressed patients tend to be small and the relationship to clinical variables, when significant, tend to be modest in strength. More sophisticated shape analysis and/or 3D surface mapping may be used to better localize structural abnormalities in late-life depression⁴. For example, the caudate nucleus was examined using traditional volumetry and a 3D brain-mapping technique in a group of patients with late-life depression and non-depressed elderly comparison subjects. Relative to comparison subjects, depressed subjects had significantly lower mean caudate volumes bilaterally. Furthermore, the 3D maps localized these reductions in volume to the caudate head and volume reductions were correlated with depression severity⁴. Another study used shape analysis to examine the amygdala in a small group of healthy elderly individuals and elderly depressed individuals. Although no significant volumetric differences were found for either amygdala, regions of specific shape variation were detected. The most notable difference was contraction of the amygdala in depressed patients relative to comparison subjects in a region associated with the basolateral nucleus¹⁹.

A number of methodological issues must be considered when interpreting morphometry studies. The specific neurohistological processes that account for the observed volume reductions in late-life depression cannot be distinguished. In addition, manual ROI morphometry is quite time consuming and a lack of standard guidelines used for delineation of ROIs across laboratories may contribute to differences between studies. VBM can overcome some of these weaknesses because of the relative ease with which it can be carried out, as well as its ability to examine the entire brain at once. However, VBM studies of ageing brains may be particularly problematic because of the requirement that MR images are transformed from native space to standardized stereotaxic space and this space is most often defined by a template that reflects a young, healthy brain. Approaches that apply templated ROI maps to MRI data in native space may increase both reliability and validity of findings from VBM studies.

Even within the context of the limitations of morphometry, the studies to date reveal a pattern of frontostriatal and limbic abnormalities, with some evidence that such abnormalities may be associated with the clinical presentation and perhaps even the course and outcome of the illness. In future studies, advancements in techniques (e.g. shape analysis) may facilitate more precise localization of structural anomalies in late-life depression.

WHITE MATTER INTEGRITY IN LATE-LIFE DEPRESSION

White-Matter Hyperintensities

Traditionally, the most common method to study white-matter abnormalities on MRI has been the examination of white-matter hyperintensities (WMH). These WMH are typically observed in T2-weighted sequences and are taken to indicate white-matter damage. They can be discrete, or punctate, or may appear more confluent with the lateral ventricles.

WMH are more frequent and severe in older depressed individuals than in age-matched controls and occur most often in subcortical grey-matter regions and frontal white-matter projections^{10,20–26}.

Even in cognitively intact individuals, WMH are often associated with subtle cognitive deficits, particularly executive dysfunction and slowed processing speed^{27–30}. Furthermore, in elderly depressed patients, increases in WMH volumes at longitudinal follow-up predict the development of dementia, especially among non-Alzheimer type dementias³¹.

Some studies suggest that WMH also may influence the course of affective symptoms in late-life depression. For example, longitudinal CHS data found that large cortical white-matter lesions and severe subcortical lesions were significant risk factors for developing depressive symptoms⁹. Furthermore, WMH burden and subcortical grey-matter hyperintensities have been associated with response to both ECT^{32,33} and antidepressant treatment^{32,34} although disagreement exists^{35,36}. One report indicated that basal ganglia lesions predicted failure to respond to antidepressant monotherapy with a sensitivity of 80% and a specificity of 62%³⁷.

Neuropathological correlates of WMH in brains of elderly depressed individuals provide rather compelling support for a vascular contribution to the pathophysiology of late-life depression. In a study of neuropathological correlates of WMH in 20 depressed patients and 20 elderly comparison subjects (see^{38–40}), all of the deep WMH examined in the depressed subjects showed evidence of ischaemia compared with less than a third of deep WMH in control subjects. Whereas large deep WMH were usually ischaemic in both groups, punctate lesions were typically characterized by ischaemia in depressed patients but not in controls. Periventricular WMH were characterized by ependymal loss, varying degrees of demyelination and cerebral ischaemia with no differences in pathological correlates detected between patients and controls⁴¹. Furthermore, in the depressed subjects, the ischaemic DWMH showed a striking predilection for the dorsolateral prefrontal white matter⁴⁰.

The methods of quantifying WMH are characterized by some of the same limitations as morphometry studies. That is, there are a number of different WMH rating scales and these scales vary widely in reliability and sensitivity. Also, postmortem studies of WMH suggest that such white-matter abnormalities reflect a number of pathological processes; however, MRI scans do not always allow a reliable discrimination among the underlying processes. Although recent advancements in measurement (i.e. volumetric measurements and regional WMH measurements) partially address these limitations, the introduction of newer MRI techniques to examine white-matter integrity may help to achieve not only better differentiation between true white-matter lesions and spurious findings, but will also help to identify the location of white-matter abnormalities and perhaps clarify their underlying causes.

MRI STUDIES OF MICROSTRUCTURAL WHITE-MATTER ABNORMALITIES

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) offers a promising approach for the examination of cerebral white-matter integrity in geriatric depression. DTI measures the magnitude and direction of self-diffusion of water. When no barriers to such diffusion are present, diffusion occurs equally in all directions (i.e. it is isotropic). However, when barriers to this diffusion are present, the diffusion tends to follow the long axis of those barriers (i.e. diffusion is anisotropic). Barriers to diffusion in the brain include cell membranes, myelin sheaths and white-matter fibre tracts. Diffusion anisotropy can be quantified by

a number of different metrics, including fractional anisotropy (FA). FA, which ranges in value from 0 to 1, is a measure of the strength of the directional dependence of diffusion and generally reflects the organization of fibre tracts. In regions with dense, highly organized fibres (e.g. the corpus callosum) FA values are the highest.

Commensurate with the morphometry findings of reduced volumes of select frontostriatal and limbic regions, DTI studies reveal that depressed elderly patients exhibit compromised integrity (i.e. reduced FA) of the white matter of prefrontal regions and the anterior cingulate^{42,43}, perhaps within the context of more subtle, widespread white-matter abnormalities⁴⁴. A study that explored the relationship of diastolic blood pressure and FA in elderly depressed patients revealed significant associations between FA and diastolic blood pressure throughout the anterior cingulate and in multiple additional frontotemporal and frontostriatal white-matter regions⁴⁵. These findings, albeit preliminary, suggest that reduced microstructural integrity of frontal-subcortical white matter may be one of the mechanisms by which high blood pressure, a known vascular risk factor, confers vulnerability to geriatric depression.

Regarding cognitive correlates of FA in geriatric depression, one study has examined the relationship of FA in depressed elders to performance on an executive task⁴⁶. Response inhibition, one aspect of executive function that has been shown to predict antidepressant response⁴⁷, was assessed with the Stroop colour-word task. Voxel-wise correlational analysis revealed significant associations between FA and Stroop colour-word interference in multiple frontostriatal-limbic regions, including white matter lateral to the anterior and posterior cingulate cortex and white matter in prefrontal, insular and parahippocampal regions.

In addition to a relationship between FA and response inhibition, there is evidence that lower FA in distributed cerebral networks is associated with poor antidepressant response of geriatric depression⁴⁸, although some disagreement exists⁴⁹. Furthermore, a preliminary study of the association of the serotonin transporter gene status to both FA and response to antidepressant treatment indicated that depressed elderly S-allele carriers had lower FA than L homozygotes in frontolimbic brain areas, including the dorsal and rostral anterior cingulate, posterior cingulate, dorsolateral prefrontal and medial prefrontal regions⁵⁰. S-allele carriers also had a lower remission rate than L homozygotes, introducing the possibility that the risk for chronicity of geriatric depression in S-allele carriers may be mediated by frontolimbic white-matter compromise.

Magnetization Transfer Imaging

Magnetization transfer ratio (MTR) is another method that can be used to study white-matter integrity in geriatric depression. MTR imaging provides information about the macromolecular structure of cerebral white matter based on the interaction of the normally observed tissue water signal with protons contained in large macromolecules (including myelin). Macromolecular structures in the brain (e.g. myelinated axons) are ordinarily not detected by MRI because of their extremely short transverse relaxation times. However, protons bound to them can be selectively excited using off-resonance radio-frequency pulses. To achieve MTR contrast, two MR sequences are used. The first is a proton density (PD) weighted sequence, which reflects the total water signal. The second uses an additional pulse prior to the basic proton density sequence and serves to null the signal from water molecules that are associated with macromolecules. The percent contrast difference between the two image

sets is usually expressed as the magnetization transfer ratio: $MTR = (M0 - MSAT)/M0$. Reduced MTR reflects reduced macromolecular volume fraction. Studies conducted in neurodevelopment and multiple sclerosis suggest that DTI and MTR may provide complementary information about white-matter integrity with DTI mostly reflecting organization of fibre tracts and MTR being particularly sensitive to myelin and axonal integrity^{51,52}.

Kumar and colleagues⁵³ were the first to demonstrate the use of MTR in geriatric depression. Their results from a small study of elderly depressed patients suggest that, relative to their elderly counterparts, older depressed patients have lower MTR in the genu and splenium of the corpus callosum, the neostriatum and the occipital white matter. In a larger study of elderly patients with major depression and elderly non-psychiatric comparison subjects, we reported lower MTR in multiple left hemisphere frontostriatal and limbic regions, including dorsolateral, dorsomedial, dorsal anterior cingulate, insula, periamygdalar, subcallosal, posterior cingulate and regions lateral to the lentiform nuclei⁵⁴. However, there have been no studies published to date that have reported the relationship of MTR to features of depressive illnesses in the elderly.

FUNCTIONAL NEUROIMAGING STUDIES

Functional neuroimaging studies in late-life depression reveal a pattern of abnormal activation of frontolimbic regions, generally characterized by hypoactivation of specific dorsal cortical regions and hyperactivation of select limbic regions. One of the first published reports of task-related activation in geriatric depression, reported results of a PET study that compared cerebral blood flow during a word activation task between elderly patients with severe depression and normal elders. During the word activation task, hypoactivation of the dorsal ACC and the hippocampus was detected⁵⁵. This finding of attenuated activation of the dorsal ACC during a verbal fluency task was later replicated by another group in an fMRI study of older depressed individuals in remission who had experienced multiple previous episodes of depression⁵⁶. In depressed elderly patients, relative to age-matched controls, Aizenstein and colleagues⁵⁷ reported decreased prefrontal activation in addition to increased caudate activation in response to an explicit sequence learning task.

Emerging evidence from functional neuroimaging studies suggests that select frontolimbic structures are not only abnormally activated in late-life depression, but these abnormalities are related to clinical features of the illness. For example, in a preliminary study of late-life anxious depression, subjects completed an executive control task. Relative to elderly depressed patients, elderly subjects with anxious depression produced a significantly greater and more sustained signal in the dorsal anterior cingulate, posterior cingulate and lateral prefrontal cortex. These preliminary results not only suggest specific activation patterns unique to anxious depression but also demonstrate the utility of using fMRI to examine the neurobiology of clinical subtypes of late-life depression⁵⁸.

Regarding the relationship of illness state to frontolimbic activation, an fMRI study of elderly depressed patients using an emotional oddball task reported that relative to healthy comparison subjects, the elderly depressed patients demonstrated attenuated activation in select frontolimbic regions, including the right middle frontal gyrus and the cingulate, as well as the inferior parietal cortex. Activation in the middle frontal gyrus appeared depressive state-related, whereas attenuated activation in the posterior cingulate and inferior parietal regions persisted in the remitted subjects, consistent with a disease-related alteration⁵⁹.

In a study examining the relationship of cerebral activation to course of illness, acutely depressed patients exhibited hypoactivation of the ventromedial prefrontal cortex in response to the emotional evaluation of negatively-valenced relative to positively-valenced words. However, this hypoactivation normalized after several months of uncontrolled antidepressant treatment⁶⁰. Furthermore, in a controlled, antidepressant treatment trial, during a cognitive control task elderly depressed patients demonstrated hypoactivation in the dorsolateral prefrontal cortex and diminished functional connectivity between the dorsolateral prefrontal cortex and dorsal ACC prior to treatment⁶¹. Although this hypoactivity in the right dorsolateral prefrontal cortex subsided after successful antidepressant treatment, the reduced functional connectivity between the dorsal ACC and the DLPFC persisted.

Taken together, the functional neuroimaging results indicate that abnormal frontolimbic activation is present in elderly depressed patients during the depressed state and these abnormalities may normalize, at least in part, in response to antidepressant treatment.

MAGNETIC RESONANCE SPECTROSCOPY

Magnetic resonance spectroscopy (MRS) provides important information about the neurochemical environment. Different molecules have unique MR spectra that can be quantified by taking the area under the signal curve. In most cases, the values are not absolute, so it is customary to take ratios of the measure of interest to some standard metabolite, for example choline.

Kumar and colleagues⁶² used MRS to examine biochemical abnormalities in left frontal WM and bilateral anterior cingulate grey matter of elderly depressed patients. They observed higher choline to creatine as well as myoinositol to creatine ratios in the white, but not grey, matter of patients relative to age-matched comparison subjects. Results from a follow-up MRS study suggested that cognitive performance was associated with levels of metabolites as measured by 2D MRS in healthy controls, but not in patients with geriatric depression⁶³. There was a significant difference in the overall pattern of associations between the four measured metabolites and verbal learning and processing speed in elderly depressed patients compared to elderly controls. The weaker relationship between metabolites and specific cognitive domains in patients with late-life major depressive disorder was interpreted by the authors to suggest that cognitive performance in geriatric depression may be associated with biochemical changes in frontostriatal circuitry.

In a recent study of elderly depressed patients and age-matched control subjects, MRS spectra were acquired from voxels that were placed in the left frontal white matter, left periventricular white matter and left basal ganglia. Results indicate that elderly depressed patients had significantly lower NAA/creatine ratio in the left frontal white matter and higher choline/creatine and myoinositol/creatine ratios in the left basal ganglia when compared with the control subjects. Furthermore, the myoinositol correlated with global cognitive function among the patients⁶⁴.

Most recently, MRS was used to examine biochemical correlates of response to antidepressant treatment⁶⁵. Using a 3D chemical shift imaging sequence, tissue-specific differences in markers of energy metabolism, including high-energy phosphate compounds (beta and total NTP, PCr) and pH, were examined in 13 older adults with major depression pre and post 12 weeks of treatment with sertraline and 10 age-matched controls. Total NTP was reduced in the white matter, but not in the grey matter, in the depressed group prior to

treatment depression group. Intracellular pH was higher in the grey matter of subjects with pre-treatment depression but similar to levels of controls after treatment⁶⁵.

Although there are only a handful of published reports that have used MRS to examine the neurochemical environment in geriatric depression, this appears to be a promising technique that, especially if used in combination with other measures of tissue integrity (e.g. DTI), is likely to be a quite powerful tool to advance our understanding of the neurobiology of late-life depression.

CONCLUSIONS AND FUTURE DIRECTIONS

For more than two decades, scientists have taken advantage of the remarkable capacity of neuroimaging to visualize and quantify patterns of cerebral abnormalities in psychiatric illnesses. As with many features of psychiatric illnesses, MRI observations are notable for the variability of findings between studies. However, when considering evidence from multiple MRI modalities across the numerous studies that have been performed, a general pattern of findings has emerged. This pattern is characterized by compromise in the structure of select aspects of frontostriatal and limbic networks coupled with hypoactivation of cortical regions critical for cognitive control and hyperactivation of limbic structures involved in emotional reactivity. Both structural compromise and abnormal activation in frontolimbic systems appear to be associated with poor response to antidepressants. These findings that relate MRI indices to antidepressant response raise the possibility that structural abnormalities may interfere with the normalization of frontolimbic activity in individuals who fail to respond adequately to antidepressants. While each neuroimaging technique alone has limitations, the concurrent application of more than one technique yielding complementary information can increase the information gleaned from future neuroimaging observations and significantly advance our understanding of the pathophysiology of depression in the elderly.

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Clinical Features of Depressive Disorders in the Elderly

Davangere P. Devanand and Steven P. Roose

Division of Geriatric Psychiatry, New York State Psychiatric Institute, and the College of Physicians and Surgeons, Columbia University, New York, USA

Late-life depression refers to depressive syndromes in people who are older than 60–65 years. Depression causes considerable personal suffering and adversely affects family members and other caregivers. In elderly subjects, depressive syndromes are often associated with chronic medical illnesses that can precipitate depression. Conversely, the presence of depression can worsen the outcomes of many medical disorders and promote disability. Depression occurs commonly in a variety of other neuropsychiatric syndromes, including mild cognitive impairment, dementia, stroke and Parkinson's disease.

In the elderly, the fear of ageing and its effects are common. Older adults commonly state that since they are getting old it is normal to feel depressed. This view is often shared by family members and even health care providers. However, the vast majority of elderly individuals are not depressed, and therefore depression should not be considered a normal part of the ageing process.

Many elderly patients describe their mood accurately as depressed or anxious, but some tend to deny and suppress it and they come to clinical attention only at the insistence of family members. Somatization is common in older patients, particularly gastrointestinal symptoms like constipation. Some patients are unsure if they are depressed because they have begun to feel less energetic and lose interest in activities in the absence of a clear-cut depressed mood. Some of these patients have dysthymia or minor depression. In the elderly, one important distinction to make is whether the first depressive syndrome began in late life or whether it represents a pattern of recurrent depression throughout adulthood, because the underlying aetiology may differ in these two types of patients. Premorbid personality does carry into old age, but its impact on the presentation of depression varies considerably. Personality itself may change with ageing and life experiences. Psychological changes in the elderly may be environmentally determined, but may also be based on changes in neurobiology; for instance, catecholaminergic neurons in the locus coeruleus decay markedly with ageing and this change may be related to the rarity of late-onset anxiety disorders and lower prevalence of major depression in the elderly population.

PREVALENCE

Depressive syndromes are common in late life¹ and represent the leading cause of poor functioning and disability worldwide that has

an overall adverse impact comparable to cardiovascular disease². A low proportion of clinically depressed elderly individuals seek help and typically they present to primary care practitioners. However, primary care physicians correctly diagnose only a minority of depressed patients and consequently few patients receive treatment for this illness. An even smaller proportion is referred for psychiatric care.

Epidemiological studies indicate that among the elderly, milder sub-threshold depressive syndromes may be more common than major depression, which ranges in prevalence from 1 to 3%³. However, the rate of major depression changes significantly depending on the setting. Studies of patients in medical clinics report rates of 10% for major depression; in non-psychiatric hospital in-patients the rate increases to 15–25%, and it is even higher in nursing homes⁴. These studies primarily used assessment instruments and diagnostic criteria that were developed for and/or validated in a younger population, and it is not known whether the adoption of age-adjusted diagnostic criteria would produce significantly different results.

DIAGNOSTIC CLASSIFICATION

A depressive disorder may be diagnosed by DSM-IV (or DSM-IV TR) clinical criteria only if the depressive symptoms adversely affect work, family or social functioning, or if the subject seeks or has received treatment for depression. The clinical entities in the current nomenclature identified in young adults that also occur in older adults are major depression (unipolar or bipolar, single episode or recurrent, with or without melancholia, with or without psychotic features); dysthymic disorder; and atypical depression. Disorders that are common in the elderly include mood syndromes secondary to a general medical condition, and subsyndromal depression including minor depression. Depression with cognitive impairment is a common presentation in elderly patients.

MAJOR DEPRESSION IN OLDER PATIENTS

Clinical observations and systematic studies suggest that patients with late-life major depression may well be different in important dimensions from younger adult patients with major depression. Such differences may reflect age-associated physiological changes, the changes associated with depressive illness (the ravages of a depressed life)

and/or the impact of co-morbid medical conditions⁵⁻⁷. For example, the differences in young versus old people may manifest in how functional impairment as a symptom of depression is expressed differently through the life cycle. Depression-associated dysfunction in childhood can present as poor performance in school or antisocial behaviour, in young adults as dissatisfaction in work or love, and for older patients as hypochondrias and increased utilization of medical resources⁸.

The cumulative impact of depressive illness itself in patients with onset of illness early in life may be a critical factor. By the time a patient with early onset depression reaches age 60, they have already suffered through recurrent episodes. There is increasing evidence that the number of depressive episodes as well as the total amount of time spent 'depressed' in a lifetime is associated with less robust response to treatment and the development of chronic symptoms⁶. Furthermore, some data suggest that the cumulative time spent in a depressed state is correlated with changes in brain structure that may subsequently affect the phenomenology and treatment response in future episodes⁵.

Moreover, changes in the brain that occur with age may also affect how the individual interacts with the environment, and can result in increased vulnerability to depression. Regional brain dysfunction, especially in the pre-frontal areas, is associated with instability of temperament, vulnerability to and the intensification of the experience of distress, and a degrading of coping mechanisms. Such alterations in an individual's psychic capacities may result in increased social isolation, loss of independence, and related behaviours that can precipitate, intensify, or prolong a depressive episode. Thus, by the time a patient with recurrent depression reaches late life, the consequences of the disorder itself, and maybe the impact of treatments received, will influence the presentation, psychobiology, treatment response and course of illness during late life.

Alternatively, the differences that exist in younger versus older depressed patients may indicate that late-life depression is a distinct disease entity and, despite some commonality, early onset and late-life depressive illness are significantly different in fundamental aetiological ways. An example of such aetiological heterogeneity is the distinction between the late-life patient with recurrent major depressive illness with onset of the first episode early in life, and the late-life patient with first onset of major depressive illness after the age of 60. The hypothesis that early-onset (before age 50 or 60) and late-onset depression may be, despite similarities, distinct entities is suggested by data from epidemiological, brain imaging, treatment, and long-term outcome studies⁹⁻¹¹. Patients with late-onset depression have a lower rate of family history of depression, and a greater frequency of MRI abnormalities compatible with ischaemic cerebrovascular disease¹⁰. These lesions have been associated with symptoms of cognitive impairment, a decreased and slower response to antidepressant medication and a deteriorating course of illness^{12,13}.

In summary, the label late-life depression may be attached to a group of patients who share some commonalities but who, nonetheless, suffer from a heterogeneous group of disorders that differ in aetiology, pathophysiology and prognosis. Indeed, some of these disorders may be relatively unique to older adults.

Diagnostic Features of Major Depression in Late Life

Whatever the reason, and whether in a medical or psychiatric setting, the age-associated changes in the presentation of depression undoubtedly contribute to the problem of under-diagnosis and inadequate

treatment of depression in late-life patients. In general, older patients report fewer emotional symptoms, for example depressed mood, and present with more cognitive/somatic symptoms, for instance sleep disturbance, fatigue, pain and memory or concentration difficulties. In fact, the older-age depressed patient may never complain of, or indeed may deny, being 'depressed'. This presentation of late-life depression has been labelled 'depression without sadness'¹⁴. Thus, if when making a diagnosis a physician adheres strictly to DSM-IV criteria, then depressive disorder may well be omitted from the differential diagnosis for an older patient presenting with non-specific physical complaints.

Diagnostic Criteria for Major Depression in the Elderly

Despite the compelling evidence that late-life depression and older people are different, the diagnostic criteria for unipolar depression in DSM-IV are not adjusted for age¹⁵. One of the five required symptoms must be either (i) depressed mood most of the day, nearly every day; or (ii) markedly diminished interest or pleasure in all, or almost all activities. The other symptoms that are counted to the total of five, but not required, are: (iii) significant weight loss, or decrease or increase in appetite nearly every day; (iv) insomnia or hypersomnia; (v) psychomotor agitation or retardation; (vi) fatigue or loss of energy; (vii) feelings of worthlessness or excessive or inappropriate guilt; (viii) diminished ability to think or concentrate, or indecisiveness (older patients with depression often have mild cognitive impairment, including disturbances in attention, speed of mental processing, and executive function); (ix) recurrent thoughts of death, suicidal ideation with or without a plan.

Though there are no separate diagnostic subtypes unique to late life, there are some considerations that are more relevant to late-life depressed patients than younger patients with the same disorder. The DSM-IV precludes the diagnosis of major depression if it can be established that the symptoms counted towards the diagnosis of depression are a direct physiological effect of a different medical disorder. However, this rule is not supported by evidence, and to the contrary, studies have suggested that the inclusive approach (i.e. if a symptom is present it is counted towards the diagnosis of depression) is justified¹⁶.

There is also the belief that unipolar major depression with psychotic features may be a more frequently occurring subtype in older than younger patients. Psychotic depression occurs in 20 to 45% of elderly depressives hospitalized for psychiatric care, and in 3.6% of elderly depressives living in the community¹⁷.

VASCULAR DEPRESSION

Hickie *et al.*¹² hypothesized that there may exist a vascular depression subtype that is unique to late life; he wrote that 'cerebral vascular insufficiency in elderly people leads to major changes in their subcortical and basal ganglia structure. The resultant late-onset depressive disorders are characterized by deficits in functions that are dependent on intact cortical striatal connections (e.g. psychomotor speed), as well as subcortical hyperintense lesions and reduced basal ganglia volumes.' The hypothesis emanated from studies that reported that patients with late-onset major depressive disorder (MDD) had higher rates of hyperintensities on MRI compared to patients with early onset MDD^{10,12,18}. The patients with late-onset depression and hyperintensities also showed deficits on neuropsychological testing including, but not limited to, deficits in executive function^{18,19}. Thus,

structural brain damage secondary to ischaemia creates a vulnerability to MDD that may be precipitated by negative life events or other stresses. Given that vascular disease of sufficient severity is the cause of the ischaemia, this form of depression will be significantly more prevalent in older adults²⁰.

Much about the vascular depression hypothesis is compelling. First, the evidence that vascular disease is the cause of the hyperintensities prominent in late-onset depression supports the hypothesis. Second, vascular risk factors, such as smoking, hypertension and high lipid levels, are prevalent in patients with late-onset depression. Actually, early onset depression is itself a very significant risk factor for both ischaemic heart disease and stroke later in life. Increased cortisol, insulin resistance and platelet reactivity, all of which can contribute to vascular damage and ischaemia, may mediate the increased risk of myocardial infarction and stroke associated with depression⁷.

Diagnostic Criteria for Vascular Major Depression

Criteria for vascular depression include vascular disease, cognitive impairment, late age of onset, and depression. However, the various research groups who study this syndrome have proposed the variables in many different combinations. For example, one group considers clinical and/or laboratory evidence of vascular disease and depression onset after age 65 as cardinal features and executive dysfunction as secondary²¹, whereas another group believes neuroimaging evidence of cerebrovascular disease to be the cardinal feature and age-of-onset over 50 as an additional secondary feature. Krishnan *et al.*²² have further refined the notion of vascular depression, requiring only MRI evidence of cerebrovascular pathology to define it, and have referred to this syndrome as subcortical ischaemic depression. Alexopoulos has proposed a depression executive dysfunction disorder of late life that only requires executive dysfunction to meet diagnostic criteria^{21,23}. Although the proposed criteria sets are important and have moved the field toward recognizing a potentially important subtype of late-life major depression, this recognition might be premature because there is no agreement on how the construct is defined. Furthermore, most studies only include patients who meet criteria for MDD; however, many patients with vascular disease have dysthymia or subsyndromal symptoms.

SUICIDAL IDEATION

Studies consistently show that elderly males, particularly white males, are the demographic group with the highest risk of committing suicide. Also, the majority of elderly patients who commit suicide have visited their primary care physician a few days to weeks before the act²⁴. These findings appear to be present across countries in several continents, although there are cultural differences in the preferred method of committing suicide²⁵.

ATYPICAL DEPRESSION

Little attention has been paid to the atypical subtype in samples of late-life depressed patients. The term 'atypical' was originally coined to describe a group of depressed patients who characteristically present with 'reverse' vegetative symptoms such as hyperphagia and hypersomnia²⁶. The diagnostic criteria and acceptance of this subtype of major depression have evolved over the past 25 years so that they are included in DSM-IV with the atypical features specifier requiring that a patient has (i) mood reactivity and (ii) two or more of the following symptoms: significant weight gain or increase

in appetite, hypersomnia, leaden paralysis, or a long-standing pattern of interpersonal rejection sensitivity¹⁵. Studies have documented that patients with atypical depression differ from other patients with major depression in a number of parameters besides phenomenology, including biological variables, treatment response, demographic characteristics and age of onset^{27,28}.

There are two studies of the atypical subtype in late-life patients. The first study has many methodological limitations but is notable because it brought attention to this subtype of depression in late life. In this study, a single practitioner in a private practice reported on 358 consecutive DSM-IV unipolar (major depressive and dysthymic disorder $N = 179$) and bipolar II ($N = 179$) outpatients presenting for treatment of a major depressive episode over the last two years²⁹. Depressed patients over the age of 60 had a significantly lower rate of the atypical subtype compared to younger depressed patients, 28 vs. 55% respectively ($p < 0.0001$), and also a significantly lower rate of bipolar II atypical subtype in the late-life patients compared to the younger sample, 35 vs. 67% respectively ($p = 0.01$). Furthermore, in comparison to atypical patients under age 60, atypical patients over age 60 had an older age of onset of illness (44 years vs. 23 years) and a lower rate of rejection sensitivity (55 vs. 83%).

The second study reported on an open trial of venlafaxine in late-life depressed patients with the atypical subtype³⁰. The sample was 17 patients, mean age 65.6 ± 7.3 years, 77% female, mean Cumulative Illness Rating Scale-Geriatric score³¹ 2.9 ± 2.8 , and 43.8% of the subjects had cardiovascular disease. The mean Mini-Mental State Examination (mMMSE) was 28.6 ± 1.4 . In this sample, 58% of the patients had recurrent depression and, most strikingly, 53% presented with late onset of depression (defined as first episode after age 50) and only 12% with onset before age 21. Of note, 15/17 patients completed the eight-week venlafaxine trial; intent-to-treat response rate was 65% and the completer response rate was 73%.

CLINICAL RATING SCALES FOR MAJOR DEPRESSION

Patients should be evaluated with a history and clinical evaluation, supplemented by semi-structured interviews, together with additional information from informants and referring physicians and mental health professionals. The Hamilton Depression Rating Scale (17, 21, 24 or 29 item versions) and Montgomery Asberg Depression Rating Scale are commonly used in young adults, and can also be used in elderly patients with depression. Specific instruments that address symptoms likely to occur in the elderly have been developed. The Geriatric Depression Scale³² has been validated in older depressed patients and can be useful in the overall assessment process. The CES-D (Center for Epidemiological Studies-D) is another short instrument with both 'positive' and 'negative' symptom assessment of depression and is widely used in epidemiological studies. Both these instruments can be completed as self-reports, though interviewer ratings often add to the nature of the information obtained. Some instruments developed for use by primary care practitioners, for instance PRIME-MD, are useful for basic office screening but require follow-up with a more comprehensive evaluation if the initial screen is positive³³. A weakness of using this type of screening approach in elderly patients is that many depressed patients do not recognize their depression as a symptom of illness or have masked depression with or without somatic symptoms. In such cases, the screen may give a false negative result. There is no objective evidence that any one of these rating instruments is superior to any other instrument in distinguishing diagnostic groups, predicting clinical

course or treatment response. Other areas of query to complete the evaluation include assessments of cognitive, nutritional and functional status, social function and general health status. Review of medications, medical work-up and laboratory assessment, if indicated, is necessary to complete the evaluation.

Depression may be reflected in behavioural changes in the elderly, with apathy, anhedonia and occasionally irritability being prominent symptoms. Although several studies show that major depression in the elderly is more likely to become chronic, it remains unclear if the likelihood of chronicity is more common in elderly patients³⁴. Some older patients show partial improvement without full remission from an episode of major depression³⁵, but the STAR-D findings suggest that this may also be the case in many young adults³⁶. While the goal is full remission, partial response without full remission remains common. In addition to antidepressant medication treatment, a variety of psychotherapies including interpersonal, cognitive behavioural and problem-solving therapy have been shown to have some efficacy, though well-controlled studies are fairly limited³⁷. Other behavioural interventions include exercise and group activity involvement, but systematic controlled studies are lacking.

DYSTHYMIC DISORDER

Dysthymic disorder is a syndrome of depression of mild or moderate severity that lasts at least two years. Dysthymia is a chronic condition that may begin early in life and extend into late life, often interspersed with episodes of major depression. In these patients, the term 'chronic depression' has been used to designate the co-morbid or sequential occurrence of major depression and dysthymic disorder³⁸. However, in the elderly, the majority of cases of dysthymic disorder are of late onset by DSM criteria (age of onset > 21 years), and the majority of patients have an age of onset above 50 years³⁹. As discussed earlier in this chapter, there is considerable evidence that patients with late-onset (onset after 50–60 years of age) major depression are less likely to have a positive family history of affective disorder and more likely to have evidence of cerebrovascular disease and cerebral atrophy than elderly patients with early onset depressive illness. These features also appear to be present in patients with dysthymic disorder^{39,40} who often have a 'pure' dysthymia uncomplicated by a history of major depression³⁹. Co-morbid Axis I disorders, particularly anxiety disorders, are far more common in early onset than late-onset patients with dysthymic disorder^{39,41}. The gender distribution in late-onset dysthymic disorder does not seem to have the female preponderance that is observed in most types of affective disorder. Personality disorders in elderly dysthymic patients are less common than in young adults with depression, and tend to be of the obsessive-compulsive and avoidant subtypes. Borderline, histrionic, narcissistic and antisocial personality disorders are rare in the elderly^{39,42}.

Co-morbid general medical conditions, cognitive disorders and frequent adverse life events, for example bereavement, can complicate the diagnosis of dysthymic disorder. Associated features may include the presence of major chronic stressors, increased physical impairment and more symptoms of anxiety. Patients with dysthymia tend to be seen in primary care settings rather than by psychiatric specialists.

DSM-IV describes the symptoms of dysthymic disorder as being similar to those in major depression, with the distinction being the presence of fewer symptoms of lesser severity. However, the DSM-IV field trials revealed a high prevalence of cognitive and social symptoms in patients with dysthymic disorder, and neurovegetative symptoms were less frequent. This led to the alternative symptom

criteria for dysthymic disorder that were listed in the DSM-IV appendix. These symptoms include low self-esteem, hopelessness, social withdrawal and lack of interest, fatigue, low productivity, poor concentration and indecisiveness. These symptoms are also more common than classical neurovegetative symptoms in elderly patients with dysthymic disorder⁴². The assessment of dysthymic disorder in the elderly can benefit from the use of the Cornell Dysthymia Rating Scale that emphasizes cognitive and social and motivational difficulties⁴³.

The optimal treatment of dysthymic disorder in the elderly remains uncertain. Fluoxetine has been shown to have marginal superiority over placebo⁴⁴ and there is equivocal evidence on whether psychotherapy or SSRIs should be the first-line treatment⁴⁵. Problem-solving therapy may have limited utility in dysthymic disorder and other types of late-life depression, but there appears to be considerable variability in treatment response when this therapy is not administered by experts^{37,45}.

OTHER SUBSYNDROMAL DEPRESSIVE DISORDERS

Subsyndromal depression is defined as the presence of depressive symptoms that do not qualify for a formal mood disorder. Subsyndromal depressive disorder tends to be a heterogeneous group of milder forms of depression with symptom patterns qualitatively distinct from more severe forms such as major depression⁴⁶. Subsyndromal depression is often used to describe patients with occasional depressed mood in the absence of other depressive symptoms. Minor depression in elderly people is associated with functional disability, and about 25% of patients develop major depression within two years. These subsyndromal depressive disorders commonly occur in patients with co-morbid medical illness, cognitive impairment, and other Axis I and II psychiatric disorders. There have been few treatment studies in the elderly, partly because the inherent heterogeneity of this set of syndromes makes it difficult to identify consistent treatment effects. Another view is that these patients' symptoms are too mild to require treatment, but the higher than expected likelihood of progression to major depression and the possible detrimental impact of even low levels of depression on medical outcomes suggest that treatment may often be warranted.

GRIEF AND PATHOLOGICAL BEREAVEMENT

Grief, a normal psychological response to the loss of a loved one, possessions or health, or unexpected adverse events, is associated with feelings of sadness, transient somatic symptoms, weight loss and difficulty in sleeping. Symptoms are often intense for several weeks to a few months and then typically begin to improve⁴⁷. Pathological grief refers to the persistence of symptoms of grief at the same intensity more than six months after the event, and may include acquisition of symptoms belonging to the last illness of the deceased, psychosomatic illness, greater interpersonal conflicts and social withdrawal, difficulty in concentration and other cognitive difficulties, low productivity and impaired overall functioning^{48,49}. Fear, demoralization and loneliness can occur. Spousal bereavement is common in late life, and is associated with declining mental and physical health and increased risk of mortality⁵⁰. Among elderly widows and widowers, 20% meet the criteria for major depressive syndrome two months after their loss, and one-third of these individuals develop persistent depression for a year or longer⁵¹. Generally, individuals who are at greatest risk for persistent depression have worse health, more

functional and social difficulties and more protracted grief than do bereaved individuals who are not depressed.

There are two schools of thought on whether grief should be treated in its early stages: some believe that it should be treated and others have the view that only persistent and prolonged grief requires intervention. The utility of antidepressant medications or psychotherapy in these contexts is not fully established, but there is some evidence for the efficacy of a specific form of therapy, complicated grief therapy, to treat patients with prolonged and disabling grief symptoms⁵².

A relatively new diagnostic concept that is especially relevant to older patients is complicated grief. In this syndrome, the grief that is normally experienced during bereavement does not resolve but instead becomes persistent. The predominant symptoms of complicated grief include recurrent intrusive images of the death, bitter or angry avoidance of situations, activities, or people, intense yearning and/or longing, seeking proximity to items belonging to the deceased, feeling that life has no meaning without the deceased, self-blaming thoughts of not helping the person or not preventing the death. This syndrome is frequently co-morbid with depressive disorder; however, complicated grief itself may be mistaken for major depression. The diagnostic criteria for complicated grief are still in development and treatment studies are ongoing. For obvious reasons this syndrome has special relevance for older patients.

STRESSFUL LIFE EVENTS AND ADJUSTMENT DISORDERS

Older adults face a variety of stresses: medical illnesses, physical disability, sensory impairments in vision and hearing, loss of family and friends, loss of social supports, changes in relationships with children and significant others, alterations in living situation, and loss of income. One or more of these factors may be related to the onset of the clinical syndrome of depression. The death of a spouse is extremely stressful, as is the death of an adult child. Patients with major depression perceive significantly greater negative emotional impact of the same life events than patients with dysthymic disorder and healthy controls, particularly for interpersonal conflicts⁵³. The resolution of stressful events probably depends on several factors, including genetic predisposition, prevailing early life experiences, adequacy of previous adaptive and coping mechanisms, patterns and profiles of premorbid personality and, in particular, the presence or absence of a strong support system. A specific scale has been developed to assess a range of stressful life events and their impact on mood and functioning in the elderly⁵³.

DEPRESSION WITH COGNITIVE IMPAIRMENT

In the elderly, depression is a major cause of suffering and disability, is often co-morbid with medical illnesses, worsens their outcome and increases mortality². Cognitive deficits are common in the elderly, and often precede Alzheimer's disease (AD) and vascular dementia, which are illnesses with enormous costs. Depression and cognitive disorders are the most common neuropsychiatric disorders in the elderly; their co-occurrence may exceed chance.

Apathetic, withdrawn behaviour is common to both depression and dementia. Paucity of speech with long latency is characteristic of major depression, particularly the melancholic subtype. However, there are many symptoms common to both depression and mild cognitive impairment or early dementia: apathy, anhedonia, insomnia, agitation, irritability, memory loss and difficulty concentrating. This

overlap in symptoms makes it difficult to make an accurate diagnosis and to estimate prognosis and plan treatment.

In patients with depression plus cognitive decline, the following symptoms commonly occur: difficulties in memory or thinking or concentration, forgetting of recent events, forgetting where things are located, problems in finding the right word to say, getting lost in familiar places, remembering appointments and to take medications, and difficulty in managing finances like balancing the chequebook or paying for items in a shop. These symptoms, especially financial management and remembering appointments or taking medications, may be the first indicators of dementia. The symptom of forgetting names of books and movies and people is common during the normal ageing process and by itself is not indicative of dementia.

The presence of depression of any type appears to be associated with an increased risk of converting to dementia during follow-up^{54,55}. Among patients with depression and cognitive impairment, a large proportion of converters to dementia are diagnosed with AD. Autopsy studies show that elderly depressed subjects who have mild cognitive impairment or dementia often have a pathological diagnosis of AD⁵⁶.

As already described, 'vascular depression' refers to major depression with higher rates of leukoencephalopathy on MRI and executive function deficits. A number of patients with both depression and cognitive impairment have evidence of cerebrovascular disease, while others have incipient AD. Patients who present clinically with 'pseudodementia', that is, depression masquerading as dementia in its clinical presentation, were thought to be common but in fact are relatively rare².

The treatment of patients with depression and cognitive impairment has been poorly studied. In one study, open treatment with sertraline showed improvement in depression with minimal improvement in cognitive deficits⁵⁷, and there is preliminary evidence that adding a cholinesterase inhibitor to antidepressant treatment may lead to improvement in cognitive test performance⁵⁸. There are no large-scale studies addressing these issues, and the standard clinical practice remains to first treat with antidepressants and then evaluate if cognition improves along with antidepressant response, even though there is little evidence to support this notion. The literature on the treatment of depression in patients with dementia, primarily AD, suggests a marginal positive effect for antidepressant medication in some studies, while other studies show no advantage of medication over placebo.

MEDICAL CO-MORBIDITY

Depression frequently accompanies other medical illnesses and is associated with considerable dysfunction and disability. Co-morbid medical illness increases the chronicity and refractoriness to treatment and it may slow recovery rates for depressed patients with various conditions, including heart disease, stroke, hip fracture and dementia.

The elderly patient typically suffers from several medical illnesses and takes a large number of medications. Benzodiazepines, steroids and anticholinergics can lead to cognitive impairment and even delirium, L-dopa and dopamine agonists prescribed for Parkinson's disease can lead to psychosis, and the use of some antihypertensives and steroids may be associated with depression.

A variety of medical disorders can first present with disturbances in mood, cognition, or psychotic features, including infections, electrolyte and metabolic imbalances, cardiovascular and cerebrovascular disease. Depression can lead to weight loss, inanition and

malnutrition. Dietary history is important in this regard; the older adult living alone may not obtain adequate nutrition and may develop vitamin and other deficiencies.

From a diagnostic classification perspective, the diagnosis of depression due to a general medical condition is given when depressed mood or anhedonia occur in patients already diagnosed with an illness that is associated with depression. A common comorbidity is depression and cardiovascular disease, and myocardial infarction is frequently associated with depression in the short term to intermediate term.

BIPOLAR DISORDER IN THE ELDERLY

Late-onset mania is not common in the elderly, but can occur as a primary late-onset mania or secondary to dementia or stroke or other neurological insult. Labile affect is believed to be typical of vascular dementia, but it remains unclear if labile affect is more common in vascular compared to other forms of dementia. Elderly patients are prone to the neurological side effects of lithium, and systematic monitoring of lithium and anticonvulsant blood levels when anticonvulsants are used is important, though the optimal treatment strategy for elderly patients with bipolar disorder is not well established. Many younger patients with bipolar disorder are maintained on the same treatment(s) as they age, and dosage reductions and other adjustments depend on the development of side effects.

CONCLUSION

While depression in the elderly shares many clinical features with depression in young adults, there are important differences. Late-onset patients, particularly those with cerebrovascular disease, may have an illness related directly to brain pathology, and those with both depression and cognitive impairment have an increased risk of developing AD. The preponderance of subsyndromal depression, and again the large proportion among them with late age of onset, indicates that the approach to diagnosis and management should not be restricted to the major depression category. Lack of social supports and life stresses do play a role in late-life depression. The high risk of suicide, particularly in elderly males living alone, should be at the forefront of the clinician's mind when evaluating the elderly depressed patient. A comprehensive biopsychosocial approach should take into account the patient's entire history, the social context and medical issues that arise during the ageing process. Medical co-morbidity needs to be addressed, and close communication with the patient's medical providers is important in elderly patients with significant medical illness. Treatment strategies should encompass both medications and psychotherapy, taking into account the reduced tolerability and increased side effects with psychotropic medication use, and the need to emphasize behavioural and problem-solving approaches in therapy when it is utilized.

CONFLICTS OF INTEREST

Dr Devanand – research support: Eli Lilly, Novartis. Consultant: Glaxo Smith Kline, Sanofi-Aventis, Bristol Myers Squibb.

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The Outcome of Late-life Depressive Disorders

Aartjan T.F. Beekman¹, Harm W.J. van Marwijk² and Max L. Stek¹

¹*Department of Psychiatry, VUmc Medical Centre, Amsterdam, The Netherlands*

²*Department of General Practice, VUmc Medical Centre, Amsterdam, The Netherlands*

THE OUTCOME OF LATE-LIFE DEPRESSION

Around the turn of the nineteenth century Kraepelin changed the face of contemporary psychiatry, primarily by systematically following up his patients after treatment. The outcome or natural history of a disorder is, since that time, decisive for any appreciation of its clinical relevance, treatment or classification, and is a cornerstone of its conceptualization. In some disorders, such as dementia, the rate of progression of the illness may vary, but the eventual outcome is fixed. Other diseases, such as diabetes or osteoarthritis, may have an extremely varied course and prognosis, but are chronic by nature. The eventual outcome of both diabetes and osteoarthritis is by no means fixed. In both disorders the outcome can vary from being a disorder that, although causing considerable discomfort, remains under control, to a debilitating and pernicious disorder. The outcome of depression is even more varied than that. Some patients suffer one episode in life, recover fully, never to run into affective trouble again. For others depression is a severe and chronic disease, omnipresent in all spheres and phases of life and discolouring all life's experience. The eventual outcome may vary from the depression having had a minor impact on the patient's life, to suicide. Between these extremes, every type of course and outcome of depression exists. This holds for depression at all ages. Indeed, it may well be that, given the changes that occur in later life, the variability of the outcome of geriatric depression is even more pronounced than in earlier stages of life.

Given the extreme variability of the outcome of depression and the obvious importance this has for our patients, it is surprising how poorly both our theories and our classification of the prognosis of depression have developed. Although a good many studies have been conducted to assess the naturalistic outcome of depression at all ages, this has not led to a well-developed prognostic theory for affective disorders. The primary aim of treatment is to influence the prognosis and outcome of a disorder. Although hundreds of trials have been conducted to test the efficacy of treatments for depression, this also has not led to an integrated theory of the prognosis of affective disorders. The result is that classification has remained where it essentially has been since Kraepelin's time: a purely descriptive system, categorizing what goes on while it goes on.

This chapter contains a reflection of this still rather primitive state of affairs. The first paragraph will discuss essential conceptual issues,

relevant to the outcome of late-life depression. Thereafter, we will summarize the available data with regard to the naturalistic outcome of depression in older people. As will become evident, the pioneering studies in this area were conducted from specialized clinical centres, following up patients after discharge from clinical treatment. Later on, larger cohort studies were put together, following patients seen in general practice and in the community. These data will be used to test the hypothesis that the prognosis is generally more favourable in the community as compared with patients referred to specialized treatment centres. A second question is whether the prognosis of depression changes with age. To this end, results of studies conducted among older people will be compared with those in younger adults. Where possible, associations between age and the prognosis will be summarized. One of the myth's surrounding age and ageing is that later life would be an age of melancholy. This myth has been falsified many times. Although some studies do show that the prevalence of depressive symptoms increases with age, this is related to age-related risk factors and not to ageing itself. The same question will be addressed with regard to the prognosis of late-life depression. Is there an effect of age? If so, is this a result of the ageing itself, or a change in age-related prognostic factors?

A related issue is whether the variation in outcomes of depression is increased in later life. If so, the potential benefit of being able to predict the individual prognosis early on in treatment is similarly increased. First episodes of depression may arise at all ages and there are subtypes of depression that generally arise only in later life (such as vascular depression or depression associated with neurodegenerative disease). It is therefore likely that the prognosis becomes more heterogeneous in later life and that there are specific aetiological or prognostic subtypes that are especially relevant to older people. Identifying prognostic factors is therefore a further aim of this chapter.

Co-morbidity is the hallmark of geriatric medicine. Studying disorders in isolation in older people is only rarely helpful or informative. This is especially true for late-life depression. Moreover, for our patients and in terms of public health, more functional and generic outcomes such as well-being, daily functioning and social integration are essential. As these generic outcomes are the product of all the co-morbid disorders the patient has to cope with, the final aim of this chapter is to consider the role the prognosis of depression plays in the overall well-being and functioning of older people.

OUTCOME BRIEFLY CONSIDERED

There are many ways to define and measure the outcome of depression. As is the case in most areas of medicine, the methods employed have evolved from studies retrospectively and rather loosely classifying each patient in predefined clinical criteria, to prospective studies, rigorously measuring symptom severity at multiple time points. By definition, the more often symptoms are measured, the more likely it is that change will be detected. That would mean that the more recent and sophisticated studies, employing multiple measures over longer periods of time, are less likely to find a patient in sustained recovery and also less likely to conclude that the patient is chronically depressed.

The way the outcome of a disorder is conceptualized has great impact on the way it is studied and treated. Frank *et al.*¹ described clear criteria for what may be called the episodic model of the outcome of depression. This model, which is summarized briefly in Figure 80.1 has been by far the most influential. Depression is modelled as an episodic disorder, with a clear beginning, symptomatic stage and resolution phase. If, very soon after the symptoms have resolved, the patient suffers a relapse, this is considered part of the illness episode. If the recovery is more sustained and the patient suffers a recurrence, this is then considered to be a new episode. This well-known model has many merits. First, it is an optimistic model. Regardless of age, most patients recover and treatment generally helps to speed up recovery. The episodic model has also been helpful in both organizing our thinking about the prognosis of depression and in designing studies of treatment.

However, longer term follow-up studies employing multiple measurements have shown that patients often do not follow the neat stages of development of the disorder depicted in Figure 80.1². The best known example is the Collaborative Depression Study, in which more than 400 patients were followed up using detailed weekly life charts. Over 12 years of follow-up, it appeared that patients moved in and out of different levels of symptom severity and diagnostic subtypes; the symptoms often waxing and waning². Using an episodic model of outcome it was reported that 70% of the patients had recovered after one year and that the mean duration of episodes was approximately six months³. Given the fact that these were patients referred (and motivated) for treatment in a tertiary treatment centre, the outcome was quite optimistic. However, after 12 years of follow-up, using life charts it appeared that these patients spent

almost 60% of the time in a state with clinically relevant levels of depressive symptoms, severe enough to disturb both well-being and functioning². The results have prompted the authors to conclude that the prognosis in depression is pleiomorphic instead of episodic². When accommodating the pleiomorphic model in research, the prognosis of depression appeared less favourable than when adopting an episodic viewpoint. In practice, there are patients in whom depression follows the path of a clearly delineated episode, there are patients in whom the symptoms wax and wane over time and there are patients with a chronic course. This has clinical relevance, as the way treatment and follow-up are organized should be determined by the expected prognosis. Indeed, as was suggested by McCullough, there is good reason to consider more chronic forms of depression as a different disorder from the more benign episodic disorders⁴.

When describing the outcome of late-life depression in the next section, both the parameters relevant to an episodic view of outcome (such as the duration of an episode, the percentage of patients remitting within a given time, relapse or recurrence) and those relevant for a pleiomorphic viewpoint (the average symptom severity over time, the percentage of time patients spend in a depressive state) will be discussed.

THE PROGNOSIS OF LATE-LIFE DEPRESSIVE SYMPTOMATOLOGY

Several systematic reviews have recently summarized the prognosis of late-life depression^{5–7}. As was mentioned, the earlier studies were conducted as follow-up assessments of patients treated in clinical facilities. Over 20 such studies have been conducted. The outcome was often determined retrospectively in rather loosely defined clinical terms, such as the patient being well, recovery with relapses or being continually ill. Given various methodological shortcomings, Cole *et al.*⁵ concluded that the majority of patients (about 60%) were well or had suffered relapses with recovery, while 14–22% were continually ill. Both Cole *et al.*⁵ and Licht-Strunk *et al.*⁶ in a more recent review have found poorer outcomes when studying depressed patients recruited from the community or primary care. Licht-Strunk *et al.*⁶ summarized the findings of 4 primary care and 17 community-based studies that fulfilled quite rigorous methodological criteria. After a period of one year, 50–75% of patients no longer fulfilled diagnostic criteria for major depression. Taking a longer time-perspective, the available studies would suggest a rule of thirds: about one in three patients has a short-term remission, another one in three develops a chronic course, while the remaining third has a more varied prognosis, with intermittent episodes⁶. Only one study estimated the duration of episodes of major depression among older primary care patients. In a three-year follow-up of 234 older (55+) primary care patients with well-defined major depressive disorder, the average duration of an episode was estimated to be 18 months⁷.

Moving from clinically defined outcomes to the more abstract pleiomorphic measures the prognosis looks even worse. In the Longitudinal Aging Study Amsterdam (LASA), which is a community-based study, 277 older depressed people were followed with six-monthly assessments over six years⁸. It appeared that almost half the sample was depressed more than 60% of the time over six years. Only one in three had a true chronic course, but another third of the patients were depressed most of the six years they were followed up, the symptoms waxing and waning over time.

Taking these results together, the prognosis seems rather good for only one in three older patients, while the majority are either

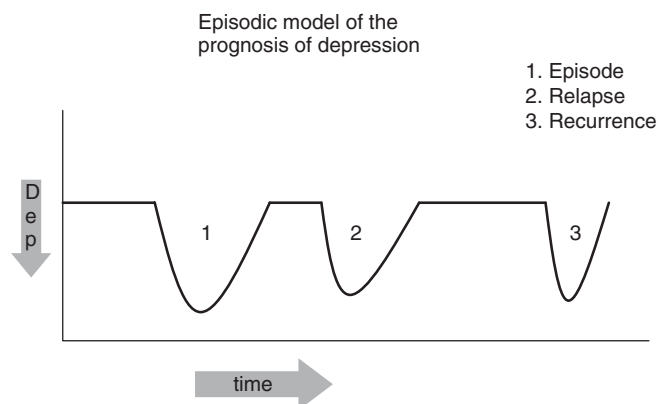


Figure 80.1 Episodic model for the prognosis of depression. From Frank *et al.*¹

chronically depressed or have frequent, but intermittent changes in symptoms. It is striking that the data from the community and primary care suggest a less favourable prognosis when compared with data from specialized mental health care facilities. This is not what would be expected, as the more severe, chronic and hard-to-treat patients are referred selectively to specialized mental health. An explanation would be that majority of older depressed patients in the community and in primary care are not treated, while those referred for treatment do receive appropriate care⁷.

MAJOR DEPRESSION, MINOR DEPRESSION AND DYSTHYMIA

Most of what is known about the prognosis of depression pertains to major depressive disorder (MDD). However, many older people with depressive symptoms do not fulfil rigorous diagnostic criteria for MDD⁹. What about their prognosis? The term 'dysthymic disorder' was introduced to replace 'neurotic depression'¹⁰. The underlying idea was that this would be a type of mild, but chronic depression, that was associated with personality disorders and therefore would arise early in life. What about dysthymia in later life? Is this common among older people and is it indeed a chronic, mild type of depression, that is primarily associated with personality problems?

The available data suggest that minor, or other subthreshold types of depressive symptoms, although clinically highly relevant to older people, do tend to have a more favourable prognosis than MDD. The prognosis of dysthymia appears to be worse than the prognosis of MDD. In the LASA study, data concerning the six-year prognoses of minor depression, MDD, dysthymia and double depression (MDD plus dysthymia) were compared⁸. Those with minor depression had the best prognosis (26% remission; 25% chronic course), followed by MDD (22% remission; 35% chronic course), dysthymia (12% remission; 52% chronic course) and finally double depression (only 5% remission and 77% chronic course). Dysthymia is quite common among older people (4.6% in the LASA study), has a symptom profile very similar to that of MDD and an earlier age of onset than MDD (average age at onset of 31 for dysthymia, compared with 53 for MDD)¹¹.

IS THE PROGNOSIS OF DEPRESSION INFLUENCED BY AGE OR BY AGE-RELATED FACTORS?

To answer this question one would like to be able to compare directly patients of different ages, recruited at similar stages of development of their affective disorder, using identical methods. As no such study is available, conclusions should be drawn cautiously as they are likely to be confounded. Given this caveat, the evidence seems to be overwhelmingly in favour of thinking that outcomes are poorer among older patients.

For instance, in a large community-based study of younger adults, the median duration of an episode of MDD was estimated to be three months, while the average duration among younger adult patients in specialized mental health has been estimated to be six months¹³. This compares very favourably with the 18 months average duration described for older primary care patients⁷. In the LASA study, direct comparisons between young-old (55–65) and older old (75–85) people is possible. It was clear that the oldest age group had a higher average symptom severity over six years of follow-up, a longer duration of symptoms and that they were almost twice as likely to have a chronic course of depression when compared with the youngest group⁸.

Cole *et al.*⁵ and Licht-Strunk *et al.*⁶ have synthesized the data on prognostic factors for late-life depression, as described in community- and primary care-based studies. Although methodological differences among studies preclude exact estimates of the prognostic strength of different variables, some conclusions do emerge. The most consistently found prognostic factors are physical illness, impairments (such as pain, loss of hearing and loss of vision), disability and the associated impairment of daily functioning. The effect of cognitive decline and dementia on the prognosis of depression is undecided. Although one would perhaps expect that massive neurodegeneration and the resulting impairments and handicaps would be a powerful factor to prolong depression, moving through different stages of the dementia process may also act as a factor ending a depressive episode.

Another set of prognostic factors that has been studied is the experience of threatening or loss-related life events. Although these are powerful aetiological factors, there is no reason to believe that depression preceded or induced by life events has a different prognosis when compared to other types of depression. A third group of candidate prognostic factors concerns what is often called long-term vulnerability for depression. Examples are genetic factors, severe life events earlier in life, unfavourable personality traits (such as neuroticism), female gender, a lack of education or a lack of adequate social support. The uncovering of genetic subtypes predicting a more chronic course of depression would potentially be of great clinical importance, but has not as yet yielded definitive results. Studies suggest that gender, level of education and social support are not strong prognostic factors^{5,6}. Both severe life events earlier in life and maladaptive personality traits have been identified as important unfavourable prognostic factors among younger adults. So far, the limited evidence has confirmed this for older adults, especially with regard to the role of neuroticism¹³.

Given the available data on prognostic factors, those that have been uncovered are clearly related to age. This may explain why the prognosis of depression is worse among older people than among younger adults.

IS THE OUTCOME OF DEPRESSION MORE VARIED AMONG OLDER PEOPLE?

As described above, the available data suggest that the outcome of depression is less favourable in older adults than in younger people. This appears from data looking at the average duration of episodes, the rate of recovery, relapse and recurrence and the likelihood of chronic depression. A similar conclusion is drawn when comparing pleiomorphic indices of the outcome, such as the average symptom severity over time or the percentage of time people are depressed. Although many uncertainties remain, it appears that this less favourable outcome is at least partly explained by an increase in exposure to unfavourable prognostic factors. Depression is well known for its aetiological heterogeneity: a myriad of different aetiological factors can play a role in the development of depression. The exposure to such factors increases with age, dramatically changing the palette of risk factors involved. It is likely that the same happens with prognostic factors: the increased variability of the prognosis in part taking responsibility for the overall change in prognosis. This is important, as it would render any sweeping statement with regard to the overall prognosis of late-life depression inadequate.

With more prognostic heterogeneity, being able to reliably predict the prognosis becomes more important. Such data are becoming

available slowly. It is clear that, besides the above prognostic, several other markers that may help predict the prognosis in an individual patient are available. The most powerful group of predictors would be the severity, duration and stage of development of the depression (first episode, versus recurrent episode)^{6,7,8,12}. Besides this, other clinical factors, such as co-morbid anxiety and substance-related disorders have been shown to predict the prognosis of depression¹².

Overall, the data suggest that old age psychiatry would do well to invest in identifying subgroups of depression by (i) a clinical staging of severity, duration and development of the disorder, (ii) the symptom profile, (iii) biological or other prognostic factors and (iv) treatment response. Examples are the vascular depression hypothesis, which, among other things, would suggest a poorer prognosis and less response to antidepressant therapy, and the recently coined amyloid depression, which would predict cognitive decline and perhaps also a less favourable prognosis¹⁴.

It may be concluded that although much work needs to be done in the area of predicting the prognosis, it is highly likely that variation increases with age and that different prognostic subgroups, highly relevant to clinical work, do exist.

GENERIC OUTCOMES

Excess Morbidity

Co-morbidity between physical health and depression is salient in late life, when both risk for illness and disability rises. Depression in old age can be a consequence of somatic illness and disability but ample research also suggests that depression in the elderly leads to restricted functioning and worsening of co-morbid conditions by a variety of behavioural and biological mediators. The pathways between depression and excess morbidity are complex and bidirectional. Large-scale longitudinal studies have been carried out trying to disentangle this complex interaction. Scott *et al.*¹⁵ recently found in their review of World Mental Health surveys that although the majority of elderly suffered from chronic physical conditions the large part had no signs of depression and anxiety. By contrast, the majority of those with mental disorders had physical co-morbidity. From another perspective findings suggest that different durations of the presence of depressive symptoms have different impact on physical health. Long-term depression had profound negative effects on illness, a short duration far less¹⁶. More specifically the association between depression and ischaemic cardiac illness is a frequently studied topic¹⁷. Depression and cardiac disease often co-occur and this association is likely to be bi-directional¹⁸. The presence of subclinical atherosclerosis due to exaggerated platelet function, activation of pro-inflammatory pathways and an altered HPA axis state has been suggested as an underlying mechanism^{19,20}.

A second field that has been studied extensively is co-morbid cognitive impairment, a clinical hallmark in old-age psychiatry because cognitive impairment is one of the immediate consequences of depression. There is a strong association between late-life depression cognitive impairment, cerebrovascular disease and progressive dementia, including Alzheimer's disease. The varied findings suggest that there are probably many pathways to poor cognitive outcomes with multiple aetiological links^{14,21}. Research in this field combines data from long-term longitudinal studies with (functional) neuroimaging and biomarkers and should lead to a better understanding of these clinically very important relationships.

Suicide and Other Causes of Excess Mortality

In most countries suicide rates remain highest in old people according to the World Health Organization. In particular, older men act more decisively on their suicidal intent than women, an effect increasing with age, which could be an explanation for the large sex differences in this respect²². In a series of psychological autopsy studies from the United States, Scandinavia and the United Kingdom more than 70% of the elderly who died by suicide suffered from a psychiatric condition, mostly depression²³. Persistent feelings of hopelessness and a long duration of depression and sleep disturbances were the most consistent predictors in the elderly²⁴. Notwithstanding the high suicide figures in elderly men the major part of the impressive rates of increased mortality in depressed elderly cannot be explained by suicide, but is related to other causes of death, probably cardiac events in the first place. In a recent study a dose-response relationship was found for late-life depression and early death, suggesting a causal relationship²⁵. There are several explanations for this pathway from depression to early death. On a behavioural level depression is generally associated with unhealthy lifestyles like smoking, use of alcohol, physical inactivity and lower compliance with medical treatment. In the elderly cognitive impairment and dieting may add to this negative cascade. Decreased heart rate variability, HPA axis dysregulation and increased pro-inflammatory activity are biological factors which probably play a part in cardiac-related death. At a subclinical level there may be depression-related illness like hypertension and endocrine dysfunctioning leading to early death. In conclusion many pathways in late-life depression lead to early death in complex interacting mechanisms^{25,26}.

Excess or inadequate use of service

Late-life depression is an important reason for both excess and inadequate utilization of non-mental care resources²⁷. Older patients and their care providers frequently persist to attribute depressive symptoms to somatic illness or ageing effects, thus creating diagnostic confusion. In a US national sample of subjects with persistent depressive or anxiety disorder, 87% had a chronic co-morbid medical disorder, most were seeing a primary care practitioner, but only 12% were receiving both appropriate medication and counselling at follow-up²⁸. In a recent Dutch general practice study, persistent frequent attendance was five times as likely to occur among persons over 65 years of age, and four times as likely when psychological or psychiatric problems were present²⁹. Depression plays an especially important role in frequent attendance of the elderly³⁰. Up to a quarter of elderly attend frequently, many of whom are depressed³¹.

Well-being and Functioning

Older depressed patients have substantial and long-lasting decrements in multiple domains of functioning and well-being that equal or exceed those of patients with chronic medical illnesses such as diabetes mellitus^{6,27}. Perhaps this strong relationship is not that surprising as depression is characterized by an absence of well-being and functioning. A prolonged lack of happiness is a key symptom for a diagnosis of major depression. To demonstrate this reciprocal relationship, positive affect, defined as emotional contentment and happiness, was directly correlated over time with social involvement and inversely correlated with negative affect (i.e. depression), instrumental activities of daily living functioning, and somatic co-morbidity³².

CONCLUSION

All the things that characterize later life also characterize late-life depression. Older people have a lifetime of experience and ageing tends to create more variability among the processes relevant to living. Depressed older people often have a long experience with mood changes and the pathways leading to depression become more complex with age. The available data would suggest that the prognosis of depression, whichever way it is conceptualized, becomes less favourable with ageing. The data also suggest that a large part of this is due to age-related prognostic factors, and much less due to ageing per se. Depressed older people are partly 'graduates': people who have suffered repeated episodes of depression throughout life and who continue to do so when they become old. Their prognosis is a function of the long-term development of their affective disorder and concurrent circumstances or events that happen while ageing. A large minority of our patients have become depressed for the first time in later life. Among them are patients becoming depressed due to life events or circumstances, and patients who become depressed in the context of specific, age-related illnesses. The prognosis of their depression is closely related to the outcome of the underlying cause and treatment more likely to be successful if this is taken into account.

It was argued that geriatric psychiatry would do well to adopt a clinical staging of affective disorders, which should include data on (i) severity, duration and clinical stage (first or recurrent episode), (ii) relevant prognostic factors, including biological markers, (iii) data on specific symptom profiles relevant to treatment or the prognosis and (iv) data on treatment outcome. This would help to build a more definitive database on the outcome of late-life depression, while simultaneously improving treatment.

Depression only rarely occurs in isolation in older people. Although clinicians are prone to focus on the disorders they have specialized in, the more generic outcomes of disorders are likely to be more relevant to our patients than the course of one specific disorder. It was shown that depression has profound impact on most of the generic outcomes that one would consider important for the public health of older people. Although it remains difficult to tease out the unique effect that depression has on these outcomes over and above the effects of co-morbid disorders, the available data suggest that depression often plays a decisive role in tipping the balance towards unfavourable outcomes. The fact that depression remains highly treatable until very late in life should inspire us to work hard to improve both the diagnosis and treatment of depression in older people.

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Physical Illness and Depression*

Mavis Evans

Elderly Mental Health Directorate, Wirral and West Cheshire Community NHS Trust, Clatter bridge Hospital, Bebington, Wirral, UK

EPIDEMIOLOGY

The prevalence of depression in the general population worldwide is usually found to be 3–8%^{1–3}. The prevalence of major depression has been shown to be no higher in the elderly than the young, although these findings do not allow for the co-morbidity of physical illnesses or dementias⁴. The World Health Organization (WHO) World Mental Health surveys⁵ of respondents in 10 developed countries ($n = 52\,485$) and 8 developing countries ($n = 37\,265$) showed that 12-month major depressive episodes (MDE) were significantly less prevalent among respondents aged 65+ than in younger respondents in developed but not developing countries. Prevalence of co-morbid mental disorders generally either decreased or remained stable with age, while co-morbidity of MDE with mental disorders generally increased with age. Prevalence of physical conditions, in comparison, generally increased with age, while co-morbidity of MDE with physical conditions generally decreased with age. The surveys concluded that the weakening associations between MDE and physical conditions with increasing age argue against the suggestion that the low estimated prevalence of MDE among the elderly is caused by increased confounding with physical disorders. Future studies are needed to investigate processes that might lead to a decreasing impact of physical illness on depression among the elderly.

Subthreshold or minor depressions have many different names and definitions, which causes widely differing prevalence rates to be quoted. Categorical definitions of depression do not fit well with the range of symptoms and severity seen in normal clinical practice. However, it is generally accepted that the burden of depression among the elderly is high and an accepted measure of diagnosis is necessary to allow communication with patients, relatives and professional colleagues.

‘Caseness’ can be considered to be the severity of depression at which the majority of professionals would consider some form of intervention appropriate. Prevalence of this degree of depression is reported as 10–15% of the elderly in the community^{6,7}, 15–30% of those attending primary care facilities^{8,9}, 15–50% of those in hospital^{9–11} and 30–40% of those in institutional care^{9,12}.

DIAGNOSIS

Depression cannot be diagnosed unless it is first considered a possibility, neither will it be appropriately treated unless it is considered

pathological. Depression may be missed when too much emphasis is placed on the presenting complaints of, for example, lethargy, anorexia or pain¹³. Depression and feelings of worthlessness may cause failure to complain of symptoms of physical illness or to ask for help. It may cause non-compliance with medication and other treatments, self-neglect or non-attendance at clinics. Alternatively, the lowering of self-esteem and decreased ability to cope can lead to increased attendance at clinics.

The lack of a concise definition for depression in the elderly makes the establishment of validity a difficult task, which can only be examined by longitudinal follow-up of patients to see what happens to their symptoms¹⁴. Somatic symptoms, such as lack of energy, poor concentration and weight loss, may be caused by the physical illness or ageing, not depression; even experienced clinicians may have difficulty attributing such symptoms to physical or psychiatric causes. Even feelings of life not being worth living and wishing to die are not always associated with depressed mood; poor subjective health, disability, pain, sensory impairment and living in an institution have been shown to be associated factors in the absence of depressive illness¹⁵.

The elderly tend not to admit to feelings of depression and relatives may be unaware of the condition¹⁶. Somatization, ‘the tendency to experience and communicate somatic distress and somatic symptoms unaccounted for by relevant pathological findings, to attribute them to physical illness and to seek medical help for them’¹⁷, is increasingly recognized. Somatization can still occur in those with genuine physical illness. The somatic symptoms of depression are similar to those of a chronic illness, such as cancer, and it must be remembered that depression and physical illness often co-exist¹⁸.

Hypochondriasis is a recognized symptom of depression in the elderly population¹⁹. However, in this age group, rigorous steps must be undertaken to exclude physical problems before ascribing symptoms to hypochondriasis or somatization^{18,20}. That such patients are depressed is inferred from their good response to standard treatments for depression²¹.

The 1991 National Institutes for Health (NIH) Consensus Statement on diagnosis and treatment of depression in late life concluded: ‘What makes depression in the elderly so insidious is that neither the victim nor the health provider may recognize its symptoms in the context of the multiple physical problems of many elderly people.’ DSM-IV allows somatic symptoms to be counted towards the diagnosis of depression if there is any possibility of psychological aetiology, a more inclusive and accurate means of diagnosis than previously.

*Updated by Mohammed T. Abou-Saleh

MORBIDITY AND MORTALITY

Psychiatric morbidity in hospitals is higher than in the general population. Surveys of wards and clinics do not completely establish an association between psychiatric and physical morbidity because they may be biased for selective referral patterns: psychological symptoms can lead to help-seeking behaviour for physical illness in an individual who had previously been able to tolerate his or her physical problems. Similarly, they may influence a GP on whether or not to refer to hospital. Stress may be as important in triggering help-seeking behaviour as in triggering actual illness. In addition to the degree of distress, many other factors determine whether or not an individual will seek help, including religious and social values, socioeconomic background and personality.

Affective disorder in the elderly is strongly associated with physical ill-health²⁰: 'whether or not such an illness has a direct aetiological relationship to the affective disorder, its practical importance must be considered, for it is bound to influence the course and outcome of the psychiatric condition.' Although overall medical burden appears comparable in elderly patients with bipolar and those with major depressive disorder, patients with bipolar disorder have higher body mass index and greater burden of endocrine/metabolic and respiratory disease²².

Other studies have found that depression leads to increased mortality²³⁻²⁵ over and above age effects, the prognosis worsening with severity of depression. Chronic illness, physical function and cognitive function all independently predict depressive morbidity in late life. The significance of depressive symptoms was demonstrated by their independent association with all-cause mortality at two-year follow-up²⁶.

Depression in the elderly may be due partly to a biological ageing process, which would directly increase mortality and morbidity^{21,27}. Burvill and Hall²⁸ showed increased mortality in depressed elderly patients ($n = 103$, aged 60+) followed for five years if they were aged 75+, had impaired mobility or showed poor recovery with residual symptoms or chronicity. There were two peaks of increased mortality, one early in the disease and one late. Cardiovascular or pulmonary disease and malignancies were the predominant causes of death. The results are similar to those of the four-year follow-up by Murphy *et al.*²⁹, who also postulate that increased mortality seen in the depressed elderly (especially the men) was not caused by differences in physical health alone. They suggest:

- inadequate treatment of the depression, leading to cardiovascular complications from the antidepressant but no benefit to the patient; the depression itself can also provoke cardiac death, especially in men;
- 'sub-intentional suicide' in those who 'turn their faces to the wall';
- residual depressive invalidism, causing poor nutrition and decreased mobility; with attendant complications of susceptibility to infection, fractures, bedsores, etc., all contributing to the increased mortality.

Mortality in hospital was found to be significantly higher in those depressed but over 30% of those discharged had died within, on average, five months, whether depressed or not³⁰. The authors also noted that survivors with depression consumed more health care resources than did the non-depressed survivors. Among the depressed elderly, 40% have chronic poor physical health³¹; they use and need more medical services^{32,33} than the non-depressed, but also use fewer social and recreational services³². An association has been found

between poor mental health and subsequent physical disease, suggesting that positive mental health may significantly retard the decline in physical health with increasing age³⁴.

Physical illness affects the capacity for independent living, resulting in altered relationships with others, lowered self-esteem and vulnerability to depression. Serious illness may be seen by some as an unpleasant reminder of mortality, bringing apprehension and fear. Continuing physical illness is a poor prognostic factor for depression, although whether this is a result of a biological relationship or the psychological strain of being ill is uncertain.

Mortality in acute medical inpatients is significantly higher in those with associated depression, although the direction of causality is not established. For example, Silverstone³⁵ followed consecutive admissions for myocardial infarction, subarachnoid haemorrhage, pulmonary embolus or upper gastrointestinal haemorrhage for 28 days post admission; 34% were depressed and 47% of these had life-threatening complications or died, compared with 10% of those not depressed.

PHYSICAL ILLNESS AND DEPRESSION

Mood disturbance can result from structural brain disease, alterations in neurotransmitter concentration or activity caused by drugs or biochemical disturbance. These affective symptoms may present during a physical illness or be the initial symptom of an otherwise occult physical disorder. Depression may be:

- the result of an illness, especially a painful or disabling one;
- iatrogenic (e.g. the result of steroid treatment);
- a symptom of the physical illness (e.g. hypothyroidism);
- an aetiological factor (e.g. alcohol abuse secondary to depression);
- a depressed patient adopting the sick role as a coping mechanism;
- a common aetiological factor, such as bereavement, causing both depression and physical illness; or
- coincidental.

The elderly are particularly susceptible to the side effects of drug treatment³⁶, especially as they are often subject to polypharmacy^{37,38}. Patients with drug-induced depression often have a past or family history of depression and the drug may have precipitated the disease by affecting the levels of available neurotransmitters³⁷. Depression can often be alleviated by cessation of the drug, although some patients will also require antidepressant treatment. The combination of a susceptible patient and a depressogenic drug may precipitate a depression sufficiently severe to lead to suicide³⁷.

Subjective rating of general health has been shown to be independently associated with depression in the elderly, including the very old³⁹⁻⁴¹. This can lead to presentation at primary care or emergency facilities, unnecessary investigations and risk of iatrogenic disease, and lower quality of life. Recognition and treatment of the depression may lead to improvement in the patient's subjective perception of his or her health.

Physically ill depressed patients are more likely to be admitted to hospital than those who are not depressed⁴². Depressed patients have higher use of all categories of medical care, including admissions, laboratory tests and emergency department visits³³.

The presence of significant psychiatric disorder has been shown to adversely affect the course of medical admission^{43,44}, affective disorders in particular prolonging length of stay⁴⁵⁻⁴⁷ (although the study by Ramsay *et al.*⁴⁸ did not confirm this) and increasing the

likelihood of admission to residential care⁴⁹. Psychiatric intervention has been shown to increase recovery rate, reduce duration of stay, reduce the need for residential care after discharge and therefore reduce costs^{50,51}. Importantly a diagnosis of major depression in older medical inpatients is independently associated with poor mental health in their informal caregivers six months later⁵².

ADJUSTMENT DISORDER

Lipowski⁵³ has proposed that the subjective significance of an illness and its treatment (e.g. amputation, cancer), combined with the patient's personality and social circumstances, is the key to the psychological response. The variety of physical illnesses found with depression would support this view. Depression may be a reaction to physical problems; it occurs more frequently in those with increasing numbers of medical diagnoses and may be precipitated by developing new physical illnesses^{23,54}. All illnesses except the very trivial involve an element of psychological adjustment. Serious medical illness is likely to be a potent psychological stressor, affecting body image, self-esteem, the sense of identity and the capacity to work and to maintain social, family and marital relationships⁵⁵. However, the majority of people adapt their lives to the demands of their illness, maximizing their prospects of recovery and return to previous levels of activity.

In the elderly, physical illness is frequently chronic and may worsen with time. This, combined with the losses suffered by many elderly people, such as loss of status and income on retirement, loss of friends and family by death and the fear of loss of independence and dignity due to the illness itself, can lead to the adjustment disorder merging imperceptibly into a depressive illness. This can be considered secondary depression⁵⁶, the depression following or paralleling a life-threatening or incapacitating medical illness. However, the prevalence of this type of depression is unknown, as it is difficult to differentiate from depression related to other stressors and previous history. Patients with this type of depression tend to have fewer suicidal thoughts but have more feelings of helplessness, pessimism and anxiety⁵⁷.

SOMATIZED DEPRESSION

This is more common than medical illness presenting as depression, especially in the current generation of elderly, who tend to somatize their psychological symptoms, having been brought up in a society which did not encourage the expression of emotion. Somatic symptoms in the elderly may represent physical illness, depression or emotional responses to physical illness. The somatic symptoms will need investigation, but depression, if suspected, should be treated.

Pseudodementia is a specific type of masked depression. One of the most important differentiating factors is that the severity of cognitive impairment fluctuates in depressed patients, remaining constant or worsening in the evenings in dementia. Depressed patients tend not to try to succeed in tasks, giving up with 'I don't know' or 'I can't'. Demented patients will try, delighting in success but possibly becoming very distressed by failure – the so-called catastrophic reaction. Biological symptoms of appetite and weight loss, sleep disturbance and headache are typical of depression and not dementia. However, depression and dementia can co-exist and the differentiation of the two conditions is not always easy. If in doubt, a trial of antidepressant treatment will help elucidate the diagnosis. The pathognomic symptoms of masked or somatized depression include:

- diurnal variation (symptoms usually worse in the mornings);
- mild impairment of cognitive processes and concentration;
- dysthymic mood changes;
- fatigue, feeling tired, lack of energy;
- sleep disturbance (waking up early and being unable to get back to sleep); and
- an anxious sense of failure or of 'impending disaster'.

LIAISON

Consultation–liaison psychiatry has become well established as an important specialty in general hospitals on both sides of the Atlantic. In an ideal situation, psychiatrists would attend ward rounds in the general hospital, particularly on rehabilitation wards, where prevalence of depression is high and the effect on delayed discharge well documented^{45–47}. However, restricted resources prevent this: psychiatric morbidity is too high for a psychiatrist to see all the patients affected – his or her main role should be educational⁵⁸, only taking an active part in the management of more difficult cases. In many areas there is increasing development of specialist liaison nurses who are able to advise on diagnosis and treatment, reducing delay before assessments. The liaison nurse is likely to be more permanent than junior doctors on rotation and can often help a patient who refuses to see a psychiatrist or whose physician refuses psychiatric referral⁵⁹. Liaison nurses can educate general nurses in the recognition of psychiatric disorders and can in turn encourage junior medical staff to institute appropriate referral or treatment. Their development and use has been compared with that of community psychiatric nurses⁶⁰.

The most common reasons for requesting a psychiatric consultation in a general hospital are⁶¹:

- diagnostic uncertainty;
- recognition of a gross psychiatric disorder;
- excessive emotional reactions (e.g. fear, anger, depression);
- a patient's deviant behaviour disturbing ward or medical procedures;
- delayed convalescence (i.e. disability incompatible with observed pathology, relapse on mention of discharge);
- crisis in the doctor–patient relationship (e.g. refusing consent!);
- patient's admission of serious psychosocial difficulties;
- selection and/or preparation of patients (e.g. pre-transplant, cosmetic surgery).

It can be seen from the above list that the depressed patient, sitting quiet and withdrawn on the ward or in a home, may not be referred for a psychiatric opinion. In practice, only about 2% of geriatric patients are referred to the liaison services^{62–64}. Suggested reasons for the discrepancy between liaison rate and psychiatric morbidity are as follows^{62,65}:

- High prevalence of transient self-limiting psychiatric disease.
- Physician's failure to recognize psychiatric disease⁶⁶. Many studies have highlighted the unrecognized psychiatric problems on medical wards⁶⁵ and the under-diagnosis of major depression in particular has been well documented⁶⁷.
- Medical and nursing staff may actively avoid questioning for psychological problems, due to fear of precipitating emotional distress that they have not been trained to deal with.
- The low priority of psychiatric disease compared to physical, especially in a busy medical ward with acutely ill patients.

- Poor access to, or dissatisfaction with, psychiatric services.
- Physician resistance to psychiatric consultation⁵⁰ due to stigma or under-estimating the severity or the potential for treatment.

Use of screening scales is appropriate for assessing depression in the physically ill: it is common, can be a difficult diagnosis and has significant morbidity and mortality if untreated. Care must be taken to differentiate between short-lived adjustment disorders, occurring as a reaction to the admission itself, or the crisis which precipitated it. Diagnosis in acute admissions should therefore include enquiry into symptoms before admission. If none can be elicited, the patient should be reassessed at a later date, either during rehabilitation or after discharge.

Screening scales serve a dual function^{68–70} – they identify patients in need of further assessment and also serve as an educational tool if given by general staff during routine admission procedures. They emphasize the associated symptoms and signs of depression in the elderly, who may not show depressed affect and will deny feeling sad. It is important, however, that education about the treatment of depression goes hand in hand with education to recognize it, or the liaison services will be swamped.

TREATMENT

The fact that one can intuitively ‘understand’ why the physically ill elderly are depressed does not mean that it should be accepted as normal and treatment not attempted. Continuing physical illness is recognized as both a precipitant of depression and a poor prognostic factor, yet despite this, 80% of elderly general hospital patients are not depressed^{45,71,72}. Successful coping mechanisms can prevent the emergence of clinical depression. Even in the terminal patient, depression or dysphoria can be relieved by euphorants, such as oral or parenteral opiates, reducing the distress of patient and relatives⁷³ without significantly reducing the length of life remaining to the patient.

It is important that the diagnosis is not missed, as this condition usually responds well to treatment, at least initially, thus improving quality of life. Follow-up and early treatment of any relapses will further improve the prognosis. Increased self-esteem and ability to cope will reduce demand on families and possibly on services.

Even when the correct diagnosis is made, the depression may not be treated adequately, if at all: physically ill patients who are also depressed are more likely to be assigned to the ‘not to be resuscitated’ group, compared with those elderly who are not depressed. The lack of effort and motivation caused by depression may be regarded as ‘not trying’ or ‘giving up’ by nurses and rehabilitation staff, who withdraw from this group of patients for more emotionally rewarding non-depressed elderly subjects on the same ward.

The elderly as a group have approximately twice as many adverse drug reactions as younger adults⁷⁴. They are frequently already on polypharmacy, so drug interactions are a real possibility. It is therefore important that physicians are advised and supported by the psychiatric services in the use of safe, well-tolerated antidepressants and other treatments to reduce the impact of this disease on both the individual and society.

Electroconvulsive therapy (ECT) is an effective treatment of depression^{75,76}. The response to treatment in older people is better than in the young^{77,78}. With the increasing safety of anaesthesia, very few patients, even those with severe physical disease, are unable to tolerate a course of treatment. It is more rapid in effect

than medication alone, but the improvement is rarely sustained unless antidepressants are also given to prevent relapse.

A review of psychological treatments in chronic illness⁷⁹ found very little empirical evidence of benefit when therapeutic interventions were applied indiscriminately. However, some evidence was found to show benefit in patients with somatization disorders rather than physical illness, and also that brief interventions following the onset of acute physical illness reduced longer term psychological morbidity. A suggested general approach to the treatment of physically ill depressed patients is as follows:

1. Investigate and give appropriate treatment to all physical problems, either curative treatment or to minimize persistent morbidity. Explain the illness, treatment and prognosis to the patient in as much detail as he/she wishes. Make sure the explanation is understood and repeat as often as necessary.
2. Give general social support (e.g. home help services, financial assistance if relevant, or residential or nursing home care).
3. Give psychological support – encouragement, continued interest in the patient (e.g. outpatient follow-up). Support groups are often beneficial for chronic conditions such as rheumatoid arthritis, Parkinson’s disease, etc.
4. Consider antidepressant therapy if the symptoms are sufficiently severe that they would be considered to warrant medication if seen in a patient without physical problems. Monitor the response to treatment; this may take 7–8 weeks⁸⁰. If no response is seen to a therapeutic dosage of antidepressant, consider a trial of an alternative antidepressant or adjunctive treatment, or specialist referral.

PROGNOSIS

Little is known of the prognosis of psychiatric disorder identified in the medical setting⁸¹, except that concomitant physical illness is a poor prognostic factor. Psychiatric disturbance often persists^{82–84}, especially in patients with a previous history of psychiatric disorder. Those with affective disorder on admission have increased mortality and make greater demands on medical, social and psychiatric services^{81,85}.

In one series of consecutive acute medical admissions⁸⁴, fewer than 45% of those patients with concomitant depression had received antidepressants at all, 20% had been given benzodiazepines, and less than 25% had been treated for more than one week. The authors concluded that an effective treatment for depression in elderly patients needed to be found, with widespread education of geriatricians in the diagnosis and treatment of depression.

In psychiatric patients, relapse has been linked with supervening physical illness⁸⁶. The presence or development of cerebral or any other irreversible physical disorder indicates poor future mental health in the great majority of patients, as well as the likelihood of early death⁸⁷.

The prognosis of the physical illness, for both morbidity and mortality, is also inextricably linked with that of the depression. Increased mortality from physical illness, especially cardiovascular disease, has been reported^{88,89}. This excess of deaths is significantly associated with groups who have been only partially treated (e.g. have not responded to antidepressants⁹⁰, especially in older men⁹¹).

Explanations for the apparent association of physical illness with poor treatment outcome might include⁹²:

- age as a confounding factor – most of the trials of treatment in the physically ill are in the elderly;

- medically ill patients may be given inadequate doses of antidepressants because of problems with side effects or over-cautious physicians;
- different subtypes of depression exist, some medication responsive, some not. Organic mood disorder (depression induced by physical illness or a specific organic factor) has been shown to have a worse prognosis at four-year follow-up⁹³.

The prognosis of depression in the physically ill elderly is therefore dependent on accurate diagnosis, intensive treatment, follow-up and early treatment of any relapses^{86,88,94}. Increased self-esteem and ability to cope will reduce demand on families and possibly on services. No studies have yet convincingly identified predictors of response in physically ill populations, although pre-existing depression prior to admission with physical problems appears to predict persistent depression, rather than if the depression develops in hospital^{82,95}.

SUICIDE

Suicide is the most dramatic of poor outcomes, and the elderly are over-represented in suicide statistics. Although the elderly are less likely to attempt suicide, they are more likely to complete it^{96,97}. The presence of physical illness, especially if associated with chronic pain and disability, increases the risk; elderly men living alone are at the highest risk. The individual's adjustment to ill-health and his or her associated feelings of hopelessness and demoralization are obviously important⁹⁸. Many elderly suicide victims are suffering from their first episode of major depression, which is typically only moderately severe but the diagnosis is missed⁹⁹, and the potential for recovery following intervention therefore lost.

Depression has been linked to decreased compliance and to voluntary refusal of life-saving essential medical treatments^{100,101}. This may reflect either conscious or unconscious suicidal motivation.

SERVICE IMPLICATIONS

It is important to note that the ageing population itself is growing older, with large numbers of very old individuals. It is this old-old group who have the highest physical and psychiatric morbidity and who make the greatest demands on services.

Undergraduate teaching programmes must be tightly integrated in order for students to develop a holistic approach to the elderly, together with an understanding of the psychosocial and economic factors that will affect presentation and treatment. Joint postgraduate meetings between the two specialties are becoming more common and should be encouraged, each maintaining their separate identities and training but working closely together in clinical practice.

Interdisciplinary research continues to grow in amount, but is mostly directed at psychiatric problems on medical wards. Little seems to be researched in the other direction, medical illnesses on psychiatric wards. All research is obviously relevant to both specialties and in practice helps to strengthen links between them.

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Depression After Stroke

Peter Knapp and Allan House

University of Leeds, UK

Stroke patients have high rates of all types of depressive disorder, although estimates of the prevalence of depression within the first month of stroke vary greatly^{1,2}, according to the type of measure used and the way the sample was derived. A recent systematic review of observational studies suggests that the point prevalence of depression at any time in the first year after stroke is about 33%³. The frequency of depression is about the same whether measured soon or later after stroke, although later rates are less certain because of patient attrition in studies. Depression remits in some patients, while in others it persists: one study reported that 50% of those depressed within three weeks of stroke remained depressed one year later⁴. Depression not only affects quality of life: patients with depression after stroke may be at greater risk of mortality⁵, cognitive impairment⁶ and poorer functional or social recovery^{7,8}.

There are claims that post-stroke depression is a distinct subtype⁹. There is little unequivocal evidence to support this claim, since psychological and biological symptoms reported by patients are found in depression seen in non-stroke patients¹⁰. What does appear to be distinctive is the increased prevalence of uncontrollable crying (emotionality) among stroke patients. A small number of patients suffer pathological laughing and crying, a syndrome which is probably neurological in origin, in which emotional expression arises after minor provocation that often appears meaningless¹¹. A more common syndrome, emotionalism, is also characterized by increased tearfulness, but is more complex. The emotional episodes are provoked by meaningful stimuli, but the crying is characterized by a lack of warning and control. There appears to be a psychological component to its origin¹². Emotionalism is associated with an increased risk of depression¹³, but patients with emotionalism may be at greater risk of psychological problems not explained by concurrent depression^{14,15}. This syndrome is probably under-recognized.

Reaching a diagnosis of depression after stroke can be complicated by the presence of problems such as communicative or cognitive impairment¹⁶. Patients with expressive communication problems can often be assessed by the careful use of closed questions. The assessment of those with receptive communication problems or significant cognitive impairment is much more complex: a non-language-based assessment of depression shows promise but is insufficiently reliable in its present form for accurate diagnosis¹⁷. The use of a 'smiley faces' symbol measure has also been shown not to be a reliable screening tool¹⁸. Screening for depression by the use of questionnaire measures can be quick and easy to do; the main disadvantage is their low positive predictive validity: they identify many false

positive cases¹⁹. A recent study suggests that such pencil and paper screening measures have greater validity when administered twice several weeks apart: patients scoring above the threshold on only one occasion are less likely to have a persistent depression that warrants treatment²⁰.

The diagnosis of depression by clinical interview might also be confused by facial palsy and a disturbance of speech prosody (rhythm in speech), both of which are relatively common after stroke and which give the patient the appearance of a person with depression²¹. The dexamethasone suppression test is not sufficiently sensitive to be used as a diagnostic tool²².

The high rate of depression reported in some stroke research has led to the suggestion that the neurological damage is a key factor in its aetiology²³. As a result, many studies have attempted to link depression after stroke with lesion location. A series of studies proposed, first, that patients with left hemisphere lesions were at greater risk of depression²⁴, and later, that those with left anterior lesions were at most risk^{25,26}. Other researchers²⁷⁻²⁹ have not replicated these findings, suggesting that patient sampling and the timing of assessment might explain the differences.

Even if lesion location is associated with greater risk of depression, the context of this relationship is important. First, it is clear that stroke patients with all sorts of lesions can suffer depression⁹, so factors other than lesion location must also be at work. Second, stroke location is extremely varied³⁰, so those with any particular lesion (such as left anterior lesions) will be a minority of patients, making the attributable risk due to any one type of lesion small. Last, although the rate of depression in stroke patients is higher than in age-matched non-stroke controls, it is about the same as in patients with non-neurological disabling illness^{21,31}, suggesting that non-neurological factors are important. Relevant non-neurological aetiological factors are likely to include the threat of disability and a sense of loss.

That psychosocial factors are likely to be relevant to both the onset and persistence of depression has been illustrated in several studies. For example, one study found that depression at four months after stroke onset was commoner among those with greater disability, those who were divorced and those with higher pre-stroke alcohol intake²⁸. Depression is more likely in those patients who perceive their stroke as a greater threat, and in those who have fewer psychological resources or social support to deal with that threat. Patients with previous history of depression or other psychological disorder are also at higher risk of depression after stroke³².

Patients with depression after stroke might be considered for pharmacological or psychological treatments. A recent systematic review of the treatment trials showed limited beneficial effects of antidepressants, with moderate reduction in symptoms compared to placebo³³. Trials are generally small with high drop-out rates and inadequate evidence on other outcomes (such as functional recovery or mortality) or adverse events. The evidence for treating emotionalism with antidepressants is rather stronger – both tricyclics and selective serotonin re-uptake inhibitors (SSRIs) have been shown to reduce the frequency of crying episodes¹⁵. There is no good trial evidence to draw upon in assessing whether psychological interventions are effective in treating depression after stroke³³.

Some services aim to intervene in an attempt to prevent the onset of depression after stroke. There is no evidence to support the use of antidepressants in preventing the onset of depression³⁴. Three recently completed studies suggest that brief psychological interventions may be beneficial³⁴. Randomized trials of motivational interviewing, care management and problem-solving therapy all showed small but statistically significant benefits. Each needs replication in further trials before these interventions can be recommended for implementation as a matter of routine, although it is encouraging that relatively brief, structured psychological interventions can show benefits. There are disadvantages to psychological management: it may be difficult to implement in patients with significant speech and cognitive impairment³⁵, and some patients find psychological treatments unacceptable, both before and after the treatment has started.

An unresearched question relates to the best means of structuring interventions. Evidence from other areas suggests that there are substantial benefits to be had when pharmacological and psychological treatments are delivered in an integrated approach according to standard protocols³⁶, when treatment is tailored to severity of depression and its response to first-line treatment, as in stepped care programmes³⁷ and when it is delivered in programmes of collaborative care that involve both primary and secondary care specialists³⁸.

In summary, depression after stroke is common, and its causes are probably multiple – biological, psychological and social – as is the case in other physical illnesses. The evidence for benefit from antidepressant drugs is accruing but remains surprisingly poor, considering their problematic side effects and how widely they are prescribed. The potential for psychological therapies is evident in several studies and its use has been under-evaluated, which is a deficit that needs correcting. The completion of several systematic reviews of intervention trials and prevalence studies has been beneficial for providing evidence for clinicians but, pending the completion of further primary research, clinicians will largely need to rely on evidence from other areas of physical medicine to inform their treatments.

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Cross-Cultural Variation in the Experience of Depression in Older People in the UK

Vanessa Lawrence¹, Joanna Murray¹, Anthony Klugman² and Sube Banerjee¹

¹*Institute of Psychiatry, King's College London, London, UK*

²*Old Age Psychiatry, South London and Maudsley NHS Foundation Trust, London, UK*

INTRODUCTION

Depression is the most common mental disorder in later life, affecting up to 15% of those over 65¹. Studies focused on the needs of people from minority ethnic groups suggest at least the same high prevalence of depression among south Asian and black Caribbean groups in the UK². It has been suggested that ethnic elders may be more vulnerable to mental illness than the majority population and the term 'triple jeopardy' has been used to describe the combined challenge of racism, ageism and socioeconomic deprivation faced by older people from minority backgrounds³. Census data reveal that the proportion of black and minority ethnic individuals over the age of 65 increased from 3% in 1991, to over 8% in 2001. Therefore, it appears inevitable that the prevalence of depression in minority ethnic groups, and the challenges that this presents to health and social services in the UK will rise². It is also of concern that older adults from minority ethnic groups appear to have lower levels of service use compared with the majority population⁴.

There are major discontinuities in the management of depression in old age throughout the health and social care system. It is estimated that only 15% of older people with depression receive appropriate treatment from primary or secondary care services⁵. This may be a function of the inherent complexities of the illness with the presentation of depression anything but uniform. From a cross-cultural perspective, there are suggestions that Asian and black Caribbean patients have their psychological problems identified less frequently than their white counterparts⁶. Again, this may in part be explained by the variable ways in which depression is manifested and reported by different ethnic groups^{7,8}. The National Service Framework for Older People has explicitly acknowledged that depression is under-treated in older people, and a key aim is to ensure the early recognition and effective management of depression across ethnic groups⁹.

BARRIERS ON THE PATHWAY TO CARE

Suggestions of unmet need among ethnic elders¹⁰ require an exploration of the potential barriers and facilitators to service use. Goldberg and Huxley (1980) described a succession of filters in the 'pathway to care' that determine whether people access mental health services¹¹. Sufferers' Beliefs about the nature of the

condition, and what is appropriate help, may act as barriers at each of these stages, influencing whether and from whom to seek help, the idioms for expressing the condition, and the acceptability of various treatments¹². At present, much of our data on these issues has been derived from studies focused on the needs of working-age adults^{13,14}; among older adult research very few studies have examined the experience of depression across ethnic groups. In the United Kingdom, as in most health-care systems, general practitioners (GPs) are the first point of access to health care, directly providing most of the treatment for common mental disorders as well as referral to specialist mental health services. The beliefs of primary care professionals may represent a further barrier in the pathway to care influencing the recognition and management of depression in older patients⁷. Thus, it is important to consider whether the large discrepancies between prevalence, identification and treatment of depression is to be found in the attitudes and behaviour of GPs, their older patients or some combination between the two.

Levkoff and colleagues (1988) hypothesized that the most common reason for older people not to seek help from their GP was that they tended to 'normalize' symptoms of depression and attribute their condition to the ageing process rather than to disease¹². Attributions of the causes of depression have been found to vary between different ethnic groups¹⁴. Bhugra (1996) found that south Asian women of all ages had a clear understanding of psychosocial aspects of depression but were not predisposed towards medical models or explanations¹⁵. Abas (1996) suggested that older Caribbean people construe mental disorders as secondary to other unmet needs (e.g. physical, social, spiritual)¹⁶. There is also evidence that south Asian and black Caribbean adults may favour self-help strategies for depression rather than seeking professional help¹⁴. Religious practices (e.g. prayer) have been identified as important ways of coping among minority ethnic groups living in the UK and traditional healers or religious leaders could be considered by these individuals to be a more appropriate and acceptable source of help than Western models of psychiatric care¹⁷. Alternatively, talking to friends and family may represent the first line of treatment¹⁸. Certainly, research suggests that south Asian and black Caribbean adults do not always envisage primary care consultations as an appropriate response to depression^{13,19}. Negative attitudes towards antidepressants and

mental health services in general, may discourage help seeking within minority ethnic groups²⁰.

Yet depression is also under-recognized and poorly managed in primary care⁵. It appears that the stigma of mental disorder is keenly felt by older adults and feelings of shame have been cited to explain underreporting of affective symptoms by older patients²⁸. Research has pointed to even higher levels of stigma surrounding depression within minority ethnic groups^{17,19}. There is evidence that GPs construe presentations by south Asian patients as being dominated by physical rather than psychological complaints⁷. Odell *et al.* (1997) speculated that a tendency in south Asians to somatise their psychological distress might contribute to low detection rates⁸. However, Bhui and colleagues (2001) commented that the frequent use by GPs of 'somatic' and 'sub-clinical' labels in relation to Punjabi patients suggests that although they did not perceive there to be 'significant psychiatric disorders' they were aware of some emotional disturbance⁷. Comino *et al.* (2001) reported substantial under-detection of depression by GPs among south Asian patients, though the patients were able to identify common symptoms of anxiety and depression themselves⁶. However, there is accumulating evidence to suggest that the language used to express psychological distress is culturally informed^{15,16,21}. Again it is important to emphasize that very few data deal specifically with older people with depression from minority ethnic groups. In order to generate services that are accessible and acceptable to older adults across ethnic groups, service providers need to understand the beliefs that underlie help-seeking behaviour and the likelihood of help being offered and accepted.

A CROSS-CULTURAL QUALITATIVE STUDY OF THE BARRIERS AND FACILITATORS TO CARE

In the light of the gaps in the evidence base identified above, we completed a programme of work to investigate the attitudes, experiences and beliefs of older adults from the three largest ethnic groups in the UK and primary care professionals concerning depression^{22–24}. In-depth interviews were conducted with 110 older adults and 30 primary care professionals (see Table 83.1).

The data incorporates the perspective of older adults with depression (both treated and untreated) and the general older population. Each group included black Caribbean, south Asian and white British older adults; this enabled us to compare and contrast attitudes among the two largest minority ethnic groups in the UK with the majority population. A 'case' of depression was defined as a score of 7 or

above on the Hospital Anxiety and Depression Scale (HADS)²⁵. Treatment was not limited *a priori* to pharmacological interventions (i.e. antidepressants) but in the event no participants were receiving psychological treatments alone. We identified participants through seven primary care practices and through day centres and lunch clubs serving the black Caribbean, south Asian and white British communities. Topics for the interview guide were generated from the research literature. We used a vignette describing an older person with symptoms typical of depression as a starting point to enable us to explore the idioms used to express mental distress and attitudes toward mental illness in our sample^{18,19,21}. Interviews then explored: what the word *depression* meant to participants; what participants thought might cause depression; what someone with depression should do, what help might someone with depression need; who should help them and how. The older adults were then asked to give their opinions on a range of treatments and services. Information sheets, consent forms, the HADS and the vignette were available in four Asian languages: Gujarati, Hindi, Punjabi and Urdu. Interviews were conducted in participants' homes, unless they stated a preference to be seen elsewhere, lasted around one hour and were conducted in the participants' preferred language. All were recorded on audio-tape and transcribed verbatim.

In-depth individual interviews were conducted with GPs, practice nurses and practice counsellors working in 18 primary care centres in south London. The sample was selected purposively to include professionals working in different settings (single-handed and group practices), serving areas of contrasting socioeconomic and ethnic characteristics. One-third of the participants were recruited from primary care research networks, and two-thirds were selected from information published on local primary care trust websites. Key topics explored in the interviews included: perceptions of the experience and presentation of depression in older people; perceptions of older people's beliefs about depression; cultural differences in the above. Analysis of the data was based on the grounded theory approach²⁶. Three members of the research team scrutinized and coded the initial transcripts. Emerging themes were identified and labelled with codes. A constant comparison technique was used to delineate the properties of the codes and to develop categories and subcategories. As the analysis proceeded, we verified and developed existing codes and added new codes where necessary. The researchers compared their coding strategies and any instances of disagreement were discussed and resolved by the wider research team. NVivo qualitative data analysis software was used to process the transcripts. The number of interviews completed in each group

Table 83.1 Number of participants

	Older adults		
	Black Caribbean	South Asian	White British
<i>Total</i>	32	33	45
Treatment status			
Depressed and treated	9	6	15
Depressed and not treated	13	12	12
Not depressed	10	15	18
	Primary care professionals		
	General practitioners	Practice nurses	Practice counsellors
<i>Total</i>	18	7	5

was determined by 'saturation of data', i.e. the point at which no new themes emerged from the interviews.

FINDINGS

The themes to be presented in this chapter emerged from the analysis of: firstly, older adults' perception of the concepts and causation of depression; secondly, older adults' attitudes towards help seeking for depression; and thirdly, primary care professionals' perceptions of the experience and presentation of depression across ethnic groups. The data will be considered in relation to the existing literature.

Older Adults' Concepts and Causation of Depression

The older adults in our study felt that the ageing process had a considerable number of physical, circumstantial and emotional implications that contributed to depression. It has been suggested that there is a propensity among the elderly to 'explain away' depression as a normal part of ageing and that this prevents them seeking help for the condition¹². However, in our study, an acceptance of the social and ageing precipitants of depression was not incompatible with the concept of depression as an illness. Roughly three-quarters of the black Caribbean elders and two-thirds of the white British participants defined depression in this way. Assigning the label 'illness' appeared to validate and legitimize the experience. Almost half of the white British and black Caribbean participants also viewed depression as a serious condition that was distinct from sadness and grief. Thus, depression was concurrently viewed by these groups as being an understandable, yet dysfunctional, consequence of old age.

It was notable that south Asian participants were least likely to identify depression as an illness or a serious condition and most likely to equate depression with 'normal' feelings of sadness and grief. The apparent incompatibility of these beliefs with the Western biomedical model of depression might make south Asian older adults less likely to seek or accept health services for depression. A further challenge to services exists in the recurring belief that emerged among south Asian and, to a lesser extent, black Caribbean participants that depression stems from a weakness or deficiency in character. This is consistent with previously reported high levels of stigma surrounding depression in these cultures²⁷. Research has suggested that fear of being ostracized by peers could act as a deterrent to help seeking within minority communities¹⁷.

The language used to describe depression also emerged as culturally influenced. A large proportion of black Caribbean participants defined depression in terms of feeling low or down, which is consistent with previous findings in younger age groups²⁸. The white British participants spoke of variations in mood and feelings of hopelessness with even greater frequency, often employing metaphors of darkness to illustrate their point. The tendency of these groups to describe depression in terms of its emotional impact implies both an ability and willingness to enter into a psychological discourse. Conversely, only a small number of south Asian elders described depression in terms of hopelessness or low mood. Along with Caribbean elders, they frequently defined depression in terms of worry, with emphasis repeatedly being placed on troubles within the mind. Notably, the south Asian participants often articulated this worry in terms of 'thinking too much', a phrase previously identified as a descriptor of mental distress within south Asian younger adults²¹.

Differences in attribution were found in the themes emerging from the three ethnic groups. Complaints of loneliness were the focus of

the black Caribbean responses, which is consistent with the suggestion that black Caribbean older adults miss the traditional social networks that characterize Caribbean society²⁹. As in research in younger adults¹⁴, black Caribbean and white British participants tended to consider mistreatment and abandonment by partners to be a likely cause of depression. Members of the south Asian group related wider family problems to depression, which similarly accords with work in younger age groups¹⁸. Participants discussed the negative impact of a difficult 'home atmosphere', and they expressed concerns about the discordance in values between their children and themselves. Interestingly, members of the black Caribbean and south Asian groups made very few references to the effects of racism on their emotional well-being, which contrasts with the expressed views of a working-age adult group¹⁴.

Over half of the white British participants cited the death of a spouse as a key cause of depression. Another major cause of unhappiness within the white British group was the feeling that they enjoyed very little contact or support from their family. Increased contact was both longed for and highly valued when received. It seems likely that this absence of family support is related to the predominant role occupied by spouses within the white British group, where loss of the spouse is likely to leave an even greater vacuum in emotional support. A large proportion of white British participants receiving antidepressants attributed their depression to bereavement, suggesting that bereavement may be used to initiate discussion about depression in this group. Research suggests that social problems may be a criterion used by GPs to make a psychiatric diagnosis³⁰. In an exploration of the reasons for low treatment rates and high suicide rates in south Asian women, mental health professionals considered it advantageous to have an understanding of the cultural background and reasons why an individual may be experiencing depression³¹.

Older Adults' Attitudes towards Help Seeking

Personal responsibility for coping was a recurrent theme. We found consensus across the ethnic groups that the impetus to combat depression must come from the individual. Forcing oneself to get out and engage in activities was identified as the most effective means of self-help. We found less of a focus on cognitive strategies compared with working age adults¹⁴, suggesting that older people tend to adopt a more behavioural approach to tackling the experience of depression. Behavioural strategies that encourage efforts to interact and remain active may provide an acceptable adjunct or alternative to pharmacological or psychotherapeutic interventions. However, it remains a fact that up to one in six older adults are depressed at any one time¹ and public education campaigns must communicate that the nature of depression often necessitates help from others.

There was a tendency among south Asian older adults to identify families as a prominent source of help for depression, which is consistent with research in younger age groups³². The black Caribbean group placed less emphasis on the role of the family but stressed the cathartic value of discussing worries and concerns with friends, suggesting a willingness within this group to discuss emotional problems in a candid way. Our results echo the importance and acceptability of religion in helping many black Caribbean people of all ages cope with emotional distress^{14,17}. Prayer was allied to the concept of self-help, and it was implied that without a true relationship with God, depression would be difficult to overcome. Seeking informal or formal help might signify insufficient faith in this context. Health-care professionals may need to work closely with religious leaders if they

are to challenge these deep-seated beliefs. Fewer south Asian participants cited religion as a coping mechanism, but of those who did, religious worship presented as an enduring and integral part of life. Participants described visiting the temple as a means of sustaining emotional well-being. In contrast to previous research^{17,21} no reference was made to traditional healers as a source of help.

Research indicates that younger south Asian people tend not to medicalize emotional distress²¹. This may account for the tendency among the south Asian group within our study to view the nature of depression as incompatible with the GP's role, which they conceived as prescribing medication and making referrals. Promoting the concept of depression as a treatable medical condition might resolve this problem and legitimize help seeking. However, it is also likely to be of value to reassure older adults that it is appropriate to voice concerns about their emotional state in a GP consultation. The black Caribbean group viewed GPs as serving the additional function of listening and discussing what was on their mind. Consequently, they praised GPs for allowing individuals to discuss their worries and concerns, yet were highly critical of instances where GPs spent insufficient time with their patients or appeared to take insufficient interest. Therefore, the belief of the black Caribbean participants that GPs *could* and *should* help resulted in polarized positive and negative evaluations. Reservations about seeking help from GPs were similar across the ethnic groups; doctors were too busy and overly reliant on medication as a form of treatment. Others explained that limited GP consultation time forced them to prioritize their physical, rather than their psychological, complaints.

Psychiatrists were generally regarded negatively and many participants were conscious of the stigma attached to this profession. This was especially pronounced within the ethnic minority groups as has been reported in other studies³³. However, experience of psychiatrists, which tended to be limited to the white British and black Caribbean groups, often predicated the more positive remarks. The idea of counselling was embraced by the black Caribbean group in particular. Their limited experience of counselling paralleled that of other groups, yet their greater enthusiasm possibly reflects the high value they place on confiding in others³³ and being genuinely 'listened to' by professionals¹⁶. For the south Asian group, their unease at discussing personal matters with strangers appeared to contribute to a negative view of counselling. This mirrors previous research that highlighted the pertinent issue of confidentiality within south Asian communities¹⁸. Medication was cautiously advocated across the groups. Participants generally felt that certain circumstances dictated its use although there was widespread concern about side effects and dependency.

Primary Care Professionals' Perceptions of Depression in Older People

All but one of the primary care professionals in our study believed that cultural differences in illness beliefs had an important influence on how older adults communicated the experience of depression. This builds upon previous cross-cultural studies of depression that have discussed the ways in which culture can shape expressions of distress³⁴. A number of GPs held the view that the Western concept of depression was less recognized in some cultures. Although GPs were reluctant to make generalizations on the basis of ethnicity most admitted that it could be difficult to engage patients from minority ethnic groups in discussions about psychological problems. Professionals were of the opinion that the belief that 'non-medical' problems were

inappropriate or not important enough to warrant medical attention prevented older people from all ethnic groups from talking about psychosocial difficulties in a primary care setting. However, black Caribbean and south Asian older adults were thought to be even less likely than their white British peers to disclose psychological symptoms. Moreover, and in accordance with previous research⁷, GPs suggested that there was a propensity among south Asian elders in particular to express psychological distress as physical pain or concerns about heart disease. One GP commented that excessive worry about physical symptoms often masked the presence of depression and that those patients who eventually received a diagnosis usually had more severe and enduring symptoms. As the first point of contact with health care, most GPs were aware there were particular requirements for sensitive exploration of symptoms, interpretation and explanation with all older adults. Some had clear strategies for introducing the concept of depression while keeping within the patient's physical formulation of their problem. Others negotiated a treatment plan or even colluded with the patient by making the requested referral to a specialist for physical tests while initiating treatment for depression. While GPs encountered more somatic presentations of depression, practice nurses and counsellors had more opportunities to identify and explore social difficulties. People with chronic conditions were often in regular contact with the practice nurse and there seemed important possibilities in using these contacts more systematically to identify and treat depression in primary care.

The suggestion that it is a lack of 'psychological-mindedness' that leads to somatic presentation of emotional distress has increasingly been rejected within the literature and research has suggested that bodily complaints may in part indicate the use of somatic metaphors³⁵. While many of the primary care professionals in our study believed that there were cultural differences in the type of symptoms presented, others believed the differences lay in the use of language and metaphor rather than the attribution of symptoms. Abas (1996) described a wide range of psychological language used by African-Caribbean elders to convey emotional distress¹⁶. Indeed expressions used to convey feelings of depression such as 'low spirit' and 'weighed down'^{16,28} explicitly reveal low mood. Similarly south Asian patients, although tending to present somatic symptoms, have been shown to articulate their distress in psychological terms³⁶. Comino and colleagues (2001) concluded that the tendency of GPs to rely exclusively on Western-based concepts and diagnostic traditions when assessing people from other cultures represented a significant detection barrier⁶. Finally, primary care staff were acutely aware of the stigma of mental disorder and had observed embarrassment, failure and shame among older patients in admitting to feelings of depression. The stigma of mental illness was thought to have more serious consequences in minority ethnic communities with a diagnosis of depression potentially bringing shame upon the family. This represented an important barrier to addressing psychosocial aspects of the illness and gaining the patient's agreement to begin appropriate treatment.

IMPLICATIONS FOR POLICY AND PRACTICE

These data have implications for policy, practice and education. The model used by older adults from all ethnic groups was more akin to a social than a classic biomedical schema. This suggests that the approach clinicians need to take in attempting to engage older people with depression in a therapeutic alliance would benefit from being framed in social as well as physical terms. Enquiries about recent

life events and losses could be used to facilitate discussion with older adults about depression. More emphasis in medical training and continuing professional development on how symptom attribution differs across ethnic groups could enable practitioners to frame their questions within an appropriate cultural framework. However, this is only a first step: clinicians need to be able to explain the interaction of the social, psychological and biological elements of causation, thus generating a shared understanding of the value of biological (such as antidepressant medication), as well as social and psychological, interventions. Recent evidence suggests that older adults incorporate medical and experiential knowledge into their model of depression³⁷. However, it has also been argued that GPs should explicitly relate diagnosis and treatment options to the individual's social experience of depression if they are to have relevance beyond the clinical context in which the diagnosis is made³⁷. Proctor (2008) takes this further, concluding that the acceptability and effectiveness of treatment for depression depends on the practitioners' ability to connect it to other medical and social problems of later life, which the study indicated occupy a higher priority among older adults³⁸.

There were striking consistencies in the barriers to care described by older people and primary care staff. Primary care professionals and older adults acknowledged that multiple health problems might prompt elderly patients to prioritize physical complaints in order to avoid 'wasting the doctor's time'. GPs considered this to be compounded by the common belief that doctors are there to deal with physical conditions rather than psychological problems. Yet white British and black Caribbean older adults displayed a willingness to disclose emotional difficulties associated with depression, which is an encouraging indication that older adults would respond to discussion with health and social care professionals about their mood. Together these data indicate that practitioners need to provide assurance that disclosure of feelings is appropriate in a medical consultation. Longer appointments might facilitate this process and enable primary care staff to address the mental health needs of older patients as a matter of routine. Practice nurses felt that they were well placed to discuss the implications of life events, family problems and other 'non-medical' crises with older patients. Given the high co-morbidity of depression in later life with physical illness³⁹, the increasing role of practice nurses in the management of chronic disease may provide a setting to explore psychosocial problems. The pronounced interest in counselling demonstrated by black Caribbean participants highlights the need for greater access to a wider range of treatments. Psychotherapy has been identified as a preferred treatment option among black American older adults and its provision in primary care has been associated with better depression outcomes⁴⁰. Unfortunately, access to talking therapies remains limited among older people in the UK despite assertions that this is an entitlement for all.

The study confirms that the language and metaphors used to describe depression can be culturally influenced. Sensitivity to the 'language of depression' used by different groups (e.g. 'excessive thinking' within the south Asian group) will increase the likelihood of reaching an acceptable diagnosis and treatment plan. An understanding of cultural variation in the expression of mental illness is fundamental to good health care, and this should form a normal part of training for health-care professionals. Ethnic differences in the conceptualization and attributions of depression also highlight the need for practitioners to emphasize, particularly with patients from minority ethnic groups, that depression is not a sign of weakness and that anyone can become depressed. In turn, cultural- and language-specific public education could be directed as modifying public attitudes and understanding of depression not only to reduce

stigma, but also to enable self-identification of the disorder. Lastly, the data point towards the need for education concerning the role of psychiatrists, as well as for accurate information regarding the risks of dependency and actual side effects with medication.

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Treatment of Late-Life Depression In Community Settings

Carolyn Chew-Graham

School of Community Based Medicine, University of Manchester, UK

EPIDEMIOLOGY

It has been stated that 10–15% of all older people meet the clinical criteria for a diagnosis of depression¹, and major depression is a recurring disorder, with the majority of older patients having a recurrence within three years². Some groups are more at risk of depression: 40% of people in care homes are depressed³ and the community prevalence of depression in South Asian older people may approach 20%⁴.

Older people have the highest suicide rate for women and second highest for men (National Confidential Inquiry into Suicides and Homicides) and is the one age group where rates have not declined. In contrast with young people, self-harm in older people usually signifies mental illness, mostly depression, with high risk of completed suicide⁵.

The over-85 population of the United Kingdom will increase by 50% over the next 15 years, from 1.2 million in 2005 to 1.8 million in 2021, compared with a 30% increase in the over-65 population. In just half that time, the older black and minority ethnic (BME) population will increase by up to 170%. This is not purely a change affecting the United Kingdom – ageing is a global issue and in the United States the number of centenarians will rise from 72 000 in 2000 to 834 000 by 2050. (www.grg.org/calment.html). The concept of multiple jeopardy postulates that ethnic elders, by virtue of age, socioeconomic difficulties and minority status are at greater risk of illness, thus in greater need of health services⁴.

Co-morbidities or multi-morbidities are the norm in later life. Thus emotional and physical health problems of older people are entwined and manifested in complex co-morbidity⁶ and those with a physical disability have five times higher rates of depression. Although there is variation between studies, it has been estimated that up to 26% of people with diabetes also suffer from depression⁷ and comparable figures have been reported for coronary heart disease⁷.

Being equipped to meet these complex needs is critical in settings like primary care and residential care.

OLDER PEOPLE'S MENTAL HEALTH PROBLEMS IN PRIMARY CARE

Primary care is on the front line in dealing with older people's mental health, supporting families and managing people with complex

co-morbidities. Older people consult almost twice as often as other age groups⁹ and 22% of older people will have attended their general practitioner (GP) within the last two weeks and 40% may have a mental health problem. In the United Kingdom primary care is a key NHS service provider for care homes, where at least 40% of older people have depression and 50–80% dementia³.

Depression is under-treated in older people with around 5 out of 6 older people with depression receiving no treatment at all. Only one third of older people with depression discuss their symptoms with their GP and less than half of these will receive adequate treatment^{10,11}. Most people with mental health problems are managed in primary care with only 6% of older people with depression receiving specialist mental health care.

MAKING THE DIAGNOSIS

The literature suggests that diagnostic difficulties of depression in later life occur largely in relation to four areas: patient factors, practitioner factors, organizational factors and societal factors.

Patient Factors

Two-thirds of older people with serious depression have symptoms that fit poorly with current classifications of mood disorders. These classifications have been generated to reflect symptoms observed in younger people, and have inherent limitations for diagnosis of depression in older people whose presentation may differ because of ageing, physical illness or both¹⁰. Thus, older people can present with non-specific symptoms such as malaise, tiredness or insomnia rather than disclosing depressive symptoms¹². Physical symptoms, in particular pain, are also common and the primary care clinician may feel they represent organic disease. Forgetfulness may also be manifest, leading to concern that the patient has cognitive impairment and early dementia¹³. Older adults may have beliefs that prevent them from seeking help for depression, such as a fear of stigmatization. They may be under the impression that antidepressant medication is addictive¹¹, or they may misattribute symptoms of major depression for 'old age', ill-health¹³ or grief. Ethnic elders in particular do not see psychiatric services as appropriate and believe they are primarily for psychosis and violence. People across cultures often present with

culturally specific idioms of distress. South Asians often describe their distress using terms such as 'sinking heart' or 'gas in abdomen' (*gola*) as a symptom of distress. This may mislead the clinicians, causing them to tend to overlook the psychological distress and focus solely on the physical aspect of the presentation¹⁵.

Practitioner Factors

Primary care practitioners may lack the necessary consultation skills or confidence to correctly diagnose late-life depression. They may be wary of opening a 'Pandora's box' in time-limited consultations and instead collude with the patient in what has been called 'therapeutic nihilism'¹⁴. In deprived areas primary care physicians have been shown to view depression as a normal response to difficult circumstances, illnesses or life events¹⁶ and depression may be under-diagnosed because of dissatisfaction with the types of treatment that can be offered, especially a lack of availability of psychological interventions¹⁴.

Organizational Factors

The trend in the United Kingdom for mental health services to be 'carved out' from mainstream medical services may disadvantage older depressed people who may have difficulties in attending different sites for mental and physical disorders¹⁷. New contractual arrangements for primary care provide no new incentives to offer re-configured services for older people with depression¹⁸.

Societal Factors

The barriers described are likely to be particularly difficult for economically poor and minority populations who tend to have more ill-health and are more disabled. The National Service Framework (Older People)¹⁸ had as its first standard the rooting out of age discrimination. However, little is known about the efficacy or implementation of the Framework at Primary Care Trust level. The 2009 Equality Billⁱ will, if enacted, make age-based discrimination in the provision of health and social care illegal for the first time in the United Kingdom. This Framework will be superseded by the New Horizons initiativeⁱⁱ which stresses the importance of well-being and resilience, prevention and early intervention. The Framework provides a focus on the mental health of older people.

THE CONSULTATION

Literature suggests that GPs experience difficulties in negotiating the diagnosis of depression with patients, including older people¹⁴. The Quality and Outcomes Framework (QOF) of the new General Medical Services (GMS) Contract¹⁹ requires that GPs and practice nurses use two screening questions within the previous 15 months with patients with chronic disease in order to increase the detection of depression in patients with diabetes and heart disease:

- 'During the past month, have you often been bothered by feeling down, depressed or hopeless?'

- 'During the past month, have you often been bothered by having little interest or pleasure in doing things?'

A 'yes' to either question is considered a positive test. A 'no' response to both questions makes depression highly unlikely.

It would be logical to consider using these screening questions in consultations with other older people who are also at high risk of depression, for example:

- those with recent (<3 months) major physical illness or hospital admission;
- patients with chronic illness/long-term conditions;
- those in receipt of high levels of home care, including residential care;
- people with recent bereavement;
- socially isolated people;
- people persistently complaining of loneliness; or
- patients complaining of persistent sleep problems.

Little evidence has yet been found, however, for this approach²⁰.

There is some evidence²¹ that a further question 'Is this something you want help with?' increases the usefulness of the screening questions in practice. It is then suggested that an assessment of severity of the depression is made by the GP using a schedule such as PHQ-9²². In addition it is vital that the GP explores with the patient ideas and plans for self-harm, and factors preventing the patient from acting on such ideas or plans.

Other authors question the usefulness of such a reductionist approach²³ and emphasize the value of professional judgement over the narrow use of schedules²⁴.

MANAGEMENT OPTIONS

Most patients with depression are managed in primary care settings, however, a substantial number of patients are not recognized, and those who are diagnosed often do not receive effective treatment²⁵. There is, however, a good evidence base for the management of depression in older people. There is evidence to show that there are effective pharmacological treatments²⁶ but only one in four depressed older people receive effective pharmacological treatment and less than 10% a talking therapy²⁷ despite the fact that many people express a preference for such treatments^{28,29}. Evidence for individual psychosocial interventions is presented in Chapter 87, but will be discussed here in the context of what the primary care practitioner can utilize. While a preventative approach to early prevention and detection of depression in older people is being evaluated and has a growing evidence base³⁰ most focus has been, and should be, on the treatment of an established, recognized disorder. Exercise is recommended by the NICE guidelines as a treatment for mild to moderate depression³¹ but there is only limited evidence for this approach in elderly people³². Training in the use of the Internet to increase social support has been shown to reduce complaints of loneliness and depression³³ and there is recent evidence that befriending has a useful function in the management of mild depression in older people³⁴. NICE guidelines³¹ recommend a stepped care approach for the management of depression, although there is limited evidence for this approach, particularly in elderly people³⁵, and it is suggested³⁶ that systematic models of care dedicated to proactively managing depression as a chronic illness are required. The PROSPECT study³⁷ (Prevention of Suicide in Primary Care Elderly: Collaborative Trial)

ⁱGovernment Equalities Office. A fairer future: the Equality Bill and other action to make equality a reality. 2009. www.equalities.gov.uk/pdf/NEWGEO_FairerFuture_may09_acc.pdf

ⁱⁱhttp://www.dh.gov.uk/en/Healthcare/Mentalhealth/NewHorizons/DH_102135

studied the effect of a depression care manager offering recommendations to GPs according to a guideline and helping patients with adherence to medication. The IMPACT^{38,39} study (Improving Mood: Promoting Access to Collaborative Care Treatment) utilized a case manager co-ordinating care and delivering a specific psychosocial intervention (behavioural activation or problem-solving treatment) with or without medication management, and liaising with both the GP and the specialist mental health services. Both studies suggest the effectiveness of such a collaborative care approach which has been shown to be acceptable to family physicians⁴⁰ and initial evidence from the United Kingdom⁴¹ is promising. Such a service, however, is not widely commissioned in the United Kingdom as it is recommended by NICE³¹ only for people with depression and chronic physical health problems.

It is vital that the GP explores the patient's view of their problem and the options that might be available to them. Thus, if antidepressants are going to be prescribed, a full discussion about these drugs, the time taken to work and the possible side effects are discussed. Similarly, a discussion about the patient's views on talking treatments or psychosocial interventions, what to expect and waiting times is vital. On-going support and review from the GP, accompanied by written information, particularly when antidepressants are prescribed, is important. In addition, the GP has a role in signposting to third sector agencies (if acceptable to the patient) and thus should be familiar with groups and local networks in his or her area.

When treatment is not leading to improvement of the patient's symptoms, it is vital that the GP considers co-morbidities, concurrent prescribing, alcohol excess, continuing loss and loneliness or a diagnosis of vascular depression⁴². At this stage, discussion with and/or referral to an old age psychiatrist is indicated.

CULTURALLY SENSITIVE INTERVENTIONS

Pharmacological and Psychological Interventions

There is little research to support any particular pharmacological therapy being specifically beneficial for ethnic elders. The general considerations about prescribing antidepressants discussed in Chapter 86 should be followed but there is a particular need for detailed explanation about the basis for suggesting medication.

Similarly, there are no culturally-sensitive psychological therapies available but again engaging the patient is critical. Abas and colleagues⁴³, working in the African-Caribbean community, provide a helpful framework to these issues. Consultation should be carried out with the following characteristics:

- a courteous, respectful and warm manner, along with interest in ethnicity and country of origin;
- flexibility about usual professional boundaries, for example, being prepared to share some experiences that facilitate rapport and acceptance of help;
- not offering false promises;
- offering a copy of written material (appropriately translated);
- comprehensive questions and not assuming that complaints or symptoms will be volunteered;
- acknowledging losses, both recent and chronic, including racism.

Encouraging ethnic elders to attend community and faith-based groups organized by the voluntary sector can often provide much needed social support which they are used to, but which is gradually eroding over time due to acculturation and changing family structure.

Working with the Family

The social stigma of depression causes families to deny, conceal, delay or even fail to seek treatment. This warrants public education within a cultural framework, as well as collaborative efforts by the ethnic community and health care providers. Particularly in ethnic elders from South Asia who still live in extended families it is important to keep the family 'on board'. This may seem difficult, as they may not share the viewpoint with the health provider on depression. So efforts to educate not only the patient, but also carers, becomes all the more important, particularly regarding issues around medication use, side effects and time delay in symptom improvement⁴⁴.

DEPRESSION IN RESIDENTIAL HOMES

Depression is prevalent in people in residential care homes yet usually goes undetected. Training care staff to recognize possible symptoms of depression can improve detection⁴⁵ and using a collaborative care approach to management is effective in improving outcomes⁴⁶. Evidence suggests that using life review to people newly moved into a residential home, compared with a 'friendly visit', can prevent depression in this group of older people⁴⁷. Other interventions such as social activation, however, have been shown to be ineffective in preventing depression⁴⁸. The usefulness in older studies such as this, when the population in UK residential homes today may be very different to that 20 years ago, is questionable. More recent studies suggest that there are effective interventions that can be implemented in residential homes, such as group reminiscence therapy⁴⁹ and introduction of a pet into the home⁵⁰. The role of the GP in detecting depression in elderly people in residential homes has not been evaluated, but is vital and probably limited due to current arrangements for provision of care for this group of people, who are dependent upon paid carers to request contact with their GP. Alternative models of primary care for residential homes may need to be explored.

POLICY IMPLICATIONS

Recent policy initiatives in the United Kingdom represent lost opportunities to invest and develop older people's mental health services through the National Service Framework for Mental Health⁵¹ which excluded older people and the National Service Framework for Older People¹⁸ which had too narrow a focus.

The publication of *Everybody's Business – Integrated Mental Health Services for Older Adults* (CSIP, 2005)⁵² helpfully set out the key components of a comprehensive service for older adults with mental health needs. Regrettably though, there has been no additional targeted investment in the United Kingdom to support implementation and in the absence of clear 'must do's', performance indicators or targets, commissioners and providers find it all too easy to disregard or distort what this Department of Health guidance states.

There is a need for education at the public health level to increase community awareness of depression as a legitimate problem to take to the doctor through media campaigns and Age Concern³, England has been active in this regard. In addition, education of health professionals in the recognition of depression in older people, a skill that requires cultural competence and different problem formulation is important, although educational initiatives alone tend to be ineffective in primary care. It is vital, then, that services commissioned are evidence-based and incorporate effective care pathways and the provision of alternative models of care, such as collaborative care,

where appropriate. There needs to be increased availability of psychological services for older people, and the Improving Access to Psychological Services (IAPT)⁵³ initiative may not fulfil this role, as there is evidence that GPs continue to refer younger rather than older people for talking treatments⁵⁴. In addition, interventions need to be tailored to older people's perspectives and the social rather than the psychological emphasized.

CONCLUSIONS

Depression in older people presents a challenge for the primary care physician or GP, particularly when compounded with a patient of an ethnic minority background, when the GP may not be culturally competent, or a person in a residential home, who may not receive adequate levels of contact with the GP, such that depression remains undiagnosed. There is, however, a good evidence base for the management of late-life depression and evidence that older people would prefer the option of a talking treatment. Thus there is a need for the education of primary care practitioners so that they develop the skills to diagnoses and support people with depression. In addition, the services commissioned need to meet the needs of older people with depression.

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Electroconvulsive Therapy (ECT)*

David G. Wilkinson

Moorgreen Hospital, Botley Road, West End, Southampton, UK

Those who decry it in the elderly are sentimental and ill-informed. ECT for suitable patients not only relieves intolerable anguish but saves lives (Pitt, 1974¹).

Electroconvulsive therapy (ECT) is an important though controversial treatment for certain subgroups of individuals suffering from severe mental disorder. These subgroups consist primarily of patients with severe depressive disorder, catatonia, mania and occasionally certain patients with schizophrenia. In addition, depending on the co-morbidity with medical and/or neurological disorders and on the risk analysis in relation to the necessity to treat, ECT is best seen as a low-risk procedure for some patients and a high-risk one for others. ECT should be administered following valid and informed consent by the patient when appropriate and in adherence to a set of guidelines of administration procedures².

Despite continued opposition to its use, ECT remains a fundamental tool in the armamentarium of the psychiatrist treating the severely mentally ill. There have now been thousands of papers and articles published concerning its use and we have a wealth of accumulated wisdom, and yet the controversy continues³.

In geriatric psychiatry there is no controversy: papers continue to confirm that in the elderly ECT is an effective treatment for severe affective disorders^{4–7} and is the treatment of choice in severe delusional depression^{8–11}. It is safe, despite the likelihood of multiple system disorders and medications¹². It is well tolerated, if not always well liked¹³, but does sometimes exacerbate confusion. There is no convincing evidence of brain damage or even of lasting memory impairment, particularly if brief pulse right unilateral ECT is used¹⁴. ECT should be considered in every patient with severe delusional depression who has either failed to respond to other treatments, or who is suffering intolerable distress, or who may die through inanition or dehydration as a result of his/her depression. It is probably for these reasons that ECT continues to be used six to seven times more frequently in the elderly than in their younger counterparts¹⁵. The fact that in the USA it has also been shown that early use of ECT reduces inpatient costs may have also been an influential factor in its greater use¹⁶.

INDICATIONS

Depressive Disorders

The introduction of ECT for the treatment of severe depressive illness is one of the most dramatic developments in psychiatry. It is widely

considered to be the most effective treatment for severe depressive illness compared with all other modalities including the range of pharmacological treatments. Since its introduction in the early 1930s it has undergone important development and improvement with the use of anaesthesia and muscle relaxation which rendered it more safe and acceptable. The recall of ECT in the USA in the 1970s was 'plagued by hostility to the treatment'¹⁷ fuelled by images of barbaric, inhumane and coercive treatment. In contrast to such an approach, many national psychiatric associations and societies have promoted ECT and many countries have introduced guidelines for practice: Australia, Canada, New Zealand, UK and the USA¹⁸. It is, however, of considerable concern that in many third-world countries, ECT is still used without the benefit and safety of anaesthesia or modern ECT devices^{17,19}.

The Evidence Base

A recent systematic review and meta-analysis of randomized controlled trials and observational studies of the efficacy and safety of ECT in depressive disorders²⁰ reported the following findings:

- ECT versus simulated ECT – ECT was significantly more effective than simulated ECT in the reduction of depressive symptoms and no difference in premature discontinuation from treatment for patients receiving ECT and simulated ECT. Patients treated with ECT were better able to retrieve remote memories than those treated with simulated ECT and had more recognition errors immediately after treatment.
- ECT versus pharmacotherapy – treatment with ECT was significantly more effective than pharmacotherapy and discontinuation was significantly lower in the ECT group than in the pharmacotherapy group.
- Bilateral versus unilateral electrode placement – Bilateral ECT was more effective than unilateral ECT in the reduction of depressive symptoms. High-dose unilateral ECT might be as effective as bilateral ECT and causes fewer adverse cognitive effects. Bilateral ECT was associated with impairment in anterograde memory impairment within seven days of the end of the randomized phase of treatment but no long-term cognitive impairment.
- Frequency of ECT – ECT administered once a week, twice and three times a week had similar effects on depressive symptoms and no difference in discontinuation of treatment but more frequent ECT led to more cognitive impairment.
- Dose of electrical stimulus – high-dose ECT led to greater reduction in depressive symptoms, but was associated with more

*Updated by Mohammed T. Abou-Saleh

impairment in anterograde memory but not in terms of personal memory.

- Stimulus wave form – brief pulse and sine wave ECT were equally effective with some indication that patients receiving brief pulse ECT recovered more quickly and had better recall of word associates learned shortly before the treatment than did those receiving sign wave ECT.

A meta-analysis of the efficacy of ECT in depression deriving from 15 randomized controlled trials (RCTs) showed ECT to be superior to pharmacotherapy and simulated ECT, with the presence of psychotic symptoms predicting better response to ECT²¹. The report found no evidence for a superior speed of action of ECT or for a difference between sine wave and brief pulse stimulation. ECT has been shown to be more effective in delusional than in non-delusional depression^{22,23}. A recent Cochrane Review assessed the efficacy and safety of ECT compared to simulated ECT or antidepressants in the depressed elderly²⁴. Only three trials could be included and all had methodological shortcomings. The results nonetheless indicated that ECT was more effective than simulated ECT, but the comparative efficacy of unilateral over bilateral ECT and safety could not be assessed adequately.

Older age confers a greater likelihood of achieving a remission with bilateral, dose-titrated, continuation ECT in comparison with continuation pharmacotherapy²⁵.

The NICE Review²⁶ of data from 90 randomized controlled trials (RCTs) of ECT in depressive disorders (not specifically in older people) concluded that:

- real ECT (where electric current was applied) is more effective than simulated ECT (no electric current was applied) in the short term;
- bilateral ECT is more effective than unilateral ECT;
- raising the electrical stimulus above the individual's threshold supported the efficacy of unilateral ECT at the expense of increased cognitive impairment.
- ECT was more effective than antidepressants notwithstanding the variable quality of RCTs and the inadequate doses and duration of antidepressants that were used in many of the trials;
- ECT is associated with cognitive impairment, particularly in those who had bilateral ECT or unilateral ECT applied to the dominant hemisphere;
- cognitive function does not last more than six months from the administration of ECT;
- there is no evidence that ECT is associated with greater mortality than that associated with the administration of general anaesthetics. Studies that use brain-scanning techniques showed no evidence that ECT causes brain damage;
- there is no evidence to suggest that the benefits and safety of ECT are age-dependent;
- there are no complications of ECT in pregnancy but the risks should be balanced against refusing antidepressant.

As mentioned studies on the efficacy of ECT, which have largely been conducted on younger patients⁸, all emphasize that ECT appears to be more effective than placebo, single-drug therapy and tricyclic/neuroleptic combinations, and that patients with more florid symptoms of recent onset fare best^{27–29}. Experience with the elderly would confirm these findings. Indicators of response are perhaps less clear in the elderly, with some authors finding

psychomotor disturbance and psychosis a positive predictor of response¹¹ and others suggesting that patients without these features can also do well³⁰. That the classic distinction between neurotic and psychotic depression appears less helpful in this group as a predictor of good response is nothing new. Post³¹ in 1976 stressed the practical irrelevance of any subclassification of elderly depressives, as he found that ECT rendered severe psychotic depressives fit for discharge only slightly more often than neurotic depressives. The presenting picture of apparent hysterical illness, hypochondriasis or other apparent neurotic illness may well be caused by an underlying functional psychosis, often depressive in the elderly. More recently, in a study of 163 elderly patients given ECT, it was found that 27% had predominantly neurotic depressive features and yet had a good response to treatment⁴. In fact, in the study by Fraser and Glass³², psychic anxiety, along with the more expected features of short duration, severity of illness, guilt and agitation, was one of the symptoms correlated with a favourable response to ECT, whereas the typical endogenous features of late insomnia and diurnal variation in mood were not. Older patients with treatment-resistant depression often do respond to ECT, although not as well as non-resistant patients³³. However, they do respond better to ECT than to SSRIs²⁹ and Flint⁶ found that ECT was significantly superior to tricyclic/neuroleptic combinations, even when the former had been augmented with lithium. A pragmatic consensus would suggest that in the elderly a trial of ECT is indicated in any depressed patient who might otherwise be regarded as a treatment non-responder, and if the illness is severe and of short duration there is likely to be a good response, regardless of the presenting symptoms. If the illness has been present for a long time, it still may respond, particularly if there is a clear history of a recent change for the worse in a patient who had previously maintained a stable personality and had coped normally with the vicissitudes of life. Prolonged or abnormal bereavement reactions with marked depressive features not responding to antidepressants or talking therapies may need to be treated with ECT before psychotherapy or counselling can be effective. ECT may need to be given within a few months of the loss if hopelessness and suicidal ideation suggest a risk to life, and should not be withheld due to the feeling that the patient must work through his/her grief naturally, as he/she may never get that chance.

Continuation Pharmacotherapy after ECT

High relapse rates of depression have been consistently reported after remission with ECT. Five controlled trials have demonstrated the efficacy of continuation treatment with antidepressants and lithium in reducing relapse after remission with ECT³⁴. Further RCTs have demonstrated the efficacy of continuation treatment with imipramine and paroxetine in relapse prevention in such patients³⁵. Nortriptyline monotherapy and its combination with lithium has also been shown to be superior to placebo over six months in preventing relapses in unipolar depression following remission with ECT³⁶.

A recent study used a longitudinal, randomized, single-blind design to compare by survival analysis the two-year outcome of two subgroups of elderly patients with psychotic unipolar depression who were ECT (plus nortriptyline) remitters³⁷. The mean survival time was significantly longer in the combined ECT plus nortriptyline subgroup than in the nortriptyline subgroup. No differences were observed between treatments with regard to tolerability. The authors advocated the judicious use of combined continuation/maintenance ECT and antidepressant treatment in elderly patients with psychotic unipolar depression who are ECT remitters.

Schizophrenia

Paraphrenia will often respond to ECT³⁸, although this is more likely if there are obvious depressive symptoms or delusions. A Cochrane Review assessed the evidence for the efficacy of ECT in terms of clinically meaningful benefits in patients with schizophrenia, and whether variations in the practical administration of ECT influences outcome³⁹. The Review included 24 trials and 46 reports and showed the following:

- Fewer patients remain unimproved with ECT, with less relapses and earlier discharge than patients treated with placebo or simulated ECT.
- Limited data indicated visual memory impairment with ECT compared with simulated ECT.
- ECT is less beneficial than antipsychotic medication.
- Continuation ECT added to antipsychotics is superior to antipsychotics alone but is associated with more memory impairment.

There is relatively little evidence specific to the use of ECT in older patients with schizophrenia. ECT has been shown to have good short-term effects and be safe in middle-aged and elderly patients with intractable catatonic schizophrenia⁴⁰ and in treatment-resistant schizophrenia⁴¹.

In schizophrenia, the NICE Review²⁶ of the data from 25 RCTs indicated that ECT may be effective in acute episodes of certain types of schizophrenia and reduces the occurrence of relapses. However, the results were not conclusive and the design of many of the studies did not reflect current practice. Moreover, there are no RCTs of ECT compared with antipsychotics. Furthermore, studies that include patients with treatment-resistant schizophrenia had not reported the use of clozapine. The Review concluded that ECT alone is not more effective than antipsychotic medication but that the combination of ECT and pharmacotherapy may be more effective than pharmacotherapy alone although the evidence is not conclusive.

ECT is certainly useful in the depressed (and usually elderly) patient with Parkinson's disease, as the motor symptoms will improve as well as the depression, and indeed, some authors advocate ECT as the treatment of choice for certain stages of Parkinson's disease, whether or not depression is a major problem^{42,43}. I have given daily ECT with excellent results to a Parkinsonian patient who had developed severe paranoid delusions. His refusal to accept his medication rendered him rigid and immobile with pressure sores, he needed intravenous fluids and nasogastric feeding until he had four treatments, whereupon his physical and emotional improvement was dramatic.

Fogel²⁷ suggests that ECT might be more readily used in the elderly if we were more objective about its virtues as compared with the severe side effects often associated with neuroleptics, which are quite readily used in the agitated elderly patient. Extrapyrarnidal effects were usually the limiting factor but are not so noticeable with atypical neuroleptics. However, he postulates that the demented patient who is very agitated and screaming might suffer less indignity and fewer side effects if treated with ECT, rather than tranquillizers, as the patient may have an underlying affective disturbance manifest only by the agitation and negativism that one often sees in this condition.

Mania

Mania is another potential indication for a trial of ECT⁴⁴, particularly in the elderly, where neuroleptics may fail to control the

symptoms and yet produce unsteadiness, postural hypotension or falls, and lithium may not be tolerated due to toxicity problems.

The NICE Review²⁶ of four RCTs indicated that ECT may be of benefit in rapid control of mania and catatonia, a suggestion that is supported by the results of observational studies. Overall, however, it concluded that the evidence for the effectiveness of ECT and for the determination of the most appropriate therapeutic strategy is inconclusive. In contrast, a recent literature review of continuation and maintenance ECT in treatment-resistant bipolar disorder reported good evidence for efficacy⁴⁵. ECT is indicated in severe and prolonged mania (excitement, delirium, psychosis, or rapid-cycling manic states), especially when the anti-manic medications (lithium, neuroleptics) have been relatively inefficient⁴⁶. It seems that the NICE Review has been restrictive in the studies it considered and the conclusions drawn from them. It must also be emphasized that the evidence reviewed above is not specific to elderly people.

CONTRAINDICATIONS

There are no absolute contraindications, only relative risks, in which the risks of ECT and associated general anaesthesia are weighed up against the morbidity and mortality of untreated depression. The limiting factor is whether the patient is physically fit for the light anaesthetic that ECT requires. The majority of risk factors are therefore associated with the cardiovascular system. Many people are denied treatment due to irrational caution. For example, pacemakers are not barriers to treatment; the bodily tissues, being highly resistant, prevent the ECT stimulus from reaching the pacemaker. The patient should remain insulated from the ground, however, to prevent the unlikely event of the current leaking to earth and being conducted down the pacemaker wire to the heart. Equally, myocardial infarction is not a contraindication to treatment if the depression is so severe as to threaten life; in less severe cases, an interval (governed by sentiment rather than science) of 4–6 weeks is usually recommended. The risks are greatest during the first 10 days post-infarct, and probably negligible after three months. I have treated a patient with hypothyroidism who had two prosthetic heart valves, was therefore on anticoagulants and had a pacemaker, with no special precautions or untoward effects. Patients with osteoporosis or with recent femoral neck fractures can be treated, provided an adequate muscle relaxant is given. Stroke is certainly not a contraindication, and ECT given as soon as one month after does not present a major risk to patients. There is now a growing body of literature attesting to the usefulness of ECT in treating post-stroke depression⁴⁷.

The case of deep venous thrombosis (DVT) is less clear. I have given ECT to a patient who had a DVT in his calf during his depressive illness, once he was adequately anticoagulated. In fact, the risk of pulmonary embolism seems, in my practice, greater in older severely depressed patients who are dehydrated and immobile depressive than in those receiving ECT.

Arterial hypertension is often regarded as a contraindication, as blood pressure is well known to rise during ECT. This can sometimes be controlled and the pressor response avoided by using sublingual nifedipine or short-acting β -blockers shortly before treatment⁴⁸. Chronic glaucoma is another condition in which ECT causes fewer problems than tricyclic antidepressants; in fact, intraocular pressures are said to reduce ECT⁴⁹. Insulin-dependent diabetes is a condition, like Parkinson's disease, which alters during ECT. Insulin requirements may decrease quite substantially during the course of ECT, so more careful monitoring of blood glucose levels is needed. It is also

necessary to avoid hyperglycaemia prior to treatment, which may significantly raise the fit threshold, and the timing of ECT administration may need consideration to prevent undue fluctuations in diabetic control.

Transient asystole occasionally occurs, for some reason less frequently in the old-old, but it is not of any long-term clinical consequence and need not prevent further treatments^{50,51}.

Epileptic patients on anticonvulsants should not stop their medication during ECT, as that might increase the risk of status epilepticus. However, they may need higher than usual electrical dosages to produce an adequate epileptiform response.

It is interesting that the seizure during ECT is invested with great powers of harm compared with epileptic seizures per se, which can of course occur in patients with any disease or at any time and seldom result in death. It seems understandable, then, that a seizure in the controlled conditions of the ECT room is probably even less likely to result in fatality. There is, of course, a mortality rate associated with ECT but, as noted by Fink⁵², the treatment rate of 0.002% compares favourably with the rate for anaesthetic induction alone (0.003–0.04%).

ADMINISTRATION

The responses of senior psychiatrists to the process of ECT vary from those who simply prescribe six treatments and leave the administration to the newest recruit, who has often had no training at all, to the surgeon manqué who may overstate the risks and precautions in order to increase the perceived risk of his (or her) job. Clearly, the ideal path lies somewhere between, but nearer the latter than the former! ECT is the only psychiatric treatment in the elderly that involves significant medical intervention with general anaesthesia, and as such, the psychiatrist should have a clear understanding of what he/she is prescribing and regular involvement in its administration. As much attention should be paid to the prescription of ECT as to any other prescription.

A clear decision as to whether bilateral or unilateral electrode placement is wanted should be made; the ECT record sheet should be reviewed to ensure that an adequate convulsive response has occurred without excessive stimulus; treatments should not be in blocks of six, but response should be evaluated after each treatment. Provided that the illness is one with a good prognosis, treatment should be continued until the expected degree of improvement is obtained, whether that is after three or 23 treatments.

There is no evidence that the habit of giving one or two extra ECTs after full recovery is effective in preventing relapse⁵³. The decision to give unilateral or bilateral ECT in the elderly is made easier by the fact that high-dose unilateral ECT does seem to produce less confusion, memory loss and headache and appears to be equally effective in many patients^{54,55}. However, there is a great deal of discrepancy in the results of comparative studies, possibly due to differences in diagnosis, age and gender, together with variance in the technique of administration of unilateral ECT. The consensus seems to indicate that, for many patients, both treatments are equally effective; some patients require more right unilateral treatments than bilateral to achieve the same result and some patients who do not respond to right unilateral ECT will respond when switched to bilateral treatment. Male gender and older age are also associated with better response to bilateral treatment.

It is my practice to use bilateral treatment initially in very severe psychotic depressives but right unilateral treatment in most other

cases, particularly if there is evidence of prior cognitive impairment, switching to bilateral treatment if there is no response after six to eight right unilateral treatments. Brief pulse ECT at a moderately supra-threshold stimulus (which is often only around 275–350 mill coulombs) appears to offer efficacy, with the advantage of much less memory loss and confusion than the modified sine wave stimulus, and should be used in all cases, with a record of dosage received by the patient to ensure adequate technique⁵⁶.

There is considerable debate about the necessity to use a dose titration technique to establish seizure threshold prior to treatment, with some viewing this as unnecessary and even detrimental in those patients requiring several non-convulsive stimuli. Adequate seizure response can be measured using interictal EEG monitoring. Some clinicians seem to have developed an excessive interest in stimulus intensity, seizure threshold and seizure duration. It is clear that seizure threshold will increase by about 40% during the course of ECT and the seizure duration will tend to decrease by about one-third. However, while it seems that outcome is not correlated with either seizure duration or threshold for bilateral ECT⁵⁷, it may be more important to keep the stimulus intensity above seizure threshold in unilateral treatment⁵⁸. Seizure duration is more difficult to evaluate, as some patients regularly have brisk and brief responses with good results. The use of propofol to induce anaesthesia consistently reduces seizure duration, although apparently without affecting efficacy^{59,60}. The use of caffeine prior to treatment to prolong seizure activity has been associated with improved efficacy in some patients⁶¹. It would seem that, as a rule of thumb, we should aim for a seizure length of around 25 s and any seizure less than 15 s or more than 120 s is likely to adversely affect response⁶². Cumulative seizure duration again seems less interesting now than it once was as a measure of the length of a course of treatment, and clinical response still seems the best measure.

There is no evidence that routine atropine premedication improves cardiac stability or lessens secretions. Theoretically it could cause confusion, but there is no convincing evidence of this either. Glycopyrrolate, which does not cross the blood–brain barrier, may be a better drug to use as a drying agent but is not widely used.

Methohexitone for the induction of anaesthesia at a dosage of 30–50 mg is adequate to ensure sleep without hangover, and muscle relaxation with a suxamethonium dosage of 20–40 mg is enough to modify the convulsion without abolishing all evidence of motor activity. If the minimum amount of anaesthetic is combined with treatment early in the morning, the patient is not required to starve any longer than usual, he/she is less likely to be dehydrated, is less likely to break his/her fast, has less time to become anxious and agitated and will recover quickly enough to enjoy a breakfast with the other patients on the ward. If this routine is combined with regular supervision of treatment by the prescribing psychiatrist, the patient will derive the maximum benefit from each treatment and the course will not be unnecessarily prolonged or ineffective. Outpatient ECT does not appear to be as effective in the elderly, except occasionally as maintenance, and consequently most patients will require admission to a specialist unit, where the effects of ECT combined with the therapeutic milieu will hasten improvement. Familiar staff administering the treatment and a well-designed ECT suite will help reduce anxiety.

MAINTENANCE AND CONTINUATION ECT

In 1990 the American Psychiatric Association task force on ECT defined continued administration of ECT over a six-month period

to prevent relapse after induction of remission as continuation ECT (C-ECT); treatment beyond six months was termed maintenance ECT (M-ECT). This was felt to be a viable form of management for selected patients.

Maintenance ECT has been used for many years: a survey of British psychogeriatricians in 1991⁶³ found that 20% were using it but there is little more than anecdote to support its use in the literature. Such studies as there are consist mainly of case studies and small series of hospitalized patients, all of a 'naturalistic' nature.

In a one-year follow-up of nine elderly patients, continuation treatment, even if discontinued fairly quickly, seemed to confer some lasting advantage in prevention of relapse⁶⁴, as did Petrides *et al.*'s study, looking at 33 courses of C-ECT⁶⁵. The conclusion seemed to be that where patients have responded to acute ECT but previously failed on continuation pharmacotherapy there was compelling evidence for C-ECT and little therapeutic alternative. The four patients in this study⁶⁵ who continued with M-ECT remained well and the five who had previously stopped did not. Naturally this result is open to other interpretations, but it does suggest that C-ECT should be considered for those with recurrent depression who respond well to ECT acutely but receive no prophylaxis from pharmacotherapy. The practicalities of using outpatient M-ECT have prevented my using it more. Bringing elderly patients to hospital for outpatient ECT early in the day, from a rural catchment area some distance from the hospital, can be problematic, they soon lose enthusiasm for the treatment and consequently often withdraw consent. This is an issue recently addressed by Kim⁶⁶. However, Schwarz's findings, that rehospitalization rates were reduced by 67% after instituting M-ECT, suggest that we should try and overcome the practical difficulties⁶⁷.

The recent NICE update of guidance on the treatment of depression⁶⁸ has recommended that further research is urgently required to examine the long-term efficacy and safety of ECT, including its use as a maintenance therapy and its use in particular subgroups who may be at increased risk particularly the elderly. This research should reflect modern techniques and the use of ECT in comparison and in conjunction with the antipsychotic and antidepressant drugs used in current practice.

CONSENT

Popular myths about ECT are always more readily believed than the reality and can be part of what the patient believes they are consenting to. Occasionally patients consent as part of their death wish. I use a video of myself administering ECT to a patient seen before and after treatment, to show anxious or interested relatives and patients; no one having seen it has then declined the treatment. There is one study suggesting that understanding is not enhanced by this method. The issue of informed consent in depressed patients is complex. As I have suggested, many care little and are prepared to do anything their doctor suggests, and patients' recollection of what was explained to them, after the ECT and when the depression has lifted, is often vague. A careful explanation should be made and recorded, and if there are doubts on either side a chance to preview the ECT room or an explanatory video may be helpful. However, it is doubtful whether the explanation of ECT is any less detailed than that of most surgical procedures and most people are willing to consent without seeing a video of the operation in question. Passive acceptance of ECT is often the case in the severely depressed but this should not prevent a full explanation, including consulting relatives if appropriate.

Involuntary ECT should never be given except within the guidelines of the relevant mental health legislation if we are to ensure the availability of ECT as a treatment option in the future. Nevertheless, depression is such a serious and debilitating illness that the chance of a cure through use of ECT should never be denied to a patient whose prognosis is favourable, simply through difficulty in obtaining actual written consent.

ADVERSE EFFECTS

As already mentioned, confusion and memory loss are often regarded as an inevitable corollary of ECT in the elderly, but this is clearly not the case and there are well-conducted studies showing no objective permanent effects on memory, and in fact this often improves as a result of improvement in the depression^{32,69,70}.

Nevertheless, there is no doubt that some patients who were given bilateral sine wave ECT experienced long-term, even permanent, memory loss, and bland reassurances that this or even brief pulse bilateral ECT will not cause any memory loss is foolish and counterproductive. Some patients given bilateral brief pulse ECT may have amnesic gaps, but can be assured that no lasting effect on memory function, i.e. new learning or intelligence will occur. The situation with right unilateral brief pulse ECT is different, with any subjective memory impairment being transient and undetectable six months later^{71,72}. Patients with existing dementia may well show signs of memory impairment, even with unilateral ECT. This may be acceptable in view of the relief from distress and agitation and improvement in behaviour and performance.

The cognitive side effects can be minimized by reducing concomitant medications, particularly benzodiazepines, anticholinergic antidepressants and lithium⁷³, although a recent study found no problems with the administration of ECT and lithium⁷⁴.

Benzodiazepines, given intravenously as the seizure ends, can be of use in controlling emergent delirium, which can last for 15–30 min after treatment and be very difficult to control otherwise.

Dementia per se does not preclude the use of ECT, provided that the co-existing depression is circumscribed. A history of depression before the dementia adds weight to the decision, particularly if there was a good response to ECT previously. Other side effects of treatment, such as headache and dizziness or muscle pain, usually only after the first anaesthetic, are minimal and soon forgotten as the depression lifts.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) involves focal stimulation of the superficial layers of the cerebral cortex using a rapidly changing magnetic field applied using an external coil. It does not require anaesthesia and can be performed on an outpatient basis. Treatment with rTMS usually involves daily sessions lasting about 30 min for 2–4 weeks and possibly longer. Its use in the treatment of depression has recently been the subject of NICE Interventional Procedures Guidance IPG 242. A recent meta-analysis for patients with treatment resistant depression which included 24 studies (1092 patients) meeting their inclusion criteria⁷⁵ found that active rTMS was significantly superior to sham conditions in producing clinical response, with a risk difference of 17%. However, the pooled response and remission rates were only 25% and 17%, and 9% and

6% for active rTMS and sham conditions, respectively. They concluded that further studies are required before adopting rTMS as a first-line treatment for treatment-resistant depression. The recent NICE update⁶⁸ concluded that the efficacy of rTMS depends on higher intensity, greater frequency, bilateral application and/or longer treatment durations and there appears to be no major safety concerns associated with its use.

CONCLUSION

ECT is a valuable and as yet essential tool in the treatment of depression in old age, a disease which untreated carries a significant mortality. It is interesting that in practice elderly patients who have attempted suicide are nearly all offered ECT. This is because those, albeit only very few in number, who have subsequently killed themselves during a depressive illness have all been patients who have either refused ECT or not been given it at the time of their index suicide attempt. However, while there are many compelling arguments for the use of ECT, it is not a universal panacea. ECT, like any potent treatment, should be prescribed with accuracy and its use monitored carefully by those prescribing it.

Depression in the elderly presents with protean manifestations. ECT should be part of an eclectic approach to treatment and as such will continue to relieve distress and save lives.

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Pharmacological Treatment of Depression

Mohammed T. Abou-Saleh¹ and Cornelius Katona²

¹*Division of Mental Health, St George's, University of London, London, UK*

²*Hon Professor, Dept Mental Health Sciences, University College London*

INTRODUCTION

Mood disorders are a major public health problem, with poor recognition, diagnosis and treatment despite the availability of reasonably safe, effective, economical treatments and the established effectiveness of continuing educational programmes for care providers¹. The magnitude of the following problems is greater in the elderly with mood disorders for several reasons: poor recognition for most somatic and cognitive symptoms; increased physical morbidity and disability; and high mortality from suicide and other causes. This situation, however, is balanced by increased recognition that pharmacological treatments are effective and reasonably safe. There is, however, marked variation in rate, stability and direction of recovery with reliable pretreatment predictors of outcome². The usefulness of pharmacological treatment for patients with subsyndromal depression, albeit to a lesser extent than major depressive disorders, has been also investigated³.

PRETREATMENT CONSIDERATIONS

There are a number of issues to be considered before starting specific pharmacological treatment of mood disorders in the elderly⁴. With advancing age, there are important and clinically significant changes in distribution, metabolism and elimination of these drugs. The age-related increase in volume of distribution results in a longer half-life for all psychotropic drugs. Hepatic drug metabolism decreases with age, also resulting in a prolonged half-life, which may be two to three times longer than in younger patients, and the decrease in renal function with advancing age is particularly relevant with regard to lithium, which also results in two to three times higher plasma levels than those in younger patients on the same daily dose. A recent review⁵ emphasized decreases in passive drug absorption, changes in the proportion of body fat (increased) and lean muscle mass (decreased) and the resultant increase in the elimination half-life of (fat-soluble) antidepressants. In addition, changes in binding proteins result in lower free levels of tricyclics but increased free levels of selective serotonin re-uptake inhibitors (SSRIs). Of particular importance, however, has been the study of the inhibitory effects of the SSRIs on the cytochrome p450 enzymes; these pharmacodynamic actions have pharmacokinetic consequences for co-administered drugs, such as tricyclic antidepressants (TCAs), which are dependent on these enzymes for biotransformation. Patients on anticoagulants in particu-

lar need close monitoring. The potential of the various SSRIs to cause significant interactions varies considerably; citalopram, escitalopram and sertraline may carry relatively low risk.

To determine the best pharmacological treatment options for individual patients requires careful consideration of a number of clinical factors, which include the following: type of mood disorder; degree of urgency for treatment; previous response to treatment; concurrent medical problems; concurrent drug therapy; risk of overdose; reasonable half-life; dosing flexibility; and affordability⁶.

TREATMENT OF DEPRESSION

Older patients with depression can be successfully treated with conventional TCAs, monoamine oxidase inhibitors (MAOIs), SSRIs and atypical antidepressants. TCAs have the major limitations of anticholinergic effects, postural hypotension, excessive daytime sedation and cardiotoxicity in overdose. Their advantages, however, are their established efficacy and low cost. Among the TCAs, the secondary amines desipramine and nortriptyline have more favourable side-effect profiles, with desipramine having the fewest anticholinergic effects and nortriptyline causing the least postural hypotension⁶. The secondary amines also have the advantage of therapeutic drug monitoring, with an established therapeutic window for nortriptyline and a therapeutic plasma level of desipramine. Therapeutic drug monitoring enables the clinician to determine the minimal therapeutic dose and to monitor compliance. Nortriptyline has been well investigated for use in elderly patients, including patients older than 80 years⁷ and patients who have had strokes⁸.

Among the MAOIs, phenelzine has been shown to be effective in treating elderly patients with depression^{9,10}, particularly for patients who could not tolerate TCAs and those with resistant depression. Their main limitation is their interaction with tyramine-rich foods, causing hypertensive crisis. For this, they are superseded by moclobemide, a reversible and selective inhibitor of monoamine oxidase type A. Comparative trials in the elderly have established its efficacy compared with imipramine¹¹, nortriptyline¹² and placebo¹³. Moclobemide also showed benefits on cognitive function in patients who had dementia and co-morbid depressive symptoms¹⁴.

The SSRIs, however, have provided the most important practical advance in the successful and safe management of depression in late life. This group of drugs includes fluoxetine, fluvoxamine, sertraline, paroxetine and citalopram. The SSRIs have replaced tricyclic

antidepressants as first-line antidepressants for older people as well as for younger adults. More recently, several other antidepressants have become available including bupropion, mirtazapine, another SSRI (escitalopram), and the serotonin and noradrenaline re-uptake inhibitors (SNRIs) venlafaxine and duloxetine¹⁴. The advantages of SSRIs over TCAs are the absence of anticholinergic effects, orthostatic hypotension and arrhythmia in the side-effect profiles, and their safety in overdose⁷. Comparison of fluoxetine with nortriptyline in in-patients with severe depression and heart disease showed that nortriptyline may be more effective in this population¹⁵. A meta-analysis of the comparative efficacy and safety of SSRIs and TCAs in elderly patients¹⁶ showed no differences in safety and dropout rates.

A recent meta-analysis¹⁷ of the efficacy of second-generation antidepressants (SSRIs, SNRIs bupropion and mirtazapine) showed response rates of 44% for active drug and 35% for placebo, suggesting only modest efficacy (number needed to treat = 11). A similarly small difference in favour of active drug was found for remission rates (33% vs. 26%). There authors reported marked heterogeneity between studies, with superiority over placebo found for fluoxetine in one of three studies, for paroxetine in two studies, for sertraline and for duloxetine but not for escitalopram or venlafaxine. Results for bupropion showed borderline superiority over placebo in terms of response rate but not in terms of remission. Studies lasting 10 weeks or more were associated with greater superiority for active drug over placebo than studies lasting 6–8 weeks, supporting the traditional view that antidepressant response may take longer to emerge in older people¹⁴.

A similar review of single versus dual action antidepressants in older people included head-to-head comparator trials as well as those with a placebo arm, and continuation as well as acute trials¹⁸. They concluded that overall, dual action agents 'do not appear to confer any additional benefits in efficacy over single action agents (SSRIs)'. Unlike the meta-analysis reviewed above¹⁷, the primary analysis in this study was by class and they did not examine whether there was heterogeneity between individual studies.

One striking feature of these trials is the relatively low overall response and remission rate for active antidepressant medication. Sneed *et al.*¹⁹ have carried out a systematic review comparing reported response rates in placebo-controlled and comparator trials of antidepressants in older people. They identified nine comparator trials and seven placebo-controlled trials published since 1985 that met their entry criteria. Response rates were considerably higher (60%) than in the placebo-controlled trials (46%); the odds of being a responder were 1.82 times higher in the comparator trials. Type of trial (placebo-controlled vs. comparator) accounted for 27% of the variation in responder rate. The authors conclude that expectation is an important contributor to outcome in such trials and that concern about possibly being on placebo may lead to a suppression of the antidepressant response¹⁴.

The side-effects profile of SSRIs includes nausea, diarrhoea, insomnia, headaches, agitation, anxiety and sexual dysfunction. The SSRIs also seem to worsen Parkinsonism. As with other antidepressants²⁰, there have been case reports of hyponatraemia, hypomania and seizures⁷. An important aspect of their use is their drug–drug interactions, and their inhibitory effects on hepatic cytochrome p450 isoenzymes, the route through which many drugs commonly prescribed for elderly people are metabolized²¹. Paroxetine, norfluoxetine and sertraline have clinically important inhibitory effects (*in vivo*) on cytochrome P2D6, resulting in increased plasma concentrations of co-administered TCAs, such as desipramine, and antipsychotics, such as haloperidol²². Sertraline,

however, had a modest effect on plasma nortriptyline levels in depressed elderly patients²³. Fluoxetine increases plasma levels of co-administered carbamazepine; alprazolam and fluvoxamine increase plasma concentration of co-administered TCAs and antipsychotics by inhibiting cytochrome P1A29. An extensive list of drugs metabolized by various p450 isoenzyme types is provided in the reviews by Catterson *et al.*⁴ and by Rivard⁶.

Despite these potential problems, two recent reviews of (SSRIs) in older people^{24,25} have found that they are generally well tolerated but that gastrointestinal (GI) problems including nausea are relatively common. Increased risk of GI bleeding is potentially important because older people are in any case at greater risk of such bleeding. SSRI-induced restlessness, sedation and extra-pyramidal movement disorders may also be particularly disabling in older people. SSRI-induced hyponatraemia is increasingly recognized to be common in older people. Older age, female gender, low body weight and co-administration of diuretics are indicators of increased risk. Inappropriate secretion of antidiuretic hormone (mediated by activation of 5HT₂ and 5HT_{1C} serotonergic receptors) is a likely mechanism. Serum sodium should be checked frequently in older patients on SSRIs, particularly in the first few months of treatment. Drug interactions involving the cytochrome P450 enzyme system may be clinically relevant in older people. Patients on anticoagulants in particular need close monitoring. The potential of the various SSRIs to cause significant interactions varies considerably; citalopram, escitalopram and sertraline may carry relatively low risk.

In the light of this it is perhaps surprising that a recent Australian study²⁶ found that although antidepressant use had increased in all age groups and most markedly in the 65+ age group, older people remained the highest users of tricyclic antidepressants whose side effects are well documented as being particularly hazardous in older people. This may, however, reflect the tendency to reuse a previously effective antidepressant for a recurrent episode of depression, and the still frequent use of tricyclics in low dose as hypnotics and analgesics in an older population.

CONTINUATION AND PROPHYLACTIC TREATMENT

Early studies indicated a poor outcome of late-life depression²⁷, with high relapse, recurrence and chronicity. This view was based on naturalistic observation without monitoring of compliance, adequate dosage and duration of treatment, including prophylactic treatment, and was therefore challenged²⁸. Controlled studies of maintenance antidepressant medication, however, showed a relatively good outcome for late-life depression²⁹. The Pittsburgh group³⁰ reported a three-year follow-up study of maintenance treatment with nortriptyline or placebo with or without interpersonal psychotherapy (IPT) and showed that 80% of patients assigned to nortriptyline, with or without IPT, remained in remission. The Pittsburgh group also identified the elderly patients who remained well after placebo-controlled discontinuation of antidepressant medication for a period of one year. Recovery of good subjective sleep quality by early continuation treatment was useful in identifying which remitted elderly depressed patients remained well with monthly IPT after discontinuation of antidepressant medication³¹. A study of the effect of treatment on the two-year course of late-life depression³² showed a 74% survival rate without relapse. This good outcome was obtained by the use of full-dose antidepressant medication, frequent follow-up and rigorous treatment of relapse.

The US National Institute of Mental Health consensus statement update³³ concluded that the overall evidence supports the recommendation for at least six months of treatment beyond recovery for those with first onset in late life, and for at least 12 months for those with a recurrent illness³⁴. Moreover, prophylactic treatment should be of the same type and dosage as that which was successful in the initial acute phase. The consensus statement also concluded that treatment response and long-term outcome for all the patients is generally similar to that observed in younger adults, but the temporal course may be somewhat slower in the elderly and risk of relapse somewhat greater³³.

The effectiveness of the tricyclic antidepressant nortriptyline in reducing relapse and recurrence in older depressed patients at high risk is well established³⁵. This study also indicated that interpersonal psychotherapy had an additional preventative effect. More recently Reynolds *et al.*³⁶ replicated their findings using the SSRI paroxetine. In this study they did not focus specifically on patients at high risk. They failed to identify any additional benefit from interpersonal psychotherapy. Klysner *et al.*³⁷ have shown that continued treatment with citalopram is associated with much lower relapse and recurrence than placebo in patients who remitted on citalopram and were then randomized to citalopram or placebo for the next two years. A similar study by Wilson *et al.*³⁸ failed to show superiority for the SSRI sertraline over placebo over two years, but the dropout rate in their study was extremely high. Gorwood *et al.*³⁹ examined relapse rates over 24 weeks in older depressed patients who remitted on open-label escitalopram and were then randomized either to continue with escitalopram or to be switched to placebo. Risk of relapse was 4.4 times higher on placebo.

Though co-morbid anxiety does not appear to affect acute response to antidepressants, the secondary analysis of data from a controlled study of paroxetine and interpersonal psychotherapy by Andreescu *et al.*⁴⁰ found that co-morbid anxiety was associated with a slower response and a higher recurrence rate.

Overall the results summarized above provide strong evidence that older people who respond to antidepressants are substantially less likely to experience relapse or recurrence if their antidepressant treatment is continued for up to two years.

The use of lithium in continuation and prophylactic treatment of depression in the elderly has also been recommended^{29,41,42}, with the use of lower doses/plasma levels³⁴. Lithium may be a more favourable prophylactic treatment than antidepressants in recurrent depression with melancholia and in depression with psychotic features (delusional depression), which are particularly common among the elderly, with a tendency to respond less well to antidepressants^{28,42}. The other advantage of lithium therapy is the evident decreased mortality, whether from suicide or other causes⁴³. A one-year prospective, placebo-controlled study of maintenance lithium in conjunction with cognitive behavioural psychotherapy in elderly depressed patients⁴⁴ showed that, although cognitive behavioural psychotherapy reduced depression severity during follow-up, lithium therapy was no better than placebo. This appears to be related to poor compliance, a finding that highlights the serious difficulties in undertaking prophylactic studies in elderly depressed patients.

TREATMENT OF BIPOLAR DISORDER

Elderly patients with late presentation or late-onset mania respond well to standard antimanic treatment with neuroleptics, lithium and

anticonvulsants⁴⁵. Neuroleptic treatment is best avoided in the elderly because of its known extrapyramidal side effects, except for floridly psychotic, agitated and behaviourally disturbed patients who need rapid control of symptoms. Lithium remains the treatment of choice, followed by valproic acid⁴⁵. The evidence for the efficacy of lithium in late-life mania is based on retrospective and uncontrolled studies; there have been no controlled studies, and there have been no controlled studies of the efficacy of anticonvulsants in late-life mania. It has been suggested that valproate is a safer alternative treatment to lithium than carbamazepine, whether used as single or adjunct treatment, in elderly manic patients⁴⁵. There are no guidelines regarding the optimal plasma concentration of valproate in relation to efficacy⁴⁵.

An evidence-based review of the treatment of mania, mixed state and rapid cycling in younger populations⁴⁶ concluded that lithium and divalproex sodium are effective in mania, whereas divalproex sodium and carbamazepine are more effective in mixed states. Divalproex sodium is the drug of choice for rapid cycling disorder. With bipolar depression, lithium is recommended as a first-line treatment and the addition of a second mood stabilizer or a TCA would be an appropriate next step⁴⁷.

The guidelines for the continuation and prophylactic treatment of bipolar illness in late life are similar to those advocated for younger patients, except for the notion of high recurrence rates necessitating prophylactic treatment, even after a first-onset manic episode. Lithium remains the medication of choice for prophylaxis⁴². An open naturalistic study of lower doses/plasma–lithium levels⁴² showed efficacy in the elderly comparable to that in younger patients at plasma–lithium levels as low as 0.4 mmol/l, with fewer side effects and renal and thyroid adverse effects.

TREATMENT-RESISTANT DEPRESSION

Treatment-resistant depression occurs in one-third of elderly depressed patients⁴⁸ and can only be ascertained after adequate recognition, compliance with treatment and effective treatment⁴⁹. It has also been related to cognitive impairment, physical and psychiatric co-morbidity, late onset and presence of melancholic and psychotic features⁴¹. Moreover, elderly patients with anxious depression are less responsive to nortriptyline than are those without significant anxiety symptoms⁵⁰.

Although TCAs¹⁵ and MAOIs⁵¹ have shown efficacy, the SSRIs are specifically advocated⁴¹. Fluvoxamine has shown efficacy (70% good response) in desipramine non-responders^{52,53}, and patients who were intolerant of fluoxetine completed a trial of sertraline with a response rate of 76%⁵⁴. Venlafaxine also has long-established efficacy in older people with refractory depression⁵⁵.

Combination and augmentation strategies have been advocated⁴⁹. Lithium augmentation in TCA non-responders is effective in 20–65% of cases^{56–58}. It is, however, associated with cognitive and/or neurological side effects in 50% of patients^{56,57,59,60}. Lithium has been successfully added to SSRIs, notwithstanding the risk of neurotoxicity with an SSRI–lithium combination⁴⁹. Advocated augmentation/combination strategies include TCA/tri-iodo-thyronine, SSRI/TCA, SSRI/anticonvulsants and SSRI/oestrogen (*ibid.*). Elderly patients requiring adjunctive medication to achieve remission may need continuation of adjunctive medication to remain well and to avoid early relapse⁶¹.

Rajji *et al.*⁵ emphasize the limited evidence base from controlled-clinical trials on optimal strategies where initial antidepressant

treatment has failed. They note, however, that remission rates of up to 50% have been reported with a 'switch' to the MAOIs phenelzine⁶² or selegiline⁶³, as well as with sequential augmentation strategies. Augmentation with lithium⁶⁴ and with the atypical antipsychotic aripiprazole⁶⁵ have also recently been reported to result in useful remission rates in treatment-resistant older people. Most of the studies to date have been small and few are placebo controlled. This is clearly an area where more research is needed.

For refractory bipolar disorders, a review⁶⁶ concluded that the safest combination of mood stabilizers is valproate plus lithium. This was also shown in a series of elderly patients with lithium-resistant rapid cycling mania⁶⁷.

CONCLUSION

Although there have been impressive advances in the pharmacological treatment of mood disorders in general, there has been a relative paucity of controlled studies in the elderly, particularly in maintenance and prophylaxis. Generalization from the results of studies of younger patients may be inappropriate in view of the significant changes associated with normal ageing and concomitant medical illness, which affect the pharmacokinetics and pharmacodynamics of psychotropic drugs.

Nevertheless, there has been a change of culture. The nihilism that had prevailed in the treatment of mood disorders in late life has been replaced by cautious optimism with regard to the results of controlled trials in naturalistic settings, as well as studies in high-risk groups, including patients with multiple medical conditions and subsyndromal states.

A large majority of elderly patients with depression could be treated successfully with antidepressants, particularly the SSRIs, because of their favourable side-effect profiles and their low toxicity in overdose. The SSRIs, however, challenge the clinician with their clinically significant drug-drug interactions. Patients who improve should receive continuation of prophylactic treatment with the same dose. For mania, lithium remains the optimal treatment, with anticonvulsants, particularly divalproex, providing a second-line treatment. The efficacy and safety of atypical neuroleptics remain to be evaluated in both acute and long-term management of bipolar illness. There is also hope for those with resistant-mood disorders with the design of augmentation/combination strategies, which require further evaluation.

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Psychotherapy of Depression and Dysthymia

Philip Wilkinson

Department of Psychiatry, University of Oxford, UK

Recent years have seen a steady but slow increase in the application of psychological treatments to manage depression in late life, both as stand-alone treatments and in combination with pharmacotherapy. This stems in part from the large body of evidence supporting the benefits of certain psychological treatments in the management of depressive illness in younger adults¹ and the need to test the benefits with older patients.

There are a number of reasons why psychological treatments warrant investigation in the older population. First, they may help to address the types of psychosocial difficulties often associated with late-life depression such as bereavement, adjustment to chronic disease and loss of autonomy. Second, they may confer benefits in reducing the recurrence of depression, which is a significant problem in older patients. Third, older patients may express a preference for psychological treatment over pharmacological treatment (although this does not necessarily predict their effectiveness)². Finally, neuroimaging data indicate that psychotherapy and pharmacotherapy may target different primary sites of the corticolimbic pathway and may therefore have synergistic effects in the treatment of depression³.

It cannot be assumed that psychological treatments for depression are as effective in older people as in younger adults. Older people are more likely to have cerebrovascular lesions which are known to be associated with poorer response to physical treatments⁴. Depression beginning in later life is also associated with greater reductions in processing speed and executive dysfunction⁵ which could impede response to psychological treatment. Symptom profiles in depressed older people, and therefore the target symptoms of psychotherapy, also differ from those in younger people, with greater motivational deficit and less affective change⁶.

This chapter reviews the different psychological therapies that have been developed, and to some extent evaluated, for use with depressed older people. It summarizes the indications and evidence for therapies and ends with a brief discussion of access to therapies and research priorities.

BEHAVIOUR THERAPY AND COGNITIVE BEHAVIOURAL THERAPIES

Behaviour therapy and its related treatments form the largest group of therapies employed in the management of depression. Although their evaluation in older adults is patchy, they offer a number of approaches to helping the depressed older person.

Behaviour Therapy

According to learning theory, depression results from reduced engagement in positively reinforcing behaviours (pleasurable events) and excessive exposure to negative reinforcement (avoidance and negative events)⁷. Behaviour therapy uses an operant conditioning model to reintroduce positive reinforcement, to reduce the time spent on negative events and to overcome avoidance. This model is presented to the patient as a vicious circle that needs breaking, based on diaries of the patient's activity and negative mood. This is then followed by scheduling of positively reinforcing behaviours and monitoring of the effect on mood. It may often be possible for patients to resume their previous activities. However, older people experiencing physical illness and disability may be unable to resume all of their previous activities and may need help in identifying alternatives.

Behavioural approaches to depression were later elaborated by incorporating the patterns of negative thinking that occur in depression, giving rise to cognitive behaviour therapy.

Cognitive Behaviour Therapy (CBT)

According to the cognitive model of depression⁸ an individual's underlying beliefs about him- or herself and the world may confer a vulnerability to depression that is then triggered in the face of specific types of event. Faulty information processing in the form of over-generalized negative thoughts shapes behaviour and maintains depressed mood.

The validity of the cognitive model as an explanation for cases of depression arising in late life has been questioned given the evidence for structural causes such as cerebrovascular disease. Another limitation of a vulnerability–diathesis model is that an older person may appear to have held the same beliefs for decades and endured previous negative events without developing depression. However, it has been observed in older patients that certain personal beliefs can be adaptive and functional throughout earlier life but can predispose to depression in response to specific age-related events, such as retirement⁹.

Cognitive behaviour therapy for depression begins with behavioural activation but in contrast with behaviour therapy it includes analysis of the thoughts that underlie inactivity. As the following case example illustrates, negative thoughts are then

addressed through direct verbal challenging and testing them out in specific situations (behavioural experiments), supported by written thought diaries.

CBT Case Example: Mrs Jacobs – a woman with physical problems and depressive illness

Mrs Jacobs was a 78-year-old woman referred for therapy by her general practitioner having developed a depressive illness following a stroke. She had been treated with a course of antidepressants, which had brought about a small improvement although she remained significantly depressed with a 'dread of the future'. She described a loss of confidence and poor concentration and had withdrawn from a number of social activities. She had also noticed a deterioration in her memory, finding it difficult to retain and use new information although this did improve at times when her mood picked up. She had three grown-up children who did not live locally.

Mrs Jacobs had enjoyed a career as a teacher until retiring at the age of 63 years. She had coped with a number of stressful events in her past, such as the loss of her husband, without becoming depressed. Her medical history included hypertension, heart disease and arthritis. Her stroke had occurred after her return from holiday, giving rise to permanent weakness of her right leg. Evaluation by a neurologist, including magnetic resonance imaging, had confirmed the presence of cerebrovascular disease. Fearing further strokes, she became anxious that she would not be able to carry on with her interests which included committee work and trips to the theatre. She feared she would be unable to continue living independently and would have to move to a nursing home. Her therapy goals included being able to manage social events and being able to plan realistically for her future.

In session 1 Mrs Jacobs began to recognize the patterns of thoughts and behaviours which were taking place in her depression. She realized that she had become very conscious of the change in her walking which resulted from her weak leg, thinking that other people were noticing it and commenting on it. This added to her anxiety and caused her to avoid social situations or to go to lengths to check that people were not likely to reject her because of it. These observations were included in a simple formulation and this set the scene for a simple diary of these thoughts and behaviours as they occurred at a committee meeting before session 2. She immediately recognized the biased nature of these thoughts, which brought about some improvement in her mood.

In session 2 Mrs Jacobs was helped to notice the link between her mood, energy and activity. At times she was quite tired with her mind 'in a fog' which caused difficulty organizing activities such as catching up on tasks at home. This led to self-critical thoughts. She expected herself to function as she had before her stroke, discounting any achievements she was now able to make. She was also disappointed by the day-to-day fluctuations in her energy. To illustrate this process she kept a diary between sessions. She was given written information about the link between activity and depression and was asked to begin activity scheduling. This caused her some difficulty as she aimed to complete the activity schedule perfectly, bringing

to attention the high standards she had always set for herself. The exercise also brought to the therapist's attention the extent to which Mrs Jacobs was struggling with mental tasks because of her cognitive slowing. Mrs Jacobs was encouraged to plan things in advance but to allow some flexibility depending on her physical state and external events. She approached larger commitments by breaking them into smaller stages and using more written records. To support these changes she successfully challenged her self-critical thoughts with responses such as 'the list of jobs will never finish, so why blame myself?', 'is it really important to do it now?'. The beliefs underlying Mrs Jacobs's high standards were examined – for example, the belief that 'I must always do everything to the best of my ability' – and she began to accept that getting older allowed her the opportunity to relax her standards and take some rest.

In session 6, Mrs Jacobs was helped to use thought challenging to deal with her fear of rejection by friends. She found questions such as 'What am I afraid might happen?' and 'Am I exaggerating the importance of events?' particularly useful. She recognized a tendency to predict that people would not want her. If others were ambiguous in their behaviour (such as not initiating conversation) it was taken as evidence that they did not want her around. She tested out her thoughts using simple behavioural experiments such as initiating conversation with people and being ready to challenge unhelpful thoughts as they arose. She found that actually putting this into practice was not always easy so she needed to plan the stages in some detail beforehand then complete her thought records and observations soon afterwards. She was successful in reducing the intensity of her thought that she was being rejected from 80% to 5%.

By session 9, Mrs Jacobs was becoming more flexible in her activities and coping better with personal relationships. She was still feeling anxious and low in the mornings. She had hopeless thoughts and although she could challenge these successfully later in the morning, she had difficulty doing this at the time. She therefore developed a list of strategies to cope with depression in the morning such as keeping a reminder by her bed of the challenges to unhelpful thoughts and activities she could engage in rather than lying in bed ruminating.

By session 10 Mrs Jacobs's mood was significantly improved. She still reported mild cognitive deficits such as difficulty naming and slower thinking, related to her cerebrovascular disease. She identified unhelpful thoughts about developing Alzheimer's disease or losing control of her life. With the therapist she also identified a distortion in her thinking that having irreversible problems (such as her cerebrovascular disease) meant she had an unmanageable problem. Understanding the physical basis to some of her problems also helped her to challenge her self-critical thoughts. At times of additional stress, such as admission to hospital, she would become anxious and depressed and her fears for the future would recur, but she managed to use thought challenging to handle this (Table 87.1). This also helped her to review the plans she had made in case of further disability in the future, such as financial planning and adding her name to the list for her preferred nursing home. At the end of treatment, Mrs Jacobs made a therapy

'blueprint' which included a summary of what she had done to achieve her improvement and what she would need to do if her problems recurred (Figure 87.1).
Abridged and reproduced with permission from Wilkinson¹⁰, pp. 67–71.

For a detailed description of CBT with older adults, see Laidlaw *et al.*¹¹

Problem-solving Therapy (PST)

Problem-solving therapy is a brief intervention of six to eight sessions that is usually delivered in primary care; it is designed to

help depressed patients to take an active approach to tackling their psychosocial problems. PST can be considered a behavioural intervention in that it tackles the avoidance and reduction in pleasurable activities that occur in depression, and as a cognitive intervention in so far as it addresses the negative perceptions that may interfere with finding practical solutions to problems.

Problem-solving therapy involves the following stages: definition of problems; establishing realistic goals; generating, choosing and implementing solutions; and evaluating outcomes. Use of a therapy manual helps patients to practise these skills and to continue their use after therapy has ended. Clearly, older people often face irreversible obstacles such as bereavement or disability, in which case goal setting is an opportunity to regain some sense of control through tackling the consequences and effects of these problems. For instance, a depressed patient unable to drive after a stroke may identify new ways to travel.

Table 87.1 Mrs Jacobs's thought diary

<i>Situation</i>	<i>Emotions</i>	<i>Unhelpful thoughts</i>	<i>Evidence that it's true</i>	<i>Evidence that it's not 100% true</i>	<i>More balanced thought</i>	<i>Feeling now</i>
Planning admission to hospital	Anxiety 60%	'I shan't be able to manage'	My children are too busy to help	If they're busy, they still haven't forgotten me	'It's OK to seek out help'	Anxiety 5%
	Depressed 80%	'I might have to ask for help'	I'm having to make all the arrangements	My neighbour did offer to help	'This is how I feel when I'm under pressure'	Depressed 10%
		'I'm all alone'	People won't ask how I'm getting on	If they don't ask, it doesn't mean they don't care	'Yes, I'm in charge of my life. It's hard work, but it doesn't mean I'm alone in the world'	

Source: Abridged and reproduced with permission from [10], Wilkinson P. (2001) Cognitive behaviour therapy. In: J Hepple, J Pearce & P Wilkinson (Eds), *Psychological Therapies with Older People* (pp. 61–73). Hove: Bruner-Routledge

1. Prioritise my time and don't be too hard on myself if I don't get things done.
2. Watch out for times when I predict the future. Just try to take things as they come.
3. Remember that having to sort things out for myself doesn't mean I am alone in the world.
4. Be aware of future setbacks, e.g. illness, practical problems.
5. If the problems recur do the following:
 - refer to therapy notebook
 - re-read my information on strokes and vascular disease
 - keep thought records
 - if necessary, seek refresher session with therapist

Figure 87.1 Extract from Mrs Jacobs's therapy blueprint

Source: Abridged and reproduced with permission from [10], Wilkinson P. (2001) Cognitive behaviour therapy. In: J Hepple, J Pearce & P Wilkinson (Eds), *Psychological Therapies with Older People* (pp. 61–73). Hove: Bruner-Routledge

Dialectical Behaviour Therapy (DBT)

Dialectical behaviour therapy has been developed to treat younger adults with personality disorder, particularly borderline disorder¹². Its underlying theory assumes a biological predisposition to increased emotional sensitivity and impaired emotional regulation. It combines individual therapy to tackle self-defeating behaviours, such as self-harm, with group training in emotional regulation and managing interpersonal relationships; these are backed up by telephone coaching from a therapist. Therapy techniques include the use of metaphor and stories (dialectical strategies) and standard cognitive behavioural strategies.

The study of personality and personality disorder in old age is in its infancy and is hampered by a lack of robust longitudinal research¹³. However, there are indications that certain personality traits in older people are associated with recurrent depressive disorder and this has led to the modification of DBT for the treatment of older patients¹⁴. Self-defeating patterns of behaviour exhibited by older patients and targeted in DBT may include repeated disengagement from treatment.

For a fuller description of DBT with older adults see Cheavens and Lynch¹⁵.

Mindfulness-Based Cognitive Therapy (MBCT)

Mindfulness-based cognitive therapy is used to prevent recurrence of depression. It is derived from both CBT and mindfulness-based stress reduction, an intervention originally developed to reduce distress in patients experiencing chronic pain and illness¹⁶. Rather than examine the content of thoughts, as in conventional CBT, MBCT teaches patients how to disengage from recurrent patterns of negative thinking by the use of meditation and refocusing on bodily sensations, particularly breathing. Techniques are taught in group classes with the intention that participants will continue to practise meditation and to employ modified techniques in everyday life. As MBCT aims to prevent rumination over insoluble problems, such as ill-health, it has obvious potential in the treatment of older people. Experience suggests that older patients value its educational approach¹⁷.

Efficacy of Cognitive Behavioural Interventions

Despite a significant number of large-scale trials supporting the acute and long-term benefits of CBT in the management of depressive illness in younger adults¹ there have been few large well-powered trials with older participants representative of clinical populations¹⁸. In one trial¹⁹ 102 adults aged 60 and over with major depressive disorder were treated over three months with CBT alone, the antidepressant desipramine alone, or a combination of the two. The authors concluded that the addition of CBT to desipramine may be of additional benefit in patients with more severe depression. A more recent trial in a UK primary care setting compared CBT with treatment as usual and treatment as usual with talking control²⁰ in 204 people aged 65 or over with a Geriatric Mental State diagnosis of depression. Based on improvement in Beck Depression Inventory score, CBT was of greater benefit than treatment as usual and talking control.

A Cochrane systematic review of trials of psychological treatments for depression in older adults included five trials comparing therapies from the cognitive behavioural schools with waiting list controls²¹. The cognitive behavioural therapies were found to be significantly more effective than waiting list controls. However, the authors of this review urge caution in generalizing these findings to clinical

populations due to the quality of the trials and their clinically unrepresentative patient populations.

Studies of MBCT

The National Institute for Health and Clinical Excellence Depression Guideline¹ recommended MBCT as a maintenance treatment to reduce the likelihood of future relapse for younger adults who have experienced three or more episodes of depression. MBCT may also be more effective than antidepressant medication in reducing overall psychiatric morbidity and improving quality of life²². There have been no randomized trials of MBCT with older people, although a descriptive study of 38 older people with recurrent depression showed it to be an acceptable treatment that required minimal modification²³.

IMPACT Trial (Improving Mood, Promoting Access to Collaborative Care Treatment)

In this large multicentre trial in the United States²⁴, behavioural activation and PST were used as components of a flexible package of treatment for depression alongside patient education, antidepressant treatment and supervision by a depression care manager. Compared with usual primary care treatment (including antidepressants) the collaborative care reduced depressive symptoms and improved rates of remission on the Symptom Check List 90 over two years.

Studies of DBT

There have been two small exploratory randomized controlled trials of DBT in older people. In the first, in which people with major depression received antidepressant medication with or without group skills therapy and telephone coaching, higher rates of remission were found with the combination treatment at six months. The second study was with participants aged 55 and over with major depression and a diagnosis of personality disorder on the Structured Clinical Interview for DSM-IV Personality Disorders and the Inventory of Interpersonal Problems (Personality Disorders) who had not remitted after eight weeks of antidepressant treatment²⁵. They were randomized to 24 weeks of either antidepressant medication management alone or medication management plus DBT. Although those receiving the combination achieved remission sooner, there was no difference between groups in overall rates of remission.

INTERPERSONAL PSYCHOTHERAPY (IPT)

Interpersonal psychotherapy is a short-term individual treatment based on the simple principle that whatever its cause, depression inevitably impacts on relationships. It arose from the interpersonal school of psychiatry and under the influence of attachment and life events theories. IPT aims to address one or two interpersonal goals that are identified during a detailed review of the patient's current and recent relationships.

Interpersonal problems are classified into four categories: complicated bereavements, role transitions, interpersonal disputes and interpersonal deficits. With older people the commonest foci are role transition and interpersonal dispute. A role transition may be the loss of a role, such as retirement from work, or the acquisition of a new role such as becoming a carer for a spouse with dementia. A role dispute may occur, for instance, when an older person dealing

with ill-health begins to require the practical and emotional support of an adult son or daughter. There is naturally some overlap between these categories: for instance, a complicated bereavement after the death of a spouse implies a role transition to being a single person²⁶.

Treatment strategies used in IPT begin with education of the patient on the nature of depression and encouragement to temporarily adopt the sick role. This should help to validate the depression as a legitimate health problem which can be important for older people. In the management of bereavement, patients are encouraged to express their feelings associated with their loss and then to build up new relationships. With role transitions, a period of mourning for the old role is encouraged followed by support in adapting to the new role. In interpersonal disputes possible treatment strategies include improving the patient's style of communication before renegotiating the basis of the relationship or seeking its dissolution.

Interpersonal psychotherapy can be used as a short-term acute phase treatment of depression (usually up to 16 sessions) or as a maintenance treatment with sessions more widely spaced over a period of months. The latter allows for a greater number of therapeutic foci to be addressed, including long-standing patterns of interpersonal behaviour that may contribute to recurrence (interpersonal deficits)²⁷. In IPT it is generally not intended that the therapeutic relationship become a focus of therapy although in tackling long-term interpersonal deficits it may provide useful insights.

IPT has also been adapted for use with cognitively impaired older people through involvement of caregivers in the delivery of therapy²⁸.

For a detailed description of IPT with older adults, see Hinrichsen and Clougherty²⁶.

IPT Case Example: Mr D – I lost my wife and my life

Mr D, a 66-year-old widower and retired lawyer, was brought to treatment by his family. He acknowledged being quite depressed in the aftermath of his wife's death from breast cancer five months earlier. On questioning, he stated that his depression had really begun when he retired from his job to care for her declining health a year and a half earlier. In fact, Mrs D had been fighting breast cancer on and off for eight years, an onslaught that he had described as having gradually taken over their lives. He was distracted from his work, and what he described as a previously warm and close relationship had suffered. 'But why shouldn't I be depressed?' he asked. 'My life is ruined, over.' He reported agitation, rumination, decreased sleep and appetite, a 15 pound weight loss, and passive suicidal ideation, with a sense that he might be reunited with his wife in death. His Hamilton Rating Scale for Depression score was 27.

Mr D reported one prior episode of depression in his early twenties; he had also abused alcohol many years before but denied current use. He reported mild prostatic hypertrophy but was otherwise in good medical condition. He was adamant that he would not take an antidepressant medication.

Given a choice between a role transition based on retirement and complicated bereavement, both therapist and patient agreed to focus for 12 sessions on the latter. Mr D felt guilty

that he had let his wife down, believed that he should have cared for her better, and considered her the love of his life, an irreplaceable loss after some 40 years of marriage. The therapist encouraged him to reminisce about what he missed about Mrs D and their marriage. She also noted that Mr D had not discussed his feelings much with his friends and had not really used the available social supports. Mr D stated that many friends and family members had either moved away or died in recent years, and he was not in any case one to talk about his feelings. He had withdrawn and kept to himself from the time of his wife's funeral. The therapist encouraged him to consider building new skills in this area, inasmuch as social supports could provide him with some comfort in his difficult situation.

As therapy continued, Mr D reported that he had begun to attend synagogue for the first time in years and that his rabbi had provided some solace. At the same time, Mr D began to discuss his ambivalent feelings about his wife – how her illness had distracted him from and ultimately ended his career and how she had annoyed him at times despite his wanting to care for her. Although they had had a wonderful marriage, there had (inevitably, his therapist noted) been some problems. He began to discuss these issues with a level of affect, initially apologizing for his tears but gradually relaxing and accepting his feelings. His Hamilton score decreased to 13, and he began to become more socially active.

In the latter part of the 12-week therapy, Mr D returned to the law, conducting pro bono work for senior citizens. He also became active as a volunteer for a local cancer society, raising funds and – somewhat to his surprise – developing new friends. Mr D saw his cancer work as a tribute to his wife. He also re-engaged with his children and other family members. By the end of treatment, his Hamilton Rating Scale for Depression score had fallen to 7. He was proud to have improved 'by myself' without medication. Given his history, Mr D and his therapist agreed to monthly maintenance IPT to help him preserve his gains.

Reproduced by permission of Oxford University Press, Inc. from [29] Weissman MM, Markowitz JC, Klerman GL. (2007) *Clinician's quick guide to interpersonal psychotherapy* (pp. 108–109). New York: Oxford University Press.

Efficacy of IPT

There is good evidence for the efficacy of IPT as an acute treatment for depression in younger adults¹ but acute phase trials with older people been fewer and smaller (e.g.³⁰). The most significant trials of IPT with older people have been in the maintenance phase of treatment; these are reviewed below.

MTLLD I and MTLLD II trials (Maintenance Therapies for Late Life Depression)

These trials examined the effect of IPT with or without antidepressant treatment in participants who had recovered from an episode of depression using a combination of IPT and antidepressant.

In MTLLD I³¹ participants were relatively young outpatients (60 years or over) who had suffered at least two episodes of depression.

In maintenance treatment they received nortriptyline alone, drug placebo alone, IPT alone or a combination of both treatments. The combination produced the lowest recurrence rate on the Hamilton Rating Scale for Depression and was superior to drug placebo, IPT alone and possibly to nortriptyline alone although this comparison did not achieve statistical significance. Participants were followed up at monthly intervals for three years (Figure 87.2). Participants aged 70 and over had the highest rate of recurrence in the first year and a secondary analysis suggested that the greatest benefit of combined pharmacotherapy and psychotherapy in reducing recurrence was in this group.

MTLLD II³² addressed the prevention of recurrence in older patients (70 years or over) (i.e. those potentially at greater risk of recurrence). Participants in this trial had more medical illness than those in MTLLD I; some had cognitive impairment and may have been developing dementia. Half of the participants were in their first episode of depression. They were randomly assigned to paroxetine alone, placebo alone, monthly IPT alone or a combination of paroxetine and IPT; and follow-up was for two years. In contrast to MTLLDI, combined treatment did not produce lower recurrence rates than antidepressant alone and IPT was no more efficacious than drug placebo (Figure 87.3).

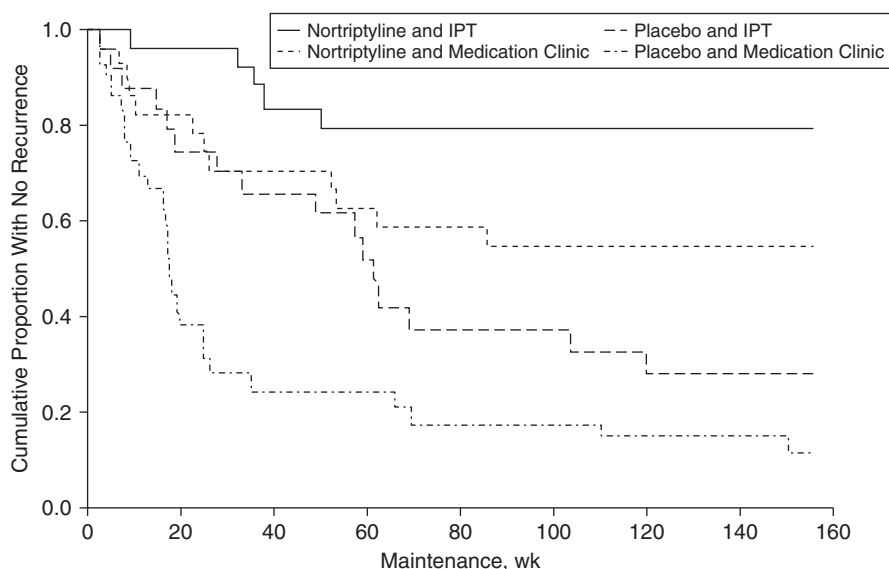


Figure 87.2 Survival analysis of the four treatment groups in Maintenance Therapies for Late Life Depression (MTLLD) I. IPT, interpersonal psychotherapy

Source: Taken with permission from [31] Reynolds *et al.* (1999), *Journal of the American Medical Association*, 281: 42. Copyright © (1999) American Medical Association. All rights reserved

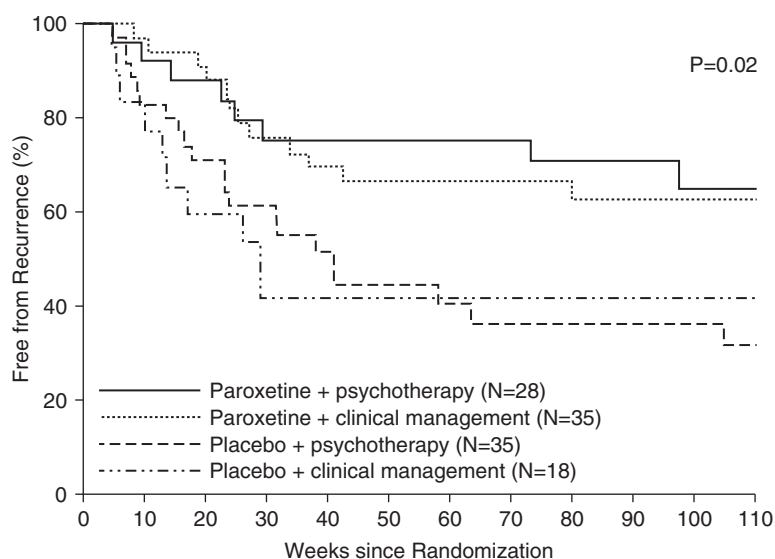


Figure 87.3 Survival analysis of the four treatment groups in MTLLD II

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PROSPECT trial (Prevention of Suicide in Primary Care Elderly: Collaborative Trial)

Although this large primary care trial principally studied the reduction in major risk factors for suicide in older people, it gives some indication of the effect on depression of a care management intervention that included IPT³³. Other components of treatment were antidepressant treatment and support from a depression care manager who also delivered the IPT in both the acute and maintenance phases of treatment. Patients receiving the intervention had a more favourable course of depression and greater rates of remission during a year's follow-up, compared with those receiving usual care.

REMINISCENCE THERAPY AND LIFE REVIEW

Designed specifically for older adults, reminiscence therapy is usually offered in groups in which participants are encouraged to discuss their earlier life experiences with the help of prompts such as photographs, music and everyday objects. Life review, by contrast, is usually an individual therapy offering a more systematic review of the patient's own life experiences.

Efficacy of Reminiscence and Life Review

A number of small, short-term trials have shown positive effect sizes for reminiscence as a treatment for depression, particularly in community-dwelling people; however, a large randomized controlled trial is lacking³⁴. In one study, reminiscence and life review appeared less efficacious than problem-solving therapy³⁵.

USING PSYCHOLOGICAL TREATMENTS IN THE PRIMARY PREVENTION OF DEPRESSION

It is known that the factors that put older people at risk of developing major depression include chronic illness, functional impairment and low-level symptoms of anxiety and depression. For this reason psychological interventions have been developed for those at risk of depression because of a medical disorder or bereavement (selective prevention) or because of having subsyndromal symptoms (indicated interventions). An example of a selective intervention is PST to prevent depression in older people with age-related macular degeneration as evaluated by Rovner *et al.* in 206 people attending an ophthalmology clinic³⁶. This study demonstrated a significant difference in depression levels between intervention and control groups at three months but this was not maintained at six months.

For a summary of prevention trials and a discussion of study design see the review by Cole³⁷.

PSYCHOLOGICAL TREATMENT OF DYSTHYMIA

Dysthymia indicates a long-standing state of milder depression, especially low mood and is sometimes accompanied by episodes of major depression. There has been little specific evaluation of psychological treatments for dysthymia, especially with older people, although there is some guidance as to how treatments can be adapted. It is suggested that both CBT and IPT for dysthymia need to take account of the strained relationships and long-term lack of achievement that can accompany it and in IPT the therapeutic focus may need to be the role transition from ill-health to health²⁹. It is likely that therapy will take place over a more sustained period with regular maintenance sessions.

OLDER PEOPLE'S ACCESS TO PSYCHOLOGICAL TREATMENTS AND THE NEED FOR FURTHER EVALUATION

Developments in the use of psychological therapies with depressed older people appear not to have significantly influenced provision. In the United States, use of psychotherapy remains uncommon among depressed older people³⁸ and in the United Kingdom availability has been patchy³⁹. The Improving Access to Psychological Therapies programme in the UK⁴⁰ has tried to improve uptake through the implementation of a stepped care approach starting with low level interventions such as behavioural activation. Although a key aim of the programme has been to enable working adults to re-enter the workforce it was also intended to improve access for older people. Despite this, older adults have been under-represented in referrals made by general practitioners. Older people appear inclined to take up the offer of psychotherapy, particularly if it presented in an educational format⁴¹.

Availability of therapies may be limited by health care providers. In the United States, for example, Medicare providers may limit the number of therapy sessions or restrict them to certain groups of patients⁴². Therapies that are more straightforward, such as PST, and that can be delivered by non-mental health workers alongside treatment of physical disorders may have more to offer and be more appealing to funders as may brief therapies designed to be delivered in group format⁴³. However, before a strong case can be made for an expansion in psychological treatment provision for depressed older people further evaluation of interventions is required. Although the effect sizes in trials with older adults appear to match those with younger people, there remains a paucity of large, robust trials with older adults representative of clinical populations^{21,44}. Trials of care management interventions in primary care have been encouraging but these do not measure the specific effects of their psychological treatment components. Indicators of likely response to psychological therapies would help guide decision making and use of resources⁴⁵.

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Acute Management of Late-Life Depression*

V. Gardner and D.C. Steffens

Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

The acute management of late-life depression may require hospitalization, both for accurate diagnosis and for effective treatment. Ambulatory management is frequently favoured because of rising hospital costs in a managed care environment. However, the elderly present special challenges that may require that diagnosis and/or treatment be undertaken in a hospital setting. The hospital provides an environment for the monitoring of symptoms for accurate diagnosis and proper personnel for regular and accurate treatment administration. Several factors may interfere with both accurate diagnosis and effective treatment on an ambulatory basis¹, including underlying chronic medical illness, pain, neurodegenerative changes, dementia, adverse life events, inadequate family support, secret self-medication, substance abuse, bereavement, interpersonal conflicts and social isolation of the elderly patient.

Actually, the elderly patient who is cognitively intact may be reliably managed on an ambulatory basis and can be instructed about medication side effects. Similarly, the more impaired elderly patient who has adequate social support for observation and medication management may only need the community support of a visiting psychiatric nurse, assuming one is available. Varying levels of care are also implemented in the hospital environment. Patients may have the usual care of routine monitoring or may have more intense one-to-one monitoring if they are an imminent risk to themselves or others.

As a general rule, the more the physical and psychiatric impairments and the fewer the psychosocial resources, the greater the need to hospitalize for accurate diagnosis and effective treatment. When deciding safe and effective management, the following factors favour hospitalization: poor or unstable physical health, high suicide risk, impaired judgement and reality testing, likelihood of poor compliance, impaired cognitive functioning, lack of social support, and severe anorexia and weight loss.

CO-MORBIDITY OF PHYSICAL ILLNESS: THE INTERFACE OF PRIMARY CARE AND PSYCHIATRY

Accurate diagnosis is a prerequisite for effective treatment. Elderly patients with depression present to their primary care physicians and psychiatrists in a complex manner, and signs and symptoms of physical illness and depression overlap. Even the normal effects of ageing may cause diagnostic difficulties and restrict treatment

options. Many primary care physicians diagnose and treat late-life depression without referral. However, those patients who fail two or three trials with antidepressants, usually selective serotonin reuptake inhibitors (SSRIs) or newer agents, are commonly referred to a psychiatrist for further management. These patients represent a treatment challenge and may require more complex medication regimens. Hospitalization may be necessary to enable close monitoring and minimise risk of self-neglect, suicidality and treatment side effects. Primary care physicians also refer for the following reasons: suicidality, co-morbidity with substance abuse, dementia, anxiety disorder, presence of psychosis (delusions, hallucinations), catatonia, bipolar disorder and inability to tolerate antidepressant treatment^{2,3}.

Depression is often co-morbid with other physical diseases. Approximately 80% of older adults suffer from at least one chronic health problem⁴. The prevalence of co-morbid depression may be up to 30% in stroke patients, 18% in myocardial infarction patients, 51% in patients with hip fracture and 50% in patients with chronic pain¹. Existence of an undiagnosed and untreated depression with these illnesses leads to higher disability⁵. The diagnosis of depression in the context of established physical illnesses may be challenging, and the hospital environment provides the necessary monitoring and support staff when complicated medication changes are required. For example, a patient with cardiovascular disease may present with decreased energy and apathy. Determining whether this is caused by a compromised cardiac status, a medication side effect, or is actually a symptom of depression may be difficult without hospitalization, close monitoring and various medication trials.

Formerly, hospitalization was favoured for the initiation of tricyclic antidepressant therapy in elderly patients with unstable cardiac disease. First-line treatment with SSRIs has made this less often necessary, though older people are also vulnerable to adverse effects of SSRIs such as hyponatraemia.

Co-morbid neurological illness is also common in geriatric depression. Patients with depressive symptoms following a cerebrovascular accident also present a diagnostic challenge. There may be communication difficulties or other neurological abnormalities. Depression may be diagnosed only by the report of the nursing staff and family, who observe apathy, irritability, tearfulness and weight loss⁷. Patients with Parkinson's disease may develop an affective illness or psychosis, which may be secondary to treatment with L-dopa or dopaminergic agonists. Hospitalization may be required for medication changes if outpatient support is inadequate.

*Updated by Mohammed T. Abou-Saleh

Severe anorexia, weight loss and refusal to eat are indications for hospitalization for safe and effective treatment^{1,8}. Poor oral intake commonly accompanies severe depression, but it may also result from a variety of medical conditions. For example, individuals with active rheumatoid arthritis may experience insomnia, fatigue and poor appetite equally from their physical illness or an associated depression⁹.

SUICIDE RISK AND THE DECISION TO HOSPITALIZE

Suicidality is the most common reason for psychiatric hospitalization. The goals for inpatient treatment are: (i) the preservation of life and safety; (ii) the elimination of suicidal intent and ideation and treatment of underlying disorders; and (iii) the improvement of intrapsychic capabilities, personal factors and psychosocial circumstances to facilitate coping after discharge and decreasing risk of the return of suicidality. However, implementation of these treatment plans is predicted on the initial detection of suicidality.

Careful assessment of suicide risk in depressed older adults is thus vital. The elderly are less likely to have made a prior suicide attempt, but they consistently demonstrate a higher rate of completed suicides¹⁰. The ratio of attempted to completed suicides decreases with age from 200:1 in young adulthood to 4:1 in the elderly¹¹. The higher rate is due primarily to the increased frequency of deaths among older, white males. In 1992, people 65 and older accounted for 13% of the population but almost 20% of suicides. Even though the frequency of suicide has increased among older persons in the United States, the prevalence is not as high as that of other industrialized societies¹².

Recognition of variables such as gender and race may influence management decisions. Risk factors for suicide in late life include increased age, with the highest prevalence of suicide of persons older than 85¹⁰. Also, being male, white, single, separated or divorced, or widowed are risk factors for suicide. Other risk factors implicated in late-life suicide include: a positive psychiatric history (especially depression and alcohol abuse and dependence); physical illness and functional disability (especially diseases of the central nervous system, malignancies, cardiopulmonary conditions, and urogenital diseases in men); previous suicide attempts; psychological factors (i.e. hopelessness); social factors (stressful life events, e.g. bereavement); and biological susceptibility (dysregulation of the hypothalamic–pituitary–adrenal axis or the serotonin system).

Most older people who commit suicide have seen a primary care provider within 30 days of death¹¹. This observation stresses the need for collaborative efforts with primary care physicians and the need to make careful assessment based on risk factors.

A number of assessment guidelines have been developed to aid in the evaluation of potentially suicidal patients. A four-item screen for identification of suicidal ideation among general medical patients was developed by Cooper-Patrick *et al.*¹²:

1. Have you ever felt that life is not worth living?
2. Have you ever thought of hurting or harming yourself?
3. Have you considered specific methods for harming yourself?
4. Have you ever made a suicide attempt?

This fourfold layered approach to assessment is useful in obtaining the necessary data without disrupting the therapeutic relationship. If the answer to the first or second question is negative, then the enquiries can cease and the older person may be considered

at low risk for suicide¹⁰. This approach has advantages over other assessment tools, which usually suggest one question to be asked to assess suicidal risk.

DELUSIONS AND LATE-LIFE DEPRESSION

Accurate diagnosis and effective treatment of depressed elderly patients with delusions can be hindered by their impairment of reality testing. Their sometimes well-organized and complex delusions may make them distrust medicine and the physician who prescribes it. This disorder is less frequent in the community and more prevalent in the hospital setting^{13,14}. Accurate diagnosis is necessary, as some studies have suggested that the depression is more severe^{14,15} and it has been associated with suicide¹³. Varying reports also demonstrate decreased cognitive functioning and social functioning among patients with delusional depression¹⁶. These patients are best treated in the hospital. They cannot be relied upon to take accurate doses of medications. Effective pharmacologic treatment for delusional depression may require combination treatment with antipsychotic medication and antidepressants¹⁵. ECT remains an effective and relatively safe treatment for the treatment of delusional depression^{17–19} and can be performed on an outpatient basis only with adequate social support.

COGNITIVE DYSFUNCTION AND LATE-LIFE DEPRESSION

A full discussion of how depression is distinguished from dementia is given elsewhere in this book. To summarize, diagnosis is difficult because several symptoms of depression and dementia overlap, such as a flattened affect, psychomotor retardation and presence, at times, of delusions²⁰. Delusions are reported to occur in up to 40%¹³ of Alzheimer's disease patients, although they are described as transient and less organized than in delusional depression¹³. Major depression occurs in over 20% of patients with Alzheimer's disease and vascular dementia^{4,21}. This significant co-morbidity may lead to profound disability²².

The diagnosis of depression in dementia usually requires the input of family members or nursing personnel^{23,24}. The patient with cognitive dysfunction and impaired reality testing cannot reliably report symptoms, take medication accurately, or reliably report side effects.

Dementia with depression and behavioural disturbance is frequently too complex to treat on an outpatient basis. These patients may even require involuntary commitment. Aggression may be verbal or physical. Aggression and agitation in dementia may be as high as 50% in the outpatient population^{25,26}. The hospital environment is the only setting with constant monitoring to make an accurate diagnosis, contain behaviour and monitor medication.

The reversible cognitive impairment that may accompany depression also increases disability²⁷. With treatment, the cognitive impairment usually improves. However, these patients are at higher risk of developing an irreversible dementia in the future²⁸.

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Bereavement

Robert J. Kastenbaum

Arizona State University at Tempe, Tempe, USA

I have lived longer than the reach of my wildest dreams. Every day is a bonus!

My body's done its job. I've done mine. So! When it's time to go, it's time to go!

Self-reflections of this kind are more common among long-lived people than those who are still making their way towards an as yet unrevealed future. Death is less theoretical, and loss a prominent feature of the lifescape. Advanced age and bereavement are normative circumstances, not psychiatric syndromes. Daily life can present a variety of concerns, such as remembering which medication to take when, fear of falling on icy pavements, and worry about paying bills and continuing to live independently. Bereavement introduces additional concerns. 'Who can I share my day with?' 'Who will do the driving/cooking?' 'Where do I go from here?' These are human rather than geriatric problems.

The psychiatry of bereavement in old age does not assume pathology or need for professional intervention, nor does it assume that all elders respond in the same way. Major research projects find a 'remarkable heterogeneity in older adults' adjustments to loss'¹. Resilient coping is more common than prolonged distress and dysfunction. Hastily prescribing psychotropic medication for a 'geriatric patient' can become part of the problem, rather than the solution. Instead, we ask, 'Who is this person?' 'What was the nature of this unique relationship that has been ended by death?' 'What does this loss mean to the bereaved person?' – and 'What coping skills and resources can be called upon to make it through?'

A perspective on bereavement in old age can be developed by following the basic sequence of events. We then identify challenges for bereaved elders and those who would offer services to them.

THE PRE-BEREAVEMENT SITUATION

Consider first the situation prior to a bereavement in old age.

1. What was the nature and status of the relationship at this time?

This question should be answered structurally and substantively, e.g. 'He was her older brother; she relied on him for advice and support more than on any other person, including her husband', or 'She was his second wife; he had expected her to look after him – actually, to wait on him hand and foot! – and suddenly he had to be the

caring person.' It is useful to explore affective and pragmatic dimensions of the relationship. Was the survivor or the deceased heavily dependent on the other person? Had the relationship been in serious trouble? If so, was this characterized by silent co-existence or stormy disputes? Did the deceased provide most of the couple's link to society? Had the survivor organized his or her life around taking care of the deceased?

An elderly person's response to the death of an adult child or grandchild is too often underestimated². There can be a deep interiorization of grief after the first shock of the loss, followed by an intensified life review. Researchers have documented a 'double pain': their own loss of a grandchild and their anguish over their adult children's grief³. There is also often a *disenfranchised grief* situation⁴. Grandparents can be subject to interpersonal signals that they are not fully entitled to mourn the loss. The extent to which grandparents might become isolated in their grief is influenced by their pre-bereavement status in the family. Counselling interventions could include resolving issues that generated intra-family tension prior to the loss. Instead of labelling the problem as 'depression' in the elder, one might instead discover a dysfunctional family pattern that is affecting all the members.

2. How was the prospect of bereavement integrated into the life scenario?

Bereavement in later life most often involves the loss of a sibling or spouse. It is not unusual for elderly people to have floating expectations regarding the loss of people they have known for much of their lives. These cohort peers are at significant risk for death because of their advancing age and accumulated vulnerabilities. Therefore, it will be a sad but not surprising day when their lives come to an end. On the other hand, they have always been around, so it is easy to assume that they will continue to go on and on. A recently bereaved elder might alternate between the more logical and the more habituated-wishful view. Psychologically, the death has been both anticipated and not anticipated.

Anticipatory grief is often a more complex response than usually assumed. Anticipatory grief is similar in many respects to the grief that is experienced after a death⁴. There are affective, cognitive and somatic components, e.g. sadness, obsession, exhaustion etc. It has often been suggested that anticipatory grief helps the survivor to cope with the loss – paid for in advance. Early studies suggested that sudden death has a much more disturbing impact than expected

death⁵. More recent studies have taken more variables into account and suggest that anticipatory grief does not always cushion the survivor's stress when the loss does occur¹. Potential caregivers would do well, then, to observe the particulars of the situation carefully, rather than assume that expectation is necessarily ameliorative. (Many elders have told me how they still feel helpless and miserable because they could not do anything to palliate the suffering prior to an expected death.)

Not all deaths are clearly expectable. Fatal accidents (especially falls and motor vehicle) are far more common among people 65 and older than in any other age group. Nevertheless, there is a greater probability the death will have been expectable, if not necessarily expected. Not only does an increasing proportion of deaths occur in old age, but modern health care has lengthened the interval between development of a life-threatening condition and the day of death. The four leading causes of death for elderly people in the USA (heart disease, malignant neoplasms, cerebrovascular disease and respiratory conditions) all involve a long period of living with progressive life-threatening conditions and, therefore, opportunity for both prolonged stress and adaptation to the prospect of death for the patient and significant others.

Physicians and other caregivers have the opportunity to strengthen the survivor's ability to cope with grief by sensitive response to the situation as it exists prior to death. Offering accurate information, suggesting other options and improving the lines of communication within the family are among the ways in which one can help to shape the anticipatory grief period into a source of strength rather than intensified anxiety. The age differential between most caregivers and the elderly bereaved people they are trying to help sometimes interferes with communications, e.g. when elders are patronized and their ability to cope with bad news is underestimated. There is also an underappreciated connection between quality of terminal care and grief recovery. A hospice physician reports that, 'The pain relief we achieve for an old man in his last weeks of life helps his wife to be more of her normal self when he really needs her – and a widow with fewer regrets and nightmares later.'

3. What was the survivor's own health status prior to the bereavement?

This is a particularly useful question to ask with respect to the older bereaved person⁶. The spouse was most frequently the principal family caregiver in the 40 hospices studied by Mor *et al.*⁷ About two thirds of the spouses were above the age of 55 and it was not unusual for the caregivers to be over 75. Elderly caregivers seldom developed new physical problems over the course of the spouse's final illness, but they tended to ignore their own existing conditions. During the first months of bereavement, the survivor's health was sometimes impaired by exacerbation of previous illnesses and impairments. It would be helpful, then, to encourage the spouse and other elderly family members and friends to look after their own health during the pre-bereavement period, and to see that health status is carefully assessed afterward. Symptoms that might appear to be part of an anxious depression syndrome could be related to physical health problems that have not received the attention they deserved.

4. Who else was there and what else was happening?

Strained interpersonal relationships and unanswered questions sometimes increase stress on patient, family and staff. It might be useful to assess the prevailing attitudinal climate. Some bereaved elders report that they felt unwelcome by staff members during their bedside visits.

'I never had a chance to really *be* with Herman. The nurses thought they owned him.' Others said they were told different things by different people. 'I can understand things if I'm told right. I worry more when I'm not sure what to worry about.' By contrast, some bereaved elders drew comfort and strength from the bedside scene. 'The people from the church were over all the time. They really cared. We were so far from the rest of the family, but they were just like family to us.' 'Miriam seemed so at peace with herself. She whispered to me once, "This is a great place to die. They're all so nice".'

A consultant can make a positive difference by identifying interpersonal issues in the end of life period and encouraging humane and effective approaches.

AT THE TIME OF DEATH

Learning what happened around the time of death can help us understand the bereaved elder's state of mind. Consider, for example, the difference between death at home and in a hospital setting. A terminally ill woman was being looked after at home by her elderly mother, with support from a local hospice service. The mother had accepted her daughter's wish to be allowed to die at home without intubation and other futile procedures. But when the daughter appeared to be actively dying, the mother panicked and called not the hospice but a visiting nurse service. Now, as a survivor, the old woman is haunted by memories of her suctioned, intubated and drugged daughter accusing her with her eyes⁸. In a more frequent scenario, an elderly person will call for assistance from paramedics when his/her spouse appears to have died. But when the paramedic team arrives, the caller may have second thoughts about seeing the spouse's body subjected to resuscitation procedures. Some bereaved elderly persons remain troubled by unanswered questions about whether they did the right thing at the right time.

Knowing only that the death took place in a hospital does not tell us whether supportive nurses encouraged a woman to be with her husband right through to the end and to have time with him afterward – or whether she was made to feel unwelcome and hustled away. Perhaps, again, she had not been notified until some time after the death. The particularities of the final scene can provide either an acceptable conclusion to the story of a marriage or friendship, or torment the survivor with resentment, self-doubt and other disturbing thoughts.

The psychiatrist often has the opportunity to increase the sensitivity of physicians, nurses and caregivers in their communication patterns around the time of death. Survivors may hold on to a word or gesture, either as a cherished or an infuriating/depressing memory. Often one can be helpful simply by validating the survivor-to-be's feelings and offering the opportunity to clarify his/her own thoughts by active listening. The generational differences between bereaved person and psychiatrist can be a source of misunderstanding. An aged widow, for example, might keep feelings bottled up in accordance with the implicit rules that characterized her generation. Patience and encouragement could help her to express and cope with her feelings. It happens the other way, too: caregivers whose own tradition is marked by subdued behaviour and restraint of emotions may not be prepared for families in which intense expressions of grief are expected, even required.

EARLY PHASES OF BEREAVEMENT

The idea that there are fixed 'stages' of either dying or grief has attracted more believers than it deserves. One can select and force

observations to fit stage theories, but to what purpose? Individual responses to grief deviate markedly from the models: this is even more common in old age, where uniqueness has been deeply engraved and polished to a high gloss.

It does make sense, though, to differentiate between responses during earlier and later periods subsequent to bereavement. Indicators of a potentially intense, disabling and protracted reaction often appear within a short time. In their classic study, Parkes and Weiss⁹ found that those who had the most difficult time coping with the spouse's death tended to smoke and drink more heavily, use tranquilizers and express depressive mood. Other investigators have also found that response to loss within the first few months provides a fairly reliable forecast of long term adjustment. The obvious lesson here is that early-appearing indicators, such as loss of appetite, withdrawal from friends and activities, sleep disturbances and escape into alcohol and drugs (including the hoarding of prescription or over-the-counter elixirs) should be taken seriously. Time alone will not necessarily prove the healer.

Dependency needs often come to the fore when the survivor is experiencing significant difficulties in coping. Counsellors and therapists can be effective in helping survivors to rekindle their sense of competency and autonomy. This is likely to be a step-by-step progression, in which the therapist may have to play the roles of protector and mentor for some time. The advanced age of the bereaved person does not necessarily stand in the way of therapeutic success. Many people bring positive coping skills and experience into their later years of life, and some continue to participate in mutually rewarding social support networks.

It is not unusual for an elderly person to seem relatively unresponsive to a death. In some situations this is the observer's failure to notice subtle but significant changes. But the lack of a strong overt response is sometimes associated with bereavement overload¹⁰. Re-activated grief from previous losses can command the person's attention so that there is not enough emotional energy available to respond fully to the most recent death. Survivors of the Holocaust and other disasters have often been burdened in this way.

An upsurge in fear of personal death is also not unusual, especially when it is a sibling who has died¹¹. A death that hits that closely to the survivor's own situation can lead to a dysfunctional pattern in which depression and anxiety vie for dominance. Here again, therapists have found it useful to bolster the individual's sense of competence and autonomy, as well as to encourage sharing of the concern.

Abundant if somewhat circumstantial research evidence supports the proposition that enhancing self-esteem can be a powerful hedge against mortal terror^{12,13}.

LATER PHASES OF BEREAVEMENT

Many senior adults have proven highly resilient after experiencing bereavement. Studies do not invariably find that widows sit around weeping and feeling helpless. The gender dimension is important here. Women outnumber men in the upper age echelons and often show themselves more skilful in providing – and receiving – social support. By contrast, the bereaved older man runs more risk of becoming isolated. In some environments, such as the retirement community with its high density of older women, the widower may be valued and looked after. Nevertheless, there is a major problem of hidden grief among older men, a problem that often persists for years after the loss. Quiet, keeping to himself, expressing little

obvious emotion, the older bereaved man is more likely to be suffering intensely than his female peer, with her greater facility in self-expression and more sensitive support network¹. Psychiatrists and other caregivers might be well advised to give more attention to the possibility of bereavement – even a remote bereavement – as the underlying factor in a variety of behavioural and somatic problems experienced by older men. Unfortunately, some of the most traumatic bereavements leave the elderly survivor with the most limited social support. This is especially the case with suicide. The high rate of suicide among elderly white men often leaves their spouses and siblings alone with their grief.

A FEW SPECIAL CONSIDERATIONS

First, grief counselling is proving effective for many adults, including those of advanced age, who had been experiencing significant adjustment problems. A false alarm received widespread attention before being revealed as such. A 'finding' that grief counselling is not only ineffective but sometimes harmful was itself found to be without empirical and scholarly credibility¹⁴. Grief counselling remains a viable option for bereaved people whose personal and interpersonal resources have been temporarily overwhelmed.

Second, bereavement is a status marker in spousal death. The survivor, no longer a husband or wife, tends to be treated in a different way, sometimes as 'the odd one out.' Counsellors can be helpful in supporting the survivor's transition to meaningful new roles, and the restoration of self-confidence.

Third, the 'little deaths' that often accompany the later years of life can both intensify and anticipate grief reactions. The old man may have been mourning the loss of his mobility even before his wife died; the older woman who was relieved of her starring role as a church soloist may have felt abandoned and rejected long before her husband's death.

Fourth, the death of animal companions can lead to authentic grief reactions¹⁵. The grief syndrome may be similar to what is experienced upon the death of a human companion, although the intensity is less likely to endure as long. Rage joins with grief when an elderly person is placed in a nursing home and then learns that his/her animal companion has been taken to the pound and destroyed.

Fifth, the profile of the senior adult population and the conditions of their lives are continuing to change. Care providers have the challenge of keeping up with these transformations instead of relying on practices and assumptions that might be outdated. Some examples of relevant population trends are:

- More elders are receptive to counselling and becoming acquainted with the internet. Each new generation of elders is bringing enhanced technological background and receptivity to mental health options.
- The burden of Alzheimer's disease is being experienced by an increasing number of elderly family caregivers both during the course of the illness and in the mixed relief and sorrow that occurs in bereavement^{16,17}. The increasing scale of caregiver stress and vulnerability presents a challenge that has not yet been fully addressed.
- Population experts see the USA as rapidly becoming 'a majority of minorities'. Familiar ways of life and death have centred on a white Christian majority. Increasing ethnic and racial diversity is bringing a new mix of attitudes and expectations, including care of the dying and mourning and memorialization practices. There are

often attitude divisions within the same family system as tradition contends with response to external influences. Care providers will have their sensitivities tested.

- Life course coherence and continuity were once bolstered by long-time residence in a relatively stable place and by other supports for familiarity, belonging and predictability. Fewer of today's elders are dying from the worlds they knew and which knew them well¹⁸. The sense of meaning, coherence, and completion is becoming more difficult to achieve both as life nears its end and as the bereaved try to come to terms with their loss. It remains to be seen whether or not mental health specialists will expand their range to include such ongoing changes in the life course.

In a sense, there are no 'little griefs', and there may be no 'getting over' the greatest losses we experience in our lives. But most elderly adults have learned to live with disappointments, limitations and suffering. When bereavement comes, as a rule they do not need drugs, hospitalization and the whole rigmarole of the health care system. To be offered companionship and to see in that companion's eyes that one is still valued and needed is often all that is required for the survivor to get on with life.

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Suicidal Behaviour

Brian Draper

School of Psychiatry, University of NSW, Sydney, Australia

Despite an increase in research knowledge about suicidal behaviour in old age, the translation into community understanding and clinical practice still lags. One common misunderstanding is about the rationality of suicide associated with age-related suffering¹. While much old age suicidal behaviour occurs in this context, that does not mean it is rational. To better understand suicidal behaviour in late life, it is also important to look at the vulnerability factors from early and mid life. This chapter will examine suicidal behaviour from a life cycle perspective and consider a framework for prevention.

Although suicide rates worldwide are highest on average in persons aged over 75 years, being approximately three times higher than in persons under 25 years of age, the pattern is variable, with about one third of countries that report mortality data to the World Health Organization having higher rates in young adults than in older persons². Furthermore, over the past 30 years many countries have reported a decline in suicide rates in older people alongside an increase in suicide rates in youth and young adults². The reasons for this reduction are unclear but may include improved physical health in middle age and old age, better community services for the disabled to enhance independence, greater financial security in later life, marriage and the prescription of antidepressants^{1,3}.

In contrast, non-fatal suicidal behaviour declines with age in most countries, with the ratio of attempted to completed suicide in old age being estimated to be between 2:1 and 4:1 as compared with 100:1 to 200:1 in young persons². Attempted suicide in old age closely resembles suicide, with high levels of lethal intent, less impulsivity and clinical features that are similar to those found in completed suicide^{4,5}. Thus suicidal behaviour in the elderly is more likely to have a fatal outcome. However, there is a recently observed trend for the 'young old' aged 65–75 years to have higher rates of less lethal and more impulsive attempts, a phenomenon described as 'elderly adolescentism'². Rates of indirect self-destructive behaviour in residential care are high, with one study reporting a weekly prevalence of 61% although the extent to which the behaviour could be regarded as intentional or part of a spectrum of suicidal behaviour is unclear⁶. Suicidal ideation in old age has prevalence rates reported between 2.3% and 15.9% in the previous month and lower rates have been reported in individuals aged over 75 years compared with those 'under 55 years of age'².

RISK FACTORS FOR SUICIDAL BEHAVIOUR

Risk factors in late life are similar to younger age groups and include demographic characteristics, psychopathology, personality

traits, traumatic life events, physical ill health and disability, previous suicidal behaviour, genetic factors and access to lethal means². However, over the age range, factors have different levels of influence, with one psychological autopsy study finding major depression was more likely in suicides aged over 55 years while substance abuse was more likely in suicides aged 21–54 years⁷. Risk factors that are more overtly important in suicidal behaviour in younger people may still convey vulnerability in late life. In a life cycle approach to understanding the development of risk for late life suicidal behaviour, it is important to recognize that some pathways begin early in life. It is often the interaction of distal risk factors with proximal factors that provides the lethal mix.

Demographic Factors

Across the life span, males have approximately a four times higher risk of suicide than females and with advancing age the male to female ratio increases¹. Females are at higher risk of non-fatal suicidal behaviour, with rates about 1.5 times higher than males, but the rates tend to converge with advancing age⁶. There is some evidence that suicidal behaviour is more common in those who are divorced or widowed^{2,4}.

There is heterogeneity of suicide rates between countries and ethnicity appears to be a factor, with different suicide rates of ethnic groups within multicultural societies². For example, in Australia suicide rates of older migrants are closely related to suicide rates in their country of origin⁸. Other cross-national research has found elderly suicide rates to be associated with population growth, the elderly dependency ratio and the proportion of elderly in the population⁹. There is also regional variation within countries, with higher rates reported in rural areas of some countries such as Australia¹⁰. In the United States, cross-state variation is related to macro-social indicators of social integration and aspects of state-level policies¹¹. Low socioeconomic status has been found as a risk factor worldwide¹.

Early Life Factors

Genetic factors contribute to suicide risk by mediating transmission of impulsive aggression or neuroticism and neurocognitive deficits¹². While there has been little research in late life, one study has suggested that an interaction between genetic factors and the physiological effects of ageing might have an important role in violent suicides¹³. Genetic factors also work indirectly by increasing the risk of mood disorders and substance abuse¹².

Childhood adversity, which includes abuse and parental neglect through death, separation and inadequate care, is a well-established risk factor for suicidal behaviour, depression and substance abuse in younger adults^{12,14}. There is increasing evidence that childhood adversity influences late life suicidal behaviour and mental disorders too. Higher rates of childhood adversity were found in older persons who attempted suicide compared with controls¹⁵; childhood physical and sexual abuse was significantly more frequently reported by older persons with a history of suicidal behaviour, mood disorders and alcohol abuse in a large general practice survey¹⁶; and the risk of attempted suicide and suicide is higher in older Holocaust survivors¹.

Childhood adversity and genetic factors also affect personality development. A number of personality traits have been linked to suicidal behaviour in late life, including inflexibility, anxious, obsessional and 'low openness to experience' (individuals that are comfortable with the familiar and have a constricted range of interests) traits^{1,17}. In essence these traits describe an older individual who has difficulty coping with the challenges related to ageing, including failing health, loss of confidants and demanding life events.

Adulthood Factors

It would seem self-evident that the lifestyle followed by an individual as an adult, including their interpersonal relationships and employment, will have some bearing on their health and well-being in late life. For example, involuntary job loss near retirement age has been found to lead to enduring depressive symptoms in individuals with low finances¹⁸.

The links to late life suicidal behaviour are indirect and largely mediated through the impact mid-life lifestyle factors have upon the development of late life risk factors such as physical health and depression. There is increasing evidence that mid-life vascular risk factors such as hypertension, smoking, diabetes and metabolic syndrome, which are associated with lifestyle factors such as diet and exercise, may lead to late life depression, cognitive impairment, and cerebrovascular and cardiovascular disorders^{19,20}. Further, a case-control of suicides over age 50 years found that cerebrovascular risk factor scores were significantly higher in suicide cases²¹.

Late Life Factors

Psychopathology

Up to 97% of older persons with serious suicidal behaviour have a mental disorder^{1,4,5,22}. A review of controlled psychological autopsy studies found that the presence of any Axis I disorder was associated with an elevated risk of suicide in older persons with significant odds ratios ranging from 27.4 to 113.1²². Depression is the major independent risk factor across cultures and although the type of depression varies, major depression is the strongest predictor of suicidal behaviour in late life, accounting for about 50% of cases^{1,4,5,7,22}. Although many cases are recurrent episodes, first-episode major depression is prominent too^{1,4,22}. Other types of depression including dysthymia, minor depression and subsyndromal depression are also important and may have a particular role in older persons with co-morbid chronic physical ill health and disability^{1,4}. In the context of recovery from a depressive episode, unrelenting hopelessness can increase suicide risk²³.

Other mental disorders are less commonly found in late life suicidal behaviour, though co-morbid disorders are common^{1,4,5,22}. Late-life psychoses, including schizophrenia and bipolar disorder, account

for less than 10% of attempted and completed suicides^{1,4,5,22}. The role of anxiety disorders is unclear, with some studies finding an increased risk though it seems usually in the context of mixed anxiety/depressive states^{1,22}. Alcohol abuse, though less frequently implicated in old age compared to younger suicides, remains a significant factor especially with co-morbid depression^{1,4,5}. Personality disorders are less common in suicidal behaviour in late life compared with younger cohorts, being present in 2.5–7% of older suicide attempters^{1,5}.

Until recently, dementia has not been regarded as a risk factor for suicide. A nationwide longitudinal study from Denmark using register data reported that hospital-diagnosed dementia was associated with an elevated risk of suicide particularly in those aged 50–69 years, where the relative risk was 8.5 in men and 10.8 in women. The risk was higher in the first three months after diagnosis, particularly in men. Controlling for mood disorders reduced but did not eliminate the increased risk. The risk was higher in Alzheimer's disease than in vascular dementia²⁴. In some, frontal lobe impairments may lead to impulsive, poorly planned attempts. It is unclear whether insight into the dementing process is a factor that increases the risk of suicidality^{1,4}.

Previous suicidal behaviour

Compared with younger age groups, a history of suicidal behaviour is less frequent in older persons with suicidal behaviour but follow-up studies of older suicide attempters have found high rates of repetition^{1,25}. In the WHO/EURO multicentre study of suicidal behaviour, 13% of older people admitted to hospital after a suicide attempt died by suicide within 12 months and 11% made further attempts²⁵. Survivors of suicidal behaviour in old age remain a high risk group and require close monitoring. Observational studies suggest that older suicide attempters are likely to receive specialist mental health management, particularly if they have a diagnosed mood disorder, but treatment studies are lacking⁵.

Physical health and disability

While physical ill health is a contributory factor in most cases of late life suicidal behaviour, its precise role is unclear¹. Some studies have found an independent effect of physical illness that is increased when there are multiple illnesses, while others have found little evidence of a physical illness effect^{1,26}. There is a lack of consistency regarding specific illnesses that might increase suicide risk, but chronic pain, breathlessness and functional impairment are frequently reported features^{1,26}. These may result in dependence on carers, loss of dignity and the fear of institutionalization that may contribute to demoralization, depression and suicidality. A threshold phenomenon may exist whereby the physically ill may become suicidal with milder degrees of depression⁴, or, put another way, physical illnesses may amplify suicide risk in those with premorbid vulnerability²⁷. Depression, pain and insomnia have the capacity to temporarily affect judgement by subtly distorting the patient's perceptions in a manner that may convince family, friends and doctor of the 'rationality' of suicide, especially in those with terminal illness, which is present in about 5–10% of older persons with suicidal behaviour. Yet the wish to die usually resolves once these symptoms are treated. Psychological reactions occur, with some people feeling overwhelmed by the knowledge of a serious illness and others convincing themselves that they have cancer, often ignoring reassurances

by their doctor²⁸. Some physical illnesses, including cancers, thyroid disorders and cerebrovascular disease, can cause severe depression and these might not be detected until after a suicide attempt⁴.

Psychosocial factors

In general, disruption of social ties increases suicide risk in old age independent of the presence of mental disorders²². As in other age groups, family discord is perhaps the most powerful psychosocial factor^{1,22,27}. In many cases the problems are chronic and there is some evidence that males are more vulnerable¹. It is likely that chronic family discord interacts with physical health issues in situations that include those who are disabled and feel a burden on others, and in caregivers who become severely stressed in caring for a disabled partner, where there is an increased risk of murder/suicide¹. A range of other life events, particularly those involving loss, including recent bereavement, and financial problems have been implicated in late life suicidal behaviour^{1,4,5,27}.

Living alone has consistently been identified as a factor and this is often regarded as a proxy for loneliness, social isolation and inadequate social support^{1,4,5,22}. Accommodation issues, including fear of nursing home placement and dissatisfaction with living arrangements, are also reported^{1,4}. It is unclear whether the suicide rate in nursing homes is different to the general population but the main risk factors of depression and physical disability are the same¹. Indirect self-destructive behaviour, including refusal to eat, drink or take medications, is common in nursing home residents and while most cases appear to be associated with severe dementia rather than depression with suicidal intent⁶, there are likely to be some suicidal individuals.

Biological factors

As with the previously mentioned genetic factors, two other biological factors associated with suicide have not been well studied in late life. Serotonergic neurotransmitter abnormalities have been found to be associated with suicidal behaviour across the age range with low levels of 5-hydroxyindoleacetic acid in cerebrospinal fluid²⁹. Non-suppression of the dexamethasone suppression test, which is a measure of the hypothalamic–pituitary axis activity in mood disorders, is also predictive of suicide²⁹.

Other late life biological factors include cerebrovascular disease and Alzheimer's disease. The risks of suicide and suicidal ideation have been reported as higher in Alzheimer's disease than in vascular dementia but studies of Alzheimer's disease neuropathological changes in late life suicide are inconsistent¹. Interestingly, older subjects with major depression who were apolipoprotein E ϵ 4 (*APOE4*) carriers had an increased suicide attempt history than depressed subjects who were not *APOE4* carriers³⁰.

Risk factors are unlikely to act independently in most cases but at present our understanding of how identified risk factors interact to determine risk in an individual is limited^{1,22}. The motivations that appear to drive the final suicidal act are quite varied and reflect this multiplicity of pathways²⁸. In addition, whether an individual has access to a lethal means that is acceptable to them plays a critical role, and this latter factor varies between cultures¹.

STRATEGIES FOR SUICIDE PREVENTION IN LATE LIFE

While an understanding of factors that are associated with suicidal behaviour provides a platform upon which to build prevention strategies, there is very little known about protective factors. There is weak

evidence that spirituality and good quality of life may be protective but more research is required¹.

A public health approach to suicide prevention considers three levels of interventions. Universal strategies implement broadly directed initiatives to prevent suicidal behaviour and related morbidity through reducing risk and enhancing protective factors at a population level. Selective strategies target 'high risk' (at a population level) asymptomatic or presymptomatic older persons with distal risk factors for suicide. Indicated strategies focus on individuals with detectable symptoms and/or other proximal risk factors for suicide¹.

Universal Prevention

These strategies should concentrate upon improvement of quality of life and prevention of depression in late life in the general population. A whole of life approach to ageing that addresses key issues such as reduction of childhood adversity, provision of basic health care, reduction of poverty, and promotion of a healthy lifestyle, including diet, exercise, and reduction of substance abuse and smoking is required. The relationship between vascular disease and late-life depression is an obvious focus of health education programmes over the life span. As such, suicide prevention would not be the main focus of the strategy but rather it would be one of the potential outcomes.

Benefits accrue for persons of all ages so programmes that focus on late life issues such as ageism, normal ageing, healthy lifestyle in late life, and stigma of late-life mental disorder are important. It is important to realize that there is still a perception that it is 'normal' for older people to be depressed and that 'nothing can be done' about it, even though the available evidence contradicts this. These negative attitudes can set the tone of society.

Psychosocial strategies that might improve well-being and reduce depression in late life could focus upon encouragement of social interaction through attendance at clubs, connection with family, participation in casual work, becoming a volunteer, and engagement in pleasurable activities such as physical exercise, music, dance, education, travel and sport. For many older people lack of transport thwarts efforts to accomplish these goals so an improved senior's transport strategy would be beneficial. An important study of a community-based programme that targeted the elderly in the rural town of Yuri in Japan involved population strategies including psychoeducation, group activities and self-assessment of depression over an eight-year period. It proved to be effective in reducing the risk of suicide in females but not males³¹.

Selective Prevention

The aim of selective prevention is to prevent suicidal behaviour and related morbidity by addressing the specific characteristics that confer high risk. Older persons with a history of depression and/or suicidal behaviour, chronic pain sufferers, and disabled older persons who live alone or with few social supports are some examples.

Education is an important strategy. Asymptomatic older persons with a history of major affective disorder should be educated about warning signs of depression to enable early intervention. Programmes that aim to minimize the effects of disability upon older people by providing services that enhance independent function are of critical importance. This has been the general direction taken in many countries where aged care service delivery has increasingly focused upon maintaining older disabled persons at home. A programme established in the Veneto region of Italy used Tele-Help,

a portable device that lets users send alarm signals activating a pre-established network of help and assistance, and Tele-Check, where trained staff members contact each client at least twice a week to offer emotional support and monitor the client's condition through a short, informal interview. At ten-year evaluation, a significantly lower than expected number of suicidal deaths was observed in the users compared to the general population³². Another approach is to focus upon the prevention of depression in the elderly with chronic physical co-morbidity. A six-session problem-solving therapy intervention in older patients with age-related macular degeneration led to a 50% reduction of new episodes of major and minor depression at two months after completion of the treatment although the effect had disappeared by six months³³.

The promotion of community groups and religious organizations to contact and support isolated older people should be encouraged. Potential target groups include rural elders, older migrants and carers. Older men are particularly vulnerable to depression and suicide in the year after divorce or death of their spouse and so could be specifically targeted for counselling in primary health care.

Indicated Prevention

The aim of indicated prevention is to identify and treat older persons with detectable symptoms and/or other proximal risk factors for suicide. Recognition of depression and suicide risk by gatekeepers (e.g. general practitioners, clergy, nurses, home care workers, police, ambulance officers, social workers) is an important component. GPs and other physicians have difficulties in the identification, assessment and management of depression and suicide risk in old age. This is accentuated with co-morbid physical illness where there are low levels of recognition, diagnosis and treatment of depression³⁴.

Studies from around the developed world consistently find that the majority of older suicide victims have been in contact with health professionals, particularly GPs, in the months before death¹. While communication of suicidal ideation occurs in up to 45% of mental health contacts, it is less likely to occur in GP contacts and with older persons¹. There is little known about contacts with nurses and other allied health professionals in the context of hospital and community treatment of physical ailments. Hence it is unclear how often health professional contacts in the weeks before suicide represent an opportunity for suicide prevention.

Despite this uncertainty, education of 'at risk' older people and their carers, gatekeepers and health professionals involved in their care is the key. The education needs to be linked to an intervention to improve its effectiveness, with strategies that include the removal of barriers to care, depression screening, and the use of treatment guidelines. A community-based 10-year suicide prevention programme for older people in the Japanese rural town of Joboji with strategies including screening for depression, follow-up with mental health care or psychiatric treatment, and health education on depression found that the relative risks estimated by the age-adjusted odds ratios for both males and females were reduced to almost 25% more than a regional historical trend, with a better response to education for females than for males³⁵.

One important component of health professional education is the assessment of suicide risk and management of older people at high risk. Even when depression is suspected, the assessment of suicide risk is often missed in older patients. A GP survey using case vignettes of older people with depression found high levels of depression recognition but only 2.4% spontaneously indicated that they

would ask about suicidal ideation, which increased to 77% with prompting. The rest either indicated that they thought the patient would communicate suicidal thoughts themselves or that they feared that they might induce suicide by asking directly³⁶. Assessment of suicide risk requires the health professional to be attentive, calm and non-threatening; to give the patient space and time to vent; to work in collaboration with the patient; and to use the word suicide without flinching. The use of open-ended questions followed up by specific questions about the nature, timing and context of suicidal thoughts is recommended. The only effective means of identifying those at risk is direct questioning³⁷. Deterrents to suicidal behaviour, including religion and fear of upsetting family or friends, need to be determined. Collateral information from family and friends should be obtained as often the family member is aware of suicide risk but will not inform the health professional unless specifically asked³⁸. The American Psychiatric Association's 'Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors' states that family and friends can be contacted without the patient's consent if suicidality is suspected³⁹.

All depressed older persons should be assessed for suicide risk but how often this should be repeated during the course of the illness is unclear. If enquiries about suicide risk are repeated too often therapeutic rapport might be undermined. Many older depressed patients were assessed by GPs to be improving in the weeks before suicide and so suicide risk assessment was not considered³⁸. Improvement in depression can be deceptive in terms of suicide risk¹.

In the absence of clinical depression there are some other situations in the context of the older person's life circumstances that might warrant a suicide risk assessment. Persons with late-life psychosis with distressing persecutory symptoms are one example. As noted earlier, suicide risk is increased in older people with obsessional, anxious and low 'openness to experience' personality traits. Such individuals may have a restricted capacity to adapt to change and the various challenges associated with ageing. Recent life stressors, including the diagnosis of cancer or other serious disorders such as Alzheimer's disease or the death of a spouse or a close friend, may be overwhelming. Chronic stressors such as pain, loneliness, complicated grief or severe disability, especially in the absence of adequate social support, are all circumstances that might lead to a suicide attempt in the vulnerable person, especially if there has been a history of previous suicide attempts and in the presence of substance abuse. There are some types of behaviour that might alert the clinician to suicidal preoccupation. These include the giving away of possessions, changing of will, stockpiling of pills and passive indirect self-destructive behaviour such as refusal to eat and medication non-compliance. However, pervasive hopelessness was the most frequently reported observation in one study of the last health professional contact with suicide victims³⁸.

High-risk management guidelines for older suicidal patients in primary care settings were developed for the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT)³⁷. The intensity of the suicidal ideation, clarity of plans and access to means should determine the location of care. Hospitalization is often indicated, particularly when there is severe depression with features of psychosis, agitation, hopelessness, refusal to eat, poor insight, ruminating insomnia or where there is co-morbid substance abuse. Impulsivity, especially in association with impairments of executive function, is another feature that might require short-term hospitalization. Other factors to consider include the lack of social supports, and presence of concurrent medical issues and associated functional impairment that impact upon safe outpatient treatment, a history of

poor compliance with treatment, or where the older person appears to have 'given up'¹.

Outcomes of hospitalization related to suicidal behaviour have not been specifically studied. The resolution of suicidal ideation before discharge is paramount and the clinician needs to be aware that the intensity of suicidal thoughts can fluctuate from day to day in the context of major depression⁴⁰. Integration of hospital and post-discharge community care improves the outcomes of older depressed patients through strategies that include having the community nurse get to know the patient before discharge, a pre-discharge home visit to check on functional needs and remove any guns or stockpiled medications, continuity of medical care post-discharge, and members of the multidisciplinary inpatient team having a transitional role to help the older patient and the family settle in at home¹.

Optimal management of the older suicidal patient requires the development of a therapeutic alliance that is often best achieved by ensuring that alleviation of the patient's suffering, whether it be physical, psychological or spiritual, is central to the care being provided. Important components of community treatment include an individualized case management approach with ongoing care (at least weekly until suicidal risk has settled), medication monitoring, and psychoeducation of the patient and carer. Explicit written instructions to the older patient and family about what to do if suicidal thoughts recur and the provision of an emergency contact are required. Avoidance of alcohol and illicit drugs should be stressed³⁷.

It is beyond the scope of this chapter to discuss treatment of depression in detail but it is essential that effective treatment be provided that not only obtains a response but also achieves remission. The available evidence suggests that electroconvulsive therapy is the most effective treatment for severe depression in late life, particularly when there are psychotic features or with high acute suicide risk. Antidepressant medication remains the cornerstone of effective treatment for major depression even with co-morbid chronic physical illness where effectiveness is reduced and should be maintained for at least two years to prevent relapse. Psychosocial treatments, including the various types of psychotherapy, activity programmes, exercise and supportive therapies, are crucial³⁴.

Improving the effectiveness of the treatment of depression in primary care can be achieved through collaborations between primary care health professionals and mental health professionals. The collaboration should involve a significant educational and supervisory approach by the mental health professional. An example is provided by the multi-centre PROSPECT study, where a depression health specialist was assigned to assist the primary care physician with guideline management based on an algorithm that included the selective serotonin re-uptake inhibitor (SSRI) antidepressant citalopram and/or interpersonal psychotherapy. Rates of suicidal ideation declined faster in the intervention patients compared with usual care after four months of treatment⁴¹.

There is debate about whether antidepressants reduce the risk of suicide, with naturalistic studies suggesting that the higher rates of antidepressant prescription since the introduction of the SSRIs have been associated with lower suicide rates¹. Concerns have been raised that SSRIs might increase the risk of suicide in the elderly, particularly violent suicide, in the first month of treatment but the absolute risk is low and probably outweighed by the benefits of treatment⁴². There is stronger evidence that lithium prophylaxis has specific anti-suicide effects apart from its prophylactic efficacy in affective disorders but there are no studies that have specifically examined whether this occurs in old age¹.

CONCLUSION

A life cycle approach is required to obtain a better understanding of suicidal behaviour in late life because the causes are complex and involve factors that arise from the entire lifespan. No single prevention strategy is likely to be successful. A multifaceted, multilayered approach to suicide prevention in old age is required.

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The Assessment of Depressive Syndromes

Adriana P. Hermida and William M. McDonald

Emory University School of Medicine, Atlanta, USA

Among community dwelling older adults, the prevalence of major depression ranges between 1% and 4% with a higher proportion of women meeting criteria for depression with no significant racial or ethnic differences¹. Although the prevalence of individuals with major depressive disorder may not be as high as for younger subjects², high levels of *depressive symptoms* are relatively common in the elderly living in the community, and the number of elders with depression syndromes increases in patients with chronic medical illnesses^{1,3,4}. The number of medically ill elders diagnosed with depressive syndromes in long-term care facilities is estimated at 10–15% with up to 35% experiencing significant depressive symptoms^{5–7}.

The diagnosis of depression in the elderly requires a multidimensional approach and should be undertaken with a clear understanding of the normal ageing process and the psychosocial factors that are unique to the elderly. These aspects of ageing are discussed in Chapter 18. Depression and depressive disorders are often misunderstood by physicians caring for the elderly as well as by the lay public, including family members and, often, the elderly patient. 'Ageism' is the term used to describe the discrimination against people because of their age and nowhere is this more apparent than in the diagnosis and treatment of depressed elders, particularly those with co-morbid medical illnesses. The oft-repeated phrases epitomize this way of thinking 'Why wouldn't they be depressed ... they are old?' and 'Of course they are depressed – they live in a nursing home and have cancer'. Underlying this viewpoint is the notion that treating the depressed elderly is futile and a waste of valuable health care resources. Among other factors ageism has been shown to be an important component in the decision as to whether to start drug therapy in elderly patients⁸.

A more rational view is to consider the costs of the treatment of depression in comparison with potential treatment benefits, including the cost savings to society of an individual remaining functionally independent in a community setting⁹. In this light the treatment of depression in the elderly has the potential for providing both benefits to the individual and health care savings. Depressive symptoms can lead to accelerated cognitive decline, physical impairment and increased health care costs¹⁰. Increased service utilization and social morbidity are common in patients with depressive symptoms even when these symptoms are not severe enough to fulfil the criteria for a major psychiatric disorder¹¹. Concomitant depression can limit compliance with medical treatments and worsen the cognitive decline

associated with dementia. Further, depression can adversely affect the clinical course of other medical illnesses and increase morbidity and mortality^{12,13}, and the elderly have the highest suicide rate of any age group¹⁴. The social and economic consequences of this disorder in the elderly are severe.

Yet the diagnosis and treatment of elderly depressive disorders can be difficult. The elderly are often subject to more adverse side effects from pharmacotherapy, and the diagnosis of depression is complicated by the overlapping symptoms of depression, concomitant medical illnesses and normal ageing¹⁵. In fact, the elderly often present with more subtle forms of depression (e.g. minor or subsyndromal depressive disorders) that can be difficult to diagnose, yet cause significant disability and make the decision to treat more difficult. Some have argued that elderly depressives should have specific age-appropriate criteria that include these subsyndromal symptoms since the elderly are not easily classified by traditional psychiatric nomenclature¹⁶.

This chapter will review the multiple depressive syndromes in depression and provide guidance on making the correct diagnosis of depression in elderly patients, particularly those with concomitant medical illness. The diagnosis and clinical significance of subsyndromal depressive syndromes will also be outlined in detail. Finally, the appropriate method for taking a history and the basic laboratory tests needed to eliminate common medical conditions that mimic depression as well as the medications that may cause depressive symptoms will also be reviewed.

THE SYNDROME OF LATE-LIFE DEPRESSION

To accurately assess the depressed older adult, the clinician must consider the range of depressive disorders from the more severe major depression to the subsyndromal depressive disorders. Depressive disorders include the mood disorders outlined in the Diagnostic and Statistical Manual of Mental Disorders Version IV (DSM-IV): major depressive disorder, dysthymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, bipolar disorder, mood disorder not otherwise specified (which include the minor and subsyndromal depression) and adjustment disorder.

Major depression is distinguished from the other mood disorders by the severity and persistence of symptoms, which by definition have lasted for at least two weeks and are associated with significant impairment in an individual's social, occupational or other

important areas of functioning. Symptoms of major depression comprise depressed mood and/or anhedonia and associated neurovegetative and cognitive symptoms, including significant weight loss/weight gain or decreased/increased appetite, insomnia or hypersomnia, psychomotor agitation or retardation, diminished ability to think or concentrate, feelings of worthlessness or excessive inappropriate guilt, and recurrent thoughts of death or suicide.

Specifiers describing the quality of the current episode include melancholic, atypical and catatonic features. *Melancholic* features consist of lack of mood reactivity to pleasurable stimuli, diurnal variation in mood (i.e. depression worse in the morning), early morning awakening, psychomotor retardation or agitation, significant weight loss or anorexia and excessive or inappropriate guilt. A melancholic depression may be associated with specific neuroanatomic changes¹⁷, and may affect response to antidepressants^{18–21}, electroconvulsive therapy (ECT)^{22,23} and psychotherapy^{24,25}. *Atypical* features include mood reactivity, increased appetite or weight gain, hypersomnia, leaden paralysis and extreme sensitivity to interpersonal rejection. Atypical depression in the elderly has been shown to respond preferentially to monoamine oxidase inhibitors (MAOIs) although the MAOIs may be more difficult to use in this population^{15,26}. The specifier *catatonic features* is appropriate when the clinical picture is characterized by marked psychomotor disturbances that involve motoric immobility, excessive motor activity, extreme negativism, mutism, peculiarities of voluntary movements, echolalia and echopraxia. Motoric immobility can be manifested by cataplexy or stupor. Catatonic states have been found to occur in 5–9% of psychiatric inpatients. Among inpatients, 25–50% of catatonic states occur in association with mood disorders, 10–15% in association with schizophrenia, and the remainder in association with other mental disorders and a wide variety of medical conditions²⁷.

An additional specifier of major depression in the DSM-IV criteria is a *seasonal pattern*, which is associated with the onset and remission of major depressive episodes at characteristic times of the year. This pattern of onset and remission of episodes must have occurred during the past two years.

In the DSM-IV, depression is subtyped according to whether the mood disturbance is associated with psychotic symptoms. Psychotic symptoms in major depression are more likely to be mood-congruent (i.e. delusions or hallucinations of a depressive nature). Psychotic depression may be more common in late life. Many elderly patients with psychosis develop delusions of poverty, somatic delusions or persecutory ideations^{28,29}. Hallucinations of derogatory voices are rare. Known precipitants of psychotic symptoms in the elderly include personal trauma, physical illness and certain medications such as corticosteroids and anti-parkinsonian medications.

Subsyndromal depressions (SSDs) include minor depression, dysthymia and syndromal depression that does not meet the criteria for major depression. SSDs are characterized by depressive symptoms that do not meet full criteria for a major depression but are associated with depressed mood and significant disability³⁰. SSD is common and associated with significant impairment in a number of areas of social and occupational functioning and an increased risk of developing syndromal major depression^{31,32}. Minor depression is a mood disorder that does not meet full criteria for major depressive disorder but which is associated with at least two depressive symptoms that are sustained for a period of two weeks (although not necessarily every day) without the degree of impairment in major depression. Technically a patient with minor depression would be coded as 'Depression, not otherwise specified' or NOS since minor depression is a research diagnosis. Research, much of it in primary care clinics, supports the

validity of minor depression as a distinct clinical entity³¹. Dysthymic disorder (dysthymia) is defined as a chronic low-grade depression, which lasts for at least two years. Personality styles and the individual's ability to cope with changing life situations may predispose the individual to develop a dysthymic disorder (see Chapter 104) and older adults with changing roles and life conditions may be particularly prone to dysthymia. Additionally, dysthymic disorder may develop secondary to a medical disorder, anxiety disorder or somatization disorder. Dysthymia preceding a major depressive episode has been shown to predict a poor outcome to treatment³³. Phenomenologically, SSD is the 'grey' zone between syndromal major depression and depressive symptoms. In geriatric psychiatry, depression is often defined as a spectrum rather than a dichotomy. There is increasing evidence that elderly subjects meeting the criteria for SSD have levels of cognitive and functional impairment intermediate between elders who are not depressed and those with major depression³⁴. Nevertheless, patients with SSD demonstrate significant disability, are more likely to have persistent depressive symptoms which worsen over a year, be at a higher risk of developing major depression, and benefit from somatic treatments and psychotherapy^{25,35}. Clearly, future research is needed to clarify the prevalence and treatment response of SSD in order to target appropriate treatments.

Substance-induced mood disorder is a prominent and persistent disturbance in mood that is judged to be due to the direct physiological effects of a substance such as excessive alcohol use. Alcohol abuse in older adults is common and may go for years misdiagnosed³⁶. The elderly are particularly prone to substance-induced mood disorders because of chronic and often excessive use of over-the-counter medications mixed with prescription medications^{37,38}. Increasingly the elderly are using herbal medications and often the effects of herbal medications are unknown, particularly in combination with other drugs³⁹.

The diagnosis of adjustment disorder with depressed mood is appropriate for an elderly patient adjusting to severe changes in lifestyle and the loss of loved ones. In the DSM-IV, the patient is not classified with an adjustment disorder unless his/her reaction is considered maladaptive and the level of impairment is significantly severe, and greater than what would be normally expected. Whether the elderly subject's reaction to these stressors is classified as a disorder is a clinical judgement. Several common life events that may prove to be stressors in the elderly include retirement, financial problems, living in high crime areas, physical illness, the death of a spouse and moving to an institutional setting. Yet older adults also may also be protected from stress as those who survive into old age are more likely to have relatively more socioeconomic security and the benefit of the wisdom that can come with older age⁴⁰. Regardless, the clinician should observe the patient diagnosed with adjustment disorder longitudinally for the development of symptoms of a major depression if the individual's reaction to stress is persistent or severe.

The symptom profile of older patients with depression has also been described as qualitatively distinct from that of younger adults. Depressed elderly patients are more likely to show cognitive changes, somatic symptoms, fatigue and loss of interest as opposed to depressed mood and guilt^{41,42}. Other researchers emphasize that these differing presentations are the result of accompanying cognitive changes with ageing and co-morbid medical illness, which are more likely to occur in older depressed patients, and that depressed elderly patients without concomitant medical illnesses have presentations similar to younger subjects⁴³. Support for this latter view has been

provided by Blazer and his colleagues⁴⁴, who compared depressive symptoms in a group of middle-aged (35–50-year-old) and older (60-year-old) inpatients with melancholic depression. The symptom profiles of these patients were markedly similar to the elderly, differing only in their more frequent reporting of weight loss and less frequent suicidal thoughts. Finally, Blazer discusses some of the misconceptions of depression in the elderly, pointing out that, as discussed above, symptomatically there is little difference when compared to adult early-onset depression.

CO-MORBID MEDICAL DISEASE

A variety of medical illnesses are associated with depressive symptoms. Mood disorder due to a general medical condition is a persistent disturbance in mood due to the direct physiological effect of a general medical condition. In the geriatric population the differentiation between mood disorder due to a general medical condition and depression as a psychological reaction to the disability due to the medical illness is challenging.

There are basically two different approaches to defining depression in medically ill patients. The *inclusive approach* counts a symptom if it is present without considering whether it is due to the underlying medical condition. Using the inclusive approach, a patient with Parkinson's disease and insomnia would be counted as having insomnia as a depressive symptom if they stated that they could not fall asleep for two hours regardless of whether they said the insomnia was due to dyskinesias or guilty ruminations. The *aetiological approach* counts a symptom towards a diagnosis of depression only if the rater determines that it is not due to the underlying medical disorder. In the example given above the clinician would try to determine if the insomnia was due to depression or dyskinesias. Clearly this distinction can be difficult, particularly because patients, their families and clinicians tend to discount many depressive symptoms because they are felt to be a symptom of the medical illness.

However, the research in this area would support the use of the inclusive approach as more reliable in diagnosing depression in patients with co-morbid medical illnesses⁴⁵ and medical conditions such as post-stroke depression⁴⁶. The inclusive approach is more objective, whereas the aetiological approach is subject to the judgement of the clinician and is inherently less reliable. The danger in using the inclusive approach is a loss of specificity and an over-diagnosis of depression. However, the real danger in evaluating medically ill patients with depression is a loss of sensitivity and missing patients who could potentially benefit from somatic treatments. As described below, co-morbid medical illnesses can have a significant detrimental effect on long-term outcomes and mortality. The available treatments for depression are increasingly better tolerated by the elderly and the risk/benefit ratio favours a modest overtreatment of depressive syndromes in the elderly.

Certain endocrine and vitamin deficiencies, medications and medical conditions are associated with depressive symptoms. Discontinuing the offending medication, and/or correcting the endocrine or vitamin deficiency should be done prior to starting an antidepressant⁴⁷. Other medical conditions, such as Parkinson's disease, multiple sclerosis, pancreatic cancer and stroke, are associated with high rates of co-morbid depression and the depressive episode should be treated while managing the co-morbid medical condition. Again, the clinician should not try to determine if the depression is due to the disability of the medical condition but should treat the depression if the patient meets criteria for the disorder.

Parkinson's disease is illustrative of a neurological condition associated with high rates of depression, overlapping symptoms of depression, and the importance of recognizing and treating co-morbid depression in patients with medical disorders. Co-morbid depression occurs in about 20–30% of patients with Parkinson's disease^{48,49}. There is considerable overlap of the symptoms of Parkinson's disease and depression, including flat affect, bradykinesia, fatigue, agitation (in the form of psychomotor agitation or dyskinesias), insomnia and cognitive problems. Yet depression in patients with Parkinson's disease can be accurately diagnosed using the inclusive approach and many depression psychiatric rating scales⁵⁰. Co-morbid depression is not simply a reaction to the medical illness and disability⁵¹; there is evidence of the underlying neuroanatomic degeneration secondary to Parkinson's disease as a cause of depressive syndromes in Parkinson's disease⁵², and the treatment of depression can lead to an improvement in the overall quality of life⁵³. The identification and treatment of Parkinson's disease with co-morbid depression is therefore important.

Cerebrovascular disease has been shown to be associated with the development of mood symptoms. Depression is a risk factor for stroke⁵⁴ and approximately half of post-stroke depressions will meet criteria for major depression, and the other half will have minor depression⁵⁵. Robinson pioneered the early work in understanding the relationship between lesion location (i.e. subcortical in the left anterior pole) as crucial to the development of depression^{56–58} and independent of the amount of physical disability caused by the stroke⁵⁹. Post-stroke depression is associated with a longer recovery time⁶⁰ and increased mortality⁶¹, and the treatment of post-stroke depression is associated with improved recovery in activities of daily living, cognition and decreased mortality⁶².

Controversy still exists whether a left-sided stroke presents with more depressive and catastrophic responses than right-sided insults, which have been described as lesions with emotional neglect, indifference and even euphoric responses^{58,63}. Hama *et al.*⁶⁴ found that the severity of affective depression was associated with left frontal lobe damage whereas apathetic depression was mostly related to basal ganglia damage. However, Robinson's relationship of anatomic lesions to psychiatric symptoms laid the groundwork for understanding the interrelationship of depression and medical disease. The body of evidence in stroke with co-morbid depression also supports the importance of the detection and treatment of depressive syndromes in the long-term course of patients with cerebrovascular disease.

The relationship between dementia and depression is complicated. Over 50% of patients with dementing illnesses such as Alzheimer's disease may also have depressive symptoms, with 20% meeting criteria for a major depressive episode⁶⁵. Depressive symptoms may also precede cognitive decline in community elders⁶⁶, and a significant number of individuals with depression and reversible cognitive deficits eventually progress to syndromic dementia^{67,68}. The biological markers of Alzheimer's disease are found in patients with major depression, including the genotype apolipoprotein E $\epsilon 3/\epsilon 4$ (*APOE4*)⁶⁹, which has been linked to Alzheimer's disease. Additionally, depressed patients with the *APOE4* genotype have more hippocampal shape abnormalities than depressed patients without *APOE4*⁷⁰, and individuals with late-onset depression and mild cognitive deficits have significant brain amyloid load in a pattern similar to the pattern found in Alzheimer's disease⁷¹.

Diagnosing depression and initiating appropriate treatment in patients with co-morbid medical disorders is therefore important in long-term outcomes and may have a significant effect on the course of the illness. The diagnosis should be made using the DSM criteria

and generally the clinician should not attempt to distinguish if the symptoms are due to depression or to the medical illness (i.e. an 'inclusive' approach).

TAKING A HISTORY FROM THE DEPRESSED OLDER ADULT AND FAMILY

The key elements in the patient's history include evidence of a previous psychiatric illness, especially a major depressive or manic episode, particularly if that episode responded to somatic therapy (e.g. lithium, antidepressants or electroconvulsive therapies). Obtaining pharmacy and other medical records regarding the symptoms, dose and the duration of medication trials can further aid in the assessment of depressed individuals. Major depression is a recurrent illness, with about half of the patients experiencing two or more episodes in their lifetime.

In general the clinician evaluating the depressed older adult should include a knowledgeable informant. Depressed elders tend to discount their depressive symptoms⁷² and the DSM criteria have been shown to be reliable in elderly patients with primary depression as well as depression secondary to co-morbid medical conditions such as stroke⁶² and Parkinson's disease⁵⁰.

In order to distinguish dementia from depression, researchers have relied upon the findings in the family and individual histories, mental status and laboratory examinations⁷³. Determining the time of onset of the depressive symptoms and the number of episodes may also be useful, since most dementias are slowly developing, with early evidence of cognitive decline (e.g. the inability to balance a cheque-book) being present months to years before the typical form of the disease becomes apparent. In contrast, the course of depressive illness may seem more abrupt. In fact Driscoll *et al.*⁷⁴ found that late-onset, recurrent depression takes longer to respond to treatment than late-onset single-episode depression and is more strongly associated with cognitive and functional impairment.

An accurate family history may also provide valuable diagnostic information, since dementing illnesses (e.g. Huntington's chorea and Alzheimer's disease, particularly the early-onset form) and major depression (especially the early-onset form) have both been demonstrated to have a genetic diathesis. The family history should also include questions about neurological and medical disease, alcohol/drug abuse, anxiety, suicide and psychosis, since these conditions are often associated with concomitant depression.

THE MENTAL STATUS EXAMINATION

The mental status examination and standardized depression rating scales may also aid in determining whether the patient has depression, dementia or (as is often the case) both⁷⁵. The depressed patient approaches the mental status examination with the same lack of interest that is also apparent in other areas of his/her life. The depressed patient may attempt to prematurely terminate the interview or consistently refuse to try to answer questions. On the other hand, the demented patient may be quite concerned about his/her declining cognitive skills and, at the same time, make attempts to cover his/her deficits with confabulation. He/she may use notes and other reminders to keep up with facts and uncovering his/her deficits might be quite distressing. This is in marked contrast to the apathetic attitude of the depressed patient⁴¹. The depressed inpatient is also more likely to be able to find his/her way around the ward and to keep track of the ward routine and personnel. In

contrast, the demented patient will forget meal times and confuse familiar faces. This confusion may often get worse as evening approaches and is incorporated in the well-known clinical syndrome of 'sundowning'.

Apathy can be difficult to distinguish from depression. Apathy is essentially the loss of interest without a loss of pleasure but can be misdiagnosed as depression since it is frequently associated with many of the same symptoms (e.g. disinterest, withdrawal, flat affect). Apathy is associated with dementia and other medical conditions that occur with depression, including stroke⁷⁶ and Parkinson's disease⁷⁷.

The mental status examination of patients with physical illnesses may show primarily problems with concentration and attention. In more severe cases, evidence of delirium may be present. Delirium is diagnosed when the level of consciousness becomes impaired. In this condition, disorientation and memory impairment may be present along with illusions (which are misinterpretations of environmental stimuli), hallucinations and disturbances in psychomotor activity and the sleep-wake cycle. As opposed to dementia, these symptoms usually evolve over hours and days rather than months and may show a waxing and waning course along with autonomic instability.

A common clinical dilemma occurs in patients who are known to be demented, but in whom the clinician seeks to make an accurate diagnosis of depression. In these patients, the clinician may need to assign more importance to neurovegetative signs, such as weight loss and insomnia, although these same symptoms may occur in non-depressed demented patients if they are too disorganized to prepare a meal or have night-time confusion. Some researchers have pointed to the presence of cognitive symptoms of depression (i.e. depressed mood, anxiety, helplessness, hopelessness and worthlessness) as being more prominent in demented patients, whereas neurovegetative signs are notably absent⁷⁸.

Monitoring the patient over time, observing for some overall consistent pattern of depressed mood and affect, is also helpful. Although there is little or no data to support empirical trials of antidepressants, given the relatively low side-effect profile of the newer antidepressants^{79,80} (SSRIs; see Chapter 86), many clinicians will often attempt a trial of an antidepressant in these difficult situations in hopes the treatment may improve cognition and function. Methylphenidate has been used to treat depressive symptoms such as fatigue, apathy, lack of energy and decreased concentration in depressed medically ill older adults. Despite the long history of its use due to rapid effect, there is little definitive evidence to support this. A few trials have been conducted. Small sampled double-blind trials suggest that methylphenidate is generally well tolerated and modestly efficacious in medically burdened patients⁸¹. Caution is advised regarding the possible exacerbation of anxiety, psychosis, arrhythmia and potential interaction with warfarin.

PSYCHOLOGICAL TESTS

Neuropsychological assessment is a useful tool to determine the level of cognitive functioning of a patient at a certain point in time but cannot be used to accurately differentiate depression from dementia, especially during the acute episode of depression. Patients suffering from depression have impairments in visuo-spatial ability, memory, psychomotor slowing, speed of information processing and executive functioning, with the executive deficits being particularly related to late age at onset of first lifetime depressive episode⁸². The demented patient will demonstrate a more global decline, with relatively lower scores on aspects of the testing requiring adaptability and processing

of information (e.g. performance IQ) as opposed to rote skills and long-term memory tasks (e.g. verbal IQ). Even though a neuropsychological assessment often does not yield a definitive diagnosis, there are some characteristics in patient behaviour that are important to consider when evaluating an older cognitively impaired patient for depression. The depressed patient will more likely show results that are inconsistent over time and are effort-dependent.

Several other factors in depression have been related to worse performance in cognitive testing, including severe depressive symptoms, severe anxiety, the presence of vegetative symptoms and psychotic symptoms. A recent study by Bhalla *et al.*⁸³ examined cognitive diagnosis among subjects 65 and older before and after depression treatment response. They found that 48% of remitted depressed subjects had persistent cognitive impairment after effective treatment of depressive symptoms. The same group found that very few depressed individuals went from cognitively impaired to cognitively normal over one year follow-up⁸⁴. It is not clear if depression represents a risk factor for or occurs in the prodromal stage of dementia^{83,85}, but some studies have reported that late-life depression may be associated with subsequent mild cognitive impairment and dementia including Alzheimer's disease and vascular dementia⁸⁶.

Standardized depression scales may yield false positive results in demented patients, particularly if they are heavily weighted for cognitive symptoms such as attention and concentration, which overlap with symptoms of depression. Depression scales that have been specifically designed to grade levels of depression in patients known to be demented include the Cornell Scale for Depression and Dementia (CSDD), the Geriatric Depression Scale (GDS), the Beck Depression Inventory (BDI) and the Montgomery–Asberg Depression Rating Scale (MADRS); all are useful tests that can help aid in evaluation of a depressed older patient^{87–89}. Each instrument has advantages and disadvantages. For example, the GDS is a self-report measure with yes or no answers that includes evaluation of subjective experience of cognitive impairment but minimizes somatic symptoms and suicidal ideation. The BDI is also self-report and has many more questions related to the somatic symptoms of depression so medically ill older patients can appear more depressed. The BDI does have an excellent question on suicidal ideation and comes in a short form, which abbreviates the questions without losing validity. The CSDD combines patient reports, interviewer observation and informant report for forming a general opinion, so reliability can be difficult if informants are not given specific instructions on how to answer the questions. The MADRS is observer reported and has been shown to be valid and reliable in a number of clinical settings. All these instruments can aid in the diagnosis but, most importantly, can track the severity of symptoms⁹⁰, and many of these rating scales are valid in medical diseases with high rates of co-morbid depression that are common in ageing such as Parkinson's disease⁵⁰.

LABORATORY TESTS

The common laboratory tests for depression may lose much of their specificity in demented patients. The dexamethasone suppression test (DST) was shown to be useful in mild dementia of Alzheimer's type in distinguishing depressed from non-depressed patients. However, findings in more severe dementia were less specific⁹¹.

The sleep electroencephalogram, however, does maintain its specificity and is able to distinguish a group of elderly depressed patients from those with dementia⁹². Several biological markers have been

associated with depression, such as higher platelet monoamine oxidase activity, platelet alpha2-adrenoreceptors, blunted thyroid stimulating hormone (TSH) response to thyroid releasing hormone (TRH), presence of a variant in a gene coding for a potassium channel, and genetic variation in a kainic acid-type glutamate receptor. Many other potential biological markers of depression have been identified⁹³.

Any physical illness that can potentially affect the central nervous system (CNS) can present with depressive and dementing symptoms; these illnesses include encephalitis, chronic subdural haematoma and normal pressure hydrocephalus. Depressive symptoms such as fatigue, insomnia, weight loss and concentration problems can occur in other illnesses that do not directly affect the CNS. These illnesses include infectious diseases (e.g. tuberculosis, influenza), cardiovascular disease (e.g. congestive heart failure), endocrine abnormalities (e.g. thyroid disease, diabetes), electrolyte disturbances (e.g. hyponatraemia, hypocalcaemia), and renal and hepatic disease. Cerebrovascular disease has also been linked to depression in the elderly, and both cerebral vascular accidents and periventricular white matter disease are related to depressive symptoms in the elderly^{94,95}.

MEDICAL WORK-UP

The work-up of medical conditions that present with depressive symptoms in the elderly includes a personal history of medical illness, mental status examination and laboratory tests^{13,41,96}. Many of these medical conditions are reversible with proper treatment, and geriatric textbooks emphasize the importance of reversible conditions presenting as dementia in the assessment of demented older adults. However, the occurrence of a reversible dementia is actually quite rare in clinical practice⁹⁷. Nevertheless, a basic laboratory work-up is important in the evaluation of depressed older adults, including those with cognitive impairment.

A complete medication history should be obtained. Medication, including the antihypertensive medications such as beta-blockers and centrally acting α -methyl dopa and reserpine, has been shown to cause depressive symptoms. Medications including steroids, barbiturates and sedatives are also frequent causes of depression in the elderly. Patients at risk should be screened for heavy metals, including lead, arsenic and the organophosphates.

The typical laboratory screening for elderly patients with depressive symptoms is outlined in Table 91.1. Clearly, the medical history and physical examination would influence the laboratory testing that was actually done. The neurological examination should be particularly thorough and include an examination of both subtle (e.g. frontal release signs) and prominent (e.g. reflex changes) signs of neurological dysfunction.

SUMMARY

Depressive symptoms are common in the elderly, whereas the syndrome of a major depressive episode is relatively rare. Regardless, depressive symptoms can have a significant effect on functioning, quality of life and mortality in the elderly. Symptoms of depression can be manifestations of either dementing or medical illnesses, both of which are common in the elderly. Psychosocial factors that are unique to the elderly may be aetiological in the genesis of depressive symptoms, but nevertheless require the clinician to assess each patient fully and treat as appropriate. Successful treatment mandates a detailed history, often with collaboration from the family,

Table 91.1 Laboratory work-up in the depressed elderly patient

Laboratory test	Underlying condition
Complete blood count	Infectious disease Encephalitis Meningitis Sub-acute bacterial endocarditis Anaemia
Electrolytes and metabolic panel	Hypokalaemia Hyponatraemia Diabetes Uraemia
B12/folate	Pernicious anaemia
Homocysteine	Vascular disease
25-Hydroxyvitamine D	Vitamin D deficiency
Thyroid panel	Hypo/hyperthyroidism
Liver enzymes	Hepatitis Liver cancer
Calcium/phosphorus	Hyperparathyroidism
Guaiac stool	Colon disease
Urinalysis	Infection Renal disease
<i>Additional tests</i>	
Electrocardiogram	Particularly patients who complain of fatigue, oedema or shortness of breath, or who are being considered for antidepressant therapy
Electroencephalogram	For patients in delirium, particularly those with a seizure history and when non-convulsive status epilepticus is suspected
Urine drug screen	For lead (exposure to paint), mercury (textile manufacturing), organophosphates and arsenic (insecticides). Also drugs of abuse (e.g. opiates, marijuana etc.)
Human immune deficiency virus (HIV)	Exposure to potentially contaminated blood products (surgery, drug use) or a history of promiscuity or homosexuality
Brain computed tomography	Neoplasia, stroke
Brain magnetic resonance imaging	Particularly to view the posterior brainstem

and a thorough medical evaluation for other co-morbid illnesses that may contribute to the patient's current presentation. The treatment of depressive symptoms in the elderly requires an understanding of both the origin of these symptoms and the proper treatment of the underlying disorder, whether the symptoms are secondary to medical, cognitive or psychosocial factors.

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Mania: Epidemiology and Risk Factors

Susan W. Lehmann

The Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Baltimore, MD, USA

In recent years there has been increased clinical interest and research regarding the syndrome of mania in the elderly. While it has become clearer that older persons with bipolar disorder are a heterogeneous group, many questions regarding differences between early-onset bipolar disorder and later-onset bipolar disorder remain. Much of the current work in this area has focused on the following: How does bipolar disorder in the elderly differ from that in younger people? Can age of onset be used to distinguish clinically meaningful subtypes of bipolar disorder?

EPIDEMIOLOGY

The manic phase of bipolar affective disorder, or mania, is an uncommon disorder in the elderly although the exact prevalence of bipolar disorder among older adults in the community is uncertain¹. In the five-site Epidemiologic Catchment Area study of more than 20 000 non-institutionalized individuals, one-month prevalence rates for mania were 0.4–0.8% for 18–44 year olds and 0.2% in the 45- to 64-year-old group. Notably, no cases of mania were identified among people over age 64². In a 12-month prevalence study of 2798 community-dwelling adults age 65 or older in Quebec, 0.6% were found to have had a manic episode³.

Nevertheless, elderly patients with mania are seen in significant numbers in a variety of clinical settings. In Roth's⁴ retrospective review of 464 psychogeriatric patients over age 60 in a long-term hospital, 14 cases were manic, representing 6% of the total number of cases of affective disorder. Two studies of first admissions to British psychiatric hospitals, using Department of Health statistics, found that the number of first admissions with mania either remained steady with age⁵ or increased with advancing age⁶. In the USA, other studies in short-stay hospitals have reported that mania accounted for approximately 5% of elderly psychiatric admissions^{7–9}. Elderly patients with bipolar disorder have been found to use disproportionately more outpatient mental health and day hospital services than older patients with unipolar major depression¹⁰. Most studies of elderly manic patients have found more females than males^{7–9,11}, though men have been reported to have an earlier age of onset¹².

For the majority of elderly bipolar patients, the first episode of affective disorder is usually a depression. Indeed, it is quite common for a first manic episode to occur 10 years or more after an initial depressive episode and to be preceded by multiple depressive episodes over many years^{7,13,14}. Generally, elderly patients have

been found to have suffered more episodes of depression before a first manic episode and to have had a long gap between an initial depression and a first manic episode than young manic patients¹⁴.

It has been estimated that about 10% of older patients with bipolar disorder experienced onset of illness after age 50¹⁵. Still, at the present time, there is no agreed-upon standard regarding which age should serve as the dividing line between early- and late-onset bipolar disorder. This uncertainty is compounded by a lack of consensus regarding how to determine age of onset itself. Different criteria have been used among various investigators to identify age of onset of bipolar disorder, including first onset of any mood symptoms, first hospitalization and first time at which the patient met full criteria for the disorder⁹.

Several studies have observed bi-modality in age of onset of mania among elderly patients. In these studies, one subgroup of patients was found to have developed bipolar disorder in early life with a mean age in their thirties, and another subgroup developed a first manic episode after age 60^{9,14}. A study of first-episode mania presenting for psychiatric treatment over a 35-year period in London found a two-component distribution in age of onset with a peak in early adult life and a smaller peak in mid-life¹⁶. A bimodal age of onset of bipolar disorder has also been reported by others^{17–19} although a trimodal distribution of age of onset has been proposed as well²⁰. While controversy continues regarding how best to define early- and late-onset cases, results from numerous studies support the relevance of distinguishing between early- and late-onset bipolar disorder. Late-onset bipolar patients tend to have had a longer gap between first depression and first mania than early-onset bipolar patients¹⁴ and in one study were more likely to be married or living with a significant other⁹. Elderly bipolar patients with late-onset have been reported to have a more favourable outcome and to be less likely to have rapid cycling compared with elderly patients with early-onset illness²¹.

RISK FACTORS

A number of studies have reported that elderly bipolar patients who had an early age of onset were more likely to have had first-degree relatives with affective disorder than late-onset elderly bipolar patients^{14,22}. This trend holds across studies that have used ages between 20 and 60 years to divide early and late cases and suggests that genetics plays a greater role in the disease of early-onset bipolar disorder. At the same time, many investigators have reported

associations between late-onset mania and cerebrovascular risk factors. In two studies comparing elderly patients with early- and late-onset bipolar disorder, researchers found that patients with late-onset mania had increased vascular risk factors^{9,17}.

In another recent study of 50 elderly bipolar patients with no known history of stroke or neurological disease, patients with late-onset bipolar disorder had higher stroke risk scores than patients with early-onset illness¹⁹. In a prospective study of mania in 35 patients over age 60, the elderly mania patients had more cortical atrophy on CT scans than age-matched controls¹⁴. However, no significant difference in cortical atrophy was found between elderly patients with early- and late-onset mania. In addition, subcortical hyperintensities have been reported on magnetic resonance imaging (MRI) in elderly patients with mania²³. These hyperintensities are believed to be due to focal loss of brain parenchyma but they do not seem to be specific to elderly patients with mania, since subcortical hyperintensities have also been found in late-onset depression as well as late-onset paranoid disorders²⁴.

Krauthammer and Klerman²⁵ proposed criteria for secondary mania that included cases of no prior family history, no past psychiatric history and a definable medical or neurological aetiology. While it is true that organic factors may precipitate mania in some elderly patients, these cases appear to be in the minority. Manic episodes can be caused by such widely prescribed medications as levodopa, procyclidine, pergolide, selegiline and bromocriptine²⁶. A variety of steroids have been reported to produce manic syndromes, as have thyroid supplements, and there have been case reports of mania associated with H₂-antagonists, antiarrhythmics, oestrogen and anti-tubercular agents²⁷. In addition, mania can occur in association with systemic infections, such as influenza, Q fever and St. Louis type A encephalitis. Cases of mania secondary to space-occupying lesions, such as meningiomas, subarachnoid haemorrhages and metastases (usually in the non-dominant hemisphere), have also been reported⁸. In these cases, mania usually resolves with removal of the offending pharmacological agent or treatment of the underlying disorder.

More commonly, mania has been reported in elderly patients with cerebrovascular and neurological disorders. A cohort study comparing 50 elderly patients with mania to 50 age- and sex-matched patients with unipolar depression found that 36% of the manic patients had neurological disorders compared with only 8% of the depressed patients²⁸. Interestingly, among these neurologically impaired manic patients, 33% had a positive family history of affective disorder in first-degree relatives. A prospective study found that 20% of patients with mania over the age of 60 had a first manic episode closely temporally related to a cerebral organic disorder¹⁴. Another prospective study of 20 manic patients with onset over age 50 found that 65% developed bipolar disorder after a silent cerebral infarction²⁹. In particular, injury to the right hemisphere appears to be strongly associated with the development of mania.

Overall, however, mania following stroke is much less common than depression after a stroke. In one large study of 700 stroke victims only three developed manic syndromes³⁰. There have been reports of secondary mania in patients with ischaemic injury to right-sided basal ganglia, orbitofrontal cortex, right basotemporal cortex³¹ and right temporoparietal cortex³². There have also been two case reports of mania secondary to infarctions in the thalamic and perithalamic areas³³. It has been hypothesized that these brain areas may be significant because of their connections to the limbic system and the modulation of emotion. Starkstein *et al.*³⁴ studied 11 patients who developed mania after stroke and found that eight had lesions involving limbic areas and nine had right hemispheric involvement. These

patients also had significantly larger bifrontal and third ventricular brain ratios than matched control patients, indicating pre-existing anterior subcortical atrophy. Moreover, almost half of the patients had family history of affective disorder in a first-degree relative.

Taken together, the current literature on mania in patients with neurological and cerebrovascular disorder underscores that genetic loading is also a factor contributing to the development of mania in these patients. Furthermore, while up to a quarter of elderly manic patients in various studies have been found to have some evidence of concurrent cerebral disease, it is still unclear to what extent these impairments play an aetiological role in the development of mania. If cases in which subjects with a known previous history of affective disorder are excluded, few cases of clear secondary mania are found^{8,14,22}. An exception to this is Shulman *et al.*²⁸, who felt that 36% of elderly patients they studied who were hospitalized with mania had true secondary mania associated temporally with clearly documented neurological disorders. Still, recent findings that late-onset mania is associated with greater vascular risk factors and greater cerebrovascular disease suggest that medical management of vascular risk factors in older patients with depressive disorders may minimize their vulnerability to developing mania¹⁹.

Mania can occur in the setting of dementia, although it is rare. In a retrospective chart review of 134 patients with Alzheimer's disease 2% were found to have had mania³⁵, although others have reported higher rates³⁶. A recent study of a large Danish cohort found that patients with dementia had an elevated probability of developing mania, depression or a first bipolar episode compared with patients with other chronic illnesses, and this risk remained increased throughout the rest of the patient's life³⁷.

As in younger patients, stressful life events have been felt by some investigators to precipitate mania in elderly patients. One study that reported on 10 elderly manic patients found that 70% had major changes in lifestyle in the six months preceding onset of mania. Stresses included marital discord and disruption of living arrangements⁷.

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Acute Mania and Bipolar Affective Disorder

M. Sajatovic¹, N. Herrmann² and K.I. Shulman²

¹Case Western Reserve University School of Medicine and University Hospitals Case Medical Center, Cleveland, OH, USA

²Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

INTRODUCTION

The term 'bipolar disorder' includes a wide spectrum of clinical expression ranging from early to very late onset, single to recurrent episodes, manic only to bipolar episodes and mild hypomania to severe mania. However, the defining feature of bipolar disorder has always been evidence of a manic or hypomanic episode. Recent notions have challenged the concept of 'bipolar disorder' to include other perspectives including treatment response and family history¹. This review of bipolar disorder in later life will focus on features that are unique to older adults including its late age of onset, long-term clinical course and the high prevalence of co-morbidity including cognitive impairment, other psychiatric disorders and neurobiological features. Ultimately, we will attempt to synthesize the determinants of mania in old age and review the implications for assessment and clinical diagnosis before addressing management issues specific to older adults.

EPIDEMIOLOGY

Data on the community incidence and prevalence of mania and bipolar disorder in old age are confounded by a number of methodological concerns. Similar to patients who suffer from paranoid disorders, manic patients are not readily amenable to interview or cooperation with community surveys. Diagnostic uncertainty is also related to the high levels of co-morbidity that cloud the diagnostic horizon². This includes the association with co-morbid medical and neurologic disorders. DSM-IV has categorized this as 'a mood disorder due to a general medical condition' (293.83). The assumption in that classification is that the mood disturbance is a 'direct physiologic consequence of the general medical condition'. However, because of the high levels of neurological and medical co-morbidity, it is difficult to ascertain with any degree of certainty whether this is the case. Further, the historical category of 'secondary mania' implies that cerebral organic factors are responsible for the syndrome³. The neurological literature complicates the issue by use of the term 'disinhibition syndrome', the features of which are identical to what is considered mania in the psychiatric literature. All of this conspires to create uncertainty as to the true incidence and prevalence of the disorder. Our best data, however, suggest that the prevalence of mania in the community decreases from a high of 1.4% in young adults to a negligible <0.1% prevalence of mania in the over-65s⁴⁻⁷.

Community epidemiological surveys, including the Epidemiologic Catchment Area Study (ECA)^{4,8}, found a very early age of onset, close to 20 years. However, in studies of mixed-age manic patients, the mean age of onset tends to be slightly higher at 30 years^{9,10}. Despite this very early onset of bipolar disorder in the general population, only a relatively small number of elderly bipolar inpatients are known to experience their first manic episode before the age of 40^{7,11}. The question 'where have all the young bipolar patients gone?' has not yet been answered.

A number of hypotheses for this phenomenon include the relatively high mortality rate from natural causes and suicide in bipolar patients⁷ while the Iowa 500 data suggested evidence of 'burn out' of the disorder over a long-term course¹². The latter phenomenon has been challenged in recent epidemiological surveys based on the Veterans Affairs database¹³. Outpatient samples may reveal a different pattern compared to hospitalized patients.

In contrast, hospital admission rates show an opposite trend to that of the community prevalence of bipolar illness. For inpatient psychogeriatric units, Yassa *et al.*¹⁴ found a relatively high 'treated prevalence' ranging from 4 to 8%. In Britain, a national survey examining first admission rates for mania showed a modest increase in the extremes of old age^{15,16}, assuming that this was associated with the increased prevalence of dementia in late life. The development of specialized inpatient units for older adults included significant numbers of individuals with late-life bipolar disorders ranging from 7 to 10 admissions per year^{11,14,17}. In Finland, 20% of first admissions with the diagnosis of bipolar disorder occurred after the age of 60¹⁸. Reconciling the opposing patterns of community prevalence and hospital admission rates has been a challenge. Are the 'bipolar' disorders in late life qualitatively different than those in younger adults or is the higher admission rate in older adults a reflection of increased frailty and the effect of neurological changes?

AGE OF ONSET

Age of onset is an important variable that might help to distinguish the subtypes of mania and reduce the genetic heterogeneity inherent in the bipolar spectrum¹⁹. Consensus seems to be heading towards a cut-off of age 50 as a distinguishing feature of 'early-' versus 'late-onset' bipolar disorder. Recently Moorhead and Young²⁰ used a UK psychiatric case registry to determine age of onset retrospectively in bipolar I patients. Those subjects without a family history tended to

have later age of onset with a modal age of onset at 49 years, consistent with the studies above. They concluded that non-genetic factors were more relevant in this subgroup and also suggested that age 50 would be a useful cut-off for the early- vs. late-onset designation. It is worth noting that age of onset is significantly influenced by the cut-off used for 'elderly' probands. Most studies use age 60 or 65 as a cut-off for 'geriatric', 'elderly' or 'older adult'.

Studies that have examined the relationship of family history with age of onset in older bipolar probands have shown a wide range of prevalence of psychiatric disorder in first-degree relatives ranging from 24% to 88%^{7,11,21-24}. Methodological issues are significant because most of the studies are retrospective in nature and the rigorous use of criteria for positive family history are not consistent in these studies. Nonetheless, a general trend towards a higher rate of family history is evident in those with early age of onset^{22,24}. The converse is true in those elderly bipolar probands with a neurological disorder mainly associated with a late onset of bipolar disorder. However, even in the 'neurological subgroup' of older bipolar patients, the prevalence of a positive family history in first-degree relatives remains quite high, at about 30%^{7,11,25}. Thus, even in those manic or bipolar patients with evidence of co-morbid neurological lesions, familial vulnerability appears to be a contributory factor.

COURSE OF ILLNESS

Early retrospective studies of bipolar disorder in late life found that about half of all index patients experienced depression as their first mood episode^{7,11,22,23}. Moreover, elderly bipolar patients whose first episode was depression (mean age of 50, went on to experience a very long latency (mean of 15 years) before their first manic episode became evident^{11,17}. In the subgroup with a latency between first depression and first mania, 25% of this group experienced a latency of at least 25 years and half of this group suffered at least three consecutive depressive episodes before developing a manic episode^{7,17,22}, begging the question of the pathogenesis of a switch from unipolar depression to bipolarity. The switch mechanism has been attributed in part to the high prevalence of co-morbid neurological disorders and cognitive changes described further below², but may also be a function of normal degenerative changes allowing for uncovering of an underlying disposition to bipolarity.

Although little is written about a unipolar mania subtype, Shulman and Tohen²⁶ found that 12% of their sample met strict criteria for a course of unipolar mania. The criteria included at least three distinct manic episodes without major depression including a minimum period of 10 years follow-up from the time of their first admission for a manic episode. This group also had a relatively earlier age of onset (41 years) compared with a mean of 65 years for a larger group of elderly bipolar patients. However, further study of unipolar manic patients has not been forthcoming.

The long-term outcome of older bipolar patients has primarily been studied retrospectively^{11,27,28}. Shulman *et al.*¹¹ found a high mortality rate in a cohort of elderly manic inpatients. About half of the manic patients had died at a mean six-year follow-up compared with only 20% of age- and sex-matched patients with depression. Berrios and Bakshi²⁷ found a poor prognosis in older bipolar patients with limited response to treatment and a higher prevalence of cognitive impairment and cerebrovascular dysfunction associated with persistent disturbances in psychosocial functioning. Dhingra and Rabins²⁸ observed a significant decline in cognition in their six-year mean follow-up study.

Lehmann and Rabins²⁹ used a retrospective chart review of patients over the age of 65 to identify factors that contributed to relapse and hospitalization in elderly bipolar patients. They noted a distribution of age of onset consistent with previous findings using a cut-off at about age 45 rather than 50 years for late onset. The early-onset patients tended to be more behaviourally disturbed prior to admission and were less adherent with prescribed psychiatric medications. Relapse and readmissions were very common in elderly manic patients with both early- and late-onset disorders. They emphasized the need for improved medication adherence in order to prevent recurrent episodes and admissions.

PSYCHIATRIC AND MEDICAL CO-MORBIDITY

Two recent studies have focused on the question of psychiatric co-morbidity with late-life bipolar disorders^{30,31}. Sajatovic and Kales³² used the Veterans Affairs database (National Psychosis Registry) to document a lower prevalence of substance abuse in older bipolar patients compared with mixed-age samples who had co-morbid substance abuse of over 60%. A total of 29% of older bipolar patients with a mean age of 70 years experienced either substance abuse, post-traumatic stress disorder, other anxiety disorders or dementia³². In this study, the anxiety disorders represented 15.2% of the sample, including post-traumatic stress disorder (PTSD) which occurred in 5.4% and other anxiety disorders in 9.8% of this group. Substance abuse was lower than other studies at 8.9% in this sample. Goldstein *et al.*³⁰ derived data from the National Epidemiology Survey on Alcohol Related Conditions (NESARC). Eighty-four elderly bipolar patients were identified and were found to have a lifetime and 12-month co-morbid prevalence of alcohol use disorders of 38%. Patients with generalized anxiety disorder had a lifetime prevalence of 20.5% and a 12-month prevalence of 9.5%. Prevalence figures for panic disorder showed a 19% lifetime prevalence and a 12-month prevalence of 11.9%. These studies show a consistently high co-morbidity that appears to be slightly lower than mixed-age and younger samples.

Medical co-morbidity has only recently been examined in bipolar elders^{33,34}. Using a prospective sample of elderly bipolar patients, Gildengers *et al.*³³ undertook to determine the profile of disease burden between elderly patients with major depression compared to those with bipolar disorder. They hypothesized that medical burden would be greater for bipolar patients, particularly in endocrine/metabolic and cardiovascular disease given the association of bipolar disorder with obesity, diabetes mellitus, dyslipidaemia and hypertension. They did not find a significant difference between the depressive and bipolar groups on the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) or body mass index (BMI). However, they did confirm that metabolic disease was higher in the bipolar group. This is consistent with the findings of Subramaniam *et al.*³⁴ who conducted a cross-sectional survey of elderly bipolar patients and showed that the late-onset group had higher stroke risk scores compared with the early-onset group of older bipolar patients but did not find any differences in cognitive functioning.

These recent studies confirm concerns that have been identified in a number of previous retrospective studies of late-life bipolar disorder where significant neurological co-morbidity was noted. This literature has consisted primarily of individual case reports and small case series, but showed a tendency for heterogeneous right hemisphere lesions to be associated with mania³⁵⁻³⁸. The findings were consistent with the psychiatric literature that used

the term 'secondary mania'³ and the neurological literature that tended to use the term 'disinhibition syndrome'³⁹. The phenomenon of pathological laughing has also been associated with right-sided lesions⁴⁰. Moreover, the right orbital frontal circuit (OFC) has been implicated in the pathogenesis of manic syndromes^{41,42}. This hypothesis is based on the observation that normal mood is dependent on the integrity of the frontal, limbic and basal ganglia circuits. Starkstein and Robinson³⁹ previously suggested that disinhibition syndromes or secondary mania cases are caused by a disruption of connections within the orbital frontal circuits. They note that the frontal lobes modulate motivational and psychomotor behaviour, limbic connections modulate emotions, and the biogenic amine nuclei in the hypothalamus, amygdala and brainstem modulate instinctive behaviours. This may be the neurobiological basis and pathogenesis for the development of mania in later life associated with a higher prevalence of neurological lesions⁴³.

Braun *et al.*⁴⁴ reviewed a series of published case reports involving focal unilateral cortical lesions, and also found a tendency towards right-sided lesions for what they termed 'mania and pseudomania'. Earlier retrospective studies of mania by Shulman *et al.*¹¹ noted a very high association of neurological disorders in the manic group (36%) compared with only 8% in a comparison group of elderly depressives. Moreover, very late-onset mania is strongly associated with neurological co-morbidity as well as high mortality due to cerebrovascular disease²⁵. In this retrospective cohort study, 10 out of 14 elderly manic patients had evidence of neurological disorders, primarily due to cerebrovascular disease.

A heterogeneous group of neurological and medical disorders have been associated with secondary mania as reported by case reports including head injuries⁴⁵, endocrine conditions^{46–48}, HIV⁴⁹ and epilepsy³⁷. However, the majority of case reports of secondary mania are associated with right-sided cerebrovascular lesions².

The presence of cerebrovascular disease associated with mania has led to the proposal of a bipolar vascular subtype³⁸. Similar to the vascular depression hypothesis of Alexopoulos *et al.*⁵⁰, vascular mania is defined in the context of a finding of cerebrovascular disease based on clinical or neuroimaging findings with further evidence of cognitive impairment. The cohort of elderly manic patients with cerebrovascular disease may fit in the proposed vascular subtype although the hypothesis still needs better data for corroboration. Using a cut-off of 49 years, Wylie⁵¹, found that the late-onset group had more cerebrovascular risk factors which are elaborated on below. Hays *et al.*²⁴ also found an increase in vascular co-morbidity in their sample of elderly bipolar patients whose mean age was 74 years. Silent cerebral infarctions were found to occur most commonly in late-onset mania when compared with age- and sex-matched group of depressive patients⁵². The proportion of manic patients over the age of 60 found to have silent cerebral infarctions was greater than 20% with a relatively modest family history in first-degree relatives.

NEUROIMAGING STUDIES

Most studies have focused on the presence of subcortical hyperintensities, decreased cerebral blood flow and evidence of silent cerebral infarctions². The relationship of hyperintensities with risk factors such as hypertension, atherosclerotic heart disease and diabetes mellitus strengthens the relationship of mania to cerebrovascular pathology.

The potential for examining structural brain changes in late-life neuropsychiatric disorders implies that hypothesis-driven theses can

now be performed⁵³. New methods may be able to help understand the pathophysiology of bipolarity within specific neural circuits. The important side benefits of studying geriatric patients is also the opportunity to integrate MRI with postmortem analysis, thus generating new hypotheses⁵⁴.

Braun *et al.*⁵⁵ collected a second series of single-case reports of unilateral lesions involving at least one manic symptom. They assembled a subgroup of 59 clearly defined manic patients, the majority of whom had right hemisphere lesions. However, elation alone without a manic symptom complex was not significantly predicted by lesion side. Rather, the association of right hemisphere lesions with mania is primarily related to disinhibition rather than a shift of mood as a result of the release of left hemisphere influence. This hypothesis is illustrated in a recent case study from Japan in which a 78-year-old woman with major depression developed a right-sided infarction in the middle cerebral artery distribution followed by acute post-stroke mania. Single photon emission computed tomography (SPECT) scan showed a unique pattern of left orbital frontal hyperperfusion with extensive right frontal hypoperfusion. Similar to Braun *et al.*'s⁵⁵ theory, they postulate a functional imbalance within the right and left orbital frontal cortices that result in the development of mania⁵⁶.

The examination of cortical atrophy has not been as frequent as that of hyperintensities and silent cerebral infarcts but Beyer *et al.*⁵⁷ found a decreased right caudate volume in older bipolar patients compared with controls related to the duration of illness. This was most pronounced in a late-onset subgroup and points to the role of the caudate in the emotional brain circuitry involving the prefrontal cortex, the amygdala, thalamus and other basal ganglia structures. Another interesting associated finding from Beyer *et al.*⁵⁸ was an increase in left hippocampal volume in elderly bipolar patients. They hypothesized that lithium treatment may have been responsible for this and point to the possible neuroplasticity and cellular resilience in this region of the brain possibly induced by lithium⁵⁹.

COGNITIVE IMPAIRMENT

Young *et al.*⁶⁰ conducted a systematic literature review involving seven studies of elderly bipolar patients and also used a cross-sectional sample of 70 bipolar patients who completed the Mini-Mental State Examination (MMSE) and the Mattis Dementia Rating Scale. The literature review identified methodological problems and differences in assessing cognitive function but overall found a pattern of significant cognitive impairment. In their clinical sample, the manic patients had lower scores on the two rating instruments compared to a comparison group. The cognitive scores did not correlate with Young Mania Rating Scale scores and were considered persistent deficits.

Tsai *et al.*⁶¹ used a retrospective chart review to study cognition in bipolar I patients over the age of 60. The cognitive screening instruments included the clock drawing test, the MMSE and the cognitive ability screening instrument (CASI). Their cut-off for early onset was age 40 and they found that 42% of early-onset euthymic older bipolar patients had impaired cognition. Gildengers *et al.*⁶² studied euthymic older bipolar patients and found that half of this group scored below the mean of the comparison subjects. They concluded that these findings were persistent changes and not associated with an abnormal mood state, similar to the finding of Young *et al.*⁶⁰.

Despite the very significant association of cognitive dysfunction with late-life mania, earlier studies have not been able to establish a clinical course consistent with the development of dementia in this

group compared to age-matched controls. However, because of the finding by Alexopoulos *et al.*⁵⁰ that reversible dementia in major depression eventually led to irreversible dementia, this issue remains of concern. Of considerable interest has been the recent finding of neuroprotection associated with lithium treatment^{63,64}.

Terao *et al.*⁶⁵ conducted a retrospective study of clinical records to show that those patients with a history of lithium exposure as well as current lithium treatment had higher MMSE scores than their comparison subjects. The putative neuroprotective impact of lithium has been postulated to be associated with its ability to decrease the enzyme glycogen synthase kinase-3 (GSK-3) which leads to the accumulation of amyloid-beta proteins and senile plaques, as well as hyperphosphorylated tau and neurofibrillary tangles in Alzheimer's disease.

A number of recent studies have addressed the relationship between cognitive dysfunction and bipolar disorder with similar findings. Schouws *et al.*⁶⁶ studied a small sample of euthymic elderly patients over the age of 60 with onset less than 50 years. A comprehensive neuropsychological test battery found that these euthymic bipolar patients were impaired across a wide range of cognitive domains and were similar to the cognitive dysfunction found in younger bipolar patients. Depp *et al.*⁶⁷ used an outpatient sample and found that bipolar disorder was associated with significant neurocognitive impairment compared to comparison subjects, and that this pattern of impairment was distinct from that found in schizophrenia. They also confirmed that the cognitive deficits in the bipolar group were not related to either the severity or duration of the psychiatric or manic symptoms, but were related to their quality of life. Sajatovic *et al.*³¹ found a co-morbid dementia in 4.5% of their sample of older bipolar patients in the Veterans Affairs database.

Similar to Tsai *et al.*⁶¹, an Argentinian study⁶⁸ used a small sample of euthymic older patients with bipolar disorders to demonstrate that their pattern of cognitive and motor dysfunction was similar to that described in younger euthymic bipolar patients. Psychosocial functioning was correlated with this impairment. Euthymic bipolar elderly patients were also studied by Radanovic *et al.*⁶⁹ who demonstrated language impairment compared to control subjects.

Gunning-Dixon *et al.*⁷⁰, also using a small sample of non-demented manic bipolar patients, showed that their performance on executive functioning was worse than controls as well as comparison depressed subjects. They hypothesized that the executive dysfunction found in this group supported the possibility that specific frontostriatal network dysfunction was associated with late-life bipolar disorder.

Lin *et al.*⁷¹ used two study cohorts identified in the Taiwan National Health Insurance Research Database. Patients hospitalized with bipolar disorder compared to those undergoing appendectomy had twice the likelihood of developing stroke.

CLINICAL PRESENTATION AND HEALTH SERVICE UTILIZATION

Various studies^{13,23} suggest that the presentation of bipolar disorder remains fairly constant across the life span, including the general range of symptoms. There is also a consistently high use of health services by older bipolar patients^{13,72}. Subsequent studies including those by Bartels *et al.*⁷² report that elderly bipolar patients have greater severity of symptoms and impairment of community living skills compared with age-matched older adults with unipolar depression. Moreover, they use almost four times the total amount of

mental health services, including hospitalization. Generally, bipolar patients are found to have greater medical co-morbidity, more cognitive impairment and a less robust response to treatment^{13,72}. Depp *et al.*⁷³ noted that elderly bipolar patients were less likely to use hospital facilities compared to younger bipolar patients, but were more likely to use case management services.

Kessing⁷⁴ used a nation-wide psychiatric registry in Denmark to study different diagnostic subtypes of bipolar disorder in patients with late-onset (over 50) and early-onset. He found that those bipolar patients whose first psychiatric hospitalization occurred after the age of 50 tended to present with less psychotic manic episodes and more severe depressions including psychosis compared with younger onset patients.

Beyer *et al.*⁷⁵ examined stressful life events in older bipolar patients. They showed that the number of serious stressful life events in the 12 months prior to a manic episode was no different in older or younger bipolar patients. In general, negative life events were more prevalent in both older and younger bipolar patients compared to a control group. Depp *et al.*⁷⁶ noted that psychotic depressive symptoms as well as cognitive impairment in elderly adults with bipolar disorder contributed to the finding of a lower health-related quality of life and functioning in this sample.

In summary, older adults with new or persistent bipolar disorder are profoundly affected by their illness, resulting in a decrease in their quality of life. Moreover, these disorders represent a significant challenge to geriatric and psychiatric services because of the high levels of morbidity and mortality.

CLINICAL IMPLICATIONS OF A NEW DIAGNOSIS OF BIPOLAR DISORDER IN LATE LIFE

One of the unique features of mania and the switch into bipolarity in late life is the association with heterogeneous brain lesions, predominantly cerebrovascular disease. This suggests that any elderly patient presenting with a manic episode, particularly for the first time late in life, deserves a rigorous neurological workup, especially for evidence of cerebrovascular disease, including brain scanning. Consequently, the management of vascular risk factors becomes an important aspect of the management of this neuropsychiatric disorder and accounts for the high rate of medical co-morbidity and increased use of health services by this subgroup of patients^{13,72}. Ruling out other neurological lesions or disorders is particularly important in late-onset cases and those without significant family history.

Our understanding of the determinants of manic illness in old age also point to the significant affective vulnerability in this subgroup manifest by a high familial prevalence of mood disorder in 50–80% of first-degree relatives^{11,24}. However, our clinical experience suggests that affective vulnerability is not based solely on genetics but also on the psychological events of early life. Early loss and trauma in childhood and adolescence may very well be significant risk factors for affective vulnerability late in life. As Beyer *et al.*⁷⁵ have shown, stressful events in old age also play a role but are not more prevalent than in younger individuals with bipolar disorder. However, it is the perfect storm of genetics, psychological stressors and the localization of brain lesions to the right hemisphere involving the orbital frontal circuit that may be critical for the manifestation of mania in old age. These findings in older adults with mania and bipolar disorders may help to shed light on the pathogenesis of mania in the much larger mixed-age population of individuals with bipolar disorder. To what extent the management and pharmacological treatment is similar or different in older adult is the focus of the next section of this chapter.

MANAGEMENT OF THE OLDER ADULT WITH BIPOLAR DISORDER

The management of bipolar disorder in the elderly is fraught with multiple challenges (Table 93.1). As noted previously, rates of medical and psychiatric co-morbidity are extremely high in elderly bipolar patients, necessitating caution during arriving at a diagnosis and ordering investigations/laboratory or imaging assessment. A careful history and collaborative history is often required to rule out comorbid substance abuse and anxiety disorders. The medical history should in particular focus on previous head injury, cerebrovascular disease and related cardiac risk factors. The use of concomitant medications must be documented in order to avoid or manage drug interactions. Baseline laboratory investigations should include a complete blood count (CBC), fasting glucose and lipid profile, liver function, kidney function, thyroid, urinalysis and an ECG. Neuroimaging has generally also been considered an essential component of the baseline investigations for elderly bipolar patients.

The next major challenge facing the clinician is the lack of randomized controlled trials and evidence-based treatment guidelines. At the present time, there is not a single published randomized trial of lithium, valproate, other mood stabilizers, antidepressants, antipsychotics, electroconvulsive therapy (ECT), or psychotherapy conducted with elderly bipolar patients. While there are numerous reviews on the management and pharmacotherapy of late-life bipolar disorders^{77–80}, none of the popular clinical practice guidelines^{81,82} provide evidence-based, specific recommendations for the elderly. Unfortunately, the situation is also unlikely to improve in the near future. A review of the clinical trial registry⁸³ revealed only four trials recruiting geriatric bipolar patients. Of these four trials, none were placebo-controlled, three were open label, and only one was

a randomized trial of lithium vs. valproate that has already been recruiting for several years.

In the absence of specific data, guidelines from adult populations have of necessity been applied to geriatric populations. For example, in a small open-label trial of 31 elderly bipolar patients⁸⁴, standardized treatment protocols were applied based on the Systematic Treatment Enhanced Program for Bipolar Disorder (STEP-BD)⁸⁵. The authors concluded that they were successfully able to apply standardized therapy even though most of the patients did not experience sustained recovery. Any adaptation of adult treatment guidelines however must consider age-specific pharmacological issues such as the fact that the elderly generally have a reduced capacity to metabolize drugs, they are more sensitive to adverse effects, and they are more likely to be taking concomitant medications, increasing the risk of drug interactions⁸⁶.

Treatment of Acute Mania in Older Adults

First-line therapy for acute mania would include lithium, divalproex (valproic acid), an atypical antipsychotic (olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone) and the combination of lithium or divalproex with an atypical antipsychotic, based on recent evidence-based clinical practice guidelines for bipolar disorder⁸². Second-line therapy would include use of carbamazepine, oxcarbazepine, ECT, and the combination of lithium and divalproex. Clozapine is included under third-line agents in these guidelines. The choice of these agents would be reasonable for elderly bipolar patients as well, taking into consideration dosing and titration appropriate for the elderly.

While other first-line agents are being used more frequently, lithium remains a commonly used mood stabilizer in old age⁸⁷. In fact, in the study of standardized treatment for elderly bipolar patients mentioned previously⁸⁴, lithium was the most commonly prescribed treatment used by over 60% of patients. Available data on the use of lithium in elderly manic patients comes from a small number of open-label case series, naturalistic and retrospective studies, which suggest lithium can be used safely and effectively^{84,89–92}. Lithium therapy highlights many of the challenges associated with pharmacotherapy in elderly bipolar patients. Lithium is eliminated exclusively by the kidney, and age-related changes such as decreased creatinine clearance and glomerular filtration rate significantly affect lithium pharmacokinetics. In a study of lithium pharmacokinetics, Hardy *et al.*⁹³ determined that lithium excretion in the elderly was half the rate of younger patients. The elderly may also be more sensitive to adverse events and toxicity even with lithium serum levels considered 'normal' in adult populations^{94–96}. This has led to some controversy regarding appropriate lithium dosages and serum levels for the elderly. Some have recommended serum levels as low as 0.5 mmol/l⁹⁷, though others have argued that higher levels are associated with better outcome^{92,98}. A review of published studies in the elderly suggested that lithium dosages were 25–50% lower in the elderly with serum levels typically below 0.7 mmol/l⁸⁰. In the study of standardized treatment of geriatric bipolar disorder, the average dose of lithium used was 657 mg per day with an average serum level of 0.67 mmol/l⁸⁴.

The potential adverse effects of lithium include a wide range of disturbances involving the central nervous system (CNS), gastrointestinal, kidney, cardiac and endocrine systems. Common CNS effects include lithium-induced tremor, aggravation of parkinsonian symptoms and spontaneous extrapyramidal effects. In an administrative

Table 93.1 Challenges in the management of elderly patients with bipolar disorder

Diagnosis	Multiple psychiatric co-morbidities: dementia, anxiety and substance use disorders are the most likely particular concerns Multiple medical co-morbidity: metabolic/endocrine, cardiovascular and neurological diseases are particular concerns
Treatment	Lack of evidence-based treatment guidelines specific to geriatric bipolar disorder Age-related changes in drug metabolism Reduced tolerance to medication side effects (e.g. falls risk) Need to treat medical co-morbidity Multiple concomitant medications increase risk of drug interactions Age-specific adverse medication affects (e.g. mortality risk associated with antipsychotics)
Service delivery	Issues related to changes in social environment (isolation, communication or transportation difficulties) and treatment adherence Intensive service needs – increased need to coordinate care between health care providers, service agencies and/or family Projected shortage in specialty care clinicians and available services for geriatric populations

health database study of 2422 elderly new users of lithium, the rate of hospitalization for lithium-induced delirium was 2.5 per 100 person years, not significantly different from the rate of valproate-induced delirium⁹⁹. The risk of lithium-induced hypothyroidism might be greater in elderly patients than that seen in younger populations. For example, in a community study of elderly lithium users, one-third were on thyroid replacement or had elevated levels of thyroid-stimulating hormone⁸⁷. In a study of 1705 new elderly lithium users, 6% were treated for hypothyroidism, about twice the prevalence expected from a mixed-age population¹⁰⁰. Finally, another major concern related to lithium use in the elderly is the risk of drug–drug interactions. Numerous commonly used concomitant medications can reduce lithium clearance including diuretics, angiotensin-converting enzyme (ACE) inhibitors and some non-steroidal anti-inflammatory drugs⁷⁷. While thiazide diuretics were classically thought to be the drugs of greatest concern, these other agents might be even more problematic. In a population-based nested case–control study with 10 000 elderly lithium users, approximately 4% were hospitalized for lithium toxicity¹⁰¹. New use of a loop diuretic (e.g. furosemide) or an ACE-inhibitor independently increased the risk of hospitalization for lithium-induced toxicity by five- to sevenfold.

In the absence of controlled trial data, it is perhaps surprising that new use of valproate therapy for bipolar elders is surpassing that of lithium use. For example, in an administrative database study conducted between 1993 and 2000, new use of lithium carbonate fell consistently while valproic acid use increased, surpassing new lithium prescriptions midway through the observation period⁸⁸. By the end of the observation period, there were almost three new prescriptions for valproate written for every prescription of lithium. While there are no published randomized controlled studies, naturalistic observational studies suggest the use of valproate for acute mania in the elderly is effective and reasonably well tolerated^{84,92,102–108}. Dosages have ranged between 250 and 2250 mg per day and serum levels between 25 and 120 µg/ml with about 60% demonstrating some degree of benefit⁷⁷.

Based on case reports, valproate appears effective for elderly rapid-cycling bipolar patients as monotherapy¹⁰⁹ or in combination with lithium^{110,111}. Successful use of intravenous valproate has also been documented for acutely manic elderly patients who refused oral medications¹¹². There are significant dose-dependent changes in valproate pharmacokinetics in the elderly, including prolonged elimination half-life, especially important at higher doses, which might predispose the elderly to toxicity^{113,114}. The most frequent adverse events associated with valproate are excessive sedation and gastrointestinal intolerance, though under-recognized and potentially important side effects in the elderly also include thrombocytopenia¹¹⁵ and hyperammonaemia potentially leading to delirium¹¹⁶. In fact, while valproate is often considered a better tolerated, safer alternative to lithium for the elderly, one study found no differences in the rates of hospitalization for delirium comparing valproate to lithium⁹⁹. Valproic acid is also highly protein-bound and a weak inhibitor of cytochrome P450 2D6. As a result, potential drug interactions exist, including drugs such as tricyclic antidepressants, acetylsalicylic acid, warfarin and diazepam¹¹⁷.

There are no randomized controlled trials of the use of carbamazepine in the elderly and only a small number of naturalistic studies reported^{118,119}. Some have raised concerns about the tolerability of carbamazepine in the elderly suggesting that relatively low serum levels (below 9 µg/ml) are necessary to avoid neurotoxicity⁹⁸. Significant potential for important drug interactions may also limit its use in the elderly¹¹⁷.

There are virtually no published studies on the use of other anticonvulsants such as oxcarbazepine, topiramate and zonisamide for mania in the elderly. One case series of gabapentin therapy in elderly manic patients suggested it was safe and effective¹²⁰.

Though typical antipsychotics are not considered first-line agents for mania⁸², they are still used frequently in the elderly as adjunctive treatments for bipolar disorder. Typical antipsychotics can cause considerable side effects in the elderly, including anticholinergic effects, orthostatic hypotension and extrapyramidal effects⁷⁹. Rates of incident tardive dyskinesia in the elderly associated with typical antipsychotics are high¹²¹. In contrast, rates of acute extrapyramidal effects and tardive dyskinesia are very much lower with atypical antipsychotics and as a result they are being used with increasing frequency for elderly manic patients¹²². Atypical antipsychotics also appear to have mood-stabilizing properties that have earned them recognition as first-line therapies for acute mania in evidence-based treatment guidelines⁸². However, in contrast to the numerous randomized controlled trials of atypical antipsychotics in elderly demented patients¹²³ and a smaller number of studies in elderly schizophrenic patients^{124–127}, there are no randomized controlled trials of atypical antipsychotics for elderly bipolar patients. While commonly used for mania in the elderly as monotherapy and adjunctive treatments⁷⁸, there are remarkably few naturalistic studies and even case series reported in the elderly. In one case series, risperidone was found to be effective for elderly bipolar patients¹²⁸ and clozapine has been reported to be effective in a couple of case reports^{129,130}. In the case of clozapine, older adults are at greater risk of developing drug-related agranulocytosis compared with younger/mixed-age populations¹³¹.

Besides their well-described metabolic adverse effects, the use of atypical antipsychotics may be associated with specific concerns in the elderly including the risk of cerebrovascular adverse events and mortality^{132,133}. Interestingly, despite the obvious increases in weight, glucose intolerance and hyperlipidaemia associated with drugs like clozapine, olanzapine, quetiapine, and to a lesser extent risperidone, neither the randomized controlled trials in the elderly dementia patients, nor population-based studies have suggested a similar concern¹³³. Whether this is because the elderly are less susceptible to these effects, or that the lower doses typically used for the elderly mitigate these effects is unclear. Despite the lack of a similar concern from the published data, it is important to note that elderly bipolar patients may have different susceptibility risks compared to dementia patients. Furthermore, it would seem prudent to be particularly cautious in patients who are at high risk for the metabolic consequences of atypical antipsychotics such as those with obesity and pre-existing diabetes and hyperlipidaemia.

With respect to cerebrovascular adverse events, while both risperidone and olanzapine carry black-box warnings for these events based on the randomized controlled trials in elderly dementia patients, it is likely that the other atypical antipsychotics as well as the typicals have similar risks¹³². Similarly, all antipsychotics, both typical and atypical, now carry black-box warnings for an increased risk of mortality based on the randomized controlled trials with dementia patients, as well as population-based observational studies¹³³. Taken together, it is unclear whether elderly bipolar patients have similar susceptibility to these serious cardiovascular/elevated mortality adverse events demonstrated in elderly patients with dementia.

Finally, there are no specific data on the use of benzodiazepines, ECT, transcranial magnetic stimulation or psychosocial interventions for elderly manic patients, even though they are clearly being used and have been recommended for the elderly⁸⁶.

Treatment of Bipolar Depression in Older Adults

Bipolar depression is a severe and pervasive problem among all individuals with bipolar illness, and mixed-age individuals with bipolar disorder experience depressive symptoms three times more frequently than manic symptoms^{134,135}. In addition to greater time duration, disability associated with bipolar depression is disproportionately greater than that associated with bipolar mania^{136,137}. Underscoring the malignant effects of dysphoric mood states in bipolar populations, bipolar depression has been reported as a major contributor to completed suicide¹³⁸.

An analysis by Depp and colleagues⁷⁶ evaluated health-related quality of life among middle-aged and older adults with bipolar disorder, finding that depressive symptoms, along with psychosis and cognitive impairment significantly contribute to reduced quality of life. In depressed bipolar elders, treatments directed at mood dysregulation can alleviate disability¹³⁹, and may help avoid 'behavioural disuse atrophy'^{140,141}.

While the earliest and largest number of prospective randomized controlled bipolar treatment trials have evaluated the anti-manic activity of various drug treatments¹⁴², the most salient issue for individuals with bipolar disorder appears to be efficacy of treatments for bipolar depression. A recent study involving 469 individuals with bipolar disorder found that patients prioritized reduction of depression severity over mania severity¹⁴³.

Unfortunately, there are few established treatments for bipolar depression, and the topic area has been severely neglected up until very recently¹⁴⁴. Commonly utilized drug therapies in mixed-age patients include lithium, the anticonvulsants valproate, lamotrigine and carbamazepine as well as the atypical antipsychotics and combination therapy with antidepressant medications adjunct to mood stabilizers^{145,146}. Fountoulakis and Vieta¹⁴⁴ noted that good research-based evidence supported by at least one placebo-controlled trial of 'sufficient' magnitude exists for selected atypical antipsychotic agents (olanzapine, quetiapine both as monotherapy or olanzapine in combination with fluoxetine). A recent International Consensus Group (ICG) suggested that only three monotherapies (lithium, lamotrigine, quetiapine) have first-level evidence for the treatment of acute and long-term bipolar depression¹⁴⁷. In addition, the use of antidepressants is controversial in bipolar depression because of potential negative consequences (switching, rapid cycling), and the ICG has not supported their general use for bipolar depression¹⁴⁷. The American Psychiatric Association (APA) guidelines for the treatment of Bipolar Disorder¹⁴⁸ recommend that the use of antidepressant agents in bipolar populations be approached cautiously and parsimoniously.

Uncontrolled and secondary analyses in geriatric bipolar depression suggest a possible role for the traditional mood-stabilizing medication lithium and for lamotrigine^{149,150}. In addition, a group of US investigators have recently initiated a preliminary, open-label trial of adjunct lamotrigine therapy in geriatric (age 60 and over) bipolar depressed populations utilizing a geriatric bipolar trials network. Preliminary data from the first seven patients (intention to treat) demonstrated significant reduction in change from baseline Montgomery Asberg Depression Rating (MADRS) scores (baseline mean 28, endpoint last observation carried forward (LOCF) mean 14.7, $P = 0.005$, with good tolerability of lamotrigine by bipolar depressed elders¹⁵¹.

Some atypical antipsychotic drugs, widely used in mixed-age bipolar populations may also be of benefit in bipolar elders. Sajatovic and Paulsson¹⁵² conducted a secondary analysis of combined results from

two eight-week, double-blind, randomized, placebo-controlled studies of quetiapine in fixed doses (300 or 600 mg/day) in the treatment of depressive episodes associated with bipolar I or II disorder^{153,154}. The primary efficacy endpoint was MADRS total score change from baseline to week 8. Efficacy populations included 72 adults aged 55–65 years (mean $\pm$ SD 58.4 ± 2.6 years; $n = 23$, 23 and 26 for quetiapine 300 mg/day, quetiapine 600 mg/day and placebo, respectively) and 906 adults aged 18 to <55 years (mean 35.7 ± 9.9 years; $n = 304$, 298 and 304, respectively). Illness characteristics, including DSM-IV diagnoses and baseline MADRS and Hamilton Depression Scale (HAM-D) scores were broadly similar between older and younger adults receiving quetiapine or placebo. In older adults, least square mean $\pm$ SE MADRS score decreased 13.4 ± 2.4 with quetiapine 300 mg/day and 14.2 ± 2.5 with quetiapine 600 mg/day vs. 8.0 ± 2.3 with placebo ($P = 0.097$ and 0.057 , respectively, vs. placebo). In younger adults, mean MADRS score decreased 16.8 ± 0.7 and 16.5 ± 0.7 vs. 11.2 ± 0.7 , respectively ($P < 0.001$, both doses vs. placebo). Quetiapine (both doses) significantly decreased HAM-D and CGI-S scores and increased CGI-I scores relative to placebo in older and younger adults. The most frequent adverse effects associated with quetiapine in older and younger adults were dry mouth, somnolence, sedation and dizziness. Rates of treatment-related withdrawals were similar in older and younger adults.

Aripiprazole, an atypical antipsychotic compound which is approved by the US Food and Drug Administration (FDA) for the treatment of bipolar mania and for the long-term treatment of bipolar disorder was recently prospectively tested in a small sample ($N = 20$) of bipolar older adults¹⁵⁵. Older bipolar I adults who were suboptimally responsive to their bipolar pharmacological treatments received 12 weeks of open-label aripiprazole added on to existing mood stabilizer¹⁵⁶. Aripiprazole was initiated at 5 mg daily and increased as tolerated. Efficacy outcomes included psychopathology scores (Young Mania Rating Scale (YMRS), HAM-D), extrapyramidal symptom assessments, and level of functioning measurement (Global Assessment Scale (GAS)). Mean age of the sample was 59.6 years, range 50–83 years. The majority of individuals had bipolar depression. Individuals had significant reductions in HAM-D and YMRS scores. There were also significant improvements in the GAS. Mean daily dose of aripiprazole was 10.26 mg/day SD ± 4.9 , range 5–20 mg/day. Overall, aripiprazole was efficacious and relatively well tolerated. Of particular note, aripiprazole therapy was associated with improvements in bipolar depression in this older population. While atypical antipsychotics offer potential promise in treating geriatric bipolar depression, this must be tempered by concerns regarding antipsychotic drugs in elders discussed above.

While the role of antidepressant agents to treat bipolar depression in mixed-age populations is controversial due to concerns regarding manic switching, mixed episodes and rapid cycling^{148,144}, preliminary data in geriatric bipolar depression suggest that antidepressants can have beneficial effects on selected health outcomes. One analysis found decreased rates of hospitalization for manic/mixed episodes during a 5135 person-years follow-up study of antidepressant use among older adults with bipolar disorder¹⁵⁶. Another report suggested that older bipolar adults with a recent history of suicide attempts were less likely to have received treatment with mood stabilizers and antidepressants compared to older bipolar individuals with no recent history of suicide attempts¹⁵⁷. Finally, ECT must be mentioned as an efficacious and well-tolerated somatic therapy for bipolar depressed elderly individuals¹⁵⁸.

Maintenance Treatment of Bipolar Disorder in Older Adults

Maintenance or longer term treatments for geriatric bipolar disorder are minimally presented in the psychiatric literature. A recent retrospective analysis of elders with unipolar depression and elders with bipolar disorder compared each patient to his or her own clinical course before and after lithium treatment¹⁵⁹. In this analysis lithium maintenance significantly reduced the probability of relapse and recurrence, suicidal behaviour, and severity of mood disturbance¹⁵⁹.

A secondary analysis of older adults (age 55 and older) from two placebo-controlled, double-blind bipolar maintenance treatment studies compared patients randomized to treatment with lamotrigine, lithium or placebo for up to 18 months¹⁶⁰. The primary endpoint was time-to-intervention for any mood episode; secondary measures included time-to-intervention for depression and mania/hypomania/mixed mood. The group of 638 patients included 98 older adults. Mean age of the older adult sample was 61 years ($\pm$ SD 6.0, range 55–82 years). In the group of older adults, lamotrigine, but not lithium, significantly delayed time-to-intervention for any mood episode compared with placebo. Lamotrigine also significantly delayed time-to-intervention for a depressive episode compared with lithium and placebo. Lithium did significantly better than lamotrigine for time-to-intervention for mania. Side effects for both lamotrigine and lithium were generally mild to moderate in severity including similar rates of skin rash (3% for lamotrigine, 5% for lithium). Lamotrigine and lithium daily doses were 240 mg/day and 750 mg/day, respectively.

Elderly and young adults from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) were compared on prescription patterns and recovery status¹⁶¹. STEP-BD was a multicentre National Institute of Mental Health (NIMH)-funded project designed to evaluate the longitudinal outcome of patients with bipolar disorder that involved extensive assessment across multiple domains including demographic data, diagnosis, symptom severity, treatment and clinical status. Patients achieved 'recovered' status when they experienced eight consecutive weeks without significant symptoms. Treatment regimes and doses were compared between younger participants ($N = 3364$) 20–59 years old, and older participants 60 and above ($N = 246$). Of the 3615 STEP-BD patients, 67.6% ($N = 2442$) achieved a recovered status – 78.5% ($N = 193$) of older patients vs. 66.8% of the younger patients. On average, participants who reached a recovered status took 2.05 medications with no difference between age groups. Lithium was prescribed to 37.8% of younger patients vs. 29.5% of older patients. Younger and older patients differed significantly on dosages prescribed of lithium, valproate and risperidone (lower dose for elderly). Significant reduction in lithium dosing was observed among individuals aged 50 and older although 42.1% of recovered bipolar elders achieved recovery with lithium alone compared with only 21.3% of the younger cohort. Thus, while recovery is achievable in the elderly, more than one medication is generally needed regardless of age.

Psychotherapy may improve illness self-management in bipolar elders. For example, McBride and Bauer¹⁶² have suggested that older adults with bipolar disorder appear to benefit from psychosocial interventions that assist in managing both mental illness and ageing-related issues. A manual-based medical care model (BCM) developed by Kilbourne and colleagues¹⁶³ appears feasible for implementation in bipolar older adult populations. The BCM includes sessions on

bipolar symptom patient self-management, use of nurse-run coordination/management, and dissemination of guidelines to care providers on cardiovascular disease risk in bipolar elders¹⁶³. Given the generally substantial medical co-morbidity seen in elderly bipolar patients, integrated therapies that address both bipolar and medical conditions are likely to be critical in order for optimal outcomes.

Emerging evidence suggests a possible neuroprotective/neurotrophic of maintenance lithium treatment^{164–166}. As noted above, lithium has been found to inhibit glycogen synthase kinase-3, which is a key enzyme in the metabolism of amyloid precursor protein and in the phosphorylation of tau protein involved in the pathogenesis of Alzheimer's disease^{59,144,167}. A cross-sectional, case-control study from Brazil found that long-term lithium treatment reduced the prevalence of Alzheimer's disease in elderly patients with bipolar disorder to levels consistent with those seen in the general population¹⁶⁶. Similarly, results from a nation-wide Danish register-based study suggest that maintenance lithium treatment may be associated with a reduced rate of dementia¹⁶⁴. In addition, in bipolar elders (mean age 66.0 ± 9.7 years), brain lithium levels and *N*-acetylaspartate (NAA), a marker of neuronal integrity, seems to be positively associated on magnetic resonance spectroscopy¹⁶⁵.

Adherence to Treatment

It has been demonstrated that nearly 1 in 2 individuals with bipolar disorder is non-adherent with prescribed medications^{168,169}. Age, marital status, gender, educational level, and psychiatric co-morbidity, in particular substance abuse, have all been reported to be related to treatment non-adherence^{168,170,171}. One study¹⁷² evaluated antipsychotic medication adherence among older (age 60 and older) vs. younger individuals with bipolar disorder using a large Veterans Affairs case registry ($N = 73\,964$). Medication adherence was evaluated using pharmacy refill patterns. Among older adults, 61.0% ($N = 3350$) were fully adherent, while 19% ($N = 1043$) were partially adherent and 20% ($N = 1098$) were non-adherent. Among younger adults, 49.5% ($N = 10\,644$) were fully adherent, while 21.8% ($N = 4680$) were partially adherent, and 28.7% ($N = 6170$) were non-adherent. In both groups, co-morbid substance abuse and homelessness were predictors of bipolar medication non-adherence.

Additional studies in populations prescribed mood-stabilizing medications note that patient knowledge of mood stabilizers correlates negatively with age, whereas sex and duration of treatment seem unrelated to knowledge^{74,173}. Older individuals on mood stabilizers have been found to have more negative views on the doctor-patient relationship and more negative views on mood stabilizers in general⁷⁴ compared to younger patients. While non-adherent rates in bipolar elders can be substantial, it is possible that adherence behaviours could be modified via intensive efforts at improving illness and medication knowledge as well as approaches that improve the doctor-patient relationship.

CONCLUSIONS

While the literature on late-life bipolarity has increased in recent years, there remain numerous and important gaps in the published data on the neurobiology, epidemiology, phenomenology and evidence base of treatment of geriatric bipolar affective disorder. This knowledge deficit limits our ability to fully understand and anticipate future healthcare requirements or to plan an optimal care-system.

Older adults with bipolar illness often experience substantial symptomatology, impaired physical and psychosocial functioning, and utilize extensive health care resources. More research is critically needed to understand expected illness trajectory, relationship to cognitive status and treatments that optimize all levels of health and functioning.

There is very limited evidence to support specific biologic or psychosocial interventions for either acute or longer term care of older adults with bipolar disorder. The current literature, based mainly on retrospective analyses or small sample and mixed-age studies, suggests that medication treatments for bipolar elders will generally require modification in dosing and titration, and should be guided by medical burden/frailty as well as the presence of medications that are co-prescribed for medical illnesses. Elderly patients with bipolar illness may be prone to specific drug-related side effects such as renal failure or extrapyramidal symptoms, and when side effects occur, the sequelae may lead to marked disability (for example, a fall leading to hip fracture). Family members and/or caregivers should be involved in treatment planning if at all possible, and clinicians need to be alert to the important issues of ageing-related reduced ability to metabolize/clear psychotropic drugs, treatment adherence and the development of medication intolerance that may develop over time. The ageing process will also often require modifications in psychosocial treatments for bipolar illness. Finally, bipolar elders will generally require close clinical monitoring, flexibility on the part of treatment providers, and utilization of available supports such as ancillary care staff and family.

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Schizophrenic Disorders and Mood-Incongruent Paranoid States

Late-Life Psychotic Disorders: Nosology and Classification

Nicole M. Lanouette, Lisa T. Eyler and Dilip V. Jeste

University of California, San Diego, La Jolla, CA, USA

With the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and 11th edition of the International Classification of Diseases (ICD-11) currently under development, it is timely to review the history of the nomenclature of psychiatric disorders. The notion that mental disorders could occur in particular periods of life, such as old age, first appeared only in the latter half of the nineteenth century¹. During this short history, there has been great inconsistency regarding the nosology and classification of late-life mental disorders, particularly psychotic disorders.

There are two groups of adults with late-life non-affective psychotic disorders. The first includes individuals who are now older, but whose psychotic illness (e.g. schizophrenia, delusional disorder) emerged early in life. Debates about the classification of these patients are the same as those for younger adults (e.g. degree of overlap between psychosis and affective disorders, issues of duration and course), and there is general consensus that these patients should retain their original diagnosis into old age unless symptoms change dramatically enough to warrant a different diagnosis. The second group of patients includes those with new onset of non-affective psychosis late in life. In the majority of these cases, psychosis is secondary to a general medical condition such as dementia. As there has been little controversy about how to classify these 'organic' psychoses in the elderly, this group is not discussed in the present chapter. In contrast, there has been extensive debate about how to classify late-onset, non-affective, non-organic psychoses. The history of the nosology of this group is replete with overlapping terms, inconsistent age cut-offs, multiple definitions of the same nomenclature, and different methods of conceptualizing similar disorders. In an effort to bring greater consistency to the field, experts in late-life psychotic disorders from 12 countries convened in 1998 and produced an international consensus statement². This statement presented an agreed-upon set of terms to describe late-life psychotic disorders, and recommended that late-onset schizophrenia (LOS, with onset of symptoms after age 40) be designated a formal subtype of schizophrenia. However, neither the ICD-10³ nor the DSM-IV-TR⁴ incorporated this recommendation, continuing the debate over how to best categorize late-onset psychotic disorders.

EARLY HISTORY

Kraepelin was one of the first clinical researchers to recognize that non-affective psychoses could arise in middle age or later in life. Although the term 'dementia praecox', with its inherent emphasis on an early age of onset, would seem to exclude late-onset cases, Kraepelin himself reported that one-third of his patients had symptom onset after age 30⁵. Kraepelin also studied a group of patients he described as suffering from 'paraphrenia'. This term had been used earlier by Guislain as a synonym for the syndrome of 'folly'⁶, and was used by Kraepelin to characterize a group of patients with minimal volitional and affective disturbance, prominent paranoia and a relatively preserved personality. While some of the subgroups of paraphrenia he described had a relatively later age of onset, Kraepelin did not consider paraphrenia to be exclusively a late-onset disorder. Furthermore, follow-up studies of these patients showed that they did not differ greatly from those classified as dementia praecox^{7,8}. Thus, many of Kraepelin's followers ultimately came to believe that dementia praecox and paraphrenia were the same disorder and that this disorder could arise early or late in life.

Other clinician investigators working during this time, however, felt that psychotic disorders arising for the first time in late life should be classified separately. The history of these classifications has been thoroughly reviewed⁹. Gaupp¹⁰ distinguished between dementia praecox and a disorder diagnosed for the first time in postmenopausal women that was characterized by depressive agitation, resulting in 'mental weakness'. Stransky¹¹ used the term 'dementia tardiva' to describe late-onset dementia praecox. Some authors emphasized the prevalence of paranoid symptoms among those with onset of psychosis late in life by using terms such as 'paranoia chronica'¹² or 'involutional paranoia'¹³. Following this tradition, Albrecht's¹⁴ classification of late-onset psychotic patients distinguished between patients with paranoid symptoms and little personality disturbance ('presenile paraphrenia') and those with 'depressive madness resulting in imbecility'. The latter category seemed somewhat similar to a late-onset form of dementia praecox. Others who described syndromes of late-onset dementia

praecox used the terms 'involuntional paraphrenia'¹⁵, 'stiffening involuntional psychosis'¹⁶ and 'paraphrenia'¹⁷. Unfortunately, the use of 'paraphrenia' to indicate an age of onset distinction led to a great deal of later confusion. Some psychiatrists employed the term to indicate a separate phenomenology independent of age of onset (much like Kraepelin's original use; e.g. Leonhard¹⁸), while others used that diagnosis to encompass most late-onset psychoses.

1940–1970

Using his father's term for dementia praecox, 'schizophrenia', Manfred Bleuler¹⁹ described individuals with 'late-onset schizophrenia' as those with onset after age 40 exhibiting symptoms similar to those with an earlier onset of the disorder and no evidence of brain disease. Very few of these patients had onset after the age of 60. This classification was adopted by most subsequent German authors⁹.

In the UK during this period, however, the classification of late-onset psychotic disorders took a somewhat different path. Studying a group of patients with onset after age 60, Roth and Morrissey²⁰ described a syndrome of paranoid delusions and hallucinations in the context of preserved intellect, personality and affect. Because of the phenomenological similarity to Kraepelin's 'paraphrenia' and due to its late onset, Roth and colleagues termed this disorder 'late paraphrenia'^{21,22}, a name that was designed to encompass all late-onset, non-affective, non-organic psychoses in which paranoid symptoms were prominent. Thus, the term was both broader than late-onset schizophrenia, in that it encompassed late-onset delusional disorder, and more restrictive, in that it did not include non-paranoid forms of late-onset psychosis. Post²³ developed a different descriptive system. He divided late-onset (after age 50) psychoses into paranoid hallucinosis, schizophreniform syndrome, and schizophrenic syndrome. Based on a three-year follow-up, however, he concluded that these three diseases were actually a continuum of the same disorder with slightly different symptom profiles.

European debates and developments were slow to influence the classification system used in the USA. The first Diagnostic and Statistical Manual of Mental Disorders (DSM-I)²⁴ used the term 'involuntional psychotic reaction', which encompassed both paranoid ideation and depression in older patients. This amalgam of affective and psychotic symptoms in the elderly was split in the second edition (DSM-II)²⁵ in favour of 'involuntional paranoid state (involuntional paraphrenia)' and 'involuntional melancholia'. The former disorder, like Roth's late paraphrenia, was characterized by 'delusion formation with onset in the involuntional period. The absence of conspicuous thought disorders typical of schizophrenia distinguishes it from that group'²⁵. Schizophrenia could be diagnosed in individuals with any age of onset.

1970–PRESENT

As European psychiatrists began to study patients with late paraphrenia more systematically, new classification systems in the USA were restricting the diagnosis of late-onset psychosis. One of the five Feighner Research Criteria²⁶ for schizophrenia was age of onset before age 40. In the third edition of the DSM (DSM-III)²⁷, a diagnosis of schizophrenia could not be made if the onset of symptoms was after age 45. Late-onset psychosis that involved persistent persecutory delusions with prominent hallucinations could be given a diagnosis of 'paranoid disorder'. This classification system was in

stark contrast to both earlier RDC (research diagnostic criteria)²⁸ and to the ninth version of the International Classification of Diseases (ICD-9)²⁹, neither of which imposed age-of-onset restrictions for schizophrenia. The ICD-9 also allowed for a diagnosis of paraphrenia at any age. The revised version of DSM-III (DSM-III-R)³⁰ rectified the omission of late-onset schizophrenia by providing a separate diagnostic category for those diagnosed with schizophrenia after age 45. In the most recent versions of the DSM (DSM-IV-TR)⁴ and the ICD (ICD-10)³, no special categories exist for late-onset psychoses, although schizophrenia may be diagnosed at any age.

TOWARD A CONSENSUS

It is clear from this historical review that there has been little consensus regarding the classification of late-onset, non-affective, non-organic psychoses. Two opposing lines of thought have pulled the terminology in different directions. On the one hand, some authors have preferred to emphasize the similarity of late-onset psychoses to the corresponding early onset disorders. This has resulted either in the use of terms such as 'late-onset schizophrenia' and 'late-onset delusional disorder' or has prompted a move toward ignoring age of onset altogether in classification (e.g. DSM-IV-TR⁴, ICD-10³). On the other hand, some members of the psychiatry community (mainly in Europe) have preferred to emphasize differences between the phenomenology of late- and early onset psychosis and thus have tended to use distinct terminology, such as 'paraphrenia' or 'late paraphrenia'³¹.

Thus, questions remain about which terminology would optimally serve the clinical and research communities. These questions have become particularly timely with the development of DSM-V^{32,33} and ICD-11. There are at least two overlapping issues to consider. First, how similar or different are the late-onset, non-affective, non-organic psychoses from early onset disorders? If late-onset patients are no different from early onset patients in terms of demography, phenomenology, aetiological factors, prognosis and treatment, then it would be redundant to classify them in a separate category. If, however, such features differ between early onset and late-onset individuals, then it would seem important to preserve a distinct diagnostic category in order to encourage further research and allow for optimal prognostic evaluation and treatment. The magnitude or extent of the differences between early- and late-onset individuals should also influence the terminology chosen for the diagnostic categorization. If a majority of critical clinical features are shared with an early onset disorder, then it would make sense to adopt a term such as 'late-onset schizophrenia'. If the extent of differences is sufficiently large, a separate term would be warranted. A second issue to consider in determining the best classification scheme is what age of onset should be called 'late'. Most of the American studies of late-onset, non-affective, non-organic psychosis have included patients with onset after age 45 and generally before age 65. In addition, among the patients in Bleuler's late-onset schizophrenia studies, only 4% had an onset after age 60⁹. In contrast, most studies of late paraphrenia have been conducted with patients whose onset was after age 65. Differences in age of onset between late-onset schizophrenia and late paraphrenia studies may help to explain some of the diagnostic confusions that have persisted.

Only relatively recently has the weight of evidence become sufficiently great in the field of late-life psychoses to allow for adequate consideration of these issues. In 1998, the International Late-Onset Schizophrenia Group met to present reviews of published data on

Table 94.1 Comparison of typical-onset (age 15–40) schizophrenia, middle-age-onset (age 41–65) schizophrenia and very-late-onset (age ≥ 65) schizophrenia-like psychosis

	<i>Typical onset</i>	<i>Middle-age onset</i>	<i>Very late onset</i>
Female : male ratio	0.6 : 1	2 : 1	up to 8 : 1
Poor premorbid functioning	++	+	–
Family history of schizophrenia	++	++	–
Sensory deficits	–	–	+
Negative symptoms	+++	++	–
Thought disorder	+++	+++	–
Structural brain abnormalities (strokes, tumours)	–	–	+
Antipsychotic dose	+++	++	+
Tardive dyskinesia risk	+	+	++

+, presence; –, absence; number of symbols indicates degree of presence.

late-onset, non-affective, non-organic psychosis and to develop a consensus statement regarding diagnostic categories². The statement recognizes two illness classifications: late-onset (onset after the age of 40 years) schizophrenia and a very-late onset (onset after age 60) schizophrenia-like psychosis. Thus, the group determined that it was important to recognize a diagnostic distinction based on age of onset, due to differences between late- and early onset patients, but that the disorders were not sufficiently different to warrant a separate nomenclature. In addition, the group felt that a further distinction was warranted within late-onset patients between those with onset in middle age and those with very late onset, based on major differences between these groups.

The similarities and differences among early onset schizophrenia, late-onset schizophrenia and very-late-onset schizophrenia-like psychosis are summarized in Table 94.1. There are many areas of similarity between both late-onset groups and early onset schizophrenia, such as symptoms^{34–36}, family history³⁵, brain imaging findings^{37–39}, and nature of cognitive impairments³⁸. The decision to retain the word ‘schizophrenia’ in the nomenclature of both disorders was driven by these strong similarities. However, while the nature of cognitive impairments and symptoms are similar, late-onset patients typically show less severe cognitive impairment compared to early onset patients^{35,40}, and a recent study found late-onset patients had less severe overall psychopathology⁴¹. On the other hand, the consensus statement’s distinction between those with middle-age-onset and old-age-onset psychoses was motivated by epidemiological, aetiological and symptom differences between these two groups. Very-late-onset schizophrenia-like psychosis is different from both early- and late-onset schizophrenia, in that these cases tend to be associated with sensory impairment and social isolation²², although these may be consequences rather than causes of these disorders⁴². Patients with very-late-onset schizophrenia are also less likely to exhibit formal thought disorder, negative symptoms^{35,43} and a wide range of cognitive biases⁴⁴, but are more likely to have visual hallucinations^{28,37,45} and have less familial aggregation of schizophrenia⁴⁶. A recent magnetic resonance diffusion tensor imaging study of frontal cortex white matter connections found no structural differences between normal controls and patients with onset of psychosis after age 60⁴⁷. It should be emphasized that the members of the International Late-Onset Schizophrenia Group were not unanimous in their support of the particular age cut-offs given in the consensus statement and also felt that the proposed nomenclature was not an end but a beginning of future research into this important topic. Their proposed groupings have

been at least partially supported by subsequent research⁴¹, but more investigations are needed.

Late-onset schizoaffective disorder and late-onset delusional disorder are not specifically addressed in the consensus statement. Late-onset schizoaffective disorder appears to share a majority of critical clinical and demographic features with late-onset schizophrenia⁴⁸. Thus, late-onset schizoaffective disorder appears to be a subgroup of late-onset schizophrenia in which mood symptoms are also present. Late-onset delusional disorder, by contrast, can be distinguished from late-onset schizophrenia by a unique preoccupation with non-bizarre delusions in the context of preserved affective and personality functioning in other domains⁴⁹. In addition, treatment of these individuals may be more challenging than in schizophrenia due to a difficulty in establishing rapport with therapists⁵⁰. Cognitive function, however, is somewhat more preserved in older patients with delusional disorder than in those with schizophrenia⁵⁰. Unfortunately, there is a lack of research comparing early- and late-onset delusional disorder.

Further research is needed to clarify the classification of late-onset psychotic disorders. Specifically, longitudinal follow-up studies are necessary to determine whether the course of illness is different in the three groups of patients and how the course of late-onset disorders compares to that of early onset syndromes. The consensus classification provided a framework for these investigations, although it remains to be seen how those guidelines will be incorporated in DSM-V and ICD-11. In summary, despite a tumultuous history, the future for research and clinical work in late-onset psychotic disorders appears to be on firmer footing.

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Schizophrenic Disorder and Mood-Incongruent Paranoid States: Epidemiology and Course

Cynthia D. Fields and Peter V. Rabins

Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, USA

OVERVIEW OF SCHIZOPHRENIA AND RELATED DISORDERS

Schizophrenia is a psychotic illness characterized by positive symptoms (hallucinations, delusions, disorganized speech with thought disorder, and disorganized behaviour), negative symptoms (inexpressive or 'flat' affect, poverty of speech, inability to initiate activity) and progressive impairment of social and occupational functioning. Typically, schizophrenia begins in late adolescence or early adulthood and follows a chronic course. Age of onset is, on average, 10 years earlier in males than in females. Recovery to baseline personality and social functioning is rare. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) requires that symptoms be present for six months as a means of ensuring chronicity. To qualify for a diagnosis of schizophrenia, symptoms cannot be due to a primary mood disorder, such as major depression or bipolar disorder, cognitive impairment, including delirium, an acute medical condition or the effects of a substance.

Less commonly, schizophrenia can begin in middle or late life. Summing up the epidemiological studies, Harris and Jeste concluded that almost one quarter of schizophrenia patients had onset of illness after the age of 40¹. In addition, late-onset psychotic symptoms, such as hallucinations and delusions, can be seen in a variety of disorders, ranging from delirium to bipolar disorder. Schizophrenia should be distinguished from delusional disorder, which tends to begin in mid-life and is characterized by the presence of non-bizarre, fixed, false beliefs. In delusional disorder, hallucinations, when present, are not prominent, and psychosocial functioning is not markedly impaired. Several subtypes of this disorder exist, with persecutory delusions being the most common in the elderly.

EARLY-ONSET VERSUS LATE-ONSET DISORDERS

It remains unclear whether early-onset and late-onset schizophrenias (EOS and LOS, respectively) are distinct disorders. Both EOS and LOS are characterized by the presence of positive symptoms, particularly systematized delusions. In late-onset cases delusions most often are of the persecutory or partition type, with partition delusions being almost unique to that group. Partition delusions refer to the belief that persons or forces (such as gas or electricity), usually of

a threatening nature, are operating or entering the home through the walls, ceilings, floors or doors, attempting to interfere. Hallucinations can also be seen in both EOS and LOS. Multimodal hallucinations (i.e. auditory, visual, sensory, gustatory and tactile) are characteristic of the late-onset group², while early-onset cases typically have auditory hallucinations only. Schneiderian first-rank symptoms, e.g. hearing a running commentary or two or more voices conversing, can be seen in both groups³.

Important differences between early- and late-onset cases include infrequent formal thought disorder and fewer negative symptoms, such as affective flattening, in late-onset cases, as well as better premorbid functioning, including better occupational and marital histories. Mental functioning and personality remain relatively well preserved in late-onset cases. Jeste *et al.* compared three groups – younger persons with EOS, older persons with EOS, and LOS – and found a similar overall pattern of neuropsychological impairment, but with some slight differences favouring the late-onset group⁴. Likewise, a recent review by Rajji and Mulsant compared older patients with EOS versus LOS and found them to be equally cognitively impaired, exhibiting deficits in executive functioning, visuo-spatial ability and verbal fluency⁵. Both groups respond well to neuroleptics but later onset cases have a more favourable short-term prognosis than those with onset before 40. In spite of the many similarities, the preservation of personality and lack of deterioration in function lead some experts to challenge the inclusion of later onset cases in the traditional definition of schizophrenia.

INTERPRETATION OF EPIDEMIOLOGICAL DATA

Epidemiological studies of schizophrenia and associated disorders in the elderly face several challenges. First, terminology has changed over time. In 1912 Emil Kraepelin introduced the term 'paraphrenia' to describe a condition characterized by schizophrenia-like delusions and hallucinations not associated with mood disorder, but in the last edition of his text book classified such individuals as having schizophrenia because the course of their illness followed that disease. Roth later revived and modified the phrase 'late paraphrenia' to describe a late-life-onset disorder characterized by prominent paranoid delusions but an absence of social and functional deterioration⁶.

Second, diagnostic criteria pertaining to age cut-offs have changed over time. Prior to DSM-III-R, schizophrenia could not be diagnosed in individuals who had onset of symptoms after age 44. Beginning with DSM-III-R, onset after 44 was allowed but cut-offs for what could be defined as 'late-onset' schizophrenia have varied. More recently, a consensus statement proposed by an international group of experts in the field defined late-onset schizophrenia as arising after 40 years of age and very-late-onset schizophrenia-like psychosis (VLOSLP) as arising after 60 years of age⁷.

Methodological challenges are a third reason why estimates of the incidence and prevalence of schizophrenic illness in late life vary widely. For example, suspicious individuals are more likely to refuse to participate in population-based surveys and this is compounded by the likelihood that such individuals are socially isolated. Furthermore, individuals with cognitive impairment are often excluded from studies in both community and institutional settings, resulting in an underestimate of the true incidence and prevalence of psychosis in the elderly. Finally, since the prevalence of psychotic disorders is much lower than that of cognitive or affective disorders, misattribution of psychotic symptoms to these other disorders is likely.

INCIDENCE AND PREVALENCE OF PSYCHOTIC DISORDERS

Methodological challenges aside, the incidence and prevalence of psychotic disorders in late life are rather low. Data from community samples suggests that the prevalence of schizophrenia is 1% or less in older age groups, regardless of age of onset. The Epidemiologic Catchment Area Study⁸, a large multisite community survey in the United States conducted in the early 1980s, estimated the prevalence of schizophrenia in the community to be 0.6% in the age group 45–64 years, and 0.2% in the 65 and over age group using DSM-III criteria. These rates were approximately one-half that of the younger age groups. Almost twenty years later, Copeland *et al.* sampled general practitioner lists in the UK and found similarly low rates of DSM-III-R schizophrenia (0.12%) and delusional disorder (0.04%) in the 65+ age group⁹. Copeland's group also reported on incidence, with 3.0 new cases of schizophrenia and 15.6 cases of delusional disorder having developed per 100 000 per year.

In a recent large study of the prevalence of psychotic disorders in the Finnish population, Perala *et al.* reported DSM-IV schizophrenia in 1.15% of 45–54 year-olds, 0.86% of 55–64 year-olds and 0.92% of those aged 65 and over. Almost 0.5% of the 65 and over age group met criteria for delusional disorder, whereas delusional disorder was not found in persons under age 45¹⁰. It is important to note that Perala *et al.*'s use of multiple sources of information, including case notes, may have resulted in higher prevalence estimates. Incidence estimates primarily come from clinical samples and suggest that the development of schizophrenia in late life is rare.

In 1975 Kay used first-admission data from England and Wales to assess the incidence of LOS and found the rates of schizophrenic illness (broadly defined) in ages 65+ to be 10–15 and 20–25 per 100 000 per year in men and women, respectively¹¹. These estimates were similar to those reported years later by Holden, with an estimated annual incidence of VLOSLP between 17 and 24 per 100 000 population¹². The incidence of LOS was reported in another Camberwell study to be 12.6 per 100 000, half that for the under 25 age group. Conversely, van Os *et al.*, using first-admission data, found that, over the age of 60, the annual incidence of schizophrenia-like psychosis increased by 11% with each 5-year increase in age¹³.

INCIDENCE AND PREVALENCE OF SINGLE PSYCHOTIC SYMPTOMS

The prevalence of psychotic symptoms in the elderly in disorders other than LOS and VLOSLP is high. For example, estimates of the point prevalence of isolated persecutory or paranoid ideation in the general elderly population are between 4% and 6%, while the incidence of auditory hallucinations and delusions in community-dwelling elderly has been estimated at 6.0% over a period of 3.6 years. Tien's analysis of ECA data showed a general rise in the incidence of hallucinations, including auditory, visual and somatic, with advanced age, especially after about age 65 or 70¹⁴. Visual hallucinations have been shown to be significantly associated with visual impairment in the elderly. The label Charles Bonnet syndrome is applied to isolated vivid visual hallucinations seen in the setting of ocular pathology, in which insight is at least partially retained. Among non-demented 85-year-olds in Sweden, Ostling and Skoog reported the prevalence of hallucinations as 6.9%; 5.5% had delusions and 6.9% had paranoid ideation not of delusional proportions¹⁵. Similarly high prevalence estimates were also found in a later sample of non-demented 95-year-olds¹⁶. As noted above, these high rates are likely due, at least in part, to the use of multiple sources of information, such as key informants and medical records, rather than a reliance on examination by researchers alone. In a related study, Ostling's group also reported a cumulative incidence of first-onset psychotic symptoms at almost 20% in non-demented elderly who survive until age 85.

RISK FACTORS SEEN IN ASSOCIATION WITH LOS AND VLOSLP

The most prominent risk factor associated with late-onset schizophrenia is female gender, with the ratio of women to men being approximately 7:1. Incidence curves for men and women also differ, with early-onset cases developing on average one decade later in women. Hearing loss and ocular pathology also appear to be risk factors. In a review of 27 studies of sensory impairment in psychotic patients, a significant association was found between hearing impairment and late-onset schizophrenia or paranoid disorder¹⁷. Premorbid schizoid and paranoid personality traits are further risk factors that predispose to the development of schizophrenia. Because very-late-onset cases often live alone, social isolation is thought to play a role. In general, family history of psychotic disorder is less common than in early-onset cases, although the evidence for genetic factors is inconsistent. Some studies have found no increased prevalence of schizophrenia in the first-degree relatives of late-onset schizophrenic probands, while others have determined the risk to be intermediate between that of the general population and earlier-onset cases. Some immigrant populations have also been shown to have significantly higher rates of VLOSLP than indigenous elders.

LONGITUDINAL COURSE AND LATER DEVELOPMENT OF DEMENTIA

Not much is known about the long-term course of schizophrenia in the elderly because most longitudinal studies provide data for only several years. The Vermont Longitudinal Study¹⁸ is exceptional in that it prospectively followed a large cohort of chronic patients, most of whom had been diagnosed with DSM-I schizophrenia at a young age, for over thirty years after their release from the

state hospital. Harding found that one third to one half of these patients did not have the expected deterioration and actually showed functional improvement. In the second part of this study¹⁹, Harding *et al.* reassessed the patients and found that almost one half of those who retrospectively met criteria for DSM-III schizophrenia at their index hospitalization had no symptoms (either positive or negative) at follow-up. Harding's studies demonstrate the heterogeneity of functioning at outcome, even when more stringent diagnostic criteria for schizophrenia are used.

Outcomes related to the development of dementia have been of particular interest. In 1955, Roth published the results from his landmark study of a group of 'late paraphrenia' patients, in which only 1 out of 45 patients (i.e. 2%) went on to develop dementia after 3–4½ years of observation⁶. Many years later, using Roth's criteria, Holden found higher rates, reporting that 13 out of 37 (i.e. 35%) patients with late paraphrenia progressed to dementia within 3 years of follow-up¹². Overall, most studies of LOS and VLOSLP have shown that cognitive deficits are relatively stable over time and that these disorders are not precursors to the development of dementia²⁰. It has been reported that hallucinations, especially visual, but not delusions, predict the later development of dementia²¹. Korner *et al.* recently studied the Danish nationwide registers of all hospital in- and outpatients making first-ever contact with late (≥ 40 years of age) or very-late (≥ 60 years) schizophrenia or osteoarthritis during an eight-year period²². Over twenty thousand individuals were identified and followed to a first diagnosis of dementia. Korner's group demonstrated that, when compared to patients with osteoarthritis, patients with late as well as very-late first-contact schizophrenia have a three times higher risk of subsequently getting a first diagnosis of dementia.

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Clinical Assessment and Differential Diagnosis

David N. Anderson

Mossley Hill Hospital, Liverpool, UK

The schizophrenias of late life, previously called late paraphrenia¹ and paranoid states in old age, present fascinating, complex, biopsychosocial problems that span the whole of psychiatry and medicine. The characteristics and associations of schizophrenia with onset in later life have been summarized by an international consensus group². These conditions usually present with paranoid ideation, most commonly persecutory in nature, with or without other schizophrenia-like symptoms.

The central abnormality implied by the term 'paranoid' is a morbid distortion of beliefs, but not all distorted beliefs are delusions and not all elderly people expressing them are mentally ill. Many aspects of old age increase vulnerability, exposing elderly people to abuse and victimization, and a thoughtful appreciation of this situation is needed when assessing the paranoid elderly patient. Furthermore, not all patients with delusions have schizophrenia³ and the first aim of assessment will be to clarify the nature of paranoid symptoms and consider a differential diagnosis. In most cases a diagnosis will be clear from the detailed historical account of symptoms and their course, abnormalities of mental state and simple physical investigations. Assessment must, then, evaluate the individual's level of functioning, independence, vulnerability, social and family support, and physical health, which will all be of relevance to aetiology and management. The assessment will aim to consider patients and their symptoms within the wider context of their social environment, and physical and psychological limitations. It is, therefore, necessary to have knowledge of premorbid personality, lifestyle, life experience and cultural background, remembering that young and older generations have important cultural differences.

Ideally, the assessment will take place in the patient's home, when environment may be maximally appreciated. Home assessment provides a more complete picture of the patient's circumstances and helps put the problem into a living context. Commonly, paranoid ideas in old age relate to the patient's immediate, local environment and people within it. Herbert and Jacobson⁴ used the term 'partition delusions' to describe the belief that things were happening just the other side of the wall, floor or ceiling. Post⁵ found that paranoid symptoms often temporarily disappeared when the patient was removed from the hostile environment, which can give a misleading impression of their nature and a reason to avoid admission to hospital when it will become difficult to gauge response to treatment.

The floridly deluded and hallucinated patient is easily recognized, but in old age paranoid ideation may be almost plausible when complaints of being abused, victimized, stolen from or manipulated are

Table 96.1 Differential diagnosis

Delirium
Dementia
Organic delusional/hallucinatory disorder, secondary to physical illness or drugs
Late-onset schizophrenia
Delusional disorder
Depression
Mania
Schizoaffective disorder
Paranoid personality disorder
Factual (basis in fact)
Sensory impairment

not beyond the bounds of possibility. Trying to establish the validity of such claims requires observation and information from a variety of sources.

We need, first, to consider the differential diagnosis of paranoid symptoms (Table 96.1) and how clinical assessment helps to differentiate diagnostic categories before discussing the process of assessment in more detail.

DIFFERENTIAL DIAGNOSIS

The point prevalence of paranoid ideas in the general elderly population is 4–6%^{6–8}. A population-based study from Sweden found 8% of non-demented 70-year olds developed first-onset psychotic symptoms during a 20-year follow-up and of those surviving to age 85 the cumulative incidence was 20%⁹. These were most commonly visual hallucinations and persecutory delusions. The more common conditions will be reviewed briefly from the perspective of clinical differentiation, although for detailed consideration reference should be made to the relevant chapters.

Delirium (Acute Confusion)

The history is short, usually days or a few weeks, and the onset rapid. A structured assessment, using validated instruments, of 100 people with delirium (17% also had dementia) found 50% experienced perceptual disturbances and hallucinations and 31% delusions¹⁰. These are typically poorly organized, fluctuating and variable in content,

while hallucinations most commonly occur in the visual modality and can be vivid and complex. Other features of delirium will normally be present.

Alcohol intoxication and withdrawal from alcohol, benzodiazepines and barbiturates may all cause paranoid delirium, and withdrawal syndromes should be particularly considered when psychosis develops shortly after a hospital admission.

Dementia (Chronic Confusion)

Ballinger *et al.*¹¹ found delusions and hallucinations in 38% and 34%, respectively, of 100 dementia admissions. Another study of 178 Alzheimer's patients revealed persecutory ideation (20%), delusions (16%) and hallucinations (17%) to be common¹². Fifty per cent of patients with multi-infarct dementia may have delusions at some time¹³. Paulsen *et al.*¹⁴ reported a cumulative incidence for hallucinations and delusions of 51% over four years for people with probable Alzheimer's disease. The clinical course of diffuse Lewy body disease is particularly characterized by psychotic symptoms, and visual hallucination is a defining characteristic¹⁵. In this case the hallucinations may precede other evidence of the disorder.

The manifestations of progressive, global, cognitive impairment will usually be present, although dementia may present with paranoid symptoms that can be indistinguishable from functional illness¹⁶. Paranoid ideas are frequently related to cognitive deficits, especially memory, leading to accusations of theft or problems arising from perceptual difficulties and misidentification¹². Like delirium, these fluctuate and may be ferociously denied, or forgotten, at interview, although the theme and content remain fairly consistent.

Depression

If depression is of delusional proportions, biological and characteristic depressive symptoms are usually marked. Delusions and hallucinations, occurring in all sensory modalities, are normally mood-congruent but incongruent symptoms occur and may be difficult to distinguish from those of primary paranoid disorders.

Kay *et al.*¹⁷ suggested six historical variables that help distinguish affective and paranoid psychoses: life events and family history of affective illness favoured an affective diagnosis, while low social class, few surviving children and social deafness favoured paranoid disorder. Premorbid personality proved the best discriminator, with paranoid patients being solitary, shy, touchy, suspicious and emotionally aloof, and patients with affective disorders reporting subjective ratings of high premorbid anxiety.

Mania

Traditional teaching suggested that mania in old age was both rare and atypical in presentation. Broadhead and Jacoby's¹⁸ prospective study found that young and older-onset patients were clinically very similar. The onset of mania in old age is more common than once thought¹⁹ and the majority of patients will have a history of affective disorder, some 50% having had three or more depressive episodes, with a latency of 15–17 years from first depression to mania^{18–21}.

Organic Delusional/Hallucinatory Disorder

Paranoid hallucinatory disorders have been associated with a variety of organic conditions^{3,8,22–25} and pharmacological agents^{3,26,27}. The

symptoms may be typical of functional disorders²⁸ and the diagnosis depends on establishing a clear aetiological link and temporal relationships between a physical disorder or drug and mental disturbance. As Kay put it, 'Had the organic diagnosis not been reached independently of the psychiatric symptomatology, most of the cases would have been regarded as, indubitably, schizophrenic'²⁸.

The more common causes encountered in clinical practice include hypothyroidism, intra- and extracerebral tumours, epilepsy and cerebrovascular disease, and pharmacological agents such as psychostimulants, anti-parkinsonian and dopaminergic drugs, and steroids.

Possibly the most common is the psychosis of Parkinson's disease. This may be seen in the presence or absence of dementia complicating Parkinson's disease, and psychotic symptoms may occur at any stage. Up to 50% of people may develop psychotic symptoms and 30% experience visual hallucinations within the first five years^{29,30}. Visual hallucinations are most common though auditory hallucination and delusions can occur.

Paranoid Personality Disorder

This is necessarily a life-long problem, which must be demonstrable from early adulthood. It is characterized by a sensitive and defensive attitude that causes people to feel they are victims of life and interpret events in a self-referential way. The effects of ageing and the vicissitudes of later life may accentuate these traits and, if dementia or functional illness supervenes, will colour the symptomatology.

Late-onset Schizophrenia

The development of ICD-10³¹ and DSM-IV³² saw the disappearance of age-defined categories of schizophrenia. This reflects the evidence that the symptoms are essentially the same regardless of age, certainly positive symptoms. It is estimated that 23.5% develops after age 40³³, and first admission data suggests the annual incidence of schizophrenia-like psychosis increases by 11% for every five-year period for people over the age of 60³⁴.

Though positive symptoms are similar regardless of age, negative symptoms are much less common with onset after age 60, when visual hallucination may be more common².

Familial risk and genetic contributions to aetiology decline with increasing age of onset. With onset over age 60, the association is weak but associations with sensory impairment, particularly deafness, and social isolation are more evident. These differences led an international consensus to recommend the nomenclature of late onset to refer to onset after age 40 and very late onset after age 60². The preponderance of females in the very-late-onset group appears to be consistent, and very-late-onset cases seem more likely to have premorbid paranoid or schizoid traits though not amounting to personality disorder. Later onset is typically associated with better premorbid educational, occupational and psychosocial functioning than early onset².

However, prevalence and gender ratio have been shown to vary in a study of first contacts with onset after age 60 in migrant populations in London^{35,36}.

Roth and Kay³⁷ provide a thoughtful discussion of the apparent similarities and differences of the associated features of late- and early-onset schizophrenia.

Delusional Disorders

These are conditions characterized by a persistent, circumscribed delusional theme, and if hallucinations occur they are not prominent.

They are defined by their delusional content, which may be erotic, jealous, hypochondriacal, persecutory or grandiose. These conditions have not been the subject of systematic study in old age, when they are thought to be relatively rare²⁶. Onset is usually in middle age but as patients normally function well outside their particular delusion and symptoms frequently persist, they may present in old age. Unlike late-onset schizophrenia, delusional disorder seems not to be associated with premorbid paranoid personality or deafness³⁸, although querulent paranoia has been related to deviant personality structure³⁹.

Familially they appear unrelated to affective or schizophrenic illnesses^{40,41}. Howard *et al.*⁴² found dilatation of lateral and third ventricle volumes by magnetic resonance imaging (MRI) to be more a feature of delusional disorder than schizophrenia in old age, as defined by ICD-10 criteria.

A small retrospective study comparing paraphrenia (schizophrenia of late onset) with paranoia (delusional disorder of late onset) found cerebral infarction on CT brain scan to be a feature of paranoia rather than paraphrenia. Furthermore, social isolation and being unmarried were not features of paranoiacs with cerebral infarction, suggesting separate groups defined by organic or social associations. Response to antipsychotic drugs was worse for paranoia⁴³.

ASSESSMENT

Interview

Interviewing paranoid elderly people may be complicated by deafness, speech problems or visual handicap, so time and patience are essential. An informant history is mandatory and often several sources may be required.

It is crucial to establish the interview situation, explain its purpose, allay anxieties and put patients at their ease. Many patients will be anxious and fearful. The patients should decide whether they prefer to be seen in private or with a confidant(e) as another's presence may equally inhibit or encourage the disclosure of sensitive material. For similar reasons an informant may wish to speak privately though discussions should never appear clandestine.

Deafness and communication problems should be openly acknowledged, hearing aids worn and working, and extraneous noise eliminated, otherwise false impressions of cognitive state may be formed. If a patient is seen in a hospital setting, insist on a separate, quiet interview room, otherwise conversation will be inhibited and information lost. Posture and attitude convey sincerity, concern and how seriously problems are considered. The patient needs to form a trusting relationship, and a respectful, honest but never patronizing approach is normally accepted. A sympathetic hand can reassure and encourage an anxious or fearful patient.

The importance of establishing a positive therapeutic relationship at this early stage cannot be overstated, as it can have far-reaching effects, not only for the openness of discussion but also for future compliance and prognosis.

History

The nature of psychotic symptoms, their form, content and course must be detailed. Late-onset schizophrenia may develop insidiously over months or a year or more, delusional depression over weeks or a few months, delirium over days and dementia over one to two years. The intensity of paranoid ideas and their effect on behaviour

assist diagnosis and the evaluation of risk. Associated symptoms, particularly affective and cognitive, should then be elicited.

Current and past medical problems and their temporal relationship to the onset of paranoid symptoms must be clearly established, including visual or auditory failure. Aetiologically significant hearing loss in very-late-onset schizophrenia is typically of long duration, severe and due to bilateral middle ear disease, often originating in early life. Details of prescribed and non-prescribed drugs, dosages and recent alterations are essential.

Previous episodes of mental disorder should be confirmed from medical records, when past diagnoses and response to treatment may quickly clarify a diagnostic dilemma. Careful enquiry might uncover past episodes of untreated, self-limiting illness, and changes in behaviour may date the onset of current problems.

Premorbid personality and behaviour are important because departures from these in old age usually signify the onset of a morbid process. Forty to fifty per cent of late-onset schizophrenics have schizoid or paranoid premorbid traits^{2,3} and the diagnosis of personality disorder depends on establishing a life-long attitude. Brenes Jette and Winnett⁴⁴ emphasized the interaction of narcissistic personality traits and the psychosocial consequences of ageing in their psychodynamic formulation of late-onset paranoid disorder.

The genetic loading of schizophrenia in old age is less marked than with younger patients but a positive family history may be found. Odd behaviour or suicide among family members may be discovered when formal psychiatric treatment is absent.

Current social circumstances and recent change are of relevance to aetiology and management. The schizophrenias of late life are particularly associated with social isolation, but rarely with precipitating life events. Paranoid patients frequently have poor socioeconomic status and multiple difficulties⁶, and social support has prognostic implications. Enquiring about alcohol and drug abuse must not be avoided for fear of offending a respectable elderly person. The elderly are not without vice and may be less inclined to confess it.

Mental State Examination

The detailed psychopathology of these conditions is described elsewhere and only points relevant to the process of mental state examination in this context will be mentioned here.

It is important to ensure that the patient understands the terminology used to elicit abnormal experiences and that a common language is being used. Eliciting paranoid and psychotic symptoms can be difficult, but with tact and careful choice of words most patients will participate in an exchange of ideas about their experiences. This must be an unthreatening process for the patient and it is unwise to challenge or trivialize complaints at an early stage. A neutral position is advisable until a firm relationship is established, when complaints may be gradually reframed so that they can be viewed by the patient as problems that can be relieved, rather than unchangeable realities that are not amenable to therapeutic intervention. Suggesting that 'it's all imagination' will be considered insulting and the patient's confidence will be lost.

Perceptual disturbance, thought process and content, mood and cognitive function are areas of particular focus.

Insight is rarely retained and patients may not volunteer experiences if they interpret questions as purely an enquiry into the state of their health. Patients have limited ability to accept the presence of illness or recognize psychiatric experiences as pathological⁴⁵. Needless to say, the mental state examination must be thorough.

Physical Examination

A complete physical examination should be performed routinely, with particular emphasis on neurological status and sensory function. The association between sensory impairment and very-late-onset schizophrenia makes attention to this area important, and remediable conditions may be found. Visual impairment, particularly due to cataracts, is often found in association with delusions and deafness⁴⁶, and visual hallucinations may be as much to do with ocular pathology as psychiatric diagnosis⁴⁷. A particular form of acute, elaborate visual hallucinosis, the Charles Bonnet syndrome, is usually related to eye disease or cerebral organic disorder⁴⁸. Simple clinical interview and self-reporting underestimate sensory impairment, and more detailed ophthalmic and audiometric examination may be necessary. A simple battery of laboratory investigations is required for all patients, including haematology, biochemistry, thyroid function, urinalysis and chest radiography.

Advanced neuroradiological techniques promise much for the future but have limited clinical application at the present time. Some authors recommend the routine use of computed tomography (CT) and magnetic resonance imaging (MRI).

Structural cerebral abnormalities, including increased ventricular size and volume reduction in various brain areas, are found in schizophrenia regardless of age at onset² and deep white matter hyperintensities in depression of late onset⁴⁹. They appear to bear little relationship to clinical state or outcome in the schizophrenia-like disorders^{50,51} but in mood disorder may indicate relative treatment resistance and associated executive dysfunction⁵². Structural imaging is important for excluding conditions like space-occupying lesions.

Functional imaging also shows abnormalities in schizophrenia and depression^{2,52}.

In dementia neuroimaging has diagnostic significance and has become a routine procedure. MRI is recommended in all cases of dementia⁵³ and single photon emission computed tomography (SPECT) has considerable diagnostic power in dementia associated with Lewy bodies and Parkinson's disease^{54–56}.

Psychometric testing may provide a useful baseline measure that can be serially repeated when the possibility of dementia arises. Psychometric testing certainly reveals cognitive deficits in late-onset schizophrenic patients, particularly affecting frontal lobe and memory function². These rarely signify dementia and are more like the deficits found with early-onset schizophrenia than Alzheimer's disease. They do not correlate with severity of psychosis or other clinical parameters. However, it appears that late-onset schizophrenia or psychotic symptoms, particularly visual hallucinations, do predict an increased risk of dementia^{9,57}.

CONCLUSION

Most patients with late-onset schizophrenia, delusional disorders, dementia and psychotic symptoms will be adequately and preferably managed from home. The need to admit to hospital seems to have declined⁵⁸ and may be determined more by social and physical factors or treatment compliance as degree of psychopathology. This is unlikely to be the case for conditions like delirium or psychotic mood disorder, which are often life threatening. For the patient requiring more than outpatient treatment, a day hospital can provide more intensive assessment of mental state, physical health and functional level.

The multifactorial contributions from ageing, physical disability, sensory impairment and social factors demand a multi-professional

approach and all relevant disciplines must be available and involved. The evaluation of these conditions requires clinical skill, rigorous attention to detail and a holistic approach. The accuracy of diagnosis and success of management will depend on the quality of initial assessment and if diagnostic doubts exist, treatment should be postponed until the situation becomes clear. Occasionally a diagnostic trial of treatment will be justified.

The paranoid disorders of old age are stimulating, complex, challenging clinical problems that encompass the breadth of psychiatry, medicine and social sciences in their assessment and management.

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Treatment of Late-Life Psychosis

Peter Connelly and Neil Prentice

Murray Royal Hospital, Perth, UK

The treatment of late-life psychosis raises a considerable number of practical and ethical issues. People with this diagnosis are likely to have developed the prodrome of their illness over a significant period of time, often measured in years, during which they might have been considered to be 'eccentric' by the general public and by health and social service professionals. Reeves *et al.*¹ found an average duration of three years of formal symptoms prior to presentation to specialist services. Compared to people with affective disorders, historical data² would suggest that they are more likely to live alone and more likely to suffer hearing loss or other sensory impairment. A significant number³ will have evidence of a premorbid paranoid personality, with associated poor interpersonal relationships, hypochondriasis, which may have alienated them from primary care services, and depressive symptoms, which inhibit their ability to initiate help-seeking behaviour. Although it is important to avoid stereotypes, and to recognize that people with psychosis in late life tend to have more family contact than younger adults with schizophrenia⁴, the description of a typical case in the key study by Kay *et al.*⁵ of a shy, reserved, touchy, suspicious person with difficulty in maintaining or establishing relationships and less likely to display sympathy towards their peers, may lead to individuals with late-life psychosis becoming intensely socially isolated with little in the way of external input during the development of their delusions, at a point where some rationalization of developing beliefs might have helped to prevent them becoming chronically established.

ETHICAL ISSUES

Although there is a fundamental need to protect the health and safety of individuals with late-life psychosis and that of their perceived persecutors – who are often neighbours or relatives – immediate recourse to emergency mental health legislation may undermine the potential to develop a therapeutic relationship in which the necessary challenges to their delusional thinking can take place. The elderly person with a well-developed and long-standing delusional system is unlikely to accept that it is they who are suffering from an illness. Much more likely they will be of the view that some intervention is required to deal with the people who are causing them problems. Patients who are intensely frightened at the thought of others being able to get into their house, despite often elaborate security systems, may well be willing to consider a change of location or temporary admission to hospital, but in many cases the only option will be to try to treat people with late-life psychosis in their existing environ-

ment. Legislation may well become necessary if there is evidence of severe self-neglect, violence or other offending behaviour towards those involved in their delusions or their property.

Persuading the patient with chronic delusions or hallucinations to take antipsychotic drugs can be problematic. Such patients will see no logic in the view that were they to take a drug it would somehow change the behaviour of people in the next block of flats. Suggesting that someone takes an antipsychotic as a way of 'protecting their body' while professionals have the opportunity to get to work on their persecutors to try to reduce the frequency or intensity of their alleged toxic behaviour can be seen as coercive and out of keeping with existing legislation on mental capacity, yet such an explanation may be readily understandable to a patient who has taken steps to protect the fabric of their property from toxic waves or sprays and is in keeping with the non-confrontational exploration of beliefs necessary to try to build cooperation. People who are fearful may accept that antipsychotics or antidepressants may have a role in reducing anxiety and agree to take medication but even with this explanation an ethical debate will continue. Although there does not appear to be specific literature on this topic, it may be surprising to find that whatever explanation has been given to the patient about antipsychotics, compliance with treatment can be surprisingly good.

DRUG THERAPY

While antipsychotics are used extensively in older patients to treat a variety of symptoms, including psychotic symptoms as features of behavioural and psychological symptoms in dementia, much of their use in treating late-life psychosis is inferred from studies of treatment for psychosis in younger patients. This is particularly problematic since older patients are more likely to suffer from major physical illness as a co-morbid feature, and a number of studies have drawn into focus concerns about the over-use of antipsychotic medication, particularly in nursing homes⁶, and excess mortality associated with antipsychotic prescribing in the elderly⁷.

While the majority of people with late-life psychotic symptoms will have hallucinations and delusions from delirium secondary to a physical cause, as a behavioural and psychological symptom of dementia, or indeed as part of an affective illness, those with schizophrenia or other late-life psychosis comprise 0.1–0.5% of the population over the age of 65⁸. Of all people over the age of 65 with schizophrenia, the majority will have developed their illness prior to age 45⁹. While there are benefits from extrapolating data derived from adults

under 65, in the absence of large multicentre double-blind placebo-controlled studies into treatment of late-life psychosis, there are a number of problems associated with this approach. Primarily the difficulties fall into areas including metabolic side effects, increased risk of extrapyramidal side effects and movement disorder, and the problems of polypharmacy, co-morbid major physical illness and pharmacokinetic changes associated with ageing.

Typical antipsychotics have been used extensively in treating older people with psychosis despite the fact that their high affinity for dopamine D2 receptors is associated with increasing extrapyramidal side effects in older people¹⁰. In addition these medications tend to be sedating and associated with quite marked anticholinergic side effects, which can cause additional confusion and disorientation in patients with mild cognitive impairment or dementia. By contrast, atypical antipsychotics are associated with less in the way of significant side effects in older people¹¹ and less hospitalization by comparison to typicals¹². Both olanzapine and quetiapine are associated with a lower incidence of extrapyramidal side effects than typical antipsychotics¹³, though sedation can be problematic and there are additional issues in relation to olanzapine and increased risk of diabetes¹⁴. Risperidone has been used extensively principally because of the low incidence of sedation or anticholinergic side effects. Clozapine has been used extensively in younger patients, though hypersalivation, neutropaenia and increased risk of agranulocytosis, particularly in older patients, limit its use¹⁵. Much of the evidence for efficacy of antipsychotics in late-onset psychosis consists of case reports and open studies though these are at times conflicting and there is not clear evidence to suggest that atypical antipsychotics are any more effective in this group of patients. However, compliance is better¹⁶.

In the absence of robust double-blind placebo-controlled data for meta-analysis, guidelines for management of late-onset psychosis focus primarily on the expert consensus approach. Focusing on the management of schizophrenia, the use of atypical antipsychotics is clearly favoured, with 93% of experts rating risperidone as first-line treatment in this group of patients, perhaps because of its low incidence of anticholinergic or sedative side effects. While quetiapine and olanzapine were also rated as first-line treatments by 67% of experts and aripiprazole by 60%, the doses recommended in this group of patients were higher than the treatment doses used in psychosis in dementia¹⁷.

A recent study of attitudes to antipsychotic prescribing in Australian specialists working within old age psychiatry identified a preference for the use of atypical antipsychotics as opposed to typical antipsychotics in an elderly population although no clear preference for any individual atypical antipsychotic was apparent¹⁸. The principal reasons for this centred on the impression that not only were atypical antipsychotics less likely to be associated with adverse events, particularly in an elderly population who were more likely to be suffering from co-morbid physical conditions, but they were also perceived as being clinically more effective than typical antipsychotics. This was supported by clinical global impression of change data within the clinicians' own patient groups, where 33% of patients with schizophrenia were rated as having improved from moderately ill to mildly ill while on atypical antipsychotics. This is similar to rates of reduction in PANSS¹⁹ total score for elderly patients with psychotic illness treated with amisulpride and risperidone²⁰ though a more recent open label study of amisulpride treatment for very-late-onset schizophrenia-like psychosis showed significant improvement over a variety of measures and 46.6% reduction in PANSS total score²¹.

Taking into account the likelihood of co-morbid physical or psychiatric symptoms in elderly patients and the altered pharmacodynamics and pharmacokinetics of older people, the limited evidence available suggests that treatment with atypical antipsychotic medication may be useful. Although there are recent concerns in relation to increased cerebrovascular risk in older patients with dementia treated with atypical antipsychotic medication²² and also concerns in relation to excess mortality associated with these drugs⁷, their cautious utilization continues to be appropriate in the absence of any clear alternative treatments.

The use of depot medication may not lead to additional advantages. Reeves *et al.*¹ found that treatment response was not increased by the use of depot and concluded that regular contact with a community psychiatric nurse, an intervention likely to increase social exposure, may be as important in maintaining treatment response.

COGNITIVE BEHAVIOURAL THERAPY

The most common types of delusions are those of reference, control or hypochondriasis²³. Partition delusions²⁴ are also over-represented in the late-life onset group. A detailed description of cognitive models and cognitive behavioural interventions lies outwith the scope of this chapter, but an understanding of the development of delusions comes from cognitive behavioural work with younger adults. Cognitive models have been used to explain delusion formation and maintenance²⁵. Similar errors in attribution have been proposed as mechanisms leading to hallucinations²⁶, although some exploratory work to examine the cognitive aetiology of delusions in people with late-life psychosis^{27,28} suggests that the wider range of cognitive distortions described in younger adults with schizophrenia may not be as pertinent in older people.

Bentall *et al.*²⁹ describe the development of persecutory thinking as a way of the person protecting themselves from perceived assaults on their self-esteem by allowing them to attribute negative events to external causes. Since many patients with late-life onset psychoses have a history of such attribution during most of their adult life, it is easy to understand the continuum of a person feeling that others are in some way hostile towards them, through the development of more eccentric beliefs with associated social withdrawal and finally explicit persecutory delusions in an intensely isolated individual. Protective behaviours become increasingly explicit and the picture of a chronically isolated, elderly lady sitting in a cold, dark house, unheated because she believes the neighbours are stealing her electricity through some tenuously understandable process, and covering surfaces of her furniture or cooking utensils with silver foil to prevent the effects of toxic spray used by the same neighbours will not be unfamiliar to clinicians treating this group of people.

Although techniques were first described by Beck in 1952³⁰, cognitive behavioural therapy (CBT) studies in people with psychosis began to appear more frequently in the early 1990s. The literature is well reviewed by Rathod *et al.*³¹, who conclude that CBT has emerged as an effective adjuvant to antipsychotic medication in the treatment of schizophrenia. However, the guidelines of the National Institute for Health and Clinical Excellence in the UK³² concluded that CBT may improve depressive symptoms but is unlikely to improve psychotic symptoms. Enlarging on this, a detailed review by Wykes *et al.*³³ suggested a clear relationship between the methodological quality of CBT studies and the effect size that they report, with better quality studies reporting a lower effect size.

Fewer CBT studies specifically report outcome with respect to delusions and hallucinations. Of these, fewer still involve a randomized design and report results with standard deviations. Durham *et al.*³⁴ is one of these few and they report no benefit for CBT over supportive psychotherapy in these domains. CBT was associated with a greater number of people achieving a 25% improvement in the overall PANSS score but with a relatively high number needed to treat of 13. No patient in this study was aged over 65 and only 2 (of 66) had delusional disorder. The review of long-term outcomes by Durham *et al.*³⁵ found a reduction of symptom severity when used for anxiety but not psychosis. McCulloch *et al.*²⁷ suggested that people with late-onset psychosis had no evidence of either overt depression or low self-esteem, so a different form of psychological approach may be required. Drawing conclusions about the effectiveness of CBT in late-life onset psychosis would be best done through quality research rather than extrapolation from younger people but limited benefits at best are likely to result. The improvement in socialization that may occur through engagement in CBT programmes may be at least as helpful³¹.

There are few studies looking at interventions in middle or late life. Patterson *et al.*³⁶ described benefits in the field of everyday living skills among older Latino patients attending a specialized clinic in the USA, such as improved use of public transportation, but no significant change in psychopathology was noted in this pilot study. Granholm *et al.*³⁷ explored the effect of cognitive behavioural social skills training in a randomized controlled trial over 24 weeks. Again, social functioning was improved, though benefits in achieving greater insight into psychotic symptoms were not significant overall and were lost after a further six months follow-up³⁸. Repetition of the programme led to no additional benefits³⁷, though social improvements were maintained at follow-up³⁸.

OTHER NON-PHARMACOLOGICAL INTERVENTIONS

A search of the Cochrane Database of Systematic Reviews reveals many interventions that have been tested in randomized controlled trials in people with schizophrenia. The list includes art therapy, music therapy, compliance therapy, assertive community treatment, distraction techniques, drama therapy and exercise. Of all the studies reviewed in these areas, virtually none include people over 65. The effects reported are influenced by the inconsistency of the data in many areas and it is difficult to recommend any of these be used routinely when dealing with someone with late-life psychosis.

One Chinese study³⁹ of a family psychoeducational programme included people up to 80 years old, but the number over 65 is not reported and would be very small. It is possible that group may have consisted of people with affective disorder rather than schizophrenia. The improvement in families of their understanding of the patient's illness and an improved problem-solving approach led to better treatment compliance by patients and less inappropriate care delivered by families. Although the culture in China is very different from Western society, these lessons are equally pertinent when considering how to maximize the effectiveness of mental health team input. The area of non-pharmacological interventions for late-life psychosis is likely to prove to be a fruitful ground for research.

UNMET NEED

There has been very little systematic research into the needs of older people with psychoses, especially the generation who have aged in

an era where, in the UK at least, the emphasis on care provision in the community has been more common than dependence on long stay care.

McNulty *et al.*⁴⁰ interviewed 58 people over 65 with a mean of 75 years, 54 of whom had schizophrenia and 2 delusional disorder. They found a total of 152 'needs' in that population, i.e. a problem requiring action for which a suitable intervention exists but which has not been given a recent adequate trial. Of these 56 lay in the social field, with an absence of social life and accommodation problems being uppermost. This group found a considerable level of cognitive impairment among their population, with a mean Mini-Mental State Examination (MMSE) score⁴¹ of 20/30 among their participants. This is considerably lower than a more recent London-based study⁴², which found a mean MMSE score of 26.5 among its 77 participants. That group also found social activity, day care and housing among the needs unmet because of lack of service, although unmet needs because of patient refusal of social activity or day care was almost four times higher.

The higher prevalence of cognitive impairment in the former study may reflect the level of deprivation in their population, although a high level of young-onset dementia^{43,44} and cerebrovascular disease⁴⁵ has also been described in the same geographical region. Services managing people with late-life psychoses should, however, be aware of the possibility of concurrent cognitive impairment, which may have detrimental effects on emotion, motivation and daily living skills, as well as further impairment of reasoning and judgement. This may complicate discussions about potential changes of accommodation, and capacity-based legislation may require to be used.

REHOUSING

The delusions experienced by people with late-life onset psychoses are often highly circumscribed and tend to be local to their present accommodation. However, although there is a plethora of literature which relates to how people hospitalized because of psychoses adapt to community living following discharge⁴⁶, there appears to be none which examines the effect of rehousing people in alternative accommodation in the community. In fact a systematic review of the health effects of housing improvement⁴⁷ found little evidence linking housing and health, and Blackman *et al.*⁴⁸ found that people over 50 had disappointing health improvement results when moved because of medical priority although this group was less likely than younger people to be rehoused on medical grounds.

LONELINESS

Among the consequences of chronic isolation resulting from late-life psychosis is the presence of loneliness. This may have adverse effects on physical health, particularly higher blood pressure, poor sleep and poor cognition⁴⁹. The importance of regular physical health checks, in people who may have disengaged with health services over long periods of time, cannot be over-emphasized.

VIOLENCE

The traditional view that older people are rarely perpetrators of violence is somewhat dispelled by the Healthcare Commission National Audit of Violence 2006–2007⁵⁰, which found that more nurses on

older people's inpatient wards reported that they had been physically assaulted than in services for adults of working age. Although the risk of physical assault was greatest in services for people with organic disorders, more than half of the nursing staff on functional units had been assaulted.

Staff may be aware of the risk of potential assault when dealing with a delusional person at home and be careful about how they challenge the delusional beliefs. However, as Taylor⁵¹ points out, relatives and friends may be much more blunt in their challenges and be at increased risk of violence. It may be necessary to include advice to the carer when formulating any treatment plan. This may include training relatives or friends in how to discuss delusional beliefs without exposing themselves to potential violence.

CONCLUSION

The treatment of older people with psychosis is an area in which high-quality research is limited. A clearer understanding of the needs of these people is required urgently. Up to one fifth of non-demented older people who survive to age 85 develop first-onset psychotic symptoms⁵² and 2.4% of 95-year-olds meet operational criteria for schizophrenia⁵³. An increased number of people with these disorders is inevitable.

As with younger adults, the use of drugs alone is insufficient to achieve stability. The place of psychological therapies is yet to be fully established and the need for an evidence base for both pharmacological and non-pharmacological interventions needs to be expanded. Reduction of social isolation and helping family members cope with the constant expression of delusional material will both help engagement with treatment. Attention to physical care and unmet social needs is vital. Realistically, the goal of treatment is to maintain people in the community and reduce the impact of symptoms. Long-term follow-up of the effects of relocation on individuals would help professionals decide on the risk and benefits of such a move.

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Neuroses (Anxiety Disorders)

Nosology and Classification of Neurotic Disorders

David Bienenfeld

Department of Psychiatry, Wright State University Boonshoft School of Medicine, Dayton, OH, USA

INTRODUCTION

The grouping of a variety of psychopathological entities under the heading of 'neurotic disorders' represents the current attempt to solve a nosological tangle dating back further than the time of Sigmund Freud. The contemporary categorization is controversial and less than satisfying to many. A brief look at its historical roots offers some explanation of the sense behind the current ICD-10 and DSM-IV structures.

HISTORY OF THE CLASSIFICATION OF THE NEUROSES

It was Hippolyte-Marie Bernheim who introduced the term 'psychoneurosis' for hysteria and allied conditions. Freud, who studied with Bernheim, differentiated the 'actual neuroses' (including neurasthenia, anxiety neurosis and hypochondria) from the psychoneuroses. The latter category included not only the 'transference neuroses', such as hysteria and obsessive neurosis, but also the psychoses (paraphrenia, schizophrenia, paranoia and manic depression), perversions and neurotic character. Both types of neurosis were related to sexual disturbance; the actual neuroses were direct somatic consequences of a noxious physical influence resulting from misdirected sexual energy; the psychoneuroses were caused by unconscious conflict between instinctual and counter-instinctual forces¹. Although Freud's thinking on the precise nature of the mental aetiology of the psychoneuroses changed over the years from about 1894 to 1906, he remained consistent in his stance that the psychoneuroses were defined by their aetiology rather than by their phenomenology². Eventually, the psychoses were classified independently, consistent with the views of Kraepelin.

In 1952, the American Psychiatric Association published the first Diagnostic and Statistical Manual of Mental Disorders (DSM-I). It identified the subtypes of psychoneurotic disorders as anxiety, dissociative, conversion, phobic, obsessive-compulsive and depressive reactions³. By the mid-1960s, the major diagnostic schemata, ICD-8 and DSM-II, codified the selection of the descriptive framework for identifying the neuroses. Anxiety was seen as the chief characteristic, whether felt and expressed directly or diverted unconsciously into other symptoms. The neuroses were also grouped by severity; they were more specifically symptomatic than the personality disorders, but entailed no gross distortion or impairment of reality testing, as in the psychoses. Categories included in the 300-code section

were anxiety, hysterical, phobic, obsessive-compulsive, depressive, neurasthenic, depersonalization and hypochondriacal neuroses. Transient situational disturbances constituted their own category (code 307)⁴.

The descriptive focus was emphasized in ICD-9 with the substitution of the term 'neurotic disorders' for 'neuroses', although the categorization was not significantly modified⁵. In 1980, the American Psychiatric Association published the DSM-III⁶, which took a substantial leap towards atheoretical descriptive diagnosis by adopting empirically validated criteria based on research diagnostic criteria. One of the most controversial changes was the elimination of the entire class of neuroses. The neurotic disorders were included in the affective, anxiety, somatoform, dissociative and psychosexual disorders⁷. The grouping by severity was abandoned in favour of clusters based on similarity of features. The diagnostic entities retained numerical codes compatible with ICD-9 and ICD-9-CM.

The other revolutionary change introduced with DSM-III was the use of a multiaxial system for diagnosis. Under this scheme, personality disorders, which often predispose individuals to the development of specific neurotic (and other) syndromes, were relegated to a separate and parallel Axis II. The 1987 revision, DSM-III-R, changed some names and criteria but retained the same hierarchy of the neurotic disorders and the same multiaxial formula⁸. DSM-IV, published in 1994, was a more substantive revision overall than DSM-III-R, with only a few changes relevant to the neurotic disorders. The diagnosis of Acute Stress Disorder was added for compatibility with ICD-10. Dissociative Identity Disorder was added to Axis I to replace Multiple Personality Disorder, which was removed from Axis II. Simple Phobia was renamed Specific Phobia for compatibility with ICD-10⁹.

Neurotic Disorders in ICD-10 and DSM-IV

The creators of ICD-10 were faced with a formidable challenge, as this version, unlike its nine predecessors, was to be designed as the last of the series to be scheduled for regular revisions¹⁰. It therefore had to contain a format that would allow for flexibility in minor revisions while establishing a more permanent structure than versions 1–9. While following the lead of the phenomenological school in separating out a major category for mood disorders that includes both psychotic and neurotic levels of severity, it retains the major classification of neurotic disorders, including somatoform

disorders and stress-related disorders¹¹. This grouping solves the objection that the term 'neurosis' groups together entities which could be better classified, e.g. by placing neurotic types of depression together with other mood disorders, rather than with anxiety disorders. It does, however, retain the historical commonality that traces to Freud's original stress on the aetiological similarity of the psychoneuroses, acknowledging the current state of scientific knowledge that is, at best, ambiguous concerning the aetiology of these disorders^{12,13}.

Table 98.1 compares the relative positions of the neurotic disorders in ICD-10 and Axis I of DSM-IV. The alphanumeric organization of the International Classification requires the constraint of all mental disorders to 10 major categories. DSM-IV, under no such limitation, separates out anxiety, somatoform and dissociative disorders but keeps them within the same gradient of severity between mood disorders and sexual disorders. Adjustment disorders are removed to a position implying less severity, as well as an implied direction that higher ranking diagnoses are to be made or eliminated first. Personality disorders, of course, are assigned to Axis II.

Under the category of the neurotic disorders, the international and American systems differ in their organization, as outlined in Table 98.2. DSM-IV groups the phobic disorders, obsessive compulsive disorder, post-traumatic stress disorder and generalized anxiety disorder together as anxiety disorders. ICD-10 separates phobic disorders, anxiety disorders and obsessive compulsive disorders. Post-traumatic stress disorders are classified with adjustment disorders. Both schemes separate dissociative and somatoform disorders. ICD-10 groups conversion disorder with dissociative states, consistent with the historical, aetiological based classification of the hysterias. DSM-IV combines it with the somatoform disorders, based on their phenomenological similarities. ICD-10 retains the diagnosis of neurasthenia; while DSM-III-R refers the clinician to dysthymia, categorized unequivocally as a mood disorder, DSM-IV eliminates the term entirely^{8,9,11}.

DIAGNOSTIC FEATURES OF NEUROTIC DISORDERS

While each of the major categories of neurotic disorders is described in the chapters that follow, the clinical features of the seven ICD-10 groupings are presented here for overview and comparison¹¹.

Phobic disorders are a set of disorders in which anxiety is invoked only, or predominantly, by well-defined situations that are not in themselves dangerous. By definition, the object of the fear is external to the individual, so that fears of bodily processes are more appropriately relegated to the category of somatoform disorders. The feared objects are characteristically avoided, and anticipatory anxiety is common.

Other anxiety disorders are those in which anxiety is the major symptom but which are not restricted to specific situations. They include panic disorder, generalized anxiety disorder, and mixed anxiety and depressive disorder. The latter is reserved for cases where symptoms of both are present, neither is predominant, and the depression is not severe enough to be classified under mild depressive disorder.

Obsessive-compulsive disorder is characterized by recurrent obsessional thoughts or compulsive acts, or both. These thoughts and acts are subjectively distressing. Subjective anxiety is usually present and depressive features are common.

Reactions to severe stress and adjustment disorders represent a unique category, in that the component disorders are identified on the grounds of both symptomatology and causation. In these disorders, anxiety follows an exceptionally stressful life event or a significant life change. While psychosocial stressors may precipitate a wide variety of psychiatric syndromes, they are elsewhere neither necessary nor sufficient to explain the occurrence and form of the disorder. The stress and adjustment disorders, however, are seen as arising as a direct consequence of the trauma or life change.

Dissociative disorder is a group of entities that share a partial or complete loss of the normal integration between memory of the past, awareness of identity and immediate sensations, and control of

Table 98.1 Relative positions of neurotic disorders in the diagnostic schemata

<i>ICD 10</i>	<i>DSM-IV</i>
F0 Organic mental disorders	Disorders usually first evident in infancy, childhood or adolescence
F1 Mental and behavioural disorders due to psychoactive substance uses	Delirium; dementia and amnestic and other cognitive disorders
F2 Schizophrenia, schizotypal states and delusional disorders	Mental disorders due to a general medical condition not elsewhere classified
F3 Mood disorders	Substance-related disorders
F4 NEUROTIC, STRESS-RELATED AND SOMATOFORM DISORDERS	Schizophrenia and other psychotic disorders
F5 Behavioral syndromes and mental disorders associated with physiological dysfunction and hormonal changes	Mood disorders
F6 Abnormalities of adult personality and behaviour	ANXIETY DISORDERS
F7 Mental retardation	SOMATOFORM DISORDERS
F8 Developmental disorders	DISSOCIATIVE DISORDERS
F9 Behavioural and emotional disorders with onset usually occurring in childhood or adolescence	Factitious disorders
	Sexual and gender identity disorders
	Eating disorders
	Sleep disorders
	Impulse-control disorders not elsewhere classified

Table 98.2 Classification of neurotic disorders

<i>ICD-10</i>	<i>DSM-IV</i>
F40 <i>Phobic disorder</i>	<i>Anxiety disorders</i>
40.0 Agoraphobia	300.21 Panic disorder with agoraphobia
.00 Without panic disorder	300.01 Panic disorder without agoraphobia
.01 With panic disorder	300.22 Agoraphobia without history of panic disorder
40.1 Social phobias	300.29 Specific phobia
40.2 Specific (isolated) phobias	300.23 Social phobia
F41 <i>Other anxiety disorders</i>	300.3 Obsessive-compulsive disorder
41.0 Panic disorder	309.89 Post-traumatic stress disorder
41.1 Generalized anxiety disorder	308.3 Acute stress disorder
41.2 Mixed anxiety and depressive disorder	300.02 Generalized anxiety disorder
F42 <i>Obsessive-compulsive disorder</i>	<i>Somatoform disorders</i>
42.0 Predominantly obsessional thoughts	300.81 Somatization disorder
42.1 Predominantly compulsive acts	300.11 Conversion disorder
F43 <i>Reaction to severe stress and adjustment disorders</i>	307 Pain disorder
43.0 Acute stress reaction	300.7 Hypochondriasis
43.1 Post-traumatic stress disorder	300.7 Body dysmorphic disorder
43.2 Adjustment disorder	<i>Dissociative disorders</i>
.20 Brief depressive reaction	300.12 Dissociative amnesia
.21 Prolonged depressive reaction	300.13 Dissociative fugue
.22 With predominant disturbance of other emotions	300.14 Dissociative identity disorder
.23 With predominant disturbance of conduct	300.6 Depersonalization disorder
.24 With mixed disturbance of emotions and conduct	<i>Adjustment disorder</i>
F44 <i>Dissociative and conversion disorder</i>	309.0 With depressed mood
44.0 Psychogenic amnesia	309.24 With anxiety
44.1 Psychogenic fugue	309.40 With mixed disturbances of emotions and conduct
44.2 Psychogenic stupor	309.28 With mixed anxiety and depressed mood
44.3 Trance and possession states	309.3 With disturbance of conduct
44.4 Psychogenic movement disorders	
44.5 Psychogenic convulsions	
44.6 Psychogenic anaesthesia and sensory loss	
F45 <i>Somatoform disorders</i>	
45.0 Multiple somatization disorder	
45.1 Undifferentiated somatoform disorder	
45.2 Hypochondriacal syndrome	
45.3 Psychogenic autonomic dysfunction	
45.4 Psychogenic pain	
F48 <i>Other neurotic disorders</i>	
48.0 Neurasthenia	
48.1 Depersonalization–derealization syndrome	

bodily movements. It is presumed that, in these disorders, the ability to exert conscious and selective control over memory, sensation or bodily function is impaired.

Somatoform disorders are those in which physical symptoms are repeatedly presented with requests for investigation or treatment, in spite of the absence of physical findings to substantiate the perception. Compared with patients who suffer from psychogenic movement or sensory disorders, those with somatoform disorders will demand attention and usually resent physicians who fail to believe in the physical nature of their illnesses. Even when the onset of symptoms is temporally related to a stressful life event, or when external manifestations of depression or anxiety are obvious to others, these patients will frequently resist speculation about psychological causation.

Other neurotic disorders feature two clinical entities, neurasthenia and depersonalization–derealization syndrome. The former,

recalling the pre-Freudian nomenclature, is a controversial category in contemporary psychiatry. Its main feature is fatigue, which may occur upon either mental or physical exercise. The diagnosis is to be made only after depressive and anxiety disorders have been ruled out. Depersonalization–derealization syndrome is a rare disorder in which the patient feels that his/her own mental activity, body or surroundings are changed in quality so as to be unreal or remote. This phenomenon is more commonly observed as a feature of depression, phobias, obsessive-compulsive disorder and some psychoses.

Special Considerations in Geriatric Patients

Anxiety, both as a symptom and as a disorder, is common among the elderly, but not remarkably more or less so than at other ages. The nature of worry and its clinical manifestations, however, change

with increasing age. The intricate relationships among psychosocial stress, physical illness, depression and anxiety in late life make the recognition, diagnosis and classification of neurotic disorders in the elderly quite complex¹⁴⁻¹⁶.

The clinician can usually compare the fears and concerns of a younger patient against those of his/her own peers and arrive at a credible assessment of whether or not the anxieties are pathological. The aged, however, have different fears; they worry about physical illness, crime, institutionalization, financial disaster, senility and physical dependency. It is often hard for the younger physician to determine whether the subjective interpretation of events, or the anticipation of future events, is in the realm of clinical anxiety or constitutes adaptive concern. Anxiety results from feelings of vulnerability, and the elderly are truly vulnerable in many ways. It is no easy task to diagnose agoraphobia in an 80-year-old person whose fear of crime in her neighbourhood may exceed its statistical likelihood. The clinician walks a fine line between pathologizing a healthy response and failing to recognize neurotic dysfunction¹⁴.

Physical illnesses with psychiatric manifestations increase in prevalence with age, as does the need to take medications with emotional or behavioural side effects. Emphysema, for example, may produce features indistinguishable from those of panic disorder. Hyperthyroidism is commonly accompanied by symptoms resembling those of generalized anxiety disorder. Further, the guiding symptom profiles for the underlying disorders may be absent or muted in the ageing person. 'Silent myocardial infarction' and afebrile pneumonia are fairly common. Finally, the elderly consume significantly more medication than do younger people and exhibit psychiatric side effects at lower doses and serum levels. Bronchodilators may produce the symptoms of many anxiety states; recommended doses of over-the-counter medications for sleep or colds may induce presentations resembling dissociative states¹⁶.

As could be expected, the diagnosis of somatoform disorders and hypochondriasis is particularly complicated in the elderly. Somatic complaints are common. To some extent, the somatic presentation of emotional disorders is a sociocultural cohort phenomenon. The generation of people over 70 in the 2000s, for example, grew up in the 1940s and earlier. At that time, words such as 'depression' and 'anxiety' were not commonplace parts of everyday conversation. Emotional introspection was not culturally normative. Thus, the older person who complains today of having 'butterflies in my stomach' may be aware of the physical concomitants of anxiety, but not of the emotional state underlying it. The clinician must 'translate' somatically phrased complaints to help determine the affective condition. Furthermore, the increase in prevalence of almost all physical illnesses with age confounds the determination of pathological perception and behaviour, necessary for making diagnoses of somatoform disorders. Both DSM-IV and ICD-10 leave room for a subjective judgement of whether the presence of physical symptoms is sufficient to explain the intensity of the patient's response. There are no objective grounds for deciding when a complaint of abdominal pain constitutes a somatoform disorder in a person with concurrent emphysema, arthritis and congestive heart failure^{14,17}.

While the delineation of the diagnosis and treatment of post-traumatic stress disorder (PTSD) followed the societal impact of returning Vietnam War veterans, the syndrome is not uncommon in older individuals. The trauma may have been a different war (Second World War or Korea), a natural disaster or a personal event such as physical assault. Symptoms may occur early and continue for decades. In many cases, symptoms may not even be manifest until many years after the traumatic event. Often, the

symptoms of delayed PTSD are precipitated by a psychologically reminiscent contemporary event; a concentration camp survivor may not experience stress-related symptoms overtly until becoming widowed and being institutionalized half a century later^{14,15}.

SUMMARY

The current classification of neurotic disorders is the most recent step in the evolution of the nosological understanding of a diverse group of syndromes. The ICD-10 grouping represents a compromise between the phenomenological grouping of neurotic conditions on a scale of severity between healthy and psychotic function, and the aetiological clustering of disorders presumed to arise from internal conflicts and vulnerabilities to external stressors. The ambiguities inherent in this system reflect the incomplete state of knowledge about the aetiologies of the constituent conditions. The North American schema of DSM-IV sets aside questions of aetiology, except in the case of adjustment disorders, and relies on ostensibly atheoretical phenomenological criteria. Although the diagnostic criteria are technically independent of the age of the patient in both systems, ageing affects the presentation of many of these disorders and makes clinical diagnosis challenging. The multiple biological and social stressors of late life blur the distinction between 'normal' and 'pathological' responses to these threats. Physical illnesses, which increase in frequency with ageing, may produce clinical symptoms easily mistaken for neurotic anxiety. The prevalence of somatic pathology forces subjective judgements about the presence of somatoform and conversion disorders. Chronic and delayed stress reactions are clinically distinct from the acute forms seen in younger individuals. The lack of clarity in the classification of these disorders, however, is probably less a manifestation of the shortcomings of the nosological systems than a reflection of the complicated function of the human mind. The neurotic disorders, as well as current science can determine, are a product not of brain disease but of human response to a complicated and stressful world. Simplicity in their nosology would belie the challenges they pose to patients and clinicians.

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The Epidemiology of Depression and Anxiety

Robert Stewart¹ and James Lindesay²

¹*Section of Epidemiology, Institute of Psychiatry, King's College London, London, UK*

²*Department of Health Sciences, University of Leicester, Leicester, UK*

GENERAL CONSIDERATIONS

Depression and anxiety are common and important disorders in later life. Before reviewing their epidemiology, it is important to consider some issues around research in old age, to the extent that these impinge on research findings.

What is Old Age?

Research in 'older people' often arbitrarily focuses on people aged 65 years and over, that is, above the usual retirement age in Western nations. This '65+' range includes very varied populations: those within a decade after retirement who can reasonably expect to be in good health, through to more advanced decades where physical and mental decline become much more common and where profound social changes are more frequent, such as bereavement and challenges to independent living. The '65+' cut-off already has little social meaning in many nations and will become steadily less relevant as retirement ages become more flexible in the West. For anxiety and depression, at least two age-group targets may be more appropriate. Retirement itself is a major life-event and may exert a substantial impact on later health; for example, whether the retirement was planned, the retiree's earlier attitude to financial planning and the resources they have put aside, their ability to find alternative occupation, and the quality of interpersonal relationships as life becomes more home centred. Research around this life-transition should have a broader age focus that includes the decade or more leading up to retirement, in order to understand better what happens afterwards. At the other extreme, more 'traditional' late-life research into the impact of physical ill health and social stressors should shift its focus towards older age groups where these have highest salience.

Constructs of Anxiety and Depressive Disorders

Anxiety and depression are applied to mental states where there are no clearly identifiable boundaries between normality and abnormality. The way in which a syndrome is defined is an important consideration. Instruments which define case-level symptoms in a broad and inclusive way will give rise to higher prevalence estimates than those which define in a more selective manner. More restricted syndromes have a higher individual impact, but more 'mild'

cases may have a stronger societal impact, because of their substantially higher prevalence. Restrictive criteria are often favoured by researchers because it is easier to achieve comparability between studies. However, they frequently encompass only a small proportion of cases seen routinely by clinical services and underestimate substantially the syndrome's wider impact. It is best not to view one approach as 'better' or 'worse' than another; they are merely different, and these differences should be taken into account when between-study comparisons are made.

Underlying Dimensions

Hypertension is an artificial category applied to a known physiological parameter (blood pressure), and it is likely that the same can be said for anxiety and depression. However, the underlying parameters are much less well understood, may not be unitary, and may not perfectly reflect traditional 'diagnosis' constructs. Criteria for depression as a diagnosis do not simply reflect the pervasiveness of depressed mood but also take into account its manifestations (tearfulness, anhedonia etc.) as well as the presence of other symptoms (e.g. appetite disturbance, insomnia), the quality of other symptoms (e.g. early morning waking rather than initial insomnia), the manifestation of the overall syndrome (e.g. duration, pervasiveness, diurnal fluctuation) and the degree to which this affects daily life. The concept of the 'syndrome' is core to psychiatric nosology. However, a substantial part of this lies in tradition rather than empirical evidence, and it may be preferable for research to clarify underlying symptoms before assuming the validity of syndromes. For example, the EURO-D instrument generates two underlying dimensions (motivation and affective distress) which have different correlates (lower motivation associated with increased age, affective distress associated with female gender¹). It is not yet established whether these findings apply beyond this instrument; however, they at least suggest that a more flexible attitude is needed towards categories and dimensions.

Are Anxiety and Depression Different Disorders?

Although anxiety and depression have traditionally been defined as separate conditions, this tradition has evolved in secondary and tertiary care settings. In community samples of any age group, mixed syndromes predominate. Furthermore, the impact of common mental

disorders appears to depend principally on the number of symptoms rather than whether they are anxious or depressive². An exception to this is mortality as an outcome, where U-shaped associations with anxiety symptom load have been found compared to more linear associations with number of depressive symptoms³, which may reflect differences in health service access and use. For example, delay in breast cancer presentation was found to be positively associated with previous depressive disorder but negatively associated with previous phobic disorder⁴. In this chapter, we shall consider depressive and anxiety disorders separately for the most part, but limitations in this approach should be borne in mind.

EPIDEMIOLOGY AND COURSE OF DEPRESSION: PREVALENCE, INCIDENCE AND OUTCOME

'Depression' as a diagnosis generally requires persistent low mood which is accompanied by other symptoms (such as disturbance of sleep and appetite), and which is causing significant distress and/or disablement. However, mood states vary across a spectrum of normality to abnormality and the prevalence of depression (i.e. how common it is in a given population) depends substantially on the cut-off severity applied. As discussed earlier, severe depressive syndromes have a high individual impact but are rare, while milder syndromes have a lower individual impact but affect many more people.

Prevalence studies using more restrictive criteria include the Epidemiologic Catchment Area (ECA) surveys in five areas of the USA, in which the Diagnostic Interview Schedule (DIS) was administered, and which found major depression in 0.4% of men and 1.4% of women aged 65 years and over⁵. Other estimates include those from the Cache County Study in Utah, also using the DIS, finding major depression in 2.7% of men and 4.4% of women aged 65 years and over⁶, as well as a survey in the Netherlands finding major depression in 2.0% of residents aged 65 years and over⁷.

An alternative approach has sought to define 'depression of clinical significance'; that is, a syndrome severity which would warrant clinical intervention. This construct in older people tends to be found 5–10-times more commonly than major depression, with prevalence ranging from 10 to 20% in most studies. These include studies which have measured 'clinically significant depressive symptoms' using brief instruments such as the Centre for Epidemiologic Studies Depression scale (CES-D); for example 16% and 9% of older residents scoring at case level (16+) in two US studies^{8,9}. A more diagnostic approach is taken by the structured Geriatric Mental State (GMS) interview schedule with its accompanying AGE-CAT computerized diagnostic algorithm^{10,11}, which has probably the most wide international use including the EURO-DEP collaboration of late-life depression surveys in Western Europe¹², the UK Medical Research Council Cognitive Function and Ageing Study¹³ and the 10/66 surveys of older people in low- and middle-income countries¹⁴. The EURO-D instrument was derived from the GMS and has been applied to EURO-DEP data^{1,12,15} as well as used more recently in the Study of Health and Retirement in Europe (SHARE) surveys^{16,17}. Principal findings from the EURO-DEP collaboration were GMS depression prevalence ranging from 8.8% (Iceland) to 23.6% (Munich) with a weighted average of 12.3% in total: 14.1% in women and 8.6% in men¹². The SHARE surveys using the EURO-D reported lowest prevalence in Denmark (18.1%) and Germany (18.8%) and highest prevalence in the three Western Mediterranean sites – France (33.3%), Italy (33.7%) and Spain (36.8%). These differences largely persisted following

standardization for demographic profiles¹⁷. Prevalence estimates for similar definitions of late-life depression in other world regions have been broadly comparable – for example a 14.8% prevalence of depressed mood in a meta-analysis of studies in China¹⁸. In three Latin American sites (Peru, Mexico and Venezuela) of the 10/66 population-based survey programme, prevalence ranges were 1.3–2.8% for DSM-IV major depression, 4.5–5.1% for ICD-10 depressive episode, 30.0–35.9% for GMS-AGE-CAT 'clinically significant' depression, and 26.1–31.2% for EURO-D caseness¹⁹.

Prevalence of depression is a product of both new cases arising (incidence) and duration of case-level disorder. A higher prevalence in one site or group compared to another may be because of higher incidence or delayed recovery. For late-life depression it could also be accounted for by delayed case mortality, although mortality has been found to be higher in older people with depression²⁰. Incidence of late-life depression has been less commonly measured. Major depression incidence was 0.15% per year in the ECA studies and, in a Swedish cohort, 0.12% per year in men and 0.30% in women²¹. One-year incidence of a broader depression syndrome (17% baseline prevalence) in the north London Gospel Oak study was 12%²², and 2.5 year incidence in Korea using the GMS (baseline prevalence 14%) was also 12%²³. Persistence of depression in the Gospel Oak cohort after a one-year interval was 63%²². However, two-point surveys give relatively crude information on clinical course. Incidence is underestimated (because depression episodes in the intervening period which have recovered by the follow-up point will be missed), and persistence is over-estimated (since some of those with depression at both times may have had an intervening period of recovery).

The course of depression, a classically fluctuating condition, is therefore poorly represented by binary concepts such as 'incidence' and 'maintenance', particularly in two-wave studies. An alternative approach has described clinical course in a more qualitative manner. The Longitudinal Ageing Study of Amsterdam investigated the six-year outcome of depression defined both by the CES-D and DIS. Only 14% of episodes were found to be short lived. Remission occurred in 23%, an unfavourable but fluctuating course was followed by 44%, and a severe, chronic course by 33%²⁴. These are similar to findings from a very early study of late-life depression where, over six years, 31% recovered, 28% had one or more relapse, 23% had a partial recovery and 17% remained depressed²⁵. In another early study with a one-year follow-up, 35% had a good recovery, 48% had had a recurrence or continuation of the syndrome, 3% had developed dementia, and 14% had died²⁶. In a more recent review of depression prognosis, no clinically significant differences were found in response to pharmacotherapy or ECT by older/younger age of onset, although older people had a higher risk of future episodes. Medical co-morbidity was a potential confounder, being more common in older people and associated with a worse prognosis. Older people with early onset depression had a larger number of previous episodes, which also contributed to a worse prognosis²⁷.

AETIOLOGY OF DEPRESSION

Age

The prevalence of depressive disorders increases from young to mid-adult age groups, often followed by a fall in prevalence for older people within a decade of the retirement age²⁸. However, studies that have focused upon depressive symptoms and broader depressive syndromes indicate either an increase in their frequency, or

stability with increasing age²⁹. Blazer concluded that, if a symptom factor structure was examined, there were no age, race or gender differences in scores²¹. Where positive associations between age and depression prevalence are found, the high prevalence of physical and social stressors in these more advanced age groups is most likely to be responsible. The exclusion, in DSM diagnostic criteria³⁰, of symptoms that are considered to be primarily attributable to bereavement and physical illness may account in part for the apparent lower prevalence of thus-defined depressive disorders in older people. The expression of depression may also be qualitatively different in older people: for example, a higher age of onset for melancholic symptoms such as non-interaction, psychomotor retardation, and agitation³¹, concurring with the positive association between increased age and diminished motivation in the EURO-D scale, both in EURODEP¹ and SHARE centres¹⁷.

Cross-sectional associations with age may reflect birth cohort effects as well as chronological age, but these have been poorly captured to date. On the one hand, rapid improvements in health and economic prosperity for the 'young elderly' (e.g. 65–75 years) have been a particular feature of demographic ageing. On the other hand, there may be a reduction in 'stoicism' and 'resilience' as well as possible differences in willingness to admit to depressive symptoms. Birth cohort differences can only really be evaluated by repeated surveys covering the same population using similar measurements and case definitions; data which have not so far been available for late-life depression.

As well as the age distribution, some research has attempted to estimate the age of onset of late-life depression; that is, the proportion which occurs as new episodes. For example, an Australian study estimated that 52% of cases had their onset at age 60 or above³², while a US study of people receiving home care estimated that 71% of those who were depressed were experiencing their first episode³³. However, this approach depends on accurate recall of previous episodes, an assumption which is questioned by a prospective study in Sweden of people who had been hospitalized 25 years earlier for major depression. Of those traced, only 50% recalled sufficient details for diagnostic criteria to be applied and 30% did not recall the episode at all³⁴. Recollections of more mild forms of depression are likely to be substantially more inaccurate.

Gender and Marital Status

Higher prevalence of depression is usually found in women compared to men, but this difference is substantially less than that found in younger age groups³⁵. The EURODEP consortium¹ reported an excess of depression symptoms in older women in 13 out of 14 European centres. This association was consistently modified by marital status, with marriage being protective for men but associated with higher risk for women. These findings are consistent with the observation from several studies that married older men cite their wife as their main confidant, whereas women more often cite a friend outside the home, and with the association between married status and relatively low mortality or good health being stronger for men than for women.

Social Support/Activity

A consistent finding has been the salience to mood and morale in older people of contact with friends, in particular intimate and confiding relationships. While older people typically receive

instrumental support from spouses and relatives, they value friends for the companionship and emotional support which they can provide. However, this generalization does not take into account the fact that some individuals may prefer a relatively isolated existence and find higher levels of social contact stressful. In the longitudinal Gospel Oak study, no contact with friends was the only social support variable prospectively associated with the onset of depression²². In this study, lack of social support and social participation were associated with maintenance rather than onset of depression, and the same has been found in a prospective French study where both social activity and disablement were associated with CES-D depressive symptoms at baseline but, for those with case-level symptoms at baseline, only higher levels of social activity predicted a reduction in symptoms at follow-up³⁶. Physical health, age and gender may modify or explain to some extent the association between social support and late-life depression. There are large gender differences in late-life social support, with women typically having more supportive and extensive networks of friends than men. These may deteriorate following bereavement. Social engagement, such as visiting friends, is impaired by disability, indicating complex relationships between these exposures.

Social Adversity and Life Events

Many surveys find associations between late-life depression and relative disadvantage in income; poverty, for example, was one of the top five correlates of late-life depression along with disability, illness, isolation and bereavement³⁷. These are highly correlated characteristics, and it will always be difficult to determine the effect of one independent of the others. At least some of the effect of poverty may be confounded by and/or mediated through physical health. Environmental measures have received less attention, although one study found that worse quality of the internal home environment was an independent predictor of incident depression one year later³⁸, particularly for cohabiting residents. Poverty, isolation and poor housing represent chronic stressors. The importance of acute stressors has also been investigated, with most studies finding some association^{39,40} although varying in exposure and outcome measurement. Specific life events may have particular salience, such as bereavement, threats to health and interpersonal conflicts^{41,42}. In British residents aged 16–74 years, associations between recent life events and common mental disorder increased in strength from early to midlife and then decreased in the oldest (65–74 year) group. Lifetime events suggesting adverse childhood exposures, however, remained strongly associated with mental disorder⁴³. In younger people, early adversity is believed to act as a vulnerability factor, increasing the risk of depression in the presence of a life event⁴⁴, but this was not found in the British survey.

The Inter-Relationship between Depression and Chronic Non-Communicable Diseases

Worse physical health may be an acute or chronic stressor. However, depression is also a risk factor for worse physical health. A large part of the relationship between worse physical health and depression is mediated through higher disability levels reflecting loss of function⁴⁵. In Gospel Oak, handicap was the most important risk factor for incident depression, with a population attributable risk fraction of 0.78²². However, as discussed above, the association appears to be with onset rather than with maintenance^{22,36}. Three studies

have suggested an interaction between disablement and social support, with the strongest effect of disablement in those with the least social support^{45–48}.

The ‘vascular depression’ hypothesis

Evidence for disorder-specific risk of depression (beyond what would be expected through disability) is fairly scant. Possibly the strongest candidate is stroke, where depression occurs very commonly⁴⁹ and where this association frequently remains robust to adjustment for disability^{50,51}. However, associations with specific arterial territory involvement have not been consistent⁵², and it is quite possible that there are additional personal impacts of stroke which account for the high risk of depression, rather than cerebral damage. Incidence of depression is also increased after myocardial infarction (15–30% major depression), principally in the first month⁵³. However, associations with conventional risk factors for cardiovascular disease have been absent or accounted for by disability^{50,51,54}, and a recent study found that vascular disorders (compared to non-vascular disorders), while specifically related to cognitive impairment, showed no specificity as correlates of mental disorder⁵⁵. The concept of ‘vascular depression’⁵⁶ therefore appears to have little epidemiological support, although may still apply to the more rare and severe (and/or treatment resistant) syndromes seen in secondary care.

Depression, mortality and cardiovascular outcomes

There is substantial excess all-cause mortality associated with mental disorder. Depression, studied most extensively, is associated with an approximately 70% increased risk⁵⁷. In a French study of late-life depression, associations with mortality varied by gender with mortality predicted by symptom severity and previous antidepressant use in men, but in women only by severe untreated depression²⁰. Associations with mortality may be mediated by disability, but not apparently by cardiovascular disease, cardiovascular risk factors or antidepressant use. There is strong evidence for associations between depression and outcomes such as angina, non-fatal and fatal myocardial infarction⁵⁸, as well as stroke⁵⁹; in many studies after 10 years or more, ruling out depression induced by preclinical cardiovascular disease as an explanation. The associations are, surprisingly, independent of vascular risk factors such as obesity, smoking and hypertension. A prospective neuroimaging study found that depression also predicted worsening of white matter hyperintensities⁶⁰.

Co-morbid depression is a consistent and independent predictor of adverse outcomes after non-fatal myocardial infarction, such as recurrent coronary heart disease (CHD) events, CHD mortality, and all-cause mortality⁵⁸; explained partly by poor adherence to prophylactic behaviour and lifestyle changes. Post-stroke depression is also associated with worse functional outcomes⁶¹ and substantially higher mortality⁶².

Depression and dementia

Dementia and depression have strong interrelationships in older people. Depression occurs commonly in people with dementia, and late-life depression is also a predictor of dementia⁶³, although it has not been clarified whether this is because depression is a risk factor or an early symptom. Common risk factors may also operate and interact over a long period. These could include cardiovascular risk factors,

cerebrovascular disease and social isolation or deprivation (predisposing to cognitive decline, and impacting negatively on access to health and social care).

Recent research strongly supports an overarching model, in which it is the disability and restriction in social participation associated with any chronic health condition that most parsimoniously explains the increased risk for late-life depression. This finding, highlighted in the UK Gospel Oak study, has been subsequently confirmed in several other cohorts.

Genetic Factors

Gene–environment interactions have attracted increasing interest for depression, with several studies finding that stressful life events are stronger risk factors in the presence of a risk allele of the serotonin transporter (*5HTTLPR*) gene⁶⁴. This was replicated for stressful life events and GMS-defined depression in an elderly sample in Korea, with brain derived neurotrophic factor (*BDNF*) also implicated²³. Similar interactions have also been found in this sample for other environmental stressors such as number of chronic disorders with *5HTTLPR*⁶⁵, and incident stroke with *BDNF*⁶⁶ which, taken together, suggest that gene–environment interactions may persist into later life. However, the interaction between stressful life events and *5HTTLPR* genotype could not be replicated for CES-D caseness in an older French population⁶⁷.

THE EPIDEMIOLOGY OF ANXIETY

Anxiety symptoms and disorders are also common in elderly populations, particularly those suffering with chronic physical illness. Like depression, they are distressing and disabling, and associated with increased mortality. However, they remain under-diagnosed and under-treated in both primary and secondary care. However, there is still uncertainty about the nature of anxiety in late life and its relationship with other disorders, such as depression and dementia.

The Nature of Anxiety in Old Age

As with depression, the experience and phenomenology of anxiety in old age may differ from that in young adulthood, and these differences may make identification difficult, in both clinical and research settings. Most instruments and diagnostic criteria were developed and validated in young populations, and may under-diagnose anxiety in older adults^{68,69}. Attributing physical symptoms to anxiety can be problematic in late life, particularly with co-morbid physical illness^{70,71}, and ‘somatization’ of distress⁶⁸. Psychological and cognitive components may also differ; for example, worry appears to be less common in late life and more strongly associated with mental disorder⁷². Severity and duration of anxiety symptoms may also alter with increasing age. Anxiety disorders might be less severe in late life because of reduced reactivity to stress, ‘healthy survivor’ cohort effects and better coping skills born of greater maturity and experience⁷³. If so, then diagnostic severity thresholds defined for younger adults may not be appropriate for elderly individuals.

The Prevalence of Anxiety in Old Age

In a recent review by Bryant *et al.*⁷⁴, a systematic database search was carried out for articles published between 1980 and 2007 reporting data on anxiety disorders or symptoms in community or clinical

populations, in subjects aged 60 years and above. A total of 49 articles met their criteria, reporting results from a wide range of North American and European epidemiological studies; however, heterogeneity precluded formal meta-analysis.

This review found wide variation in the estimated prevalence of anxiety and its disorders. A few studies reported the prevalence of anxiety symptoms, which ranged from 15% (two or more symptoms on HSC⁷⁵) to 52.3% (one or more symptoms on GMS⁷⁶). Regarding anxiety disorders, overall prevalence rate ranged from 1.2% (GMS-AGECAT⁷⁷) to 14% (DSM-IV⁷⁸). The prevalence of phobic disorders ranged from 1.4% (GMS-AGECAT⁷⁷) to 25.6% (PDS⁷⁹), with specific phobia the most common phobic disorder, and social phobia the least common. Generalized anxiety disorder (GAD) prevalence ranged from 1.3% (CIDI⁸⁰) to 7.1% (HSC⁸¹) and, overall, was the commonest anxiety disorder reported. Prevalence data on the less common anxiety disorders in old age are much more limited. The Longitudinal Aging Study in Amsterdam reported six-month prevalence of 0.9% for case-level PTSD and 13.1% for sub-threshold PTSD⁸². The episodic nature of panic attacks and panic disorder render them difficult to capture in cross-sectional surveys, so it is not surprising that very low prevalence has been found of 1% or less.

In clinical studies, data are limited, but overall the results are again very variable, with anxiety symptoms ranging from 15% (geriatric hospital, GMS-AGECAT⁸³) to 56% (general hospital, GMS-AGECAT⁸⁴), and anxiety disorders from 1% (general hospital, GMS-AGECAT⁸⁴) to 24% (primary care, CIDI-SF⁸⁵).

While some of the differences in the reported prevalence rates may reflect genuine differences between populations, Bryant *et al.*⁷⁴ conclude that much is due to conceptual and methodological differences between studies. As with depression, a key factor is variation in the level of severity that is used to define a case. Studies using GMS-AGECAT demonstrate this: typically, they report quite high prevalence for sub-cases but very low prevalence for cases, indicating a high threshold. Another important factor is the application of different diagnostic rules. Instruments and diagnostic algorithms applying hierarchical rules exclude cases of anxiety co-occurring with other disorders such as depression and dementia (e.g. GMS-AGECAT, DIS-DSM-III) and, not surprisingly, identify far fewer cases of anxiety disorder than measures that do not operate such rules. The magnitude of this effect in relation to phobic disorders is shown by Lindsay and Banerjee⁷⁹, who applied different diagnostic criteria to the same population; a hierarchical system (GMS-AGECAT) yielded a prevalence of 3.6% as against 25.6% when a non-hierarchical system (PDS) was used. This problem is most pronounced in elderly populations, where there is extensive co-morbidity between depression and anxiety, particularly GAD^{86–88}. Indeed, the extent of this co-morbidity has led some to question the utility of depression and GAD as distinct diagnoses, and propose instead a dimensional construct^{89–91}.

To what extent do the prevalence rates of anxiety disorders change with increasing age? A number of epidemiological studies have examined prevalence across the adult age-range, but findings have been heterogeneous. In the US ECA study, the prevalence of anxiety disorders generally declined with increasing age, although this was less pronounced for some categories, such as phobic disorder. In the UK National Survey of Psychiatric Morbidity, the prevalence of GAD peaked in 50s and declined thereafter. Few studies report data on the very oldest age groups, but there is some suggestion that rates of anxiety may increase in extreme old age. However, most findings are drawn from cross-sectional data which must be interpreted with caution. Although it is possible that vulnerability diminishes with

age, findings may also be the result of excess mortality associated with anxiety, or birth cohort differences⁹². Measurement validity may also vary, with risk of under-diagnosis in elderly subjects⁹³.

Evidence regarding the incidence rates of anxiety in older age groups is still sparse. In studies that have looked retrospectively at age of onset, such as the ECA, most of the cases of GAD had their onset prior to the age of 65 years⁹⁴. In a three-year follow-up of the Liverpool survey using GMS-AGECAT⁹⁵, the estimated incidence rate of neurotic disorders overall was 0.44% per year; the limitations of two-point surveys to determine incidence discussed above should be noted, however.

Risk Factors for Anxiety in Old Age

Factors influencing the risk of developing an episode of anxiety may be classed as premorbid vulnerability factors, those that trigger the onset of a particular episode (destabilization), and those that determine the duration of the episode (restitution)⁹⁶. It is likely that the exposure to and impact of specific risk factors will change over the lifespan, with some, for example chronic physical ill health and disability, having more effect in old age compared to young adulthood, and vice versa. However, ageing *per se* does not appear to be a risk factor for anxiety⁹⁷; indeed, it may be protective⁹⁸. Vink *et al.*⁹⁹ reviewed studies of factors associated with anxiety and depression in elderly subjects published between 1995 and 2005. The number of studies of risk factors for anxiety, either alone or with depression, was limited compared to the number examining depression alone. Heterogeneity between the studies was also high and no formal meta-analysis was attempted. Risk factors were classified as biological, psychological or social. The principal biological risk factors associated with anxiety disorders in cross-sectional studies were: number of chronic health problems, poor self-perceived health, and functional limitation^{91,100}. Evidence from the few longitudinal studies was limited, with only poor self-perceived health and sensory deprivations emerging as predictors of anxiety symptoms^{82,101}. The psychological risk factors for anxiety identified in both cross-sectional and longitudinal studies were: external locus of control and neuroticism, poor coping strategies, and psychopathology^{82,91,100}. Not many studies have examined social risk factors for anxiety in late life in any detail. Social demographic associations such as female gender and lower educational level are reported^{91,97,98}, and the size and quality of social network has been identified in some studies^{82,97,102}. The evidence base for social risk factors for depression is larger, and there are some differences. In comparative studies, infrequent social contacts, childlessness, adverse life events and low income were associated with anxiety only, whereas small social network size and being unmarried were associated with depression. Regarding life events, depression seems to be associated more with losses, and anxiety with threats and trauma. Overall, however, the risk profile for anxiety and depression and for symptoms and disorders appear very similar, supporting the dimensional rather than categorical modelling of these conditions⁹⁹.

CONCLUSIONS

While there are many commonalities in the epidemiology of depression and anxiety across the adult lifespan, there are also some important differences due to the effects of ageing, survival and changes in the physical and social environment. These point to the need for some different interventions for older adults, aimed at increasing

social engagement and reducing the impact of physical disability, if these disorders are to be effectively prevented.

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Psychopharmacological Treatment of Anxiety

John L. Beyer

Duke University Medical Center, Durham, NC, USA

INTRODUCTION

Though the prevalence of anxiety disorders declines with age (a finding consistent with most other mental disorders), anxiety disorders remain the most common psychiatric illness in the elderly¹. An estimated 10–20% of older adults experience clinically significant symptoms of anxiety². Unfortunately, many individuals may never seek treatment, or their anxiety may not be recognized. The result has been a significant under treatment of a very treatable illness.

There are no 'perfect' anxiolytic medications for treating the elderly^{3,4}. Medications may vary in effectiveness or have problems with side effects. Further, there are significant gaps in the literature about best treatment practices, which makes evidence-based decisions difficult⁵. Therefore, we will first review general considerations about treating anxiety in the elderly before reviewing current pharmacological options. Classes of medications rather than specific recommendations for each anxiety disorder will be reviewed since research has not clarified primary treatments for most anxiety disorders in the elderly. Finally, guidelines for the evaluation and selection of pharmacological treatments are suggested.

GENERAL CONSIDERATIONS

Recognition of Anxiety

Despite the ubiquity of anxiety, either as a disorder or a symptom, recognition is not always apparent. This is especially true in treating the elderly patient. Elders often are less willing to discuss 'anxiety', but may report 'anxiety-equivalent' symptoms and physical illnesses. Thus a patient may deny feeling 'anxious', but admit to feeling 'jittery', 'sick', 'uneasy', 'flustered', 'restless', 'ill', 'achy' or 'bad'. Alternatively, the patient may deny having anxiety, but report having physical symptoms, such as 'heart pain', 'insomnia' or 'indigestion'. These complaints may obscure the true diagnosis or complicate another. The physician must therefore be sensitive, not reactive, to the presenting complaint.

Differential Diagnosis

The DSM-IV-TR has identified 12 types of anxiety disorders (Table 100.1). They are based on a cluster of symptoms with a characteristic course and treatment. Anxiety may present as a primary disorder (such as panic disorder, generalized anxiety disorder,

obsessive-compulsive disorder etc.) or as a symptom of another disorder. For example, many common medical disorders (like chronic obstructive pulmonary disease, coronary artery disease, early dementia) or common prescription and non-prescription medications (especially caffeine-containing products, cold and flu medications, alcohol or nicotine withdrawal, and certain herbal remedies) may cause anxiety (see Table 100.2). Finally, environmental and social stressors common to late life, such as bereavement, relocation or hospitalization may also cause anxiety. Thus, differentiating the source or sources of anxiety may be difficult.

When to Treat

When considering the treatment of anxiety in older adults, it is important to remember that anxiety is an adaptive emotion that occurs as a normal consequence of stressful experiences⁶. Stressful life events that frequently occur with age, such as loneliness, fear of isolation, diminished sensory abilities, diminished physical abilities, increased incidence of illness, financial limitations, and the prospect of dying, often generate considerable amounts of anxiety⁷. While anxiety may be a normal response to life events, it may also become maladaptive, meeting criteria for one of the 12 anxiety disorders. The decision to treat the anxious older patient with medication depends on the severity of the anxiety and the degree to which it interferes with the patient's functioning^{8,9}. This frequently is seen in decreased coping skills, worsening of cognitive function, exacerbation of physical illnesses, or even a breakdown in support systems¹⁰. Therefore, the first task is to assess the impact of the anxiety symptoms on social and emotional functioning or the severity of a co-existing physical illness.

Challenge of Treatment

Research in the treatment of anxiety disorders for elderly patients is limited. A National Institute of Mental Health Workshop on Late-Life Anxiety⁵ noted three significant research gaps: (i) little consensus on the 'best' approach to measure and count anxiety symptoms, syndromes, or disorders in late life; (ii) insufficient numbers of studies that examine anxiety among older adults; and (iii) limited knowledge of the differences in 'early' and 'later' onset of various anxiety disorders. These limitations become especially significant when making treatment recommendations for elderly anxiety patients. There are very few controlled clinical trials of medication or psychosocial interventions for anxiety disorders in the elderly⁴. Most recommendations

Table 100.1 DSM-IV anxiety disorders

Panic disorder without agoraphobia
Panic disorder with agoraphobia
Agoraphobia without a history of panic disorder
Specific phobia
Social phobia
Obsessive-compulsive disorder
Posttraumatic stress disorder
Acute stress disorder
Generalized anxiety disorder
Anxiety disorder due to . . . [<i>a general medical condition</i>]
Substance-induced anxiety disorder
Anxiety disorder, NOS

are usually based on case reports or open-label studies in the elderly, or extrapolated from the clinical studies of younger mixed-age adult populations and personal clinical experience. For the most part, there is little reason to doubt the applicability of the studies to the elderly patient, yet the clinician should be aware of the limitations of the research, and sensitive to the developing research in this area.

Special Adaptations for the Elderly Patient

Before prescribing anti-anxiety medicines for the elderly, the physician should also be aware of the several age-related physiological changes that may alter drug pharmacokinetics and contribute to increased risk of adverse reactions (see also Chapter 10). These include changes in drug absorption, drug distribution, protein binding, cardiac output, hepatic metabolism and renal clearance^{11–13}. In addition, changes in neurotransmitter and receptor function in the central nervous system (CNS) may make a patient more sensitive to psychotropic drugs¹⁴. In general, the usual starting dose of psychotropic drugs for elderly patients is roughly one-half of the starting dose for younger adult patients.

PSYCHOPHARMACOLOGICAL DRUGS

Over the past century, a variety of agents have been used for the treatment of anxiety and anxiety disorders, with varying degrees of success. These include antidepressants, antihistamines, antipsychotics, benzodiazepines, beta-blockers and buspirone. Despite the multiple medicines available, Zimmer and Gershon's (1991) conclusion¹⁵ that the 'ideal geriatric anxiolytic' has yet to be developed still holds true today. Therefore, effective treatment for excessive anxiety is especially dependent upon a thoughtful, accurate assessment of the patient, as well as a thorough knowledge of the patient's medication history, medical problems and social support/stress.

BENZODIAZEPINES

Since the 1960s, the benzodiazepines have been the mainstay of drug treatment for patients with situational anxiety, generalized anxiety disorder, and panic disorder¹⁶. They are also frequently prescribed for insomnia, relaxation prior to medical procedures, seizure disorders or 'agitation'. However, in the last two decades, increased attention has been given to the prescription pattern of benzodiazepines in the elderly. In the recent past, benzodiazepines were prescribed at a much higher rate among elderly patients

Table 100.2 Medical disorders associated with anxiety as a symptom

Cardiopulmonary
Asthma
Chronic obstructive pulmonary disease
Hypoxic states
Angina pectoris
Mitral valve prolapse
Cardiac arrhythmias
Congestive heart failure
Cerebral arteriosclerosis
Hypertension
Pulmonary embolism
Neurologic
Partial complex seizures
Early dementia
Delirium
Post-concussion syndrome
Cerebral neoplasm
Huntington's disease
Multiple sclerosis
Vestibular dysfunction
Endocrine
Carcinoid syndrome
Cushing's syndrome
Hypoglycaemia; hyperinsulinism
Hypo- or hyperthyroidism
Hypo- or hyperparathyroidism
Menopause
Pheochromocytoma
Premenstrual syndrome
Medications
Anticholinergic medications
Caffeine
Cocaine
Steroids
Sympathomimetics
Alcohol
Narcotics
Sedative-hypnotics

than that of the general population^{17,18}. The percentage of use has declined, especially since the introduction of the SSRIs; however, benzodiazepines remain extensively used in the elderly.

Benzodiazepines are usually classified in two groups based primarily on their length of action: anxiolytics and sedative-hypnotics. Currently, seven benzodiazepines are available for the treatment of anxiety. Listed in their order of introduction, they are chlordiazepoxide, diazepam, oxazepam, clorazepate, lorazepam, alprazolam and clonazepam¹⁹. The most common sedative-hypnotics are triazolam, temazepam and flurazepam. Table 100.3 lists the currently available benzodiazepines and their individual characteristics.

Pharmacokinetics

Each benzodiazepine follows one of two biotransformative pathways: oxidation or glucuronide conjugation. Oxidative transformation occurs slowly, contributing to a longer half-life and producing many active metabolites. Conjugative transformation usually occurs

Table 100.3 Commonly used benzodiazepines in the elderly

<i>Generic name</i>	<i>Trade name</i>	<i>Onset of action</i>	<i>Indication</i>	<i>Half-life (h)</i>	<i>Metabolism</i>	<i>Active metabolites</i>	<i>Geriatric dose (mg/day)</i>	<i>Route of administration</i>
<i>Short to intermediate half-life</i>								
Triazolam	Halcion	Fast	Hypnotic	2–5	Conjugation	None	0.125–0.5	Oral
Oxazepam	Serax	Intermediate to slow	Anxiolytic	5–15	Conjugation	None	5–30	Oral
Alprazolam	Xanax	Intermediate	Anxiolytic	6–15	Oxidation	Yes	0.125–3.0	Oral
Lorazepam	Ativan	Intermediate	Anxiolytic	10–20	Conjugation	None	0.5–3.0	Oral, IV, IM
Temazepam	Restoril	Intermediate to slow	Hypnotic	12–24	Conjugation	None	15–30	Oral
<i>Long half-life</i>								
Chlordiazepoxide	Librium	Intermediate	Anxiolytic	8–30	Oxidation	Yes	5–30	Oral, IV, IM
Diazepam	Valium	Fastest	Anxiolytic	26–53	Oxidation	Yes	2–10	Oral, IV, IM
Clorazepate	Tranxene	Fast	Anxiolytic	30–200	Oxidation	Yes	7.5–15	Oral
Clonazepam	Klonopin	Intermediate	Anxiolytic	30–40	Oxidation	Yes	0.25–3.0	Oral
Flurazepam	Dalmane	Fast	Hypnotic	64–150	Oxidation	Yes	15	Oral

more rapidly and the metabolic products are pharmacologically inactive. As a general rule, benzodiazepines that are inactivated by conjugation are less likely to interact with other medications. For example, cimetidine has been found to inhibit the metabolism of benzodiazepines that require oxidation, but not benzodiazepines inactivated by conjugation. Table 100.4 lists several important drug interactions with benzodiazepines.

When used for their sedative properties in the elderly, effects of ultra-short, short and intermediate half-life benzodiazepines do not extend to the next day²⁰. Ultra-short benzodiazepines are generally used to treat insomnia rather than daytime anxiety. However, they can cause rebound insomnia after abrupt discontinuation. Safety concerns about triazolam (i.e. after being noted to cause confusion, agitation and hallucinations) have led to its ban in several European countries¹⁸. Benzodiazepines with long half-lives can significantly contribute to increased risk of falls and hip fracture in elderly patients²¹.

The onset of action after a single dose is primarily dependent upon the drug's absorption rate. Most benzodiazepines are highly lipophilic. Benzodiazepines that are more lipid soluble have a faster

onset of action because they are absorbed and diffused into central synapses more rapidly^{22,23}. This rapid onset of action can produce euphoria and thereby enhance abuse potential.

Efficacy

Although benzodiazepines have been shown to be effective in younger populations, systematic studies in the elderly are lacking. Benzodiazepines are effective for generalized anxiety disorder (GAD). Clonazepam has been shown to be effective for social phobia. Clonazepam and alprazolam are effective in panic disorder. Efficacy and use in posttraumatic stress disorder (PTSD) is limited. A paradoxical reaction has been documented when some patients with PTSD are treated with benzodiazepines. None of the benzodiazepines appear effective for obsessive-compulsive disorder. Of note, though short-term efficacy has been well documented, there are no data on long-term results.

Dependence and Withdrawal

True physiological dependence, resulting in a withdrawal and abstinence syndrome, develops for benzodiazepines usually after three to four months of daily use¹⁴. Withdrawal symptoms are likely to be more severe with abrupt discontinued therapy, and with patients receiving short half-life benzodiazepines, or higher daily doses. The symptoms of withdrawal include tachycardia, orthostasis, intention tremors, diaphoresis, hyper-reflexia, anxiety, insomnia, nightmares, malaise, anorexia, headache, muscle pain and twitching, tinnitus, hyperacusis, photophobia, metallic taste, strange smells and, in more severe cases, hyperthermia, nausea, vomiting, delirium, seizures and psychosis.

Side Effects

Adverse drug reactions with benzodiazepines are almost twice as common in patients over the age of 70 years compared with those aged 40 years or less²⁴. Benzodiazepines have a greater effect on the central nervous system of the elderly than younger patients^{8,12,13}. The most common side effect is a dose-dependent dampening of central nervous system activity. The resulting symptoms include fatigue,

Table 100.4 Drug interactions with the benzodiazepines

<i>Drug</i>	<i>Effect</i>
Alcohol	Increased CNS sedation
Neuroleptics	Increased CNS sedation
Narcotics	Increased CNS sedation
Antihistamines	Increased CNS sedation
MAO inhibitors	Increased CNS sedation
Cimetidine	Increased elimination half-life and decreased clearance of alprazolam, diazepam and chlordiazepoxide
Isoniazid	Decreased metabolism of diazepam
Rifampicin	Increased metabolism of diazepam
Antacids	Decreased absorption of clorazepate and chlordiazepoxide
Digoxin	Increased digoxin levels
Levodopa	Decreased control of parkinsonism by levodopa
Fluvoxamine	Increased levels of alprazolam

drowsiness, muscle weakness, blurred vision, nystagmus and (of special concern in the elderly) impaired psychomotor and cognitive performance that may lead to falls and fractures^{12,25,26}. The impairment of motor coordination causes drivers taking benzodiazepines to be five-times more likely to be involved in a serious road accident²⁷. Cognitive impairment can be severe enough to present as a pseudodementia in susceptible elderly patients. The risks of side effects appear to persist or worsen with chronic treatment²⁸, making the risk/benefit ratio for benzodiazepines appear unfavourable in the long-term treatment of anxiety disorders in the elderly⁶.

Benzodiazepines may also cause a paradoxical reaction of restlessness, confusion, irritability and even aggression. Outbursts of anger in elderly patients receiving benzodiazepines may indicate the need to consider an alternative medicine. Benzodiazepines may cause mild respiratory depression in patients with chronic obstructive lung disease. Mixing benzodiazepines with other CNS depressants such as alcohol can lead to severe intoxication or (potentially lethal) respiratory depression.

Selection

In general, benzodiazepines are equivalent in terms of overall efficacy²⁹. The selection of a particular benzodiazepine is primarily based upon the patient's particular problem and the medication properties (route of metabolism, length of half-life, onset of action and presence of active metabolites)³⁰. In general, the following guidelines should be considered when using a benzodiazepine:

1. Benzodiazepines which undergo conjugation (e.g. temazepam, lorazepam, oxazepam) have no active metabolites and their pharmacokinetics are not significantly changed by the ageing process¹². They are probably the wisest choice for elderly patients with impaired hepatic function.
2. Short (but not ultra-short) half-life drugs are preferable to long half-life medications since they appear less likely to increase the risk for hip fractures²¹.
3. Accumulation of benzodiazepines is directly related to the amount of fat. Therefore, the thin or medically frail patients may be at increased risk.
4. Avoid benzodiazepine use in patients dependent on alcohol or other drugs.
5. Begin with lower doses and titrate upwards gradually. ('Start low and go slow.')
6. Try to limit the length of use to three to four months. Taper benzodiazepines over a four to eight week period.
7. Evidence suggests that early anxiolytic benefits from benzodiazepines improve overall compliance to antidepressant treatments in older patients³¹.

BUSPIRONE

Buspirone is a novel anti-anxiety medicine whose mechanism of action is probably related to its high affinity for the serotonin type 5-HT_{1A} receptor, which causes reduced serotonergic activity. In addition, it enhances brain dopaminergic and noradrenergic activity^{32,33}.

Efficacy

Buspirone was shown to be effective in the treatment of generalized anxiety disorder (GAD) in the elderly in a small (40 patient)

and short (four week) double-blind study³⁴. It is well tolerated and as effective as the benzodiazepines for GAD^{35–37}; however, buspirone does not appear effective in the treatment of panic disorder³⁸. Some researchers suggest that buspirone may be helpful in mixed anxiety/depression symptoms. It may also be effective as an adjunct treatment for obsessive-compulsive disorder. Its use in posttraumatic stress disorder and social phobia appears to be limited.

Administration

Therapeutic doses of buspirone range from 20 to 60 mg daily. Because of its short half-life, buspirone is usually given three times a day. Further, as opposed to benzodiazepines, the anxiolytic effect of buspirone may not become apparent for one to three weeks. Some researchers have also suggested that the efficacy of buspirone may be reduced in patients who have previously been treated with benzodiazepines³⁹.

Side Effects

Buspirone is usually very well tolerated, but potential side effects may include nausea, headache, nervousness, dizziness, light-headedness and fatigue. Unlike the benzodiazepines, buspirone does not appear to cause psychomotor impairment, dependence, withdrawal or abuse⁴⁰. Further, it does not interact with alcohol and other sedative drugs. Therefore, it may be of particular value in the treatment of patients unable to tolerate the sedative effects of benzodiazepines⁴¹, or patients with a history of substance abuse.

ANTIDEPRESSANTS

Tricyclic Antidepressants

Efficacy

Tricyclic antidepressants (TCAs) have been shown to be effective in treating mixed anxiety-depression states, panic disorder, and generalized anxiety disorder in the elderly^{42–45}. In the general adult population, TCAs are frequently used in posttraumatic stress disorder, and clomipramine has been approved by the FDA to treat obsessive-compulsive disorder. However, the overall use of TCAs has decreased as other options (especially the SSRIs) have become available. This is primarily due to the significant side effects TCAs have at therapeutic doses, which also increases the risk to physically ill patients and potentiates toxicity in overdose. Further, like all other medications used for the treatment of anxiety (except the benzodiazepines), TCAs usually require several weeks to show maximal benefit. Despite their shortcomings, tricyclic antidepressants remain an alternative treatment for generalized anxiety disorder⁴⁶.

Side effects

Common side effects may be mediated by alpha-adrenergic blockade, anticholinergic effects and antihistaminergic effects. The alpha-adrenergic blockade of TCAs may cause significant orthostatic hypotension or cardiac conduction irregularities. The elderly are particularly susceptible to injury from orthostatic falls. Patients with complete heart block should not be given TCAs because these medications can cause a prolonged QRS complex. Trazodone, a

heterocyclic antidepressant, is sometimes used as a sedative or in the treatment of agitation for demented patients, but the side effects of postural hypotension may limit its use²⁰.

Anticholinergic side effects of TCAs are dry mouth, blurred vision, constipation, urinary retention and confusion or even psychosis. This may be particularly significant in patients with Alzheimer's disease or other disorders which impair memory. The major antihistaminergic effect is sedation.

Guidelines for use

Imipramine and amitriptyline have long been established in the adult population for use in various anxiety disorders. However, their tertiary amine structure tends to cause increased anticholinergic, adrenergic and sedative side effects. The secondary amines, nortriptyline and desipramine, are preferred for use in the elderly due to their less intense side effects. In general, anxiety disorders appear to respond at doses lower than those used in mood disorders. A baseline EKG is highly recommended prior to starting therapy since TCAs can cause a prolonged QRS complex.

Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase inhibitors have been effective in treating mixed anxiety-depression and panic disorder but not pure generalized anxiety^{43,44}. MAOIs are rarely used now because of their potential side effects (especially the drug/diet interactions) and the wider availability of newer antidepressant choices. Phenelzine and tranylcypromine are the best MAOI choice for the elderly in the United States⁹. Interestingly, phenelzine was found to be more effective in the elderly than in younger patients⁴³, and just as well tolerated as nortriptyline⁴⁷. The starting dose is 15 mg daily in the morning, increasing by 15 mg every few days to an average dose of 45–60 mg⁴⁸.

Orthostatic hypotension is a frequent side effect of MAOIs; however, the major concern is the possibility of an acute hypertensive crisis due to the drug and dietary interactions.

Selective Serotonin Re-Uptake Inhibitors (SSRIs)

Efficacy

The introduction of selective serotonin re-uptake inhibitors has transformed the treatment of both depression and anxiety in the adult population. Seven SSRIs are now available for use in the US: fluoxetine, sertraline, paroxetine, paroxetine CR (controlled release), fluvoxamine, citalopram and escitalopram. Since their introduction, certain SSRIs have obtained indications for the treatment of not only depression, but also panic disorder, bulimia, obsessive-compulsive disorder and social phobia. They have also been shown to be effective for use in posttraumatic stress disorder and generalized anxiety disorder. Surprisingly, there has still been little research into the use of SSRIs for the treatment of anxiety disorders in the elderly. Fluoxetine has been shown to be effective in treatment of elderly depressed patients with agitation²⁰. Fluvoxamine was found to be effective in a sample of elderly patients with a mixture of anxiety disorders (mostly GAD)⁴⁹, though near-maximal doses of fluvoxamine were needed to achieve remission. A study of 60 elderly patients with anxiety disorders (primarily GAD) found citalopram to be effective, with improvements noted through the first 20 weeks of treatment⁵⁰. Fluvoxamine and fluoxetine have been shown to be

effective in clinical trials for obsessive-compulsive disorder that have included some elderly patients^{51,52}. Case studies have shown sertraline, paroxetine, venlafaxine, fluoxetine and fluvoxamine effective in social phobias and anxiety^{53–56}.

Side effects

All SSRIs can cause gastrointestinal effects (nausea and diarrhoea), sexual arousal and performance changes, and a decrease in appetite and weight. The nausea and diarrhoea are usually dose dependent and resolve for most patients within the first week of treatment. An increasing concern has been SSRI-associated weight gain seen with extended use. Paroxetine has been noted to have some anticholinergic activity that may be more apparent in elderly, sensitive patients. A significant potential side effect of SSRIs includes a tendency to stimulate patients, causing tremor and jitteriness.

Guidelines for use

SSRIs have now become the first line treatment for most anxiety disorders. Some researchers have found that an initial use of benzodiazepine augmentation improves overall compliance with treatment³¹ without an increased risk of falls⁶. Smith and colleagues⁵⁷ have recommended that SSRIs which have shorter half-lives and are less activating, such as paroxetine or sertraline, be used preferentially to fluoxetine. However, it should be noted that fluoxetine has been shown to be effective in treating anxiety symptoms associated with depression.

Newer Antidepressants

Venlafaxine, an SNRI (serotonin-norepinephrine re-uptake inhibitor), is approved for the treatment of generalized anxiety disorder in adults. A retrospective analysis of elderly subjects in the phase III studies for venlafaxine ER (extended release) found a 25% greater response rate than placebo (similar to that observed in younger adults)⁵⁸. Older subjects had a lower rate of side effects than younger subjects, though the side effect-related discontinuation rate was the same (15%). Overall, the side effect profile of venlafaxine is similar to the SSRIs. Small elevations in blood pressure may be seen at dosages above 200 mg/day.

Nefazodone may be a useful antidepressant for depressed elderly patients who have concomitant anxiety symptoms²⁰. It has an acceptable level of daytime sedation for the elderly⁵⁹, but minimal anticholinergic and other side effects. Its more moderate serotonin re-uptake inhibition may make it less likely to create agitation than the SSRIs⁶⁰. Nefazodone does inhibit P-450 isoenzymes and is contraindicated for use with terfenadine, astemizole and cisapride. It will also increase the plasma levels of alprazolam, midazolam and triazolam.

Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA) has shown beneficial effects on the concomitant symptoms of anxiety and sleep disturbances in depression trials⁶¹. It has few anticholinergic, adrenergic and serotonin-related adverse effects, but can be very sedating due to the antihistaminergic effects. There are no current data on its effectiveness in the elderly.

BETA-BLOCKERS

The usefulness of beta-blockers for treatment of anxiety in the elderly is unclear since the data for the elderly are restricted to clinical case

reports³⁰. Beta-blocking agents have been shown to be specifically beneficial in younger patients with predominantly somatic symptoms associated with generalized anxiety or anxiety related to stressful situations⁶². They may also have potential use in the treatment of aggression and agitation in patients with organic brain disease⁶³. Although beta-blockers decrease autonomically mediated symptoms such as diaphoresis, palpitation, tremor and gastrointestinal upset, they usually do not reduce the inner subjective effects^{3,7}.

Propranolol in small doses (such as 5–10 mg one to four times a day) may be effective in elderly patients²⁰. These drugs should not be used in patients with chronic obstructive pulmonary disease, congestive heart failure, heart block, insulin-dependent diabetes, severe renal disease or peripheral vascular disease.

ANTIHISTAMINES

Sedating antihistamines such as hydroxyzine and diphenhydramine hydrochloride are sometimes useful for anxiety or insomnia in the elderly. They have been rarely recommended because they are less effective than benzodiazepines, and their anticholinergic side effects outweigh their weak anxiolytic effects³. They may be used in patients with mild symptoms, in severe chronic obstructive pulmonary disease, in patients with substance misuse, or in patients for whom more traditional drugs are not effective⁶⁴. However, physicians must be aware that the elderly patient is much more susceptible to their anticholinergic properties, which may cause blurred vision, tachycardia, dry mouth, urinary urgency, constipation, restlessness, hallucinations and confusion.

GENERAL GUIDELINES

Despite the limited data on treatment of anxiety disorders in the elderly, the clinician can successfully treat patients with a conservative and thoughtful use of medications. The following guidelines have been adapted from Small (1997)²⁰:

1. Conduct a complete psychiatric evaluation. Listen specifically for expression of anxiety. Does this patient have anxiety that significantly affects their quality of life or functioning?
2. Consider the full differential diagnosis. Does the pattern of anxiety identify itself as a formal anxiety disorder, or as a symptom of another psychiatric or medical disorder? Geriatric psychiatry has been called the specialty of co-morbidity. There may be several potential aetiologies for anxiety symptoms that should be considered before initiating treatment.
3. Consider non-pharmacologic treatments first. Education and reassurance are invaluable in the treatment of anxiety, and may themselves be adequate treatments. Specifically address social stressors and evaluate the effectiveness of the support systems. Attention to family caregivers may facilitate the positive response to other treatment. Remember, the ability to benefit from therapy is not based on age.
4. Minimize polypharmacy. In the elderly population (especially those in the nursing care facilities), the use of multiple medications is the rule rather than the exception. Most clinicians stress the importance of reviewing the medication list for potential areas of reduction, prior to adding new treatments. Reducing the number of medications may actually treat the anxiety symptoms²⁰.

5. When selecting an anxiolytic, consider the full presentation rather than just the anxiety when choosing an initial medication. For example, use an antidepressant if depressive symptoms are apparent. Avoid anticholinergic medications in patients with dementia. Avoid benzodiazepines when the patient's ability to ambulate is compromised.
6. Presently, treatment recommendations for elderly with anxiety disorders are similar to those in younger patients. In general, SSRIs and venlafaxine are considered first line pharmacotherapy for anxiety disorders in the elderly⁶.
7. As far as possible, make medication changes one at a time in order to clarify whether a complaint results from a medication side effect or an underlying illness.
8. 'Start low and go slow.' Most medications are started at lower doses than those used for younger adults, but it is generally necessary to increase to usual therapeutic doses.

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Obsessive-Compulsive Disorder

James Lindesay

Department of Health Sciences, University of Leicester, Leicester, UK

Although obsessive-compulsive disorder (OCD) is known to occur in old age, studies are few and information is limited. This may be because it is often not perceived as a disorder of late life. The mean age of onset of the condition is 20–25 years^{1–3} and it is unusual for OCD to have its first onset after the age of 50 years. However, OCD can become a chronic disorder; as a recent 40-year follow-up study has shown, while most patients improve to some extent, less than half show complete or partial recovery⁴. A significant proportion of cases persist into old age, at which point they may present to services for the first time. It is important, therefore, that old age psychiatrists are aware of this disorder and of its management.

CLINICAL FEATURES

Diagnostic Criteria

OCD is characterized by intrusive, persistent obsessive thoughts, images or impulses and/or compulsive behaviours that are a significant source of distress, or interfere with the patient's personal or social functioning. The current diagnostic criteria, as set out in DSM-IV⁵ and ICD-10⁶, apply to all patients, irrespective of age. The limited evidence available indicates that the clinical features of OCD in elderly patients are very similar to those of younger adults. In their comparative study, Kohn *et al.*⁷ found that concerns about symmetry, need-to-know and counting rituals were less common in elderly patients, and hand-washing and fear of having sinned were more common, but otherwise there were few differences in clinical features compared with younger OCD patients. Extreme ego-syntonic religiosity has been proposed as a variant of OCD that may be more common in older patients⁸.

Differential Diagnosis

Unpleasant, intrusive thoughts and abnormal stereotyped behaviours occur in other mental disorders, and OCD is not diagnosed if their content is exclusively related to another disorder, for example guilty preoccupations in depression, worries in generalized anxiety, concern with illness in hypochondriasis, weight control in anorexia or avoidance in phobic disorders⁵. It should be borne in mind that conditions such as depression, generalized anxiety and substance abuse may be co-morbid with OCD. In elderly patients, increased anxious orderliness may be a prodrome of dementia; however, this behaviour is not resisted or associated with the tension that occurs

in OCD. The compulsive behaviours of OCD resemble the stereotyped behaviours that occur in certain other disorders, such as Tourette's syndrome, Sydenham's chorea, encephalitis and partial complex seizures. Tourette's syndrome and OCD commonly co-occur⁹, and patients with OCD may have a history of Sydenham's chorea in childhood¹⁰. There is currently some debate as to whether conditions such as OCD, body dysmorphic disorder, trichotillomania and hypochondriasis might form an obsessive-compulsive 'spectrum of disorders'.

Despite its similar name, obsessional personality disorder is quite distinct from OCD. It is characterized not by obsessions and compulsions, but by a preoccupation with orderliness, perfection and control dating back to early adulthood⁵. Individuals who are unable to discard personal possessions may present as the so-called 'senile squalor' syndrome after a lifetime of accumulating rubbish. This syndrome overlaps both obsessional personality disorder and OCD¹¹.

Not all patients with OCD have insight into the irrationality and inappropriateness of their obsessions and compulsions. If the obsessional thoughts are held with delusional intensity, an additional diagnosis of delusional disorder may be warranted. The ruminative delusions and stereotypies of schizophrenia are usually not ego-dystonic, and therefore would not be regarded as OCD⁵.

Clinical Assessment

An effective treatment plan for OCD requires a detailed clinical assessment. What exactly are the main problems? What, if anything, exacerbates or improves the symptoms? How long has the condition been present, and how has it evolved since its onset? What treatments, if any, have been tried in the past? What other symptoms or disorders are present? Any concomitant depression, mania, psychosis or alcohol dependency will require specific management before behavioural treatments for OCD can be effective. If the patient is cognitively impaired, this will have implications for the choice of treatment; for example, some behavioural strategies will not work if information cannot be retained or recalled. In elderly patients with OCD of recent onset, it is important to investigate carefully for any underlying cerebral disease. Late-onset cases are associated with frontal dysfunction¹², which may be caused by a variety of focal and generalized disorders, including cerebrovascular disease, tumours and primary neurodegenerative dementias. Late-onset OCD may also be the result of external factors, such as adverse life events and exposure to trauma, that weaken an elderly individual's resistance to long-standing subclinical obsessionalities¹³.

EPIDEMIOLOGY

Most of our knowledge about the epidemiology of OCD in old age derives from the US National Institute for Mental Health (NIMH) Epidemiologic Catchment Area (ECA) Program. Overall, the one-year prevalence for those aged 65 years and older was 0.85% (men 0.75%, women 0.93%), as opposed to 1.65% for the sample as a whole¹⁴. A more detailed analysis of the elderly population at the Eastern Baltimore site found prevalence rates of 1.3% for those aged 65–74 years and 0.6% in those aged 75+¹⁵. Following the second wave of the ECA, annual incidence rates were estimated. In males aged 65+, the incidence rate of OCD was one-third of that for males of all ages, but in females there was a non-significant upturn in the incidence rate after age 65¹⁶. In common with a number of other psychiatric disorders, the lifetime prevalence of OCD decreased with age in this study. The reason for this is unclear, but it may be the result of cohort effects, differential mortality or age-specific differences in symptom ascertainment and recall. A rather higher overall one-year prevalence rate of 1.5% in over-65-year-olds has been reported in a more recent community study in Quebec, greater than that found for major depression (1.1%)¹⁷.

AETIOLOGY

OCD is familial; it occurs in 40–50% of parents, 19–39% of siblings and 16% of children of probands with the disorder¹⁸. Just what is inherited is not clear; other anxiety disorders are also more common in the families of OCD probands¹⁹. At least part of this familiarity is due to genes, and most of the studies that have been carried out have focused on candidate genes in the serotonergic and dopaminergic neuronal pathways²⁰. However, to date most of these studies have been too small to establish linkage with an acceptable level of significance, and apart from the glutamate transporter gene, there has been no replication of findings. It is not known how the expression of any genetic susceptibility to OCD may vary across the life span.

Most of the evidence from clinical, neuropsychological and neuroimaging studies implicates the basal ganglia and their connections with the thalamus and the cerebral cortex in the aetiology of OCD²¹. Specifically, it has been proposed that there are structural and functional abnormalities in a neuronal circuit involving the orbitofrontal cortex, the basal ganglia, the substantia nigra and the ventrolateral pallidum²². Recent developments in imaging, such as voxel-based morphometry and multivoxel analyses have confirmed abnormality of the orbitofrontal-striatal areas in OCD, but indicate that other regions such as the dorsolateral and ventrolateral pre-frontal and parietal areas are also involved²³. The specific response of OCD to serotonin (5-HT) re-uptake-inhibiting drugs (see below) suggests that serotonergic neuronal systems are involved, directly or indirectly. In the cognitive behavioural model of OCD, obsessions and compulsions result from pathological, anxiety-provoking over-control of normal intrusive cognitions²⁴.

TREATMENT

There are no randomized, controlled trials of treatment of OCD in elderly patients. Accordingly, the guidelines that follow are based upon case reports and extrapolations from studies in younger adults²⁵. The current evidence-based UK NICE Guideline on OCD recommends a stepped care approach, with low-intensity psychological treatment for mildly impaired patients, and more intensive

psychological treatment or pharmacotherapy for the more severely impaired, or those who fail to respond to low-intensity treatment²⁶. This document also outlines some useful principles underlying the effective care of this group of patients.

Non-Pharmacological Treatments

Behavioural therapy, in the form of exposure and response prevention (ERP), is well described as an effective intervention for OCD in younger adults²⁷. This involves exposing the patient to the feared situation, and helping him/her to resist the urge to perform the compulsive behaviours that would normally follow this exposure²⁸. ERP is least effective in those who have obsessional thoughts and covert rituals unaccompanied by compulsive behaviour. In these patients, a cognitive approach directed at modifying the misinterpretation of intrusive thoughts is more appropriate²⁹. A recent systematic review of randomized trials of psychological treatments for OCD in comparison with treatment as usual has concluded that treatments based on cognitive behavioural models are effective in younger adults, although larger studies with longer periods of follow-up are still needed³⁰. Another systematic review has found that group cognitive behaviour therapy for OCD is effective in comparison with several control conditions, although it is not yet clear how this compares with individual treatment formats³¹. There are a number of case reports of effective behavioural interventions in elderly OCD patients^{24,32–35}, which suggest that it is reasonable to extrapolate the available evidence from randomized, controlled trials involving younger adults. It should be borne in mind, however, that most of the case reports are difficult to interpret because of the concomitant administration of medication, although in the case described by Calamari *et al.*³⁵, significant improvement following ERP was maintained without medication at eight-month follow-up.

Sigmund Freud originally proposed that obsessional symptoms were a regression to a pre-genital anal–sadistic phase of development. However, despite this and subsequent psychodynamic formulations of the disorder, there is no evidence that psychodynamic psychotherapy is an effective treatment for OCD at any age.

Pharmacological Treatments

Studies in younger adults indicate that 30–60% of patients with OCD show improvement on appropriate medication, and that drug treatments appear to be more effective for obsessional thoughts than for compulsive behaviours. In practice, drug treatment and behavioural therapy are often given in combination, and there is some evidence that this is an effective strategy³⁶.

The theory that OCD is a disorder of serotonergic function is based upon the empirical observation that it can be effectively treated by drugs that inhibit serotonin re-uptake. Clomipramine is the most extensively studied drug treatment for OCD, and its effectiveness has been established in a number of double-blind, placebo-controlled trials in younger adults³⁷. However, its lack of receptor sensitivity means that it has significant anticholinergic and antihistaminergic side effects that limit its usefulness in elderly patients³⁸. In this age group, the current drug of first choice is one of the specific serotonin re-uptake inhibitors (SSRIs). Fluoxetine, paroxetine, fluvoxamine and escitalopram are currently licensed in the UK for the treatment of OCD, although none of the trials supporting this indication specifically involved elderly patients. A systematic review of trials of SSRI drugs for OCD in comparison with placebo has concluded that they

are effective, at least in the short term, and that there are some differences between the different SSRIs with respect to their adverse effects³⁹. The effective dose for the treatment of OCD with these drugs tends to be higher than that required to treat depression, and the time taken to respond is typically much longer: 10–18 weeks. Studies suggest that long-term therapy is required, as discontinuation of medication leads to relapse of symptoms⁴⁰.

There is little evidence for the effectiveness of other drug treatments in OCD. There are some case reports suggesting that monoamine oxidase inhibitors (MAOIs) may be useful in patients with concomitant panic or severe anxiety. Anxiolytic drugs may also help with the anxiety associated with OCD, but do not appear to have any effect on the core symptoms. A possible exception is buspirone, which may augment the effect of fluoxetine^{41,42}. A recent meta-analysis of randomized, controlled trials supports the use of antipsychotic drugs in combination with an SSRI in patients resistant to first-line drug treatment⁴³; the best evidence is for haloperidol and risperidone. Several other drugs, including carbamazepine, gabapentin, memantine and mirtazapine have been reported to be effective in combination with SSRIs in small uncontrolled studies. Lithium augmentation of fluoxetine has also been reported as effective in one elderly case⁴⁴.

Physical Treatments

There is very little evidence to suggest that ECT is effective in the treatment of OCD in patients who are not also depressed⁴⁵. Similarly, the therapeutic potential of transcranial magnetic stimulation in this disorder has yet to be demonstrated⁴⁶. Some good results have been reported for stereotactic neurosurgical procedures in patients with severe and treatment-refractory illness, including elderly subjects²⁵, but since negative outcomes are rarely described, this evidence is difficult to interpret.

CONCLUSIONS

OCD may present for the first time in old age, and many elderly patients with chronic illness will not have been exposed to the full range of pharmacological and cognitive behavioural interventions that are now available. It is important that old age psychiatry services are aware of these treatments and develop some experience in their delivery. There is some evidence that they are effective in elderly patients, but further research is needed. Patients with a new onset of OCD in late life need careful assessment to exclude underlying organic brain disease.

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Somatoform Disorders and Unexplained Physical Symptoms

Bart Sheehan

Health Sciences Research Institute, Warwick Medical School, Coventry, UK

HISTORY

Mysterious physical symptoms of uncertain origin have been noted as long as medical matters have been written about. Early explanations of mysterious symptoms involved the abnormal movement or function of the womb, hence the origin of the term hysteria from the Greek word *hysterikos*. Such explanations may now seem absurd, but were influential till at least the seventeenth century, when Sydenham first wrote of hypochondriasis (a male condition) and hysteria (a female equivalent). Sydenham described the two conditions as alike 'as one egg is to another'. He recognized that psychological disturbance was primary, that symptoms were changeable and that these conditions cause great diagnostic difficulty. Over the next 200 years, acceptance of a psychological origin for some ill-defined physical symptoms grew, along with the concept of a group of psychological illnesses called neuroses.

Interest in these ill-defined symptoms really accelerated with the popularization of Sigmund Freud's early ideas about unconscious conflicts and psychological disturbance. Freud was struck by Charcot's demonstrations in Paris of hysterical physical symptoms. He developed the idea that unconscious conflicts were manifest as physical symptoms, as a form of defence mechanism. After the First World War, no-one who had seen the victims of 'shell-shock' could doubt the ability of psychological trauma to cause physical symptoms.

Proponents of psychoanalytic ideas developed terms like somatization and psychosomatic illnesses. As the influence of these ideas eventually waned after the Second World War, clinicians became less focused on aetiology and more on careful description of patients with persistent troublesome physical symptoms. By 1980, when DSM-III was published, the term hysteria was dropped. Somatization disorder, in which multiple physical symptoms persist over years, with no organic explanation, and hypochondriasis, in which patients dread a particular disease and cannot be reassured despite investigation, became the prototypical somatoform disorders. Thus, Sydenham's observations from 300 years previously were confirmed in modern medicine.

MODERN TERMINOLOGY

Both DSM-IV and ICD-10 have categories of somatoform disorders. Both include core somatization disorder and hypochondriacal disorder, and a handful of other disorders like conversion disorder and body dysmorphic disorder (DSM-IV), Somatoform autonomic disorder (ICD-10) and persistent pain disorders (both classifications).

Clinicians dealing with older patients are likely to mainly encounter less differentiated admixtures of unexplained symptoms and hypochondriacal beliefs. The diagnostic categories in DSM-IV are unlikely to be especially helpful when faced with a persistently complaining patient who is likely also to have at least one organic illness. The term 'medically unexplained symptoms' is sometimes used to cover the wider range of patient presentations. This term avoids diagnostic confusion and can sometimes be useful in the presence of real physical illness.

CLINICAL PRESENTATIONS

Case 1

Mr W is a 76-year-old man admitted with worsening depression to a psychiatric ward. In the last two weeks he has become increasingly preoccupied with his bowels, plaguing his primary care doctor for consultations. He is now convinced that his bowels have stopped working due to 'a blockage ... cancer or something'. He is reluctant to eat or drink and feels that any treatment is futile. Examination and investigation shows mild constipation but no evidence of any other organic lesion. Reassurance is ineffective. He eventually requires intravenous rehydration and ECT. He begins to improve after about a week, initially saying 'I am not so sure', then later 'I suppose I was worrying too much'. He regains much of the weight he had lost and is discharged home after seven weeks in hospital.

A case of severe depressive disorder with psychotic features (hypochondriacal and nihilistic delusions). Rapid improvement in physical complaints noted with definitive treatment of underlying psychiatric disorder.

Case 2

Mrs K is a 64-year-old woman who is referred to psychiatric services for the fifth time in her life. She is well known to primary care as a frequent attender and for the last three years has seen her general practitioner at least once a week. She complains of multiple symptoms including pain in the head, back and limbs, abdominal discomfort, bloating and frequency of bowel motions, blurred vision, dry mouth, urinary frequency, some shortness of breath and chest pain, and is 'unable to settle at night'. She has had multiple referrals to secondary care over 40 years. Investigations by gynaecology, general surgery, cardiology and gastroenterology have been negative but did not help. She does not feel taken seriously and is 'fed up with doctors ... the whole time they just try to get rid of me'. She has mild depression but is very reluctant to see a psychiatrist or counsellor. The psychiatrist writes 'No sign of formal mental illness' and discharges the patient back to the general practitioner.

A probable case of somatization disorder. Psychiatry is unhelpful here, maintaining the disorder by rejecting the validity of the complaint and offering nothing helpful to the GP.

Case 3

Mrs T, a 76-year-old widow, presents to her GP with abdominal pain. This has come on in the last three weeks. There are no findings on examination and she has no significant medical or surgical history. Her husband died about six years ago. She becomes tearful during the consultation and says she is 'desperately worried' that the marriage of her only daughter is in trouble. This daughter is her main social support. She thinks she may not see her grandchildren again for some time. She agrees that stress makes the pain worse, and agrees that the family situation is stressful. She comes back to see the GP after two weeks. The pain has lessened, though she is still worried. She has told her daughter of her worry, and been reassured that she will not lose contact with any family members.

Illustrates how mild physical symptoms may follow psychological distress, and how watchful waiting and a sympathetic approach may be associated with improvement and no unnecessary referrals.

somatized symptoms are probably the most common way for depressive disorders to present in primary care. In secondary care, psychological distress and outright somatoform disorders have both been consistently linked with frequent attendance, high costs and chronicity of presentations.

Good-quality evidence on the prevalence and incidence of these presentations among older people is lacking. Somatoform presentations are often defined in loose or confusing ways, or highly selected populations may be sampled. Some studies define somatoform presentations as strict classical presentations with a primary hypochondriacal or somatization disorder, others are rates of ill-defined somatic symptoms. Prospective studies which follow somatoform presentations among older people are especially rare.

Community Samples

Surveys among community samples of older people have tended to show very low prevalence (0.0–3.9%) of strictly defined hypochondriacal or somatization disorders. A consistent finding in studies comparing younger with older people is that older people are no more preoccupied with physical health than younger people. This counters a widespread stereotype of older people concentrating introspectively on physical health.

Primary Care Samples

In older UK primary care patients¹, 5% were reported to have hypochondriacal neurosis, but many more had at least a few somatoform symptoms (unexplained symptoms). In the same study, primary care physicians were asked about the likely origins of the older patients' physical symptoms. A third were rated as having physical symptoms that were equally or mainly of psychological origin. A careful Italian primary care study² showed a similar figure of 8.1% having a primary somatoform disorder.

General Hospital Samples

Rates of somatoform disorders, or unexplained physical presentations, in secondary care have consistently been shown to be high. The few studies which have included secondary care patients from across the age range have shown very similar rates between young and old. Unsurprisingly, older hypochondriacal patients at general hospital settings do have higher rates of other true organic illnesses.

Psychiatric Samples

Most interest has been in the prevalence of somatoform presentations among older people with depression. Older patients with either anxiety disorders or depressive disorders have been consistently shown to commonly present with somatized physical symptoms, and these presentations are more common than among younger patients with depressive and anxiety disorders. Unexplained physical symptoms among frail older people are more strongly associated with depressed mood than with the burden of 'real' physical illness. This is an important clinical point: the presence of unexplained symptoms should trigger consideration of psychiatric as well as physical illness.

EPIDEMIOLOGY

While strictly defined somatoform disorders are relatively rare at all ages, somatoform presentations are very common. In all cultures,

AETIOLOGY

Many theories about the origins of somatoform presentations have been advanced. Some, like the ancient view that such symptoms

arose from uterine causes, are now dismissed due to modern understanding of anatomy and physiology. Others, including the influential psychoanalytic view that somatization arose from the 'conversion' of unacceptable unconscious mental conflicts, have been highly influential but difficult to examine in scientific study. Modern theories on aetiology have three key themes:

1. Somatoform presentations as manifestations of other psychiatric disorders – Somatoform presentations are undoubtedly found most frequently among people with higher rates of psychiatric disorder, especially depressive disorder.
2. Somatoform presentations as reflecting a stable, internal personality style – Research has shown that neurotic personality styles are much more common among somatizers. It is common when dealing with chronic severe somatizers to note the early appearance of unexplained physical symptoms and persistent pattern of medical help-seeking. In some cases this may be related to early maternal loss, abuse or other trauma. People who have a tendency to negative self-evaluation and to somatosensory amplification (a tendency to interpret normal physical symptoms as aversive) are much more likely to report physical symptoms to a health professional.
3. Somatoform presentations reflecting a social construct (i.e. an understandable reaction to the medical system or societal norms that a person lives in). It is widely held that somatoform presentations are more common in non-western cultures. The largest international study of somatization³ reported rates of somatization in primary care in 14 centres. Somatization was found commonly in all centres and especially so as a means of presentation of psychiatric disorder. Only South American centres showed higher rates; even here, rates of depressive disorder were as common among those presenting somatically. Another possibility is that somatoform presentations are encouraged by the medical or social system people live in. Somatizing patients consume large amounts of resources, and early recognition of the problem, fewer prescriptions and fewer hospital referrals are associated with better outcomes.

Among older people, the strongest aetiological link has been with depressive illness. While some older people are simply chronic somatoform presenters grown old, new somatoform presentations remain common in old age. Depressive disorders are the most common association, with certain symptoms including fatigue, dizziness, weakness, pain and heavy feelings in the limbs among the symptoms most commonly reported. Moreover, the association with depressive illness is independent of that with physical disorder. Among older people, the traditional concept of 'masked depression' has held up better than many other theories of the origins of somatoform presentations.

OUTCOMES

Most studies at any age indicate that somatoform disorders will tend to persist if they are severe and outcomes also depend on the medical response to the initial presentation. The clinical context is important; mild somatoform presentations in primary care may be transient though the style of presentation, that is, the tendency to present with physical symptoms when emotionally distressed, tends to persist. Among patients with clear-cut severe somatoform disorders in secondary care, persistence is part of the diagnostic criteria.

Patients have often had a very persistent course with 10–20 years of relentless presentations despite multiple investigations and failed reassurance. Such patients are difficult to treat, but may greatly trouble health professionals.

Among older patients, few studies have followed somatoform presentations prospectively. Among UK older primary care patients, a prospective study¹ found that severe cases of full somatoform disorders tended to remit, but vague or unexplained physical symptoms were highly persistent at nine-month follow-up. The attribution of physical symptoms to a physical cause was also highly stable over time. These findings are somewhat contrary to reports among younger people. Somatized symptoms were prospectively associated with frequent attendance in primary care. Though research is limited, it is fair to assume that among older patients, milder somatoform presentations use significant amounts of primary care time and are likely to persist. More severe somatoform presentations, especially when secondary to depressive disorder, may be likely to respond to treatment.

TREATMENT

Specific Treatment of Somatoform Disorders

Many controlled trials have been carried out among patients with somatoform disorders. The most frequently evaluated interventions have been cognitive behavioural therapy (CBT) and antidepressant medication. These interventions have been subject to systematic review⁴. This review specified the somatoform disorders addressed, including both pure somatization disorder and lower threshold disorders. Of good-quality trials of CBT, 11 of 13 studies showed benefit above control treatment, while among studies of antidepressant medication, 4 of 5 trials showed benefit. Of those trials addressing health care resource use, 10 of 11 studies showed cost reductions for the intervention group. The author concluded that the best evidence was for CBT. The cognitive behavioural model requires highly trained and skilled therapists and represents a challenge among older patients. Problems may include inadequate provision of psychological therapy for older people and the fact that these patients are likely to have admixtures of somatoform symptoms as well as symptoms from organic illness. A further challenge is to find ways to amend CBT to integrate its use into primary care. No intervention studies have been carried out among older patients with somatoform disorders.

Studies among Patients with Psychiatric Disorders

Studying somatoform presentations among older patients being treated for depressive or anxiety disorders tends to show improvement in somatoform presentations over time. Those trials of antidepressant medication that have examined which symptoms predict positive outcomes tend to consistently show that hypochondriacal or somatization symptoms predict a poorer outcome, though those clinicians with experience of treating severe hypochondriasis among people with depression will be aware that severe hypochondriasis does resolve along with other psychotic symptoms.

AN APPROACH TO MANAGEMENT OF MEDICALLY UNEXPLAINED SYMPTOMS IN OLDER PEOPLE

This approach draws on what is known to be effective among younger people with somatization. Older people have a high prevalence of

physical illness so a commonsense approach to management of new or uncharacteristic physical symptoms must be taken. It may be easier for medically qualified staff to tolerate uncertainty with such patients.

Is There a Physical Illness?

Is it being adequately dealt with?

In the majority of cases the patient will be adequately investigated and treated before somatization is considered.

Is There a Psychiatric Illness?

In depressive disorder, the low mood and biological symptoms such as poor sleep, weight loss, poor appetite, poor concentration and retardation/agitation usually precede the physical complaints. Patients usually admit to gloomy introspection and are likely to admit to depression rather than reject such suggestions.

Is it being adequately treated?

Antidepressant medication will usually resolve depression, with resolution of somatized symptoms.

Do Medically Unexplained Symptoms Need Independent Treatment?

If both physical and psychiatric illness is being reasonably dealt with, but unexplained symptoms are persisting and causing distress, then a positive and structured response is needed.

- Stop investigations and hospital referrals. Explain that investigations are not helping but as a clinician you believe the patients' symptoms and will continue to monitor them.

- Schedule regular appointments with the patient. The patient should be seen regularly but not necessarily frequently. This means they do not need to report symptoms in order to be seen and may reduce demands for appointments at short notice.
- Explain that investigations have shown no condition that they cannot recover from. This allows the prospect of recovery to be available, maintaining hope.
- Use cognitive behavioural techniques. Identify dysfunctional beliefs ('headaches usually mean brain tumour', 'muscle aches mean exercise has damaged the muscle fibres') and dysfunctional behaviours ('I will stay in bed all weekend to give my muscles a chance to recover').
- Identify positive thinking and behaviour strategies. For example, demonstrate that holding a book in an outstretched hand causes pain – to show effect of muscle tension. Exercise increases blood flow and fitness of muscle fibres. Schedule increasing levels of activity and record symptoms in fatigue diary.

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Other Neurotic Disorders

Jerome J. Schulte, C. Michael Hendricks and David Bienenfeld

Department of Psychiatry Wright State University, Boonshoft School of Medicine, OH, USA

REACTION TO SEVERE STRESS AND ADJUSTMENT DISORDERS

Before the Second World War it was generally held that psychiatric patients were constitutionally different from 'normals'. During the War it was observed that previously asymptomatic individuals experiencing unusual environmental stress sometimes suffered from transient psychiatric difficulties. This observation led to a reclassification of psychiatric disorders to allow for behavioural and emotional symptoms in people who would return to their premorbid state with the removal of the unusual environmental precipitant¹. DSM-I and ICD-6 classified these transient difficulties as 'gross stress reaction' and 'adult situational reaction'; DSM-II and ICD-8 classified them as 'transient situational disturbances'. ICD-9 introduced the categories of 'acute reaction to stress' and 'adjustment disorder'. ICD-10 defines 'acute stress reaction', 'post-traumatic stress disorder' and 'adjustment disorder'; although DSM-III-R recognized only the latter two of these, DSM-IV-TR recognizes all three².

ACUTE STRESS REACTION

Clinical Features

According to ICD-10, acute stress reaction is a transient disturbance occurring in persons without apparent mental disorder, in response to exceptional physical and/or mental stress and subsiding in hours or days. The diagnosis should not be made for an exacerbation of symptoms of a diagnosable psychiatric disorder already present, except for accentuation of personality traits. Previous history of another psychiatric disorder does not invalidate this diagnosis. An immediate, clear connection between the stressor and the onset of symptoms should be seen.

Symptoms of this disorder show a mixed and changing picture, with no one symptom predominating for long. They appear within minutes of the stress and resolve rapidly when the stressor is removed or, if the stress remains, symptoms decrease after 24–48 hours and are minimal after three days. Typical symptoms include an initial state of 'daze', constriction of consciousness, narrowing of attention, decreased comprehension of stimuli and disorientation. Withdrawal, agitation or overactivity may follow. Autonomic signs of panic (tachycardia, sweating, flushing) are common. Amnesia for the traumatic present may also be present. In the elderly, organic factors and life stage events can be predisposing factors to acute

stress reaction³. The multiple bereavements that are not uncommon in late life can be the precipitants for acute stress reaction. However, recent data do suggest the older population may tolerate acute stress better than the younger and middle-aged⁴.

DSM-IV differs somewhat from ICD-10 in its diagnostic classification of acute stress disorder. Unlike ICD-10, which requires that symptoms appear within minutes of the stress and diminish to minimal intensity after three days, DSM-IV requires symptoms to last a minimum of two days and allows for persistence up to four weeks. DSM-IV also includes dissociative symptoms not included under ICD-10: a subjective sense of numbing, detachment or absence of emotional responsiveness; derealization and depersonalization. Another DSM-IV requirement is that the traumatic event is persistently re-experienced in at least one of the following ways: recurrent images, thoughts, dreams, illusions, flashback episodes, or a sense of reliving the experience; or distress on exposure to reminders of the traumatic event. DSM-IV also requires marked avoidance of stimuli that arouse recollections of the trauma⁵.

Differential Diagnosis

The differential diagnosis includes post-traumatic stress disorder (PTSD) and adjustment disorder. PTSD (see below) occurs after a latency period of weeks or longer, while the symptoms of acute stress reaction begin immediately after the traumatic event. The repetitive, intrusive imagery characteristic of PTSD is not usually a feature of the ICD-10 diagnosis of acute stress reaction. DSM-IV, however, does include repetitive intrusive imagery among the features of acute stress disorder. If psychotic symptoms follow an extreme stress, acute (brief) psychotic disorder should be considered. Adjustment disorders are less severe, and longer lasting, than acute stress reactions. Events that precipitate adjustment disorders are also less intense than those responsible for acute stress reactions.

Therapy

By definition, the symptoms of acute stress reaction are time-limited and will resolve without specific therapeutic intervention. Treatment may be requested, however, for intolerable tension or insomnia. For tension, short-term use of benzodiazepines with simple metabolic pathways and short half-lives, such as lorazepam or oxazepam, are safest in the elderly. For insomnia, temazepam or

the non-benzodiazepine sedative hypnotic zolpidem⁶ are justified. Families and patients may be reassured that the acute response does not indicate a psychotic decompensation, and that the prognosis for rapid recovery is favourable. Acutely, and in the aftermath of the traumatic event, it is useful to help the patient gain mastery over the trauma⁷ by using a brief treatment model, consisting of fostering abreaction and integration of the event as quickly as possible, with the expectation that the trauma victim will return to full functioning. Abreaction can be fostered through individual or group psychotherapy⁸.

POST-TRAUMATIC STRESS DISORDER

Post-traumatic stress disorder (PTSD) first appeared in DSM-III but was based on older concepts tied to the history of warfare. Da Costa wrote of 'irritable heart' following the American Civil War. In the First World War the disorder was known as 'shell shock'. Early twentieth century psychoanalytic theory called it 'traumatic neurosis' and in the Second World War it was known as 'traumatic war neurosis' or 'combat neurosis'. In DSM-I it was renamed 'gross stress reaction', a reaction to great stress in a normal personality. During the relatively peaceful time between the Second World War and the Vietnam War, the category was omitted from DSM-II⁹. ICD-9 defined catastrophic stress and combat fatigue as two diagnoses under the category of acute reaction to stress. DSM-III defined intrusive re-experience of the trauma, together with emotional numbing, as the central features of PTSD. DSM-III-R placed more emphasis on the avoidance of stimuli associated with the trauma and less on numbing.

DSM-IV changed the definition of the trauma to an event where a person experienced, witnessed or was confronted with threatened death or serious injury or threat to physical integrity of self or others. Here, the response to the trauma involves intense fear, helplessness or horror. Also, where DSM-III-R required either numbing or avoidance behaviour, DSM-IV requires both⁵. ICD-10 criteria more closely resemble those of DSM-III, highlighting the restriction of emotional responsiveness. In ICD-10 the late chronic sequelae of devastating stress (i.e. those manifesting decades after the stressful experience) should be classified under enduring personality change after catastrophic experience³.

Clinical Features

The prevalence rate of PTSD in the elderly is about 1%¹⁰⁻¹². The ICD-10 diagnosis of PTSD requires evidence of trauma, or a response to a stressful event or situation of exceptionally threatening or catastrophic nature, likely to cause pervasive distress in anyone. The central symptoms are repetitive and intrusive recollections (flashbacks) or re-enactment of the event in memories, daytime imagery or dreams. The onset follows the trauma with a latency period of a few weeks to months (rarely exceeding six months).

There may also be a sense of 'numbness' and emotional blunting, and avoidance of activities and situations reminiscent of trauma. Anxiety, depression, suicidal ideation and insomnia are also common in many PTSD patients, particularly with advancing age⁹. PTSD is also associated with alcohol and drug abuse, possibly reflecting attempts to cope with PTSD symptoms. Dissociative symptoms, commonly described in younger PTSD victims, become less prevalent with increasing age^{13,14}. However, psychotic symptoms tend to be more common in older PTSD patients¹⁵.

It remains a subject of debate what factors, if any, predispose individuals to the development of the post-traumatic stress syndrome. Some traumas, particularly the concentration camp experience, are so severe that symptoms are almost universal in survivors. Because retrospective assessment of function before the traumatic event is always coloured by the response to the event, correlations are difficult to draw and empirical analyses have been inconclusive¹⁶. Certain personality traits (e.g. compulsive, asthenic), neurotic illness, and a history of adverse events in early childhood¹⁰ may all lower the threshold for manifestation of the disorder³. PTSD can also develop from bereavement. One study surveyed surviving spouses two months after their spouses' deaths and found that 10% of those whose spouses died after a chronic illness met criteria for PTSD; 9% of those whose spouses died unexpectedly met PTSD criteria; and 36% of those whose spouses died from 'unnatural' causes (suicide or accident) had PTSD¹⁷. Other late life events, including falls, stroke, myocardial infarction and breast cancer, have also been shown to put the elderly at increased risk of developing PTSD¹⁸⁻²¹.

Although PTSD symptoms can persist for many years, with increased frequency of symptoms towards the end of life²², the typical course is one of fluctuating symptoms²³. One study, examining current PTSD symptoms in elderly Second World War and Korean War prisoners of war (POWs), suggested that severity of exposure to trauma and lack of post-military social support were moderately predictive of PTSD. In this study, 53% of POWs met criteria for lifetime PTSD, with 29% meeting criteria for current PTSD, but for those POWs most severely traumatized, the lifetime PTSD rates were 83%, with current PTSD at 59%²⁴.

There are two types of PTSD to which the elderly seem susceptible: delayed-onset PTSD and chronic PTSD. In delayed-onset PTSD, patients may exhibit signs of the disorder decades after the trauma, and in chronic PTSD symptoms have been persistent since the time of the trauma. Delayed-onset PTSD may be a reactivation of remote PTSD earlier in life. A typical pattern is the onset of symptoms after initial exposure, a gradual decline in symptoms over several decades, followed by a reemergence in late life²⁵. In some elderly Second World War veterans, media coverage commemorating the 50th anniversary of the end of the War triggered PTSD symptoms²⁶. Commonly, guilt, distorted memory, emotional numbing, estrangement and feelings of detachment are seen²⁷. Patients in this group can present with physical symptoms of cardiovascular, gastrointestinal and musculoskeletal diseases¹⁶.

In general, the onset of severe symptoms can be linked to a profound recent life event, such as death of a wife, job retirement or loss of physical integrity from illness²⁷. Most often, the contemporary precipitant reawakens emotions and perceptions from the original trauma. Holocaust survivors and POWs have been noted to begin displaying symptoms of PTSD after admission to nursing homes, where they re-experience a loss of freedom and autonomy. Second World War veterans found the loss of physical integrity due to somatic illness particularly upsetting, since it evoked memories of a traumatic period when their physical integrity was in jeopardy¹⁴.

Differential Diagnosis

Although adjustment disorders also occur in response to life events, these events are in the normal range of human experience, unlike the extraordinary traumas responsible for PTSD. Specific features of numbing and flashbacks do not occur, and adjustment disorders, by definition, do not last more than six months. Acute stress reaction

is characterized by a more variable clinical picture that resolves within days. Whether PTSD is predicted by acute stress reactions remains unclear²⁸. While anxiety and depression are common features of PTSD, generalized anxiety disorder and phobic disorder have anxiety as a more specific and central symptom. Major depression is marked by deep and persistent mood disturbance, usually with loss of reactivity; dysthymia results in chronic, indolent dysphoria. None of these disorders includes the specific symptom of intrusive recollections.

Therapy

The signs and symptoms of PTSD include distorted expectations and perceptions, mood disturbances, psychophysiological symptoms and social withdrawal. Thus, common sense dictates, and empirical data confirm, that multimodal treatment is most advisable^{11,29}. Psychosocial intervention and pharmacotherapy each has its place. Historically, dynamic psychotherapy has been a useful approach, but recent treatment guidelines support exposure-based psychotherapies as the most evidence-based form of treatment for PTSD²⁹. Antidepressants can offer symptomatic relief by diminishing dysphoria, intrusive thoughts, insomnia and nightmares³⁰. In particular, selective serotonin re-uptake inhibitors (SSRIs) have been shown to be effective pharmacotherapeutic treatment for PTSD, especially in reducing avoidant symptoms^{31–37}.

Other second-generation antidepressants do show promise in the management of PTSD but sufficient evidence is lacking at this time³⁵. Prazosin, an alpha-1 adrenergic receptor antagonist, has been shown to be helpful with the sleep disturbance and nightmares of PTSD, but should be used with caution in the elderly because of the risk of orthostatic hypotension, particularly in combination with other medications that may lower blood pressure^{29,38}. Beta-adrenergic blocking agents have been used in younger PTSD patients for relief of symptoms of autonomic arousal, tremors and startle reactions³⁹. Older patients, however, are less likely to display a clinical profile of hyperarousal, and are more susceptible to the cardiovascular complications and organic mood disorders associated with adrenergic blockade. There are case reports of positive results using atypical antipsychotics as augmenting agents when added to SSRIs for treatment of refractory PTSD^{35,40}. However, this class of medications must be used with caution in the older population given current concerns of increased mortality in older demented patients. Conversely, benzodiazepines do not appear to be a helpful treatment for PTSD³⁵ and should be avoided as much as possible in ageing individuals since they can cause paradoxical excitation and frequently induce subtle cognitive impairment⁴¹. Similarly, divalproex (valproate) has been demonstrated to be ineffective as monotherapy for PTSD in older veterans⁴².

ADJUSTMENT DISORDER

The diagnosis of adjustment disorder refers to a state of subjective distress or emotional disturbance, interfering with social functioning or performance, arising in a period of adaptation to a significant life change or subsequent to a stressful life event. It is assumed that the condition would not have arisen without the stressor. According to DSM-IV, onset is within three months of the stressor. The duration of symptoms should not exceed six months, except in the case where the stressor is chronic (e.g. a chronic general medical condition) or the stressor has enduring consequences (e.g. the financial and emotional

difficulties resulting from a divorce)⁵. ICD-10 describes onset as arising in the period of adaptation to the stressor³.

Clinical Features

Symptoms of adjustment disorder may include: depressed mood, anxiety, worry, impairment in performance of daily routines and inability to cope or plan ahead. Adjustment disorders can be specified as brief depressive reaction, prolonged depressive reaction, adjustment disorder with predominant disturbance of other emotions, adjustment disorder with predominant disturbance of conduct, or adjustment disorder with mixed disturbance of emotions and conduct. The precipitating events for adjustment disorders can affect social network or values, and may involve the individual, his group or community. Common events causing such symptoms in older patients include physical illness or injury, placement in a nursing home and retirement⁴³. The events, while subjectively profoundly meaningful, are of considerably smaller magnitude than those precipitating acute stress reaction and PTSD. Individual predisposition and vulnerability to these stressful life events thus plays a greater role in the occurrence of adjustment disorders. Poor pre-stressor social and co-existing physical problems⁴⁴, current dementia⁴⁵ and a history of a past psychiatric disorder⁴⁶ all increase vulnerability to adjustment disorders. However, while these premorbid risk factors are frequently observed, they do not appear essential. In a recent large study of elderly veterans with no recent psychiatric history admitted to medical/surgical units, adjustment disorder was diagnosed in over 20% of the patients post discharge⁴⁷.

Therapy

The cornerstone of treatment for adjustment disorders is focal psychotherapy, although it appears that antidepressants may be of value in the successful management of adjustment disorders in some outpatient settings that often lack ready access to psychotherapy⁵⁰. Based on a psychodynamic understanding of emotions and behaviour, focal therapy identifies the most specific nidus of current distress and views it in the context of the patient's core conflicts or deficits. The therapy is of relatively brief duration, usually 6–20 sessions. The major techniques employed are clarification and confrontation⁴⁸. Quite frequently, the precipitating event can be framed as a narcissistic threat or injury. In psychotherapy, the patient will come to view the therapist as a self-object, looking for restoration of the self-esteem provided by the lost function, role or friend. The therapist helps restore the wholeness of self by allowing the patient to modify his or her expectations of him- or herself and environment⁴⁹.

DISSOCIATIVE AND CONVERSION DISORDERS

In the last three decades of the nineteenth century, dissociation was studied extensively by Janet and conversion by Freud. DSM-I incorporated the concepts of dissociation and conversion into its classification scheme. Conversion reaction was assigned to hysterical neurosis, and amnesia was placed in the category of dissociative reaction. In DSM-II they were united under the heading of hysterical neurosis, but divided into conversion type and dissociative type. In DSM-III, DSM-III-R and DSM-IV the two conditions were renamed and separated once again. Hysteria, conversion type, became conversion disorder and was assigned to somatoform disorders. Hysteria,

dissociative type, was expanded into the dissociative disorders⁵¹. ICD-10, however, continues to contain both under the heading of dissociative disorders.

Dissociative Amnesia

Dissociative amnesia is characterized by loss of memory, usually of important recent events, that is too great to be explained by ordinary forgetfulness or fatigue; and amnesia, either partial or complete, for recent events that are of a traumatic or stressful nature. The amnesia is usually partial and selective. The extent and completeness of the amnesia varies from day to day and between inquirers, but a persistent common core cannot be recalled in the waking state. Complete, generalized amnesia is rare and is usually part of a dissociative fugue. Affective states in amnesia are varied but severe depression is rare.

Perplexity, distress and varying degrees of attention-seeking behaviour may be evident, but calm acceptance is also sometimes striking. Purposeless local wandering may occur, but is rarely accompanied by self-neglect and rarely lasts more than a day or two. Often in dissociative amnesia, new learning is preserved⁵². Disturbing external circumstances causing despair or anxiety may predispose an individual, but a single event is usually at the centre of the syndrome.

As a rule, dissociative amnesia becomes less prominent with age and is uncommon in the elderly^{53,54}. However, it has been seen in First World War combat soldiers⁵⁵ and soldiers in other conflicts. In most patients the amnesia is short-lived, 75% of cases lasting between 24 hours and 5 days⁵⁶. Its features resemble those of more frequently observed disorders. Organic amnesia is usually anterograde⁵². In postconcussional syndromes there may be a combination of hysterical and organic amnesia that can be difficult to untangle. In dementia, memory loss is seen in the context of global cognitive impairment, which is stable over a period of weeks to months. The syndrome of pseudodementia also features variable memory impairment, but affective disturbance, usually severe depression, is evident⁵⁷.

Dissociative Fugue

Fugue exhibits all the features of dissociative amnesia, plus an apparently purposeful journey away from home or place of work during which self-care is maintained. A new identity is assumed and organized travel may be undertaken to places previously known and of possible emotional significance. Although there is retrograde amnesia during the fugue, behaviour during fugue is normal. A severe precipitating stress is almost universal as a precipitant of dissociative fugue. Times of marital discord, financial difficulty, major role change or personal loss may precede the fugue. Depressed mood is frequently present before fugue symptoms are displayed⁵². Fugue is rare in elderly people. Because its features, with the exception of travel, are identical to those of dissociative amnesia, it has been proposed that the two disorders be considered as one.

Treatment

Therapy for dissociative amnesia and that for dissociative fugue are virtually identical. Patients usually seek treatment after the amnesic period has ended. They desire help in recovering memory of events during the fugue. Hypnosis⁵⁸, benzodiazepines⁵⁹ and short-acting barbiturates have been used to reconstitute repressed memories,

although typically they return spontaneously. Psychodynamic psychotherapy has been used to facilitate resolution of conflicts that lead to fugue states. This treatment may decrease the vulnerability of the patient to dissociate in future times of stress⁶⁰.

DISSOCIATIVE DISORDERS OF MOVEMENT AND SENSATION (CONVERSION DISORDERS)

In conversion disorder, there is a loss or alteration in movements or sensations (usually cutaneous) in a patient presenting as having a physical disorder. No somatic condition can be found, however, that explains the symptoms. Instead, the symptoms represent the patient's concept of the physical disorder, which may be at variance with physiological or anatomical principles. Here, mental state and social situation suggest that disability resulting from the loss of function is helping the patient to escape an unpleasant conflict, or helps the patient to express dependency or resentment indirectly. Conflicts may be evident to others, but the patient often denies their presence and attributes distress to the physical symptoms or the resulting disability.

In making the diagnosis it is essential that: (i) evidence of a physical disorder is absent and (ii) sufficient knowledge of the psychological and social setting and personal relationships of the patient allows a convincing formulation of the reasons for the disorder.

Predisposing factors to conversion disorder are premorbid abnormalities of personal relationships, childhood sexual abuse⁶¹, and personality disturbance, with histrionic personality being the most common⁶². Also, close relatives or friends may have suffered from physical illness with symptoms resembling the patient's. A few patients establish a repetitive pattern of reaction to stress by production of these disorders, which can continue into middle and old age³.

The most important differential diagnosis is the group of somatoform disorders (although DSM-IV classifies conversion disorder as a somatoform disorder instead of a dissociative disorder). In the latter, the patient's presentation centers around persistent requests for medical attention and pervasive concern with the perceived medical disorder; patients with conversion disorder are much more likely to take their presumed illnesses in stride. Conversion disorders generally begin in adolescence and young adulthood, and occur in single or recurrent episodes with substantial remission. Somatoform disorders may not increase in prevalence with increasing age, but they tend to assume the quality of a pervasive character style with little remission.

Most conversion disorders remit with non-specific, supportive interventions. Hypnosis⁶³, anxiolytics and behavioural relaxation exercises may be helpful. Also, psychotherapy aimed at helping the patient recognize and cope with the psychosocial stress that provoked the symptom can be impressively beneficial if the patient can be engaged in a cooperative alliance of therapeutic curiosity. The prognosis of conversion disorder is generally good, since conversion symptoms are of short duration with abrupt onset and resolution. A few become chronic, and some recur, most commonly when the precipitating stress is chronic or recurrent, when there is other psychopathology or when there is marked secondary gain.

NEURASTHENIA (FATIGUE SYNDROME)

Historical Perspective

George Beard introduced the term 'neurasthenia' in 1869. He viewed neurasthenia as a physical illness caused by loss of nerve strength. Janet differentiated psychasthenia from neurasthenia. Freud similarly

separated anxiety neurosis, a 'psychoneurosis', from neurasthenia, an 'actual neurosis' he attributed to misdirected libidinal energy. In the First World War, the syndrome was defined by the term 'shell shock'; in the Second World War, 'operational fatigue'. Although it remains in ICD-10, the diagnosis of neurasthenia was deleted from DSM-III and replaced by dysthymia. In the United States the symptom cluster known as chronic fatigue syndrome is almost identical to the current ICD classification of neurasthenia^{64–66}.

Clinical Features

Neurasthenia is characterized by persistent, distressing complaints of fatigue after mental effort, or complaints of bodily weakness and exhaustion after minimal physical effort, along with at least two of the following: muscular aches and pains, dizziness, tension headaches, sleep disturbance, inability to relax, irritability or dyspepsia. If autonomic or depressive symptoms are present, they cannot be sufficiently persistent and severe to fulfil the criteria for any more specific disorder³. Premorbid fatigue may be the single most reliable predictor of the development of neurasthenia⁶⁷.

Differential Diagnosis

Differential diagnosis includes primarily major depression and somatoform disorders. In the elderly it is especially important to rule out depression, since somatic complaints and fatigue are common presentations of depressive disorders in late life. Physical symptoms with no demonstrable organic pathology are the essential features of somatoform disorders. However, these complaints do not include the specific physical symptoms of fatigue or exhaustion found in neurasthenia.

Therapy

Specific treatment for neurasthenia has not been established. Given the high likelihood, particularly in old age, that the neurasthenic picture is a manifestation of a mood disorder, treatment with antidepressant medication and psychotherapy, as for depressive conditions, is generally warranted⁶⁸.

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Personality Disorders

Personality Disorders: Description, Aetiology, and Epidemiology

Victor Molinari¹ and Daniel L. Segal²

¹University of South Florida, Tampa, FL, USA

²University of Colorado at Colorado Springs, Colorado Springs, CO, USA

According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR)¹, 'A Personality Disorder is an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment' (p. 685). Also included in the definition of personality disorder is that the traits have to be rigid, maladaptive and pervasive across a broad range of situations rather than expectable reactions to particular life experiences or a normal part of a developmental stage. An important caveat in the DSM-IV-TR is that, although the definition of personality disorder requires an onset no later than early adulthood, it is often the case that a person with a personality disorder may not be diagnosed or treated until later life.

One possible explanation for this caveat is that the individual with personality disorder may have presented clinically with the more obvious signs of an Axis I clinical disorder such as anxiety, depression, disordered eating or substance abuse, whereas the underlying personality disorder features may not have been examined as closely. Another important factor is that in some cases, personality traits can be adaptive at one phase of life but become maladaptive at a later developmental phase. For example, an extremely aloof, reserved and emotionally detached man may have functioned successfully in the occupational sphere by choosing a job requiring little social interaction (e.g. a computer programmer who writes code at home). He managed to live alone and had little use for others during much of his adult life. Imagine the discomfort and distress he would face, however, if in later life he becomes physically frail and debilitated and out of medical necessity is re-located to a nursing home where he is forced to cope with the presence of medical professionals, caregivers and other residents. In this case, it would be only after the person has failed to adjust to his new living situation that his personality traits would be viewed as dysfunctional (and a personality disorder diagnosis given). Thus, the *context* in which personality traits are expressed is an extremely important concept in determining their relative usefulness or hindrance across the lifespan.

Personality disorder in older adults is an important area of study for a number of reasons. First, since personality disorder affects the way an older adult copes with life, individuals with specific person-

ality disorders may be less able to successfully negotiate age-related losses (e.g. a histrionic person who has relied on her physical attractiveness and sexual provocativeness to garner attention for herself may feel neglected as she ages and loses some of her seductiveness; an obsessive-compulsive individual may feel out of control because he feels his medical problems reduce his control over his body; a dependent person may lose his main source of support due to the death of a spouse, siblings, adult children etc.) or the interpersonal compromises necessary for peaceful institutional living (e.g. anger episodes erupt when the interpersonal needs of a borderline or narcissistic person are not immediately met). Second, personality disorder can influence the presentation of Axis I symptomatology, frequently generating complicated diagnostic and assessment dilemmas. For example, disruptive behaviour in the nursing home may camouflage the fact that the person is suffering from a depression that is exacerbating premorbid antisocial personality features. Third, just as for young adults, the presence of personality disorder warrants modification of treatment strategies and prognosis for those with co-morbid Axis I disorders in certain geriatric settings.

In recent years, there has been an ever-expanding body of knowledge about personality disorder in older adults. Notably, there has even been the publication of two books solely devoted to personality disorder in older adults^{2,3}. However, as we shall see, there remain many unanswered questions spawned by thorny conceptual and methodological quandaries in this controversial area. This chapter will summarize what is known about the aetiology, diagnosis, epidemiology and prognosis of personality disorder in older adults.

AETIOLOGY

Because personality disorders and personality disorder features begin relatively early in life and have a generally persisting impact across the lifespan, it can be assumed that the aetiology of personality disorders includes psychosocial and biological factors³. Concerning personality disorder among older adults, it is helpful to focus on dimensional aspects of personality as well as the categorical diagnosis of personality disorder.

Psychosocial Factors

Freud noted the importance of Axis II traits in the aetiology of Axis I symptoms. He embedded the idea of personality within his psychosexual schema regarding oral, anal, oedipal, latency and genital stages. Inborn temperamental traits combine with parental influences in these early developmental periods to shape an individual's personality. How early figures react to the growing child's bio-psycho-social needs forges a rigid template that is operative throughout the person's life, and reflects whether the person will satisfy his or her intrapsychic and interpersonal needs in an adaptive manner or in an exaggerated repetitious fashion. Acute symptomatology erupts when current stressors intersect with the psychosocial dynamics and interpersonal sensitivities laid out in early childhood forming this hard bedrock of personality traits. Working from this grand model, Freud erroneously concluded that by the age of 40 personality patterns were invariably set, and advised psychoanalysts to spend their time with younger analysands.

Erik Erikson⁴ enhanced the Freudian framework to include three stages of adulthood that were yoked to specific life challenges. Those in young adulthood are faced with the crisis of deciding on a career and achieving intimacy; those in middle adulthood raise their family, maintain a career and hopefully become generative; those in late adulthood are confronted with preparing for death, gaining wisdom and achieving ego integrity. Unfortunately, the heuristic value of these conceptualizations has not been realized because limited research has been conducted to validate these stages.

Coming from a more empirical tradition, Costa and McCrae⁵ conducted both cross-sectional and longitudinal research with their well-validated NEO Personality Inventory (which measures five broad lexically derived personality factors of neuroticism, extraversion, openness, agreeableness and conscientiousness) and concluded that there is general continuity of personality across the life span. However, other researchers have argued that Costa and McCrae's five-factor model tends to minimize personality change in adulthood, particularly with respect to environmental factors⁶. Indeed, in his 50-year follow-up study of Harvard undergraduates, Vaillant⁷ discovered that significant change can occur for certain individuals, related either to specific negative or positive adult life events (e.g. alcoholism; supportive spouse). Consistent with these formulations, Identity Process Theory⁸ postulates that older adults tend first to assimilate and (if assimilation is non-successful) then to accommodate discrepant experiences to maintain self-esteem via a consistent sense of self. Those with rigid understandings of themselves that characterize personality disorders may be less able to employ these more mature coping mechanisms and negotiate the vagaries of ageing. From this conceptual basis, too much or too little stability in personality as we age may become maladaptive.

Finally, a well-researched cognitive model of psychopathology suggests that personality disorders may be characterized by cognitive distortions which are derived from biases in information processing and dysfunctional schema or core beliefs that influence people's perceptions and thoughts at the conscious level⁹. Examples of cognitive distortions include all-or-none thinking (seeing personal qualities or situations in absolutist 'black and white' terms, and failing to see shades of grey), catastrophizing (perceiving negative events as intolerable calamities, commonly referred to as 'making mountains out of molehills'), magnification and minimization (exaggerating the importance of negative characteristics and experiences while discounting the importance of positive characteristics and experiences) and personalization (assuming one is the cause of an event when other

factors are also responsible). Schemas are often expressed as unconditional evaluations about the self and others. Some examples include beliefs that: 'I am incompetent', 'I am defective', 'I am unlovable', 'I am special', 'Others are hurtful and not to be trusted', 'Others need to take care of me', and 'Others must love and admire me'. Schemas are generally thought to be formed early in life but to persist if no conscious effort is made to identify, examine and challenge them.

Some examples of cognitive distortions and schema relevant to specific personality disorders include:

- an individual with paranoid personality disorder is prone to habitually and chronically perceive others as deceitful, abusive and threatening;
- an individual with borderline personality disorder is prone to sort people into categories of either 'all good' or 'all bad';
- an individual with obsessive-compulsive personality disorder tends to be a slave to the belief that he or she must be perfect and always in control;
- an individual with dependent personality disorder sees him- or herself as weak, incompetent and inadequate, requiring constant reassurance, nurturance and direction.

Whereas a few studies have attempted to validate the specific relationships between core beliefs and personality disorder pathology¹⁰, notably lacking are studies that specifically examine these relationships in older adult samples.

Genetic Factors

A growing literature base has focused on the genetic factors that contribute to personality disorders. In a study of 483 adult twin pairs, Jang *et al.*¹¹ found a median heritability of 0.44 for 66 of 69 personality disorder facet traits. Similar data were reported by Coolidge *et al.*¹² who found a median heritability coefficient of 0.75 for 12 specific personality disorders in their sample of 112 child twin pairs. Interestingly, Jang *et al.*¹³ found in their cross-sectional twin study that genetic contributions to personality disorder traits actually increase with age. Torgersen *et al.*¹⁴ used a structured interview to diagnose the full range of personality disorders, finding an overall heritability estimate of .60. Finally, a very recent study with a large sample of young adult Norwegian twins found one genetic factor reflecting a broad vulnerability to personality disorder pathology and negative emotionality whereas two other genetic factors more specifically reflected high impulsivity/low agreeableness and introversion¹⁵. In summary, there is clear evidence of heritability for some personality disorders but much that remains unexamined. Perhaps the best conclusion from this data is that heritable traits play a significant role in the formation of personality disorders but heritability alone does not directly cause an individual to develop a specific personality disorder.

DIAGNOSIS

The diagnosis of personality disorders is known to be particularly challenging across the lifespan. Specifically, in adulthood, it is generally difficult to distinguish one personality disorder from another¹⁶. Later life adds further complications to diagnosis. There are, for instance, problems in obtaining a reliable diagnosis and, at present, there is no 'gold standard' of diagnosis for personality disorder

in older adults. Molinari *et al.*¹⁷ studied geropsychiatric inpatients with depression, and found general discordance between patient self-report, family informant ratings, social worker evaluations and consensus case conference categorical diagnosis of personality disorder. It appears that there are varied perceptions of an individual's personality, all of which should be taken into account for a comprehensive evaluation of Axis II pathology.

Personality disorder is commonly seen in practice settings yet seldom formally identified. Mental health professionals are loathe to diagnose it, particularly in old age, due to concerns over pejorative bias, pessimistic beliefs about the prospects of therapeutic change for personality disorder pathology, managed care reimbursement biases, and focus on medical or Axis I pathology (particularly cognitive impairment) in old age. Often the patient with personality disorder presents in a demanding, blaming manner with an inappropriate, rigid interpersonal stance and limited insight. Unfortunately these same features are sometimes erroneously interpreted as part of the natural ageing process¹⁸. Perhaps it is most important to recognize that 'either/or' thinking is often incorrect in the diagnosis of older adults. Comorbidity is the rule rather than the exception, with research consistently finding that older adults with depression also may have longstanding maladaptive personality disorder traits^{18–20}.

Another factor that impacts identification and diagnosis of personality disorders in later life is that, in some cases, there is an emergence of personality disorder symptoms that were 'hidden' earlier in life³. For example, consider a highly dependent woman who was supported by a caring, perhaps dominating, spouse who did not mind making all of the decisions for the couple and essentially took care of his wife throughout much of their adult lives. It would not be until she struggled to take care of herself after becoming a widow that the extent of her 'disorder' would become recognized and perhaps diagnosed. A final diagnostic challenge is that the sets of diagnostic criteria do not fit older adults as well as they do younger adults³. In an empirical investigation of potential age-bias using item analysis, Balsis *et al.*²¹ found evidence of age-bias in 29% of the criteria for seven personality disorders. In this study, some diagnostic criteria were differentially endorsed by younger and older adults with equivalent personality disorder pathology, suggesting a bias.

EPIDEMIOLOGY

Some early anecdotal reports suggested that personality characteristics become uniformly less harsh with age^{22,23}. Other clinicians working with older adults believed that the 'high-energy' personality disorders (e.g. Cluster B) mellow whereas the 'low-energy' personality disorders (e.g. Cluster C) may be aggravated by the ageing process^{24–26}. DSM-IV-TR¹ states that 'Some personality disorders tend to become less obvious or remit with age, whereas this appears to be less true for some other types' (p. 688). Early research yielded wide variability in personality disorder prevalence rates due to inadequate definitions of personality disorder, non-standardized measures and different samples of older adults. With the employment of better diagnostic criteria, some consistent findings have emerged. This section on epidemiology will therefore largely focus on studies using standardized measures, and will be divided into community, institutional, outpatient and depression studies.

Community Settings

In community settings, two studies^{23,27} compared young and older adults utilizing the Coolidge Axis II Inventory. Coolidge *et al.*²³

found a greater need for organization and more restricted affect in older adults, whereas Segal *et al.*²⁷ found that older adults were significantly higher on obsessive–compulsive and schizoid personality disorder, but lower on the antisocial, borderline, histrionic, narcissistic and paranoid scales. Ames and Molinari²⁸ used the Structured Interview for Disorders of Personality scale (SIDP-R) and detected a trend of less personality disorder in older adults, with significantly fewer older adults meeting the criteria for more than one personality disorder. Cohen *et al.*²⁹ used the Structured Psychiatric Examination and found that individuals 55 years old and older were less likely (6.6% vs. 10.5%) to have personality disorder, due to a threefold decrease of Cluster B personality disorder in older adults. These data documenting personality 'mellowing' in older adult community samples are in stark contrast to the results of a study by Segal *et al.*³⁰, who found that a high number (63%) of community-dwelling older adults surveyed at a senior center met personality disorder criteria by self-report. However, this study used a measure known to be overly sensitive to personality disorder pathology, and the cognitive status of the participants was also not taken into account.

Institutional Settings

Early personality disorder prevalence rates in nursing home settings were reported to be 12–15%^{31,32}, whereas for geropsychiatric inpatients, personality disorder estimates were more variable (7–58%). In a large sample of hospitalized male veterans, Molinari *et al.*³³ conducted a cross-sectional investigation of personality changes across different age groups for those clinically diagnosed with personality disorder. Older adults with personality disorder were more responsible and less impulsive, paranoid, energetic and antisocial than young adults diagnosed with personality disorder. Kunik *et al.*³⁴ studied 547 older psychiatric inpatients, and found that a consensus case conference diagnosis of personality disorder varied widely, depending upon the specific co-morbid Axis I diagnosis (e.g. 6% for patients with an organic mental disorder, but 24% for those with depression). Only a few studies of geropsychiatric institutionalized patients utilized standardized instruments. Molinari *et al.*³⁵ used the SIDP-R and found that older adults had personality disorder rates similar to those of a young adult comparison sample; however, older adults were less likely to meet criteria for more than one personality disorder, and clinical diagnoses yielded fewer personality disorders than the SIDP-R. Likewise, Coolidge *et al.*³⁶ used the Coolidge Axis II Inventory and found similarly high personality disorder rates among young (66%) and old (58%) chronically mentally ill patients, but the younger group was more likely to be specifically diagnosed with antisocial, borderline, and schizotypal personality disorder. Finally, among older inpatient veterans, Kenan *et al.*³⁷ found a 55% personality disorder prevalence rate.

Outpatient Settings

The findings from the lone study conducted with a structured personality disorder scale in a geropsychiatric outpatient setting are consistent with the latter inpatient studies. Molinari and Marmion³⁸ found that older adults were less likely to meet the criteria for more than one personality disorder than younger adults, and clinical diagnosis again yielded fewer personality disorders than the SIDP-R.

Depression

One area of intense study has been the relationship between personality disorder and depression in older adults. Kunik *et al.*²⁰ studied 154

depressed older inpatients and identified 24% with co-morbid personality disorder, whereas Molinari and Marmion³⁹ determined that 63% of depressed geropsychiatric outpatients met personality disorder criteria. Thompson *et al.*⁴⁰ found that 33% of depressed older adults who were being treated with psychotherapy in a geropsychiatric outpatient clinic met personality disorder criteria. In a study investigating the relationship between personality disorder and functioning in acutely depressed older psychiatric patients, Axis II pathology was found to be associated with greater disability and more impaired social and interpersonal functioning⁴¹. In their review of the literature on personality disorder in older adults, Agronin and Maletta⁴² posit that personality disorder in late life may be intrinsically related to Axis I pathology, particularly major depressive disorder.

Summary of Epidemiological Studies

In an attempt to lend clarity to the burgeoning literature on personality disorder in older adults, Abrams and Horowitz⁴³ conducted a meta-analysis of the most methodologically sophisticated epidemiological studies. They inferred a personality disorder prevalence rate of 10% (with a range of 6–33%) for those over the age of 50, and concluded that research neither substantiates nor disconfirms an age effect. However, these authors remark that the bulk of the evidence supports, at least for certain personality disorders, a decline in frequency and intensity with age. The cause for this decline is one of the most controversial and debated topics in the literature on personality disorder in older adults. Four main reasons have been postulated.

First, there is a general mellowing of the 'high-energy' Cluster B personality disorders due to biological (reduced testosterone in males) and developmental changes (those with personality disorder finally master a single interpersonal strategy to manage stresses). This accounts for the consistent result that older adults are less likely to meet the criteria for more than one personality disorder, and is also supported by the study of Segal *et al.*²⁷, who discovered lower levels of dysfunctional dispositional coping styles among older adults compared with younger adults.

Second, the decline in 'high-energy' personality disorder relates to the greater mortality rates of those with Cluster B personality disorder in their younger years. Older adults with personality disorder are thereby a selective sample of less extreme personality disorder 'survivors'. Third, personality disorder is generally under-diagnosed, particularly in older adults, where cognitive and medical causes are emphasized or personality disturbance (avoidance, dependency, emotional lability) is viewed as normal⁴⁴.

Fourth, the decline in personality disorder with age is a methodological artefact, since some DSM criteria are age-insensitive. For example, occupational and vocational impairment are often irrelevant to older adults. From this point of view, there really is no true decline in personality disorder rates with age, just a change in form that is inadequately assessed. These so-called 'geriatric variants'⁴⁵ reflect the more subclinical, non-specific or age-relevant personality disorder traits that account for personality disorder NOS (not otherwise specified) to be diagnosed with particular high frequency in older adults. These formulations are consistent with the theory of heterotypic continuity⁴⁶ which proposes that core psychological constructs remain constant, but that they are manifested in different ways throughout the life cycle (e.g. failure to conform to social norms may be reflected by repeated fights in younger individuals with antisocial personality disorder, but by repeated rule infractions in long-term care settings by older adults with antisocial

personality disorder). The construction of a new geriatric nosology has been proposed to accommodate the late life changes in Axis II pathology^{42,43,45}. Such re-classification will need to: (i) reconsider the diagnostic requirement that maladaptive personality disorder behaviour be rooted so early in young adulthood; (ii) routinely address Axis II pathology in the context of more acute Axis I symptomatology; and (iii) integrate age-related developmental, medical (Axis III) and psychosocial/environmental stressors (Axis IV) with Axis II manifestations⁴².

PROGNOSIS

Unfortunately, only a few seemingly contradictory studies have investigated the prognosis of personality disorder in late life. In two separate studies of geropsychiatric outpatients, personality disorder was found to be a poor prognostic sign for the psychotherapeutic treatment of depression^{40,47}. However, Molinari⁴⁸ examined the one-year relapse rates for 100 male geropsychiatric inpatients and found no significant differences for those diagnosed with and without personality disorder. Consistent with the finding of Kunik and colleagues²⁰ that personality disorder diagnosis had no impact on the acute response of inpatient treatment for depression with older adults, no differences were found in relapse rates for a subgroup of depressed inpatients with and without personality disorder⁴⁸. It appears that in inpatient geropsychiatric settings, Axis I symptomatology overrides Axis II pathology as an outcome predictor, probably related to the complex combination of medical, cognitive and psychiatric symptoms often observed in those older patients needing acute care. More generally, the prognosis for older adults with personality disorder is highly variable and contextualized. Some adults with personality disorder clearly mature with advanced age, some seem to deteriorate in the face of challenges associated with ageing (e.g. loss of prestige, reduced physical stamina and attractiveness, increased need for assistance from others) and yet the third pattern is the unabated continuity of similar levels of dysfunctional behaviours from younger life to later life³.

SUMMARY

1. There are psychosocial and genetic determinants of personality disorder in older adults.
2. The assessment of personality disorder in older adults is challenging, especially due to the presence of Axis I and Axis III co-morbidities.
3. There are poor concordance rates of personality disorder diagnosis between clinical examination, structured interviews and self-reports, suggesting the need for data collection from a variety of sources.
4. There may be an age-related mellowing of the 'high-energy' personality characteristics of individuals with personality disorder, and/or there are 'geriatric variants' of personality disorder not tapped by DSM.
5. There is a positive association between depression and personality disorder diagnosis.
6. Identifying personality disorder in older adults may be more useful prognostically in outpatient settings, where the Axis I symptomatology is less severe.
7. DSM-V must do a better job of accommodating late life changes in personality disorder presentation.

Although age-related changes in personality disorder expression may be in the less volatile and impulsive direction, novel geriatric manifestations still can create a significant burden in stressful caregiving contexts for family members, friends, health care professionals and administrators of institutions attempting to support a flawed and vulnerable older adult. Future empirical research guided by conceptual advances in psychodynamic, self/identity, cognitive and life span developmental theories of personality that address the interrelationship of genetic, biological, psychological and social variables promises to yield exciting progress in the creation of gero-specific assessment instruments and treatment protocols for personality disorder in older adults.

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Diagnostic and Treatment Issues Regarding Personality Disorder in Older Adults

Richard A. Zweig¹ and Dana Scherr Parchi²

¹*Ferkauf Graduate School of Yeshiva University, Bronx, NY, USA*

²*The Child and Family Institute at St Luke's and Roosevelt Hospitals, New York, NY, USA*

A growing body of epidemiological and observational studies support the notion that personality disorder is highly prevalent in community and clinical samples of adults and older adults (see Chapter 104) and that personality disorder moderates the presentation, course and outcome of Axis I disorders in both younger^{1,2} and older adults^{3–5}. The potential import of such findings for prevention and treatment cannot be overstated; recent findings, for example, suggest that personality pathology in the elderly may be a risk factor for coronary heart disease⁶ and late-life suicidal behavior⁷. Even normative variations in personality appear to play a salient role, as inter-individual differences in personality have been linked to outcomes such as physical and psychological well-being, functional ability and longevity in older adults^{8,9}. Yet, much personality pathology remains undetected and undertreated in clinical settings.

It is likely that efforts to translate these findings to practice settings have been hampered by differing conceptual models and methods (e.g. dimensional versus categorical)¹⁰ as well as myriad obstacles to the assessment of personality pathology in the elderly¹¹. Additionally, the lack of appropriate detection and treatment of personality disorder exacts a heavy cost, as personality disorders have been associated with long-term functional impairment¹² and a doubling of treatment expenses¹³. In this chapter, we review methods and measures for assessing personality pathology, describe obstacles to accurate detection, and delineate some common challenges in the differential diagnosis of personality pathology from other late-life disorders. We also discuss the psychotherapeutic and pharmacological management and treatment of these disorders.

DETECTION OF PERSONALITY PATHOLOGY

Methods and measures for detecting personality pathology have advanced considerably in the past four decades, such that an array of structured clinical interviews, multiscale self-report inventories and other measures have been developed and refined for this purpose^{14,15}. Most current measures are derived from categorical or dimensional models of personality. Broadly speaking, measures based upon a categorical model tend to adhere closely to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) constructs of personality disorder¹⁶, and determine presence/absence

of personality disorder based upon whether an individual meets or exceeds DSM thresholds for each personality disorder type and manifests significant functional impairment or distress, in a manner analogous to the diagnostic assessment of Axis I syndromes. Measures of this type, such as the Structured Interview for DSM-IV Personality (SIDP-IV)¹⁷ and the International Personality Disorders Examination (IPDE)¹⁸, are more reliable than unstructured interviews, allow for the use of informant data to control for biased reporting of symptoms, and incorporate clinician judgement as to whether personality disorder symptoms are maladaptive, pervasive and inflexible across situations and contexts. Dimensional measures of personality (e.g. NEO-PI-R)¹⁹ are derived from models that view personality disorder typologies as extreme variants of normative personality traits (e.g. neuroticism/emotional stability; introversion/extraversion; compliance/antagonism). Such measures, which typically rely on a patient's self-report of inner experiences and behaviours, allow for a more heterogeneous picture of patients' personality traits, and rely less on clinician inference, but vary in their accordance with DSM criteria for personality disorder.

Recent trends favour a dimensional approach to assessments of personality pathology, as flaws in the current categorical model of personality disorder, including arbitrary diagnostic thresholds with limited empirical support, high co-occurrence of personality disorder typologies, and inadequate coverage of diverse presentations of personality disorder in practice settings, appear insurmountable¹⁰. Moreover, recent research suggests that select dimensional personality traits (e.g. neuroticism, agreeableness) independently predict remission in adults with borderline personality disorder (BPD)²⁰, adding incremental validity to efforts to assess for personality pathology.

BARRIERS TO DETECTION OF PERSONALITY DISORDER IN OLDER ADULTS

Avoidance of Disclosure

Personality disorder may be undetected or inaccurately assessed due to difficulties engaging in the personality assessment process on the part of patients and clinicians, and due to limitations in applying current measures and constructs for this purpose. Specifically, many older adults grew up in an age when it was not acceptable

to openly talk about discordant feelings or interpersonal conflicts. Perceived stigma may impede inquiry into deviant inner experiences or behaviours, and would also make it unlikely that an older adult would have received a previous personality disorder diagnosis of which they can inform their current physician²¹. In a complementary manner, some clinicians adhere to the erroneous belief that older adults simply do not have personality disorders¹⁴. In addition, personality disorders may increase risk for developing Axis I disorders and it is often for this subsequent condition that patients seek professional help. Axis I conditions may be easier to recognize and accept, for both the clinician and patient, and are therefore often deemed the focus of diagnoses and treatment.

Assessment Measures

The structured interview is often considered an ideal assessment tool for diagnoses of personality disorder, but is subject to biases and inaccuracies when assessing older adults. As longitudinal evidence is required for a diagnosis of personality disorder, older adults may be asked to recount events and trends from 30–50 years before, and it is often doubtful that such information is valid or reliable²¹. Furthermore, measures of personality disorder cannot fully account for the potential influences of current psychological states, medical or neurological problems, situational or environmental contexts, or sociocultural roles on reporting of current symptoms or behavioural patterns²¹. Self-report inventories face similar vulnerabilities^{14,15}, and must be supplemented by a practitioner's clinical judgement.

Diagnostic Criteria

DSM-IV criteria for many personality disorders may not be generalizable to experiences and behaviours displayed by older adults. For example, symptoms of personality disorder such as increased dependency, social withdrawal, or rigid and moralistic thinking may be misinterpreted by clinicians as part of the natural ageing process and therefore may not enable discrimination between normal and pathological behaviour. In a large epidemiological survey which compared younger and older adults with equivalent levels of personality disorder pathology, an item analysis found evidence for age bias in two thirds of personality disorder criteria sets^{22,23}. Difficulties determining when impairment in social and occupational functioning is significant enough to warrant a diagnosis of personality disorder may also impede diagnosis. In the lives of older adults, where retirement and smaller social circles are common, this may not be an accurate measure of impairment^{14,21}. Finally, discrete behaviours upon which inferences as to personality are based may be more fallible in older adulthood. As individuals age, changing physical and developmental capabilities may limit their repertoire of behaviour, and thus the likelihood that behaviours are completely representative of their inner character. In this context it may be dangerous to rely on a solely behavioural framework for diagnoses^{11,24}.

DOES THE AGEING PROCESS ALTER PERSONALITY PATHOLOGY?

One of the most prominent barriers to accurate detection of personality disorder pathology is uncertainty as to whether and how age-related biopsychosocial changes affect the phenomenology of personality disorder, and a definitive answer remains elusive. Tyrer

and Sievewright²⁵ suggested that personality disorders can be divided into mature and immature types, in which the mature types, such as obsessive–compulsive, paranoid, schizoid and schizotypal, remain stable with age. In contrast, the more dramatic disorders, termed immature (borderline, narcissistic, histrionic), are hypothesized to decrease in intensity with age.

Empirical studies of normal personality find evidence for both stability and change over the life span. Major personality traits, such as those represented in the five-factor model (FFM) of personality (neuroticism, extraversion, openness, agreeableness and conscientiousness) have a prominent genetic basis, appear universal across cultures, and demonstrate substantial stability over the life course^{10,26,27}. Hence, one might expect that maladjusted individuals with personality disorder tend to remain so as they age. However, a recent meta-analysis of 92 longitudinal studies of reports of personality traits over the life span found that 'people tend to become more socially dominant, conscientious, and emotionally stable through midlife' (p. 21)²⁸, suggesting a positive maturational effect for most adults likely linked to age-graded roles (e.g. work, marriage, parenthood). Personality processes, such as emotion regulation, also display favourable age-related changes in cross-sectional studies of younger and older adults^{29,30}. Such findings are in accord with case series reports and cross-sectional studies of late life personality disorder³¹, and suggest that normative, maturational effects may favourably modify the phenomenology of personality disorder in older adults, especially in areas such as affect regulation and impulsivity.

Longitudinal studies of personality disorder are limited, but extant research provides further insight into stability and change in the phenomenology of personality disorder over the life span. McGlashan³² performed a longitudinal study on inpatients diagnosed with BPD, unipolar depression, or schizophrenia. He obtained follow-up data for over 288 participants (mean age of 47) at an average of 15 years after discharge (range 2–32 years). Compared to the other groups, the BPD group displayed the highest level of global functioning at follow-up, particularly in those conducted 10–19 years after discharge compared to subsequent follow-ups. Instrumental and global functioning increased for participants with BPD, whereas their interpersonal relationships often remained problematic or non-existent. McGlashan speculated that as patients with personality disorder age and lose employment capabilities, earlier improvements in instrumental functioning become less relevant and the lack of close relationships becomes more significant, potentially resulting in diminished functioning later in the life span. Similarly, a 16- to 45-year longitudinal follow-up of male inpatients diagnosed with antisocial personality disorder (ASPD) found that over half had improved or remitted, but that many also had enduring problems with occupational performance, interpersonal discord and social isolation³³.

Perry³⁴ reviewed 26 longitudinal studies on personality disorders, with the majority focusing on BPD. At an average follow-up of 8.7 years, only 57% of BPD patients continued to meet diagnostic criteria. This relationship was reportedly linear, with approximately 3.7% of borderline cases remitting each year. A more recent 10-year follow-up study of inpatients with BPD found that 88% achieved remission (many within 2 years), and that symptoms such as impulsivity were likely to resolve, while chronic dysphoria and interpersonal symptoms persisted^{20,35}.

In sum, investigations into the temporal stability of personality traits, disorders and processes find evidence for substantial continuity, particularly for major traits and for interpersonal functioning, but

also for favourable change in select areas, such as emotion regulation and impulsivity. Although we are unaware of studies that follow personality disorder into older adulthood, such findings suggest shifts in the phenotypic expression of personality disorder, and provide further empirical support for recommendations that clinicians consider possible attenuation and exacerbation of personality disorder traits and symptoms over the life span, apply time course criteria flexibly, and appreciate the salience of subsyndromal presentations of personality disorder in late life^{11,24}.

CHALLENGES IN THE DIFFERENTIAL DIAGNOSIS OF PERSONALITY DISORDER IN LATE LIFE

In addition to the barriers described above, clinicians who work with older adults face added diagnostic challenges, as personality disorder is often embedded in a complex matrix of age-related changes in cognitive and physical health, functional ability, interpersonal roles, and coping resources and behaviours. Although co-morbidity is the rule rather than the exception in geriatric practice, the DSM-IV-TR 'General Criteria for Personality Disorder'¹⁶ require that manifestations of personality disorder be disentangled from major psychiatric syndromes, medical and neurological disorders, situational behaviours or coping styles, and social/cultural roles. Among the most vexing issues are difficulties differentiating personality disorder from (i) an unremitted Axis I disorder; (ii) context-dependent roles and behaviours; (iii) subtle neurocognitive impairment; or (iv) a difficult doctor–patient relationship.

Personality Disorder Versus Unremitted Axis I Disorder

In practice settings an older person's long-standing and unremitted Axis I pathology, especially if associated with features of irritability, negativism and caregiver exhaustion, is often attributed to personality pathology. Although personality pathology is correlated with poorer treatment outcomes and persisting decreases in functioning in older depressed samples^{3–5}, it is not a 'diagnosis of exclusion' and such a conclusion may confuse personality disorder with illness duration and/or treatment responsiveness. This challenge may be addressed through careful application of the general diagnostic criteria for personality disorder, supplemented by dimensional personality measures and informant reports, with special attention to temporal relationships between the onset of Axis I and Axis II symptoms. If core features of personality disorder persist following maximal treatment of Axis I syndromes with combination therapies, a definitive diagnosis of personality disorder may be warranted.

Personality Disorder Versus Context-Dependent Roles and Behaviours

Older adults confronted with significant, ongoing life stressors such as serious medical illness (e.g. becoming disabled), interpersonal loss or role transition (e.g. becoming a caregiver), or the need to navigate a novel social environment (e.g. long-term care setting) may exhibit behaviours that mimic aspects of personality pathology. For example, confronted with medical problems or physical limitations, some elderly may express their distress somatically as if to manipulate the responses of caregivers; others may become antagonistic and demanding; still others may regress to a child-like dependency. Although significant psychosocial stressors may lead underlying personality disorder features to emerge²⁴, it is often the case that such

behaviours are context-dependent, or only loosely tied to personality traits rather than disorders. A longitudinal history, supplemented by informant data and dimensional measures of personality, may help clarify whether personality disorder symptoms and behaviours preceded the change in life context, thus meriting a diagnosis of personality disorder.

Personality Disorder Versus Subtle Neurocognitive Impairment

Neurological disorders such as Alzheimer's disease, Parkinson's disease, and vascular and frontotemporal dementias are common in late life, and both their characteristic features and associated behavioural manifestations are well recognized. Recent evidence suggests that personality changes (such as increased egocentricity, emotional lability, rigidity or apathy) may represent early or prodromal manifestations of dementia³⁶. Further, neuroscience research affirms that impairment of discrete brain regions often manifests as personality changes: orbital frontal lobe dysfunction is associated with reduced empathy and disinhibition; dorsolateral frontal lobe impairment is related to impaired initiation, planning and social awareness; parietal and temporal lobe insults are associated with misperception of the emotional context of speech²⁴. Personality manifestations that are prominent, have insidious onset or long duration, and overshadow evidence of neurocognitive impairment (which may be subtle) may be mistaken for personality disorder. When such personality features are the consequence of a medical condition, result in functional impairment and are not attributable to a diagnosis of dementia, delirium or another Axis I disorder, they are best described in DSM-IV-TR nosology as 'Personality Change Due To ... (a general medical condition)'¹⁶. A careful historical review of the temporal relationship between medical or neurocognitive and personality symptoms, assisted by a neuropsychological evaluation or diagnostic neuroimaging may clarify this differential diagnosis.

Personality Disorder Versus a Difficult Doctor–Patient Relationship

Patients who are especially challenging to treat due to prominent mood states such as irritability/hostility or fearfulness/mistrust, who deny emotional distress or express this through somatic complaints, or whose interpersonal behaviour violates 'expected rules' of the doctor–patient relationship are often experienced as difficult by their clinicians. Although clinicians' emotional experiences may signal the presence of a patient with personality disorder, difficulty experienced in the doctor–patient relationship can also occur in the context of somatization disorder and other Axis I disorders^{37,38}. Hence clinicians' emotional experiences provide important data, but may be non-specific regarding presence/absence of personality disorder. For purposes of differential diagnosis, such data might best be evaluated alongside informant information, clinical history and other assessment approaches described above.

One might expect that the above challenges would result in many false positive diagnoses of personality disorder in late life, but more commonly, behavioural problems that mimic personality disorder are informally and erroneously attributed to 'personality' in much the same way that ambiguous medical problems are ascribed to 'ageing'. Both practices may serve to reduce clinicians' discomfort with diagnostic uncertainty or other dissonant experiences, but can also result in failure to detect or properly manage an underlying, potentially treatable condition.

MANAGEMENT AND TREATMENT OF PERSONALITY DISORDER IN OLDER ADULTS

Progress in the development of strategies to manage and treat personality disorder has been slow, and evidence-based guidelines regarding the treatment of personality disorder in older adults currently do not exist. Hence clinicians engaged in the psychotherapeutic or pharmacological treatment of older adults with personality disorder often extrapolate from treatment models developed for younger adults. Generally, approaches for managing late-life personality disorder are based on the following premises: (i) evidence-based treatments for Axis I disorders require augmentation when personality pathology is present; (ii) standardized psychotherapeutic treatments developed to target aspects of personality disorder in adults are more effective than usual care; (iii) initial studies suggest that older adults may also benefit from these targeted treatments; (iv) guidance regarding the treatment of personality disorder in late life may be derived from common ingredients of effective approaches, extant research and clinical observations.

Studies of depressed younger or older adults provided with standardized brief treatments demonstrate that those with co-morbid personality disorder achieve less favourable outcomes^{4,39}. Importantly, these data do not suggest that depressed older adults with co-morbid personality disorder cannot derive some benefit from treatment for Axis I conditions⁴⁰, but they underscore that those with personality disorder are at higher risk of slower treatment response or adverse outcomes⁵. The presence of a personality disorder may interfere with the success and efficacy of such treatments in a variety of ways: longstanding maladaptive interpersonal patterns can pose challenges to forming a working therapeutic alliance; patients may be unwittingly invested in their symptoms and reluctant to get better for fear that secondary gains (attention, sympathy, intimacy) of illness may be lost; other aspects of the patient's life may be so chaotic that treatment adherence is difficult; or a patient may act out in offensive or self-destructive ways, causing the clinician to decrease their commitment to and optimism about treatment.

Empirical studies of psychotherapeutic approaches developed for the treatment of personality disorder in adults demonstrate promising findings. Dialectical behaviour therapy (DBT), schema-focused therapy, transference-based psychotherapy, and interpersonal group therapy have displayed efficacy in treating characteristic maladaptive coping styles and behaviours common to BPD in adults^{41–43}. Preliminary findings suggest that at least some of these models may have utility in treating depressed elderly with co-morbid personality disorder. In a recent trial, older adults with chronic depression and co-morbid personality disorder demonstrated improved remission rates when antidepressant treatment was combined with an adapted form of DBT. Those offered combined treatment also showed reduced interpersonal sensitivity and aggression, although it is unclear if other components of personality disorder were ameliorated⁴⁴.

Since effective approaches to treating personality disorder appear to share common ingredients, Livesley has argued for an integrative, common factors therapeutic approach^{1,45}. Such an approach would combine treatment modalities (psychotherapeutic and psychopharmacologic; individual and group psychotherapies) and techniques (behavioural, cognitive and psychodynamic) and maximally draw upon common factors found to be effective across treatments as part of an intensive, long-term intervention. Although this model has yet to be validated for older adults, it is consistent with models, emerging research and clinical reports regarding the treatment of late-life personality disorder^{31,44,46–50}.

PSYCHOTHERAPEUTIC MANAGEMENT: BASIC PRINCIPLES

Collaborative Multimodal Treatment, Managing Crises and Ensuring Safety

Effective treatment approaches for personality disorder tend to utilize a collaborative multimodal approach, in which clinicians of different disciplines combine treatment interventions to help the patient. Since older adults with personality disorders are likely to experience functional impairment in multiple areas (health, mood, social functioning), a multimodal approach in which the person may receive individual and group therapy, pharmacotherapy, medical attention for health concerns and case management is often ideal.

As with any psychiatric illness, the utmost priority in the treatment of patients with personality disorder is ensuring the patient's safety. Older adults with personality disorder may be prone to act in impulsive and self-destructive ways, arousing clinicians' concerns regarding their potential for self-harm or suicidal behaviour. A collaborative and cohesive treatment approach, often including all treatment team members and enlisting the patient's family or significant others to ensure safety, may assist to defuse such crises. This approach can also help clinicians evaluate the patient's need for hospitalization, closely monitor symptoms, and modify treatment parameters as needed.

Treatment Parameters

Effective psychopharmacological or psychotherapeutic treatment of individuals with personality disorder requires that clinicians attend carefully to treatment parameters such as session frequency and duration, availability of clinicians during non-treatment hours, policies regarding confidentiality and consent, and the respective roles and responsibilities of the patient and team members. Individuals with personality disorders may be more likely to cross boundaries with clinicians, or in some cases, encourage clinicians to cross boundaries for them. When clinicians find themselves stepping outside their normal repertoire of behaviour for a patient, whether in a positive or negative way (avoiding sessions, letting the session go overtime, doing tasks for patients that one would expect other patients to do for themselves, having intrusive thoughts or fears about a patient), this can reflect an enactment of the patient's interpersonal problems. When a clinician conceptualizes such boundary disturbances in a therapeutic manner (i.e. this person crosses boundaries because it is likely that someone crossed boundaries inappropriately with them in the past), it may be easier for the clinician to intervene using a combination of empathic clarification and limit-setting approaches, while maintaining a therapeutic alliance with the patient.

A common clinical occurrence when working with individuals with personality disorder is the propensity for the patient to split the treatment team. Splitting describes a tendency to engage in dichotomous thinking, such as categorizing people or experiences as all good or all bad, often evoking responses that appear to confirm this polarized and distorted perspective. When splitting does happen, it is of utmost importance that the treatment team recognizes it, retains solidarity and acts towards the patient as a unified front, especially in regard to treatment parameters, expectations regarding the patient's responsibilities in the treatment, and consequences regarding a failure to meet these expectations.

Patients with personality disorder may be especially prone to acting out or becoming more symptomatic when there is a transition

regarding the treatment team. Whether prompted by a clinician's departure or the patient's need for a different level of care, such personnel changes may be interpreted implicitly as rejection or abandonment, and it is essential that transitions be handled with sensitivity and increased alertness regarding safety issues. Anticipatory discussions of these transitions permit an exploration of how the patient perceives them, and a respectful and empathic response by the clinician may serve to diminish the chance of exacerbated symptoms or maladaptive behaviours. An interdisciplinary treatment team of providers may also serve to offer some constancy during such times.

Therapeutic Relationship and Treatment Alliance

Some of the most effective treatments for people with personality disorders are those that highlight the importance of the therapeutic relationship. For example, dialectical behaviour therapy, schema-focused therapy, transference-based psychotherapy and interpersonal group therapy all include a focus upon emotion regulation and the recognition of maladaptive interpersonal patterns, with special attention to how these problems may affect the therapeutic alliance. Several of these models, tested primarily in adults with BPD, suggest that clinicians assist patients to recognize and expect the emergence of underlying insecurities that would normally rupture the therapeutic process. For example, when conflicts in therapy arise, the clinician may enquire about past relationships in which the person had a similar experience or felt the same way. Clarifying similarities and differences between experiences of current and past relationships, and recognizing and correcting cognitive distortions about relationships, can be beneficial. During this process, as individuals with personality disorder come to recognize and label their own underlying emotions and experiences, they tend to engage less in acting out unacknowledged affective states, prompting interpersonal relationships to improve.

Since maladaptive interpersonal behaviours are core aspects of personality disorder, clinicians often find it difficult to form and maintain the alliance that is needed as a foundation of treatment. Clinicians challenged by this ongoing struggle may find it helpful to keep the aetiological factors of personality disorder, such as early trauma or aversive psychosocial experiences, in mind. Without understanding the underlying issues which often drive patients with personality disorder to act in offensive or self-destructive ways, clinicians are bound to be put off and frustrated by such patients, and it is likely that a clinician's instinctive defensive or avoidant response may reinforce the patient's pathological beliefs and interpersonal patterns. Thus, clinicians need to draw on their reservoir of knowledge to understand the underlying motivations for such behaviour so as not to contribute to its negative effects. Accordingly, a useful clinical guideline to keep in mind when treating individuals with personality disorders is to respond to underlying anxieties rather than maladaptive coping styles or defences. If one conceptualizes an individual's personality disorder in terms of an underlying vulnerability (e.g. sensitivity to issues of abandonment, loss of control, rejection etc.), one may be better able to respond to these insecurities as opposed to the maladaptive behaviours they can inspire. When the clinician can maintain a therapeutic stance (often putting their own ego and pride aside) and respond to the patient by acknowledging and validating fears, they are more likely to be able to successfully set limits, break interpersonal patterns, and provide patients with a new experience that can lead to real change.

PSYCHOPHARMACOLOGICAL MANAGEMENT

As mentioned above, psychopharmacological intervention is often an important component of a multimodal integrative approach to the treatment of personality disorder, and both theoretical and practical rationales may be presented for pharmacotherapy for late-life personality disorder. First, there is evidence that neurochemical abnormalities (e.g. serotonergic dysfunction) mediate the relationship between adverse genetic or environmental diatheses (e.g. temperament) and manifestations of personality pathology (e.g. impulsive aggression; suicidal and compulsive behaviours)⁵¹. Similarly, there is some evidence that dimensions of personality pathology (e.g. affective dysregulation, cognitive-perceptual dysfunction, impulse dyscontrol) may share common psychobiological substrates with Axis I disorders, and thus targeted pharmacotherapies might address neurotransmitter systems linked to these underlying substrates^{49,52}. A second, practical rationale for adjunctive pharmacotherapy is that personality disorder is often associated with Axis I disorders, brief destabilizing symptoms such as agitation or psychotic-like experiences, and behavioural crises, in which cases pharmacotherapy can be employed to manage acute symptoms, restore emotion regulation and reduce overall functional impairment.

Controlled studies find that psychopharmacological interventions have some effectiveness in treating circumscribed symptoms related to personality disorder, but research has been limited to three personality disorder types (borderline, schizotypal and antisocial personality disorder) and has only been conducted in young adult samples³¹. Studies of patients with BPD have found that atypical antipsychotic, anti-epileptic, and SSRI or SNRI medications effectively treat symptoms of cognitive-perceptual disturbance, mood instability and negative emotionality or aggression, respectively⁵¹. However, a review of forty randomized controlled trials of pharmacotherapy for adults with personality disorder (borderline, schizotypal and antisocial types) cautioned that although useful, psychotropic medications tend to only induce partial improvement in circumscribed areas⁵³.

A general framework for psychopharmacologic management of older adults with personality disorder augments general principles of geriatric psychopharmacology with an understanding of both the potential goals and challenges of managing symptoms in the context of late-life personality disorder. Once the best possible diagnostic formulation is reached, clinicians are advised to review with the patient all medications and remedies currently in use, and to attend to possible medication interactions⁴⁹. The presence of comorbid medical illnesses, cognitive impairment and other factors that may affect adherence should be identified. Even when target symptoms and goals are identified and agreed upon, it is important that both clinician and patient recognize that pharmacotherapy will not cure the personality disorder, and so the potential benefits and risks of treatment should be carefully reviewed and documented. In regard to specific agents, recent reviews suggest that SSRIs be used as first-line interventions for low mood as well as suicidal, aggressive or obsessional behaviours, and that mood stabilizers be considered to control affective fluctuations, which may occur in the context of cluster B and C personality disorders. Atypical antipsychotic medications may be helpful when psychotic-like symptoms are present, or in cluster A personality disorders. All reviews emphasize the prescribing clinician's need to carefully attend to the doctor-patient relationship, as a tenuous alliance and medication misuse or non-adherence are common in work with patients with personality disorders^{11,31,53,54}.

CONCLUSIONS

Personality and personality pathology exert profound effects on psychological well-being in older adults, yet are often underdetected and undertreated. Barriers to effective diagnostic assessment include the limitations of current measures, the differing phenomenology of late-life personality disorder and problems in differential diagnosis. Current findings favour a two-step, multimethod assessment approach in which presence/absence of personality disorder is first identified according to DSM-IV 'General Criteria for Personality Disorder'¹⁶ and then supplemented by collaterally informed semistructured interviews, and dimensionally-based personality self-report measures to characterize personality disorder type⁴⁵. Longitudinal assessment may be required to fully sort out personality disorder from Axis I disorders, subtle neurocognitive impairment, context-dependent behaviours, or other causes of difficult doctor–patient relationships.

Although randomized controlled trials of the treatment of late-life personality disorder are rare, recent findings in young adults suggest that components of personality disorder are amenable to targeted psychotherapies and pharmacotherapies. An integrative approach that combines treatment modalities and the common therapeutic ingredients of efficacious approaches may offer the best hope for the management and treatment of late-life personality disorder.

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Part I

Mental and Behavioural Disorders Due to Psychoactive Substances

Alcohol Abuse and Treatment in the Elderly

Helen H. Kyomen¹ and Benjamin Liptzin²

¹*McLean Hospital, Belmont, MA and Harvard Medical School, Boston, MA, USA*

²*Department of Psychiatry, Baystate Medical Center, Springfield, MA and Tufts University School of Medicine, Boston, MA, USA*

INTRODUCTION

Alcohol abuse in the elderly involves the persistent and intended use of ethyl alcohol despite problems caused by its use^{1,2}. It is often overlooked, as elderly with alcohol abuse may present with non-specific concerns such as confusion, mood lability, depression, anxiety, unusual behaviour, self-neglect, falls, injuries, diarrhoea, malnutrition, myopathy, incontinence, hypothermia³⁻⁵ and motor vehicle accidents⁶. However, as these conditions are evaluated, signs of the characteristic addictive use of ethyl alcohol may be uncovered with: (i) tolerance; (ii) withdrawal symptoms; (iii) loss of control of use; (iv) social decline; and (v) mental and physical decline². Late-life alcoholism is a substantial problem. In a recent population representative study which included 4236 non-institutionalized elderly, at-risk alcohol use was described by 13% of men and 8% of women, and binge drinking was reported by over 14% of men and 3% of women⁷. In another recent study of 24 863 elderly primary clinic patients, 21.5% were moderate drinkers, 4.1% were at-risk drinkers and 4.5% were heavy or binge drinkers⁸.

EFFECTS OF ALCOHOL IN THE ELDERLY

Older people are at greater risk and more vulnerable to the toxic effects of alcohol for two main reasons:

1. The elderly have a decreased volume of distribution due to decreased muscle mass, a greater proportion of fat and a smaller water compartment. These all result in a higher blood alcohol level than in a younger adult for the same amount of alcohol consumed^{9,10}. In a younger person, larger amounts of alcohol consumption may be necessary before detrimental effects from alcohol abuse become grossly evident. A susceptible elderly person may reach this threshold for hazardous use of alcohol after drinking relatively less.
2. The general decrease in the capacity to withstand stress and maintain homeostasis as well as a higher risk for medical illness and disability in elderly people may hinder adaptation to the noxious effects of alcohol and magnify the consequences of alcohol abuse in the elderly¹¹.

The interaction of these two main factors places the elderly alcohol-using person at greater risk for multiple impairments resulting from the use of alcohol.

There are many possible detrimental effects from alcohol abuse in the elderly. Among them are the following:

1. Driving ability can be adversely affected with the consumption of minimal amounts of alcohol. In some elderly, relatively small amounts of alcohol can exacerbate or lead to confusion, visuospatial impairment, problem-solving deficits, motor impairment¹² and motor vehicle accidents⁶.
2. Cognitive impairments suggesting dementia may be caused by alcohol abuse. Though some cognitive impairment can result from even social drinking, chronic consumption of higher doses of alcohol has been shown to cause marked cognitive deficits with associated cortical atrophy and ventricular dilatation on brain scan¹².
3. Elderly alcoholics have a higher prevalence of alcohol-related medical conditions than the elderly population at large. Such conditions include alcoholic liver disease, alcoholic cardiomyopathy, hypertension, chronic obstructive pulmonary disease, neurological diseases (including cognitive disorders and peripheral neuropathy), malnutrition, osteopenia, psoriasis, peptic ulcer disease and various cancers^{3,12,13}.
4. Alcohol use can adversely affect the elimination of some drugs and add to the toxicity of others. This places an elderly person with medical illness or disability who is taking prescription medication at great risk for having subtherapeutic or adverse effects from the medication^{14,15}. The magnitude of this problem is evident when one considers that the elderly are the largest per capita prescription drug users¹⁶ and the most at risk for medication associated adverse events¹⁷.
5. The depressant effects of alcohol on the central nervous system may mimic or contribute to depression in the elderly. Some elderly with depressed mood may resort to drinking in order to 'self-medicate' themselves. This may alleviate the depressive symptoms initially, but later lead to an increase in depression, anxiety, sleep disturbances and impotence^{18,19}.

6. Alcohol can contribute to malnutrition in the elderly. Malnutrition can result from the interaction of the following factors^{20,21}:
 - (a) Food intake can be hindered if the elderly alcoholic develops depressed mood, becomes apathetic and experiences loss of appetite. If the elderly alcoholic's impaired ambulation or driving results in a reduced capacity to obtain food, or if limited financial resources are used to purchase alcohol instead of food, dietary intake may be restricted further.
 - (b) The effect of alcohol on the gastrointestinal tract is to produce malabsorption of fats, fat-soluble vitamins, calcium, magnesium, iron and zinc. The active transport of B vitamins is also impaired.
 - (c) Alcohol can contribute to increased losses of magnesium, phosphate, potassium and zinc through the urine. If vomiting and diarrhoea occur, there may be increased loss of sodium, potassium and chloride.
 - (d) Alcohol use increases the requirements for folate and pyridoxine.
7. Alcohol use contributes to accidents and injuries that may lead to fractures or subdural hematomas^{3,6,22}.
8. Heavy use of alcohol is associated with greater mortality^{23–25}.
9. Alcoholism can disrupt the elderly alcoholic's family structure and cohesiveness, and may even lead to family violence. This can result in dysfunctional family relationships, with consequent increased difficulty in treatment of the alcohol-related problems.

Despite the many unfavourable effects of alcohol abuse in the elderly, researchers have also reported positive aspects of alcohol use. Light to moderate alcohol consumption has been associated with decreased mortality risk^{24,25}, reduced risk of substantial functional health decline²⁶, better cognitive health and well-being^{27,28}, improved bone mineral density²⁹ and, in elderly coronary patients, elevated high-density lipoprotein cholesterol³⁰.

CHARACTERISTICS OF ELDERLY ALCOHOL ABUSERS

Elderly alcohol abusers differ from younger alcohol abusers in a number of ways. Alcohol abuse in the elderly is often associated with clusters of stressors such as job retirement, widowhood, the deaths of close friends and relatives, medical illness and disability in oneself and one's peers, and perceived loss of meaningful roles or functions. Some authors consider late-onset alcoholism to be associated with tension reduction, where alcohol is used to regulate stress. However, the extent to which alcohol abuse in the elderly is precipitated by stress is unclear. Some researchers have found little or unexpected change in alcohol consumption or drinking behaviour due to life stressors^{31,32}.

The time of onset of alcohol abuse may also significantly differentiate the younger alcoholic from the older one^{10,33,34}. The early-onset alcoholics have a greater amount of psychopathology and family history of alcoholism than the late-onset alcoholics. The early-onset alcoholics are characterized by being male relatives of alcoholic men with histories of violence with and without alcohol, legal problems due to alcohol use and illegal substance abuse. The late-onset alcoholics are characterized by having isolated alcohol-induced problems with health, marital relationships, or self-care, and much reduced histories of arrests, violence or other substance abuse. Many elderly with alcohol problems fall into the late-onset alcoholic group. These findings suggest that the aetiology and predisposition of a person to an alcohol use disorder may differ by onset age. If this is so, the

treatments and interventions for an alcohol use disorder may also differ with age of onset and need to be individualized accordingly.

Individual feelings towards alcohol use are affected by exposure to cultural and historical attitudes³⁵. For example, the experience of the American elderly alcoholic may differ from that of younger alcoholics in that the elderly alcoholic and his peers may have been exposed to the turmoil of the Prohibition era³⁶. The moral issues highlighted in this historical period may influence the willingness that some elderly may have in recognizing and accepting a diagnosis of and treatment for alcoholism. In some retirement communities, evening cocktails are a part of the social routine, leading some individuals to increase their prior alcohol consumption.

THE RECOGNITION OF ALCOHOL ABUSE IN THE ELDERLY

Alcohol abuse in the elderly often comes to the attention of health professionals through presentation with a non-specific medical or psychiatric symptom, such as self-neglect, falls, confusion, emotional lability, depression, unusual behaviour, injuries, diarrhoea, malnutrition, myopathy, incontinence or hypothermia. In cases where alcohol abuse is suspected, alcohol dependence must be considered. Alcohol dependence is suggested when there is: (i) tolerance; (ii) withdrawal symptoms; (iii) loss of control of use; (iv) social decline; and (v) mental and physical decline^{2,37}.

Tolerance to alcohol may be assessed by establishing a reliable history of the patient's drinking pattern. Corroboration from family members and others close to the patient may be crucial. Tolerance is suggested if the patient exhibits a quantity and frequency of drinking which is increased over his baseline pattern of drinking. A patient with tolerance to alcohol will require a greater quantity of alcohol to achieve the same amount of inebriation that a lower quantity had been able to achieve previously. Tolerance is strongly suggested if there has been at least a 50% increase in the amount of alcohol required to attain a given effect^{2,37}.

Withdrawal symptoms occur when a patient who is physically dependent on alcohol experiences a rapid decrease in blood alcohol concentration. In an older person, the onset of withdrawal may be delayed by days after drinking cessation, and the duration of withdrawal may be prolonged^{37,38}. Symptoms of the alcohol withdrawal syndrome stem from autonomic hyperactivity and include tachycardia with a pulse of greater than 110 beats per minute, tachypnea, hypertension, low-grade fever, sweating, nausea, vomiting, hand tremors and increased anxiety. In some cases, the patient may develop seizures or delirium tremens with confusion, agitation and visual or tactile hallucinations. An elderly patient undergoing withdrawal may experience one or all of these symptoms^{37,38}.

Loss of control means that the patient is no longer able to consistently choose the amount of alcohol consumed in a given situation³⁷. The patient may also experience blackouts, and behave and feel in unpredictable ways.

Social decline in the elderly alcoholic is assessed from a baseline of age-appropriate behaviours^{2,37,38}. Many elderly people no longer hold a steady job, do not drive or hold a driver's license, and have lost many of their close friends and associates with whom they used to socialize. Thus, it may not be as appropriate to assess for social decline by investigating these areas of the elderly patient's life as it would be in a younger patient. However, it is relevant and revealing to ask elderly people if they are in contact with their children or grandchildren, and to what extent. It is also useful to find out whether

the patient's relatives express any concern about the patient's alcohol use. Investigating the patient's functioning with respect to hobbies or other enjoyed activities can also be useful.

Physical, psychological and laboratory findings may also uncover problems with alcohol use^{37–39}. Addictive alcohol use can lead to malnutrition, gastrointestinal upset and bleeding, delirium, falls, depression, hypertension and neglect of self. Recurrent diseases of the stomach, pancreas or liver may also be caused by excessive alcohol abuse. These medical conditions often bring the elderly alcoholic to clinical attention. Laboratory results of macrocytosis, elevated mean corpuscular volume and increased liver enzyme levels, especially gamma glutamyl transpeptidase, may correlate with alcohol abuse in the elderly. Carbohydrate-deficient transferrin is approved by the Food and Drug Administration (FDA) as a clinical diagnostic test for identifying heavy alcohol use³⁹. Blood alcohol levels, and urine or breath tests for alcohol, may be used to confirm alcohol intoxication.

Assessment of tolerance, withdrawal, loss of control, social decline and mental and physical decline are useful clinical parameters to recognize and diagnose alcohol addiction. Several screening instruments have been devised to help clinicians recognize alcoholism. These scales typically assess the quantity and frequency of drinking, social and legal problems resulting from alcohol abuse, health problems related to excessive alcohol use, symptoms of addictive drinking and/or self-recognition of alcohol-related problems^{40,41}. Three screening instruments that are commonly used with the elderly are the CAGE screen⁴², the Short Michigan Alcoholism Screening Test-Geriatric Version (S-MAST-G)⁴³ and the Alcohol Use Disorders Identification Test (AUDIT)⁴⁴.

The CAGE screen is the most widely used. 'CAGE' is a mnemonic for the questions: Have you ever felt a need to Cut down on drinking? Have you ever felt Annoyed by others enquiring about your drinking? Have you ever felt Guilty about drinking? Do you ever use alcohol for an Eye-opener? If two or more of these questions are answered positively, a need for more extensive evaluation for alcohol abuse is indicated. The validity of the CAGE screen for alcoholism in the elderly has been examined empirically⁴².

A more detailed screen is the 10-item S-MAST-G⁴³ or the original 24-item MAST-G⁴⁵. The S-MAST-G was developed for screening older adults in various settings and has excellent psychometric characteristics. Scores of ≥ 2 on the S-MAST-G or of ≥ 5 on the MAST-G are indicative of possible problems with alcohol.

The AUDIT⁴⁴ emphasizes the identification of harmful drinking and need for current treatment. It was validated in a sample of non-elderly adults and is composed of two parts: a 10-item AUDIT Core Questionnaire and an 8-item AUDIT Clinical Procedure. The AUDIT Core Questionnaire includes specific questions about the quantity and frequency of drinking and can be incorporated into a general interview or medical history. In the original study sample, all alcoholics scored ≥ 9 on the AUDIT Core Questionnaire. The AUDIT Clinical Procedure complements the AUDIT Core Questionnaire and includes questions about clinical signs associated with harmful drinking, such as fractures, tremors and hepatic abnormalities. The AUDIT Clinical Procedure may be especially helpful in evaluating patients who underestimate their alcohol-related problems. A short version of the AUDIT, the AUDIT-C⁴⁶, is a 3-item screen composed of the alcohol consumption questions of the AUDIT. The AUDIT-C has been reported to be a valid primary care screen for heavy drinking and/or current alcohol abuse/dependence. Various versions of the AUDIT have been used widely, but for older adults, the overall accuracy is low and multiple screening methods are recommended^{47,48}.

THE TREATMENT OF ALCOHOL ABUSE IN THE ELDERLY

In acutely intoxicated patients, a thorough evaluation for and treatment of other co-existing medical or psychiatric problems must be initiated at the same time as the patient is being detoxified. Providing adequate nutrition and hydration is especially important in the elderly alcoholic due to increased nutritional problems and impaired thirst mechanisms in the elderly. Benzodiazepines are generally avoided in most elderly due to their potential for causing delirium. However, if significant withdrawal symptoms occur, benzodiazepines should be administered according to assessments of alcohol withdrawal severity^{38,49}. Withdrawal severity may be evaluated using the revised Clinical Institute Withdrawal Assessment Scale for Alcohol (CIWA-Ar)⁵⁰ and taking sequential vital sign measurements. Elderly patients may experience a delayed onset of and more severe withdrawal from alcohol and require higher doses of benzodiazepines than younger patients³⁸. In general, detoxification using a symptom-triggered regimen with benzodiazepines with a shorter half-life is recommended in the elderly. Longer acting benzodiazepines may allow a smoother course of withdrawal but may cause more sedation in elderly patients³⁸. They may also cause ataxia which can lead to falls. Non-benzodiazepine GABAergic medications are considered to be potential agents to treat alcohol withdrawal⁵¹, but their effectiveness in elderly patients is unclear. There is anecdotal experience for trying an anticonvulsant such as divalproex to prevent withdrawal seizures.

Once the elderly alcoholic patient is detoxified, adequate relapse prevention and rehabilitative treatment is crucial for the patient to maintain sobriety. The elderly alcoholic must first come to an acceptance of the alcohol abuse problem. Family members or others who are close to the patient may intervene to help the patient break through the denial regarding alcohol abuse seen in many alcohol abusers. Family members may also be instrumental in motivating the patient to stop drinking. Patient and family education about the effects of alcohol must be provided, and the need to abstain from alcohol must be stressed. Although light-to-moderate drinking has been reported to be health promoting^{24–30}, abstinence may be the healthiest goal for those who are unable to drink normally, tend to lose control of their drinking, or lose control of themselves when drinking. Early intervention includes brief alcohol counselling (BAC) to patients and family which encompasses expressions of concern, feedback associating the patient's drinking with health issues and explicit advice to reduce drinking⁵². Age-specific relapse prevention and rehabilitative programmes may improve treatment participation and completion⁵³. A behavioural and self-management treatment module has resulted in marked success in treating alcohol-use problems in the elderly⁵³. This module educates the elderly alcoholic about drinking behaviour, the acquisition of self-management skills and the reestablishment of social networks.

The elderly alcoholic patient's recovery and rehabilitation is an ongoing process. The patient needs to learn to readjust to life without alcohol. The patient's family and close relatives and friends can help him in this endeavour by supporting sobriety in the patient and incorporating the non-drinking patient into their lives without the presence of alcohol. Family members may have been 'enabling' the patient to drink, and they need to be made aware of these patterns of behaviour and change them through family education and family therapy. Sometimes, even when relatives are aware of the harmful effects of alcohol, they still provide alcohol if the patient insists. If the elderly alcohol abuser is a parent and the enablers

are his children, the role reversal that is inherent in the children's setting limits on their parents may make this task especially difficult. Group therapy may help the patient adjust to a non-alcoholic lifestyle. In this setting, he can develop non-alcohol-related social skills and learn to bond with others in safe surroundings, free of the context of alcohol. If elderly alcoholics can be treated in age-specific groups, they may remain in treatment significantly longer and be more likely to complete treatment than those treated in mixed-age groups⁵³. Involvement in Alcoholics Anonymous with people with whom the patient feels comfortable and can consider his peers is important, especially if he has no close relatives or friends. The relationships with others that can be formed in these settings can provide a replacement for the alcohol to which he was bonded previously. Family involvement with the patient in Alcoholics Anonymous and in other affiliated groups such as Alanon, Alateen or Alatot is important, as alcoholism adversely affects family members who also need support, education and treatment.

Use of alcohol-deterrent medication such as disulfiram or anti-craving medication such as naltrexone may serve as adjunctive treatments. Disulfiram is infrequently used in the elderly due to concerns about adverse effects. Naltrexone was approved by the FDA for the treatment of alcohol dependence, based on efficacy studies with middle-aged patients with alcohol dependence^{54,55}. It seems to be well tolerated in many elderly. A study in older veterans aged 50–70 found that treatment with naltrexone 50 mg/day resulted in decreased rates of relapse to heavy drinking, but no improvement in total abstinence⁵⁶. These drugs may help motivated alcohol abusers reduce the quantity of alcohol used or the number of drinking days. However, these medications generally are not effective unless prescribed and monitored as part of an overall, multidisciplinary treatment and relapse prevention plan. Acamprosate has anti-craving therapeutic effects and also has been FDA approved for the treatment of alcohol dependence. It seems to be well tolerated by elderly, but there are no clinical trials focusing on its use in elderly⁵².

The cultural aspects of alcohol abuse intervention are also worthy of consideration. In instituting any type of treatment or intervention, it is important to consider the context of the problem that is being addressed and the context into which the treatment or intervention will be instituted. The consumption of alcohol can take on a variety of cultural meanings. To some groups, ethanol is a food or is associated with religious rituals. For others, it is a means to relax and calm one's nerves. For still others, alcohol is considered to be a sinful intoxicant used by those of weak moral fibre. To intervene most effectively with an aged person for whom alcohol consumption has become a problem, it is important to understand what meaning the use of the alcohol has for him as an individual, a family member and as part of the greater society, including his cultural group. The contextual meaning of the change in alcohol use must likewise be considered. To understand these contextual meanings most effectively, the clinician must be aware of what his inherent assumptions may be about these contextual meanings and try not to confound with his own biases, his understanding of the situation. Members of the patient's contextual and cultural groups may be very helpful in providing meaningful insights into these understandings. Once these cultural factors are understood, interventions to reduce the problematic alcohol consumption to the desired outcome of abstinence or, perhaps, of less harmful alcohol use can be creatively formulated and instituted more effectively and efficiently.

CONCLUSION

In summary, alcohol abuse in the elderly is a significant problem that needs to be addressed aggressively. Recognition and diagnosis of alcohol abuse may be more difficult in the elderly. The biological and psychosocial losses and decline that are often used to identify alcoholism in younger people can occur in many elderly who do not abuse alcohol. The clinical presentation of an elderly alcoholic is often with a medical condition that may be masked by other medical diagnoses. For these reasons, the clinician must be especially alert to the possible presence of alcohol abuse in this age group. If alcohol abuse is identified, the clinician must then be prepared to direct or initiate treatment in a culturally appropriate, sensitive, flexible and creative manner that is geared to the elderly individual and his family and significant others.

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Epidemiology of Alcohol Problems and Drinking Patterns

Celia F. Hybels and Dan G. Blazer

*Department of Psychiatry and Behavioral Sciences, Center for the Study of Aging and Human Development,
Duke University Medical Center, Durham, NC, USA*

Alcohol use in excess of recommended limits is an important clinical issue for older adults. This chapter begins by summarizing the epidemiology of alcohol use disorders. Some older adults, however, fail to meet criteria for alcohol abuse or dependence yet engage in heavy drinking. The chapter continues with a discussion of patterns of alcohol use and problem drinking as well as the factors and outcomes associated with alcohol problems in this population. Issues of detection and co-morbidity are also addressed.

PREVALENCE OF ALCOHOL USE DISORDERS

Over the past decade, large community-based epidemiologic studies have provided new information concerning the prevalence of alcohol use disorders in the general population. In the National Comorbidity Survey Replication (NCS-R), conducted in the USA between 2001 and 2003 with a representative sample of 9282 adults, the lifetime prevalence of DSM-IV alcohol abuse disorder was 13.2%, a lifetime prevalence similar to that of major depression, specific phobia and social phobia, and therefore one of the more common lifetime psychiatric disorders. The lifetime prevalence of alcohol abuse disorder among those 60 years or older was 6.2%, lower than that observed for those aged 45–59 years (14.0%), 30–44 years (16.3%) and 18–29 years (14.3%). The lifetime prevalence of alcohol dependence was not as high as that of alcohol abuse, and among those aged 60 or older was 2.2%¹. Although higher estimates were reported from the 2001–2002 National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) in the USA (the lifetime prevalence of any alcohol use disorder was 16.1% among those aged 65 or older), younger or middle-aged adults were still 2.5 to 3.5-times more likely to have a lifetime alcohol use disorder than those aged 65+². These estimates are similar to those obtained in the landmark Epidemiologic Catchment Area (ECA) surveys where the lifetime prevalence of alcohol abuse/dependence was 13.52% among older males compared to 26–28% among males aged 18–44. The lifetime prevalence among older females was 1.49%³.

Similar to lifetime estimates, the current prevalence of alcohol use disorders has been shown in cross-sectional studies to decline with age. In the NESARC, the 12-month prevalence of DSM-IV

alcohol abuse was 7.0% among those aged 18–29, 6.0% among those 30–44, 3.5% among those 45–64 and 1.2% among those aged 65+. A similar decline was observed for alcohol dependence with a 12-month prevalence of 9.2% among those aged 18–29 and 0.2% among those aged 65+². These estimates are in agreement with the 12-month prevalence of any alcohol use disorder in the ECA among those aged 55+ (2.6–2.8%)⁴. One-month prevalence estimates of any alcohol use disorder among those aged 65+ in the ECA were 1.8% in males and 0.3% in females⁵.

The prevalence in clinical samples of older adults can be higher. In one sample of 2405 patients aged 60+ seen in the emergency department, the prevalence of any current alcohol use disorder was 5.3%. The disorders occurred more frequently among men. Compared to older patients without disorders, those with alcohol use disorders were more likely to be homeless, live alone, be divorced or be never married. The most common alcohol-induced disorders were alcohol intoxication and alcohol-induced mood disorders. Falls and delirium were frequent emergency admission circumstances in the elderly drinkers⁶.

While the proportion of older adults with defined alcohol use disorders may be low in comparison to younger adults, alcohol consumption at any level may potentially be problematic in this age group due to increased sensitivity to alcohol⁷. Because of decreased lean body mass and smaller volume of distribution, higher peak ethanol concentrations per dose are found in older compared to younger adults⁸. Also, even in small amounts, alcohol may exacerbate or mask symptoms of illness. Finally, many older adults are users of both prescription and over-the-counter medications that may interact with alcohol⁷. In a study of 700 persons aged 75+ from Finland, the prevalence of alcohol consumption was 44%. However, 86.9% of the alcohol drinkers used medications on a daily basis and 87.8% used medications as needed, including medications known to interact with alcohol⁹. In another study, 19% of older adults who used alcohol-interactive drugs also reported concomitant alcohol use¹⁰. These factors suggest alcohol use in older adults, especially in excess of recommended limits, may have adverse consequences. The number of older adults is projected to increase significantly over the next few decades as the post-Second World War generation ages, bringing

a higher lifetime prevalence of alcohol disorders. This could potentially result in higher numbers of older adults with alcohol-related problems¹¹.

Defining recommended limits given these age-related issues can be difficult. Chermack *et al.* examined the relationship between alcohol consumption patterns and the presence of DSM-III-R alcohol symptoms among 443 current drinkers aged 55+, and found that both average daily consumption and days of heavy drinking in the past year independently predicted symptom status. Consumption levels for men and women were only different for symptomatic drinkers. The authors reported that their results supported the recommendation that moderate consumption levels should be lower for older than for younger adults, and the recommendation not to exceed one drink/day to reduce the risk of symptoms¹².

PREVALENCE OF ALCOHOL USE

Alcohol use declines with age. In the 2001–2002 NESARC, 45.1% of the participants aged 65+ reported that they had consumed one or more drinks in the past year, compared to 64.3% among those 45–64, 72.9% among those 25–44 and 70.8% among those 18–24. Among those aged 65+, 28.5% reported former alcohol use and 26.4% reported lifetime abstinence. Among older adults, the prevalence of current drinkers was 48.3% among Whites, 23.4% among Blacks, 37.9% among American Indians/Alaskan Natives, 32.7% among Asian/Pacific Islanders, and 36.6% among Hispanics. Among current drinkers aged 65+, 64.3% were classified as light drinkers, 20.7% as moderate drinkers and 13.9% as heavy drinkers. A total of 58.0% of older adults with excellent/very good self-perceived health were current drinkers compared to 29.1% of those who rated their health as fair/poor¹³.

This decline in alcohol use by age is also observed among the oldest old. Ruchlin examined the prevalence of alcohol consumption in adults aged 55+ and found 46% had consumed alcohol in the past year, with a continuous decline across age groups, from 52.9% of those aged 55–64 categorized as current drinkers compared to 24.7% of those aged 85+. A total of 17% of the sample reported that they had consumed alcohol every day in the past two weeks. In controlled regression analyses, more people aged 65–74 drank every day, compared to those 55–64 (odds ratio = 1.36), but people aged 75+ drank less than those aged 55–64. Males and Whites used alcohol more frequently and were more likely to be heavy drinkers than females and non-Whites. The lower one's perceived health status, the lower the odds of drinking every day. Believing excessive drinking increased the chances of getting cirrhosis of the liver decreased the odds of moderate and heavy drinking¹⁴.

There are various explanations as to why the prevalence of alcohol use is lower in older adults. Selective survival may be a factor, in that persons who drink may be less likely to survive to older ages. Cohort effects are also possible. Persons who grew up before the Second World War may have had lower alcohol use throughout their lives. In the NESARC, the proportion of lifetime abstainers was highest in the 65+ age group (26.4 vs. 13.7% among those aged 25–44 years)¹³. Studies have also shown that some older adults decrease their use as they grow older. Busby *et al.* investigated alcohol use in a community-based sample of adults aged 70+ in New Zealand. Both frequency and quantity of intake decreased with age. A total of 60.1% of the men and 30.3% of the women said they drank less compared to middle age, while 7.4% of the men and 11.1% of the women said they drank more. The main reasons cited for decreased

use of alcohol were change in health and fewer social opportunities, with reasons cited for increased intake being more time and money¹⁵.

Adams *et al.* followed a cohort of 270 healthy community-dwelling adults aged 60+ over seven years. At baseline, the investigators found a decline in percentage of drinkers with increasing age. In the seven-year follow-up, there was a 2% per year decline in the percentage of subjects consuming any alcohol, but the mean alcohol intake did not change for those who continued to drink, except among heavy drinkers, suggesting an age-related decline rather than a cohort effect¹⁶. A study from Denmark of adults aged 50–74 interviewed at five time points between 1987 and 2005 reported that the unadjusted probability of heavy drinking declined with age but increased by calendar year and year of birth for both men and women¹⁷.

Using data from four time points over 20 years, Karlamangla *et al.* found evidence for age and period effects for heavy drinking but not cohort effects across all age groups. The prevalence of heavy drinking decreased with increasing age, an age effect, and also tracked declines in USA per capita alcohol consumption, a period effect. The prevalence of heavy drinking in specified age groups did not differ by birth year¹⁸. Cohort effects have been noted across all age groups, however, for beverage-specific consumption, with adults born before 1940 more likely to drink spirits than those born after 1940, and elevated beer consumption among those born between 1946 and 1965¹⁹. In the NESARC, beverage preference among current drinkers aged 65+ was coolers (long drinks with ice, 1.3%), beer (23.6%), wine (31.1%), liquor (14.2%) and no preference (29.7%). Preference for beer was lower and preference for wine and liquor was higher compared to other age groups¹³.

While the NESARC reported that less than half of older adults in the USA had consumed any alcohol in the previous year, regional studies have shown much variation. In a sample of 270 healthy men and women aged 65–89 living in the Southwestern USA, 48% of the participants reported in their three-day diet record that they had consumed alcohol, with 66% reporting they had consumed alcohol at least monthly²⁰. The prevalence of alcohol use reported from the Established Populations for Epidemiologic Studies of the Elderly (EPESE) studies of persons aged 65+ varied by site. In East Boston, 70.5% of the sample drank alcohol in the past year and 54.7% had used alcohol in the past month. Similar findings were reported from New Haven, where 65.8% had used alcohol in the past year and 51.9% in the past month. The proportions were lower in Iowa and North Carolina. In the Iowa sample, 46.3% had used alcohol in the past year, while 31.2% had done so in the past month. In the North Carolina EPESE, 37.4% had consumed alcohol in the past year and 24.6% in the past month^{21,22}.

Samples from clinical populations have also found a range of alcohol use among older adults. Saunders *et al.* reported, among men and women aged 65+ randomly selected from patient rosters, that 10.5% admitted to drinking more or less every day (17.7% men and 6.1% women). At the three-year follow-up, one-fifth of the participants were regular drinkers, drinking at least on one occasion per week²³. In a sample of 539 medical admissions aged 65+, the prevalence of alcohol abuse was 7.8%. An additional 29.7% of the sample who were neither abstainers nor occasional drinkers or alcohol abusers drank regularly: 43% of the men and 16% of the women²⁴.

PREVALENCE OF HEAVY DRINKING

Heavy drinking in older adults has been documented in research studies in various ways. In the EPESE baseline studies, the percentage of

persons who drank two or more ounces of absolute alcohol per day in the previous month was 8.4% in East Boston, 6.6% in New Haven, 5.4% in Iowa and 7.2% in North Carolina^{21,22}. Goodwin *et al.* found in their sample from the Southwestern USA that 17% of the drinkers drank more than 30 g alcohol per day on average²⁰. In a study of older Medicare beneficiaries, 9% reported exceeding recommended drinking limits. The prevalence was higher in men (16%) than women (4%). Exceeding limits was defined as monthly use exceeding 30 drinks per typical month, or consuming four or more drinks a day in a typical month²⁵. In a report from the 2004 Behavioral Risk Factor Surveillance System (BRFSS), the prevalence of binge drinking decreased with age, from 27.4% among those aged 18–24 to 3.7% among those aged 65+. However, among binge drinkers, those aged 65+ reported the highest average number of binge drinking episodes during the previous month. The number of drinks consumed during the most recent binge episode decreased with age, from 9.8 among those aged 18–24 to 6.4 among those aged 65+²⁶.

The prevalence of heavy alcohol use among drinkers has also been reported. In the NESARC, daily limits across all age groups were defined as 5+ drinks per day for men and 4+ for women. A total of 3.9% of older drinkers reported excess drinking 1–11 times in the previous year, and 6.1% reported excess consumption 12+ times in the past year. Weekly limits were defined as 14 drinks per week for men and 7 per week for women. A total of 13.9% of the older drinkers exceeded the weekly or both daily and weekly limits during the previous year¹³. Saunders *et al.* found that 19.5% of the men and 19.6% of the women who were regular drinkers were exceeding sensible limits²³.

The prevalence of heavy drinking in clinical samples is similar. Adams *et al.* screened 5065 primary care patients aged 60+ and found that 15% of the men and 12% of the women regularly drank in excess; 9% of the men and 2% of the women reported regularly consuming more than 21 drinks per week²⁷. Iliffe *et al.* studied 241 patients aged 75+ from general practice and found that 51% of the men and 22% of the women reported using alcohol in the past three months. Among drinkers, 3.6% of the men admitted consuming more than 21 units and 3.2% of the women more than 14 units of alcohol per week. Weekly alcohol consumption was not associated with age, cognitive impairment, depression, falls or inpatient or outpatient care²⁸. Callahan and Tierney found the prevalence of CAGE²⁹-defined alcoholism was 10.6% among primary care patients aged 60+. Patients with alcoholism were more likely to be younger, have fewer years of education, and be male, Black, smokers and malnourished³⁰. In another sample of adults aged 65–103 years selected from primary care, 70% reported no alcohol consumption during the past year. A total of 21.5% were moderate drinkers, 4.1% were at-risk drinkers and 4.5% were heavy or binge drinkers³¹.

Bristow and Clare interviewed 650 medical and geriatric admissions over age 65 and found 9% of the men but few of the women drank in excess of recommended safety limits. Another 10% had drunk heavily over the age of 65 but cut down because of medical, social, financial or other reasons. Compared to the non-drinkers and light drinkers, the heavy drinkers were more likely to smoke, to be unmarried and to have some impairment of mobility³². In a similar sample of hospital patients aged 65+, 54% reported no alcohol consumption and 9% screened positive for alcohol problems (17% among male and 2.5% among female patients). Seven percent of the patients were discharged with an alcohol-related diagnosis³³.

IDENTIFICATION OF PROBLEM DRINKING

Clinicians may have difficulty detecting and diagnosing alcohol problems in older adults for a number of reasons. Screening instruments used in younger populations to detect problem drinking may not be as reliable for older adults^{34,35}. Adams *et al.* compared responses to a beverage-specific self-administered questionnaire about the quantity and frequency of alcohol use and episodes of binge drinking to the widely used CAGE questionnaire (Cut down, Annoyed by criticism, Guilty about drinking, Eye-opener drinks)²⁹ in 5065 primary care patients age 60+, and found the CAGE performed poorly in detecting heavy or binge drinkers²⁷. Many of the screening instruments enquire about frequency and quantity of alcohol use, but even small amounts may be problematic for older adults with chronic health conditions and in combination with certain medications. Criteria for alcoholism often include problems with social and/or occupational functioning. However, older adults are less likely to be married or employed, and therefore less likely to report marital or job problems. Older drinkers may also be less likely to cause public disturbances resulting in legal problems³⁶.

Clinicians may be reluctant to enquire about alcohol use out of embarrassment or because the patient doesn't fit the stereotype of an alcoholic. They may also fail to diagnose alcohol problems because symptoms of alcohol misuse may be similar to symptoms of ageing such as cognitive difficulties³⁷. Adams *et al.* screened patients 65+ seen in the emergency department for alcoholism. Using their criteria of either CAGE-positive or self-reported drinking problems and alcohol use within the past year, they found the current prevalence of alcohol abuse was 14%, with a high prevalence (22%) among those presenting with gastrointestinal problems. Physicians, however, detected only 21% of current alcohol abusers³⁸. In a study from primary care, only 41.6% of older patients who screened positive for alcoholism had a diagnosis of alcoholism recorded in their medical record³⁰. In a study where all new admissions to the medical service were screened for alcoholism using the CAGE and the Short Michigan Alcohol Screening Test (SMAST)³⁹, the prevalence of alcoholism was 27% in patients under 60 and 21% among patients aged 60+. These age differences were not significant. However, 60% of screen-positive younger patients were identified as having alcoholism by their house officers compared to only 37% of those aged 60+. Older patients with alcoholism were less likely to be diagnosed if they were White, female, or had completed high school. Even when diagnosed, older patients with alcoholism were less likely than younger patients to be referred for treatment⁴⁰.

Another identification problem is establishing what constitutes excessive drinking in older adults. Moos *et al.* compared several guidelines defining excessive drinking in a sample of 1291 older adults. Depending on the criteria used, 23 to 50% of the women and 29 to 45% of the men engaged in potentially unsafe drinking patterns. The number of drinks per week and per day was associated with alcohol use problems. The authors concluded that safe alcohol consumption levels should not necessarily be higher for men⁴¹. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Center for Substance Abuse Treatment Improvement protocol recommends that persons aged 65+ consume no more than one standard drink per day or seven drinks per week. Also, they should not consume more than four standard drinks on a given day⁷.

In a study of community-dwelling older adults from New Zealand, the prevalence of hazardous alcohol consumption was 9.9%, and the lifetime prevalence of DSM-IV alcohol dependence was 24.8%. None of the physicians identified by the participants, however, had

diagnosed alcohol problems in the past year, and only 4% reported a history of alcohol problems. The adults with hazardous patterns of alcohol use were twice as likely to be hospitalized but less likely to have seen their physician in the past year⁴².

FACTORS ASSOCIATED WITH ALCOHOL USE

In general, older adults who consume alcohol are more likely to be male, be married, and have higher income and years of education, have a good social life and have fewer health conditions^{13,20,43}. Older drinkers are also more likely to be current or former smokers¹³. Goodwin *et al.* found no differences in social support between elderly drinkers and non-drinkers, and no relationship between alcohol intake and emotional status. They also reported that those older adults who consumed alcohol performed better on cognitive functioning tests, but no relationship was found between past alcohol consumption and present cognitive performance²⁰.

A somewhat different profile emerges for older adults with drinking problems. Heavy drinking has been shown to be associated with male gender, younger age, being unmarried, fewer years of education, smoking, depressive symptoms, impairment in cognitive functioning and poor self-rated health^{25,30,32,44,45}. While some studies have shown an association between alcoholism and functional limitations^{32,45}, Mangion *et al.* found that men aged 65+ classified as alcohol abusers were more independently mobile than those not abusing alcohol, suggesting greater physical fitness²⁴. As another example of conflicting results, in a sample of Medicare beneficiaries, unhealthy drinking patterns were associated with higher education and income and better health status²⁵.

In a study of 209 patients selected from a geriatric inpatient ward in France, 54.5% of the patients had consumed alcohol in the past month and 52% consumed at least once per week. A total of 9% of the patients (3% of the women and 18% of the men) met criteria for DSM-IV alcohol dependence. In a comparison between those with and without alcohol dependence, those with the disorder were more likely to be younger, male, to consume alcohol at least one day a week, consume alcohol alone, to begin to drink in the morning, to have more drinking days per week, to more often consume >5 drinks on one occasion, be treated with benzodiazepines, and be dependent on nicotine⁴⁶.

In a study of adults aged 70–75 in Italy, higher self-reported alcohol consumption was associated with: male gender; better mood, daily function and somatic health; not living alone and being married; while CAGE-detected alcoholism was associated with male gender, poorer cognitive function and income dissatisfaction. There was not much overlap between the groups⁴⁷. Mirand and Welte studied the relationship between health-oriented lifestyle and heavy drinking among older adults in Erie County, New York, and reported that the prevalence of heavy drinking was 6%. Heavy drinking was positively associated with being male, having suburban residency and currently smoking, and negatively associated with socioeconomic status, rural residency and degree of health orientation. Age and level of active lifestyle were not related to drinking⁴⁸.

Changes in alcohol use have also been studied. Moos *et al.* followed a cohort of adults aged 55–65 for 10 years and found overall that health-related problems increased and alcohol consumption and drinking problems declined over the follow-up interval. Medical conditions, physical symptoms, medication use and acute health events predicted a higher likelihood of abstinence and less frequent and lower alcohol consumption. Increased health problems predicted

reduced alcohol consumption but more drinking problems⁴⁹. Perreira and Sloan examined the relationship between the experience of life events and changes in alcohol consumption using four waves of the Health and Retirement Study. Alcohol consumption did not change for the majority of older adults (68%) over the six years. Hospitalization and onset of a chronic illness were associated with a decrease in consumption, while widowhood was associated with a short-term increase in drinking. Onset of retirement was associated with increased drinking. Getting married or divorced was associated with both increases and decreases in drinking⁵⁰.

ONSET OF PROBLEM DRINKING

In research focusing on the age of onset among elderly problem drinkers, two groups have emerged. There are older adults who have had problems with alcohol for most of their adult life and have survived to old age, generally referred to as 'early-onset' problem drinkers. There are also older adults who may or may not have consumed alcohol earlier in their lives, but who do not become problem drinkers until later in their adult life, a group referred to as 'late-onset' problem drinkers.

Atkinson *et al.* studied the age of onset among 132 men aged 60+ admitted into an outpatient treatment programme and found onset after age 60 in 15% of the sample and in 29% of the sample aged 65+. Later-onset alcohol problems were milder, associated with less family alcoholism and associated with greater psychological stability. Treatment variables were better predictors of outcome than age of onset⁵¹. In a similar sample of patients admitted to an alcoholism treatment programme, late-onset alcoholism was present in 39% of the men and 46% of the women. Few differences were noted between the two groups⁵².

Symptom presentation may differ by age of onset. In a study of 268 patients on an alcohol detoxification ward in Germany, alcohol dependence was diagnosed in 94.1% of those with an earlier onset but in only 62.2% among those with a later onset. Those with late onset were less likely than those with a younger onset to report a strong desire to drink alcohol, impaired capacity to control drinking, and preoccupation with drinking⁵³.

Brennan and Moos reported that late-middle-aged problem drinkers reported more negative life events, chronic stressors and social resource deficits than did non-problem drinkers. Among problem drinkers, those with late onset consumed less alcohol, reported fewer alcohol-related problems, functioned better and had fewer stressors than early-onset problem drinkers^{54,55}.

Age of onset may differ by gender. Brennan *et al.* found that women with drinking problems consumed less alcohol, had fewer drinking problems, and reported more recent onset of drinking problems than did male problem drinkers. The female problem drinkers also used more psychoactive medications, were more depressed and were less likely to seek treatment⁵⁶. Osterling and Berglund examined gender differences in age of onset among older first-time admitted alcoholics in Sweden across two time periods. During the period 1978–1982, they found that age of onset of problem drinking occurred significantly later in females compared to males. One decade later, during the period 1988–1992, sex ratios indicated a significant convergence in age of onset for female patients to that of males⁵⁷.

Moos *et al.* followed a cohort of problem drinkers aged 55–65 for one year. Remitted problem drinkers were those who did not experience any problems in the follow-up period. Late-onset drinkers were

more likely to remit during the year. At baseline, the to-be remitted problem drinkers consumed less alcohol, reported fewer drinking problems, had friends who approved less of their drinking, and were likely to seek help from a mental health practitioner⁵⁸.

OUTCOMES ASSOCIATED WITH ALCOHOL USE

The relationship between alcohol use and physical health is not straightforward. In cross-sectional studies, patients with alcoholism have an increased likelihood of some chronic diseases and decreased likelihood of others. Callahan and Tierney reported that patients with alcoholism were less likely to have a diagnosis of hypertension, arthritis or diabetes, and more likely to have obstructive lung diseases, injuries and gout³⁰. Hurt *et al.* described 216 older inpatients treated for alcoholism. The frequency of serious medical disorders among this group was higher than what would be expected for the overall population aged 65+. Hypertension was less frequent among these patients, but alcoholic liver disease, chronic obstructive pulmonary disease, peptic ulcer disease and psoriasis were more prevalent among the alcoholic group compared to the population at large. The frequencies of ischaemic heart disease, cerebrovascular disease and diabetes were about the same as what would be found in an older population⁵².

In longitudinal studies, moderate alcohol use in older adults has been shown to decrease the risk of stroke⁵⁹, heart failure^{60–62} and incident diabetes⁶³. It is not clear whether there is a true protective effect of alcohol or whether older adults who consume alcohol are already in better health. In the Framingham Study, alcohol consumption was not associated with stroke across all age groups, but alcohol intake among those aged 60–69 was associated with a lower risk of stroke. In addition, former drinking of 12 or more grams of alcohol per day was associated with 2.4-times higher risk of stroke among men⁶⁴. Drinking in excess has been associated with adverse health outcomes as well as protective effects. For example, heavy consumption of alcohol may be associated with an increased risk of stroke⁵⁹. In the Cardiovascular Health Study, however, consumption of 14 or more drinks per week was associated with a reduced risk of coronary heart disease⁶⁵. In the NESARC, women aged 65 or older who consumed alcohol had better self-perceived health, improved cardiovascular health and lower rates of hospitalizations. No associations for men were significant⁶⁶. Older adults, particularly those with pre-existing drinking problems may use alcohol to manage pain. Older men with drinking problems who used alcohol to manage pain had more health problems and injuries while female problem drinkers who used alcohol for pain had more drinking problems three years later⁶⁷.

Studies have also shown that alcohol problems in older adults are associated with psychiatric co-morbidity. Saunders *et al.* reported that 44% of men aged 65 or older with a history of heavy drinking were given current psychiatric diagnoses, compared with 12% of the men without a history of heavy drinking. The most common diagnoses were depression and dementia. The association between drinking history and current psychiatric morbidity was not explained by current drinking habits⁶⁸. The prevalence of alcohol use is three- to four-times greater among depressed older adults compared to those who are non-depressed. Among older adults with major depression, the prevalence of an alcohol use disorder is 15–30%. Depression can put the older adult at risk for alcohol problems, and alcohol use disorders can be a risk factor for late-life depression⁶⁹.

Increased hospitalizations have also been linked with alcohol use in the elderly. Callahan and Tierney reported that older patients with

alcoholism were more likely to be hospitalized within the year following the interview, compared to those without alcoholism (21.5% vs. 16.9%)³⁰. Using 1989 hospital claims data, the prevalence of alcohol-related hospitalizations among persons age 65+ in the USA was 54.7 per 10000 population for men and 14.8 per 10000 for women, a proportion similar to that seen for myocardial infarction⁷⁰.

The relationship between alcohol use and mortality is also complex. In a study from Finland, drinking had an independent protective effect on 10-year mortality among older adults. Mortality was lowest among frequent and occasional drinkers, second lowest among abstainers, and highest among ex-drinkers. In analyses controlling for variables such as chronic disease and smoking, frequent drinkers had a reduced risk compared with abstainers⁷¹. Paganini-Hill *et al.* studied changes in alcohol intake over 23 years in a sample of residents of a California retirement community. Those who drank 2+ drinks per day had a 15% reduced risk of death. Stable drinkers also had a reduced risk compared to non-stable drinkers. Women who quit drinking had an increased risk of death, suggesting persons who quit may do so for reasons that affect mortality⁷². In a community-based longitudinal Australian study of women 70–75 years old at baseline, women who did not consume alcohol or drank rarely were more likely to die compared to women in the low-intake category⁷³.

In contrast to moderate drinking, alcoholism has been linked to increased mortality. In a sample of elderly male veterans from primary care clinics at Veteran Administration medical centres, where the prevalence of alcohol use can be higher than in the general older population, 48% of the veterans reported drinking in the past year. Half of the drinkers and non-drinkers screened positive for problem drinking. Overall health status and survival were better in drinkers compared to non-drinkers, but worse in those who screened positive for problem drinking compared to those who screened negative⁷⁴. Callahan and Tierney found that patients with alcoholism were more likely to die within two years than those without evidence of alcoholism; 10.6% compared to 6.3%, controlling for age, gender, race, education and smoking history³⁰. Hurt *et al.* followed a sample of inpatients treated for alcoholism for an average of 5.2 years. A total of 32% had died by follow-up. Of those who died, 47% of the deaths could be attributed to the patient's alcoholism⁵². In the Canadian Study of Health and Aging, alcohol abuse was associated with short-term mortality⁷⁵. In a retrospective case control study of 1735 older people that died of falls, motor vehicle crashes or death by suicide and 13381 controls, having 12+ drinks in the past year was associated with an increased risk of fatal injury⁷⁶. Finally, at-risk drinking was associated with increased 20-year mortality in men when 'at-risk' was determined by the amount of alcohol consumed in the presence of relevant co-morbidities (e.g. an illness or medication use)⁷⁷.

Heavy drinking has also been shown to be associated with impairments in physical function. In a study of 161 primary care patients aged 60+, 16% of the patients consumed 8–14 drinks, and 22% had more than 14 drinks per week. Forty two percent of the sample (33% of the men and 51% of the women) reported binge drinking (four or more drinks on one occasion for men and three or more for women) in the past year. Compared to those having fewer than 7 drinks per week, those consuming more than 14 drinks per week were more likely to have impairments in instrumental activities of daily living (IADLs) and advanced activities of daily living (ADLs). Those having 7–14 drinks per week were more likely to have impairments in IADLs but not ADLs. Binge drinkers were more likely to have impairments in IADLs⁷⁸.

Other studies have reported different findings. Using data from the Health and Retirement Study in the United States and the English

Longitudinal Study of Ageing, samples of adults aged 65+ followed from four to five years, Lang *et al.* reported that 10.8% of US men, 28.6% of English men, 2.9% of US women and 10.3% of English women drank above USA recommended limits for this age group. Functional outcomes did not differ between those who drank >0–1 drink per day and those who drank >1–2 drinks per day⁷⁹. Karlamangla *et al.* found that light to moderate drinking was associated with a decreased risk of incident disability compared with abstinence. Disability risk decreased with light to moderate drinking among men and women with good or better self-reported health, but not among those with fair or worse self-rated health⁸⁰. La Croix *et al.* found, by following three of the EPESE cohorts for four years, that older adults who did not consume alcohol had an increased risk of losing mobility, defined as the ability to climb up and down stairs and walk half a mile, compared to those with small to moderate amounts of alcohol consumption⁸¹.

The relationship between alcohol consumption and cognitive performance has received considerable attention in this population. In the Honolulu-Asia Aging Study, non-drinkers and heavy drinkers had poorer scores on cognitive functioning tests compared to those who consumed 1–60 ounces (28.4–1701 g) of alcohol per month⁸². A protective effect has also been reported from longitudinal studies. In the Cardiovascular Health Study, older adults who consumed one to six drinks weekly had a lower risk of incident dementia compared to those who abstained⁸³. In a study of adults aged 75+ from Sweden, light to moderate drinking was associated with a decreased risk of six-year incident dementia and Alzheimer's disease compared with non-drinking⁸⁴. In a two-year study of older adults in China, light to moderate drinking was associated with a lower risk of dementia compared to non-drinking, while excessive drinking was associated with a higher risk of dementia⁸⁵. In the Canadian Study of Health and Aging, the occurrence of all types of dementia except probable Alzheimer's disease was higher in those older adults with definite or questionable alcohol abuse⁷⁵. Other studies have not found an association between drinking and incident cognitive impairment⁸⁶. A study from China reported among older adults with mild cognitive impairment that those with light to moderate alcohol consumption had a decreased risk of transition to dementia over two years when compared to abstainers or heavy drinkers. Heavy drinkers with mild cognitive impairment had a higher risk compared to those with light to moderate use and abstainers⁸⁷. Researchers from the Italian Longitudinal Study on Aging reported that older adults with mild cognitive impairment who were moderate drinkers had a lower rate of progression to dementia than abstainers. Older adults with mild cognitive impairment and higher levels of drinking, however, did not have a higher rate of progression to dementia compared to abstainers. Incidence of mild cognitive impairment was not associated with any level of drinking compared to abstainers⁸⁸.

In the NESARC, only 3.54% of current drinkers aged 65+ with an alcohol use disorder in the past year and 1% of older adults classified as heavy drinkers received any alcohol treatment in the past year¹³. Long-term remission among older untreated problem drinkers followed for 10 years was predicted by being female, having a recent onset of drinking problems, having fewer and less severe drinking problems, having friends who approved less of drinking, and drinking less and less frequently at baseline. Long-term remitted problem drinkers attained levels of functioning and life context similar to those of lifetime non-problem drinkers, but remitted problem drinkers continued to report more incipient drinking problems, depressive symptoms, health and financial stressors, psychoactive

medication use, less social support and dependence on avoidance coping strategies compared to lifetime non-problem drinkers⁸⁹.

SUMMARY

Alcohol use, including drinking in excess, among older adults is prevalent, particularly among males. Because of interactions with chronic disease and prescribed medications, the use of alcohol among older adults is an important health concern. Given the higher prevalence of alcohol use disorders among middle-aged adults, the numbers of older adults with alcohol-related problems is expected to increase in future generations. Screening and questioning for alcohol problems should be routine. Drinking within recommended guidelines could potentially decrease the proportion of alcohol-related illness, hospitalizations and mortality seen in this population.

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Drug Misuse in the Elderly

Martin M. Schmidt and Mohammed T. Abou-Saleh

Division of Mental Health, St George's University of London, London, UK

Substance misuse occurs mainly in young adults, with most research focusing on this group. Several factors, however, suggest a growing trend towards substance misuse in the elderly. Increasing age is associated with chronic illnesses and multiple medications, with the attendant risk of dependence. There is also evidence to support a growing trend to increased alcohol consumption in the over-65s, while a generation of lifetime drug users are now entering old age¹. Along with the increase in ageing of European and North American populations, the number of older adults requiring treatment for substance misuse is predicted to double between 2001 and 2020². The need for age-appropriate treatment interventions has never been greater.

USE, ABUSE AND HARMFUL USE

When considering drug use among the elderly it is helpful to consider substances of misuse in three broad categories: medications, both prescribed and non-prescribed; socially sanctioned psychoactive substances; and illicit substances. Self-evidently this will differ between countries due to religious, cultural and legal differences³. Some of the consequences of drug misuse are determined by the status of the drug rather than its physical effects. Difficulties in obtaining a drug supply and financing that use may account for as much harm as the physical effects of the drugs themselves in younger adults. Among the elderly, drugs from the medicines category are over-represented in cases of misuse when compared to other age groups⁴. This reflects the increased access to medicines among this group, allied to the physical and social barriers that make accessing other drugs harder for this group. This chapter will focus on drug misusers who display 'harmful use'. This is defined as 'a pattern of psychoactive drug use that causes damage to health, either mental or physical'⁵. This definition allows consideration of individuals suffering damage as a result of drug use, irrespective of the nature or the source of the drug of abuse. It excludes cases where omission of a psychoactive medication may be harmful, e.g. in cases of underuse of antidepressants.

Harmful use may be related to a single episode of drug misuse resulting in harm, such as a fall while intoxicated. More often it is a chronic condition associated with a dependence syndrome. 'Dependence syndrome' describes the cluster of cognitive, behavioural and physical phenomena that are observed when use of a substance becomes a greater priority for the individual than other previously more valued activities. It is characterized by:

- a compulsion to take the substance;
- difficulties in controlling the substance use in terms of timing and levels of use;
- withdrawal symptoms on discontinuation of the substance, with relief of these symptoms on reinstatement of use;
- tolerance or neuroadaptation, where increasing amounts of the substance are required to achieve effects previously possible at lower doses;
- progressive neglect of alternative activities, due to prioritization of drug-related behaviour;
- persistent use of the substance in spite of evidence of harmful consequences.

Presence of three or more of the above features simultaneously in the past year supports a definite diagnosis of dependence syndrome, using World Health Organization criteria⁶.

PHARMACOKINETICS

Ageing is associated with a series of physiological changes that significantly alter the fraction of an ingested drug available for a psychoactive effect. Drug absorption shows little variation with age, despite changes in gastrointestinal motility and acidity, reduced absorption surface and slowed gastric emptying. However, once absorbed, the volume of distribution in an elderly subject is likely to have changed.

Ageing results in an increase in percentage body fat and a fall in total body water. Hydrophilic drugs, such as alcohol, are distributed in body water, such that with increasing age the volume of distribution falls and the peak concentration for a given dose may rise by 20%⁷, resulting in lower levels of intake giving the same intoxicant effect. Conversely, lipophilic drugs, such as benzodiazepines and other psychotropics, that are stored in fatty tissue will remain in the body for longer but at lower peak concentrations. A fall in plasma albumin in old age results in increased bioavailability of protein-bound drugs, such as warfarin and diazepam.

Drug elimination occurs primarily through direct excretion or metabolism. Both routes are reduced in the elderly. Glomerular filtration rates fall steadily in old age, leading to the accumulation of renally excreted drugs. This may be compounded by renal damage due to drug misuse, e.g. analgesic abuse⁸. Hepatic metabolism is impaired due to a loss of liver mass and a reduced blood flow, which may also be compounded by toxic drug effects. The efficiency

of microsomal oxidation also falls with age, leading to reduced drug excretion of hepatically metabolized drugs⁹. The combination of these effects may greatly alter pharmacokinetics in the elderly. For example the half-life of diazepam in the very elderly has been shown to be over 3 days, compared with 20h in a younger subject¹⁰.

Multiple drug use complicates the pharmacokinetics of a substance, due to competition for binding sites and metabolic pathways. Polypharmacy may have different effects, depending on whether it is acute or chronic. Alcohol will inhibit microsomal enzyme activity in acute use, while prolonged administration will induce the same enzymes. Hence, alcohol will acutely raise concentrations of benzodiazepines, while lowering them if used chronically¹¹.

Pharmacodynamics also alter in the elderly. Sensitivity to drugs, particularly those acting on the central nervous system, tends to increase, while drug receptor populations also change with increased age. The particular effects of age-related brain changes on the reward effects of abused substances is currently difficult to predict¹².

As a consequence of all these variables, the extrapolation of a drug's effects in the elderly, based on observation in younger adults, is foolhardy.

CONCLUSION

The terms 'old age' and 'substance misuse' are both terms that have a wide range of meaning to different readers. The current literature is based primarily upon chronological age banding of individuals, as opposed to banding by overall health, possibly a more valid measure. Definitions of substance misuse are similarly varied. Often in transgenerational studies, definitions of caseness are set at a level to prevent false-positive reports for younger adults. In older age groups, where less of a substance may have a greater effect, there is the possibility of missing cases if such standards are applied.

PREVALENCE AND CORRELATES

The elderly may display harmful use of any psychoactive substance. However, access to a potential substance of abuse is key to determining what an individual may misuse. Alcohol is obtainable with ease in most industrialized nations and is a socially acceptable and accessible psychoactive drug. Sedatives, hypnotics and analgesics are easily accessible through prescription and consequently, along with alcohol, are responsible for the majority of cases of harmful use. Over-the-counter medication is also easily obtained and may be misused. Illicit drugs are usually only available in potentially dangerous environments from individuals who may pose a significant risk to vulnerable older adults. Illicit drug use is therefore not commonly observed in the elderly, but numbers are on the rise¹³. Shah and Fountain identified the following as factors associated with illicit drug use in the elderly: male gender, 'young old' age group, belonging to the post-war cohort, African American ethnicity, prior convictions, diagnosis of mental illness or alcohol misuse, serious medical illness and past history of substance misuse with onset before age of 30¹⁴.

BENZODIAZEPINES

Benzodiazepines replaced barbiturates as the mainstay of pharmacological interventions in both anxiety and sleep disturbance. Benzodiazepines accumulate more readily in the elderly due to

changes in body composition, leading to a greater volume of distribution for lipophilic drugs¹⁰. Chronic use may contribute to toxic effects, including cognitive impairment, poor attention and anterograde amnesia, cerebellar signs such as ataxia, dysarthria, tremor, impaired coordination and drowsiness¹⁵. Increased falls and hip fractures are associated with benzodiazepine use in the elderly¹⁶ while withdrawal may be accompanied by rebound insomnia, agitation, convulsions and an acute confusional state. If benzodiazepines are required for the elderly then short-acting drugs (i.e. with half-life less than 24 hours) at the lowest effective dose may be used for a short duration¹⁷. There is no 'safe' period of use but tolerance and dependence levels increase with prolonged use¹⁸.

Prevalence of Benzodiazepine Use

Establishing levels of benzodiazepine among the elderly is problematic. National prescription audits can reflect trends in use but are unhelpful when considering particular population subgroups.

Following the publication of guidance for the appropriate use of benzodiazepines by the UK Committee on Safety of Medicines (CSM) in 1988¹⁹, prescribing of benzodiazepines has fallen dramatically. In England and Wales prescriptions have fallen by 32% from 1987 to 1996²⁰, while prescribing of benzodiazepines by general practitioners in England has fallen from 15.8 million prescriptions in 1992 to 12.7 million in 2002²¹. Of concern, however, is that 30% of prescriptions were for long-term treatment and 56% of prescriptions for the three most commonly prescribed benzodiazepines were issued to patients over the age of 65²¹. More recent trends for England show a relatively stable annual prescription rate of 10 million items for hypnotics; however, Z drugs (zopiclone, zolpidem, zaleplon) appear to be responsible for a larger proportion of prescriptions, rising from 33% in 2001 to 44% in 2004²².

A community follow-up study of 5000 over-65s in Liverpool²³ revealed that 10% were using benzodiazepines on first assessment and that of these some 70% were taking a benzodiazepine two years later. A further four-year follow-up revealed that 69% of these were still on benzodiazepines. Women were twice as likely to be taking a benzodiazepine as men at any stage in the study. In the USA, a study found 6.3% of a large sample of over-65s used a hypnotic, one third of these daily and nine tenths for at least a year²⁴. Five-year follow-up found 46.6% still using hypnotics, but with a switch away from barbiturates and longer-acting benzodiazepines towards short-acting ones²⁵.

Use of benzodiazepines in institutional samples has traditionally been higher and associated with female gender, greater age, bereavement and poor health²⁶. Chronic benzodiazepine use in older adults' nursing homes has been associated with depression, sleep disturbances and demand for medication²⁷. In the USA a study found that one quarter of nursing home residents were prescribed a benzodiazepine and nearly 10% of all residents had chronic benzodiazepine use²⁷. Studies from other countries reveal similarly high levels of benzodiazepine use among institutionalized older adults²⁸.

The level of morbidity among institutional residents is likely to be higher than community-dwelling elders. While chronic pain may require treatment with dependence-inducing medication, there are few indications for long-term benzodiazepine use. It has been argued that the regular use of benzodiazepines in institutions is a form of behavioural control, used more for the benefit of staff and others than these users. In many cases, the individual may be incapable of giving valid consent to taking such medication. The use of medication in

such circumstances may be considered benzodiazepine misuse by some and as elder abuse by others²⁹.

Correlates

Psychiatric morbidity

Significantly high rates of psychiatric disorder have been described among elderly benzodiazepine users³⁰. Among elders using short-acting benzodiazepines as hypnotics, one third reach caseness for depression, while a further third have a diagnosable anxiety disorder. Among users of anxiolytic benzodiazepines, half are depressed and one fifth are anxious in spite of treatment. As with alcohol misusers, one third of elders requiring inpatient treatment for benzodiazepine misuse are of late onset, while two thirds have graduated from misusing benzodiazepines or other drugs while younger³¹. The incidence of co-morbid alcohol abuse has not been consistently shown to be significantly greater among benzodiazepine misusers³¹. However, more recent research suggests that a prior history of alcoholism may predispose to later benzodiazepine misuse in the elderly³². An all-age study found that DSM-III-R Axis I co-morbidity existed in all cases of a sample of benzodiazepine-dependent users in Spain³³. The commonest diagnoses were insomnia, anxiety disorders and affective disorders. Obsessive-compulsive, histrionic and dependent personality disorders were found in half of the cases and physical problems in one third of the cases.

Gender and age

Benzodiazepine use is over-represented among women of all ages. The likelihood of use of a benzodiazepine increases with age. There is little evidence that this gender divide narrows on reaching old age. Legislative approaches and prescribing guidelines have made some inroads into the over-representation of prescribing to the elderly³⁴. Increasing public awareness of the side effects of benzodiazepines and an increase in advocacy services for the elderly are likely to have a similar effect.

OTHER PRESCRIBED AND OVER-THE-COUNTER MEDICATION

The elderly routinely receive a wide variety of medications, the majority of which may be misused. One quarter of prescription drugs sold in the United States are used by the elderly often for conditions such as chronic pain, insomnia and anxiety³⁵. Ten per cent of over-64s are on prescribed analgesics at any one time, with at least an equal number using over-the-counter medication. Edwards and Salib³⁶ found 3% of a community sample of over-65s to have been using mild opiate analgesics for a period of at least a year; 40% of this group were deemed to fulfil the criteria for dependence. In addition to the dependence caused by these drugs, physical harm may also result, e.g. nephropathy may be caused by the use of paracetamol, salicylates and pyrazole derivatives, while renal impairment occurs with non-steroidal anti-inflammatory drug use³⁷. Chronic nephropathy may also be caused by the excessive ingestion of analgesic mixtures combining two or more antipyretic analgesics, along with codeine or caffeine (both independently capable of causing addiction). Such acute and chronic effects are more likely among the elderly, where relative drug levels are higher and less biological reserve exists. Similar physical complications may arise from the

misuse of other medications, the commonest being laxatives and cough mixtures.

ILLCIT DRUG MISUSE

Little is known about levels of illicit drug use among the over-65s, although the general perception is that it has been less of a problem than the misuse of prescribed medication. Overall the prevalence of illicit drug use in the elderly is low compared to younger people¹⁴.

In the Epidemiological Catchment Area Study (ECA), only 0.1% of elders met the criteria for drug abuse for an illicit substance in the previous month. Lifetime prevalence was 1.6% for over-65s³⁸. Figures from the 2005 and 2006 National Survey on Drug Use and Health found similar low rates in the elderly along with higher rates in the middle aged, lending further evidence to the suggestion that prevalence rates may rise in the elderly as the younger cohort ages³⁹. Current predictions are that the number of older adults requiring substance abuse treatment in the USA will increase from 1.2 million in 2000 to 4.4 million in 2020¹³.

The 2007/8 British crime survey reported the following in 55–59 year olds: 17.9% had used illicit drugs at some point in the past, 1.7% had used in the last year, and 0.9%, in the last month⁴⁰. No figures were available for older age groups because respondents over 59 were not asked about illicit drug use. The decision to omit drug use questions in this age group was based on previous surveys which showed a lifetime prevalence of less than 1% for people aged 60 and over¹⁴.

In the UK, few cases of illicit drug use among the over-65s have found their way into the literature; one exception is a series of seven elderly reported to have initiated injecting heroin in later life. They attributed their behaviour to a combination of loneliness and depression⁴¹.

In the USA, in a study of a Veterans Administration old age psychiatry inpatient facility, 3% of the patients were found to have a primary drug misuse disorder involving prescribed medication, while 1% were addicted to illicit substances³². Also in the USA, attendance at methadone maintenance clinics by the elderly is reported to be rising, although over-60s still form 2% of those attending⁴. Similarly, a number of elders are reported to continue their use of cannabis into late life⁴². Anecdotal evidence also points to some individuals initiating the use of cannabis in later life in a search for its reputed therapeutic benefit in conditions such as multiple sclerosis.

On balance, it appears that illicit drug use is less of a problem in the elderly than the abuse of legally sanctioned drugs.

POLYSUBSTANCE MISUSE

The elderly have access to a variety of drugs of misuse. In many cases they may misuse one drug without misusing others. This is often the case with prescribed medication, where one medication is overused while compliance with the prescription is maintained for the others. Where non-prescribed substances become involved, the possibility of abuse of more than one substance is elevated. Finlayson and Davis³⁰ found 15% of over-65s requiring inpatient detoxification from alcohol were also dependent upon a second substance, usually a hypnotic, anxiolytic or analgesic. The phenomenon of cross-tolerance must also be considered. Psychoactive substances may have a cumulative effect, due to either a shared outcome effect or to different drugs acting as interchangeable substitutes for one another (cross-tolerance). Cross-tolerance exists within each class

of drug, such that the clinician should always consider the total benzodiazepine or opioid dose, using class-specific equivalence charts⁴³. Cross-tolerance for some drugs may also occur outside of the class, most notably for alcohol and benzodiazepines. While this phenomenon is widely exploited for detoxification, failure to consider the clinical possibility may lead to overlooking cases of dependence.

CONCLUSION

Alcohol and prescribed medication remain the most prevalent substances misused by the elderly. There is little clear evidence of great changes in individuals' addictive behaviour patterns with increasing age. However, a convincing body of evidence points towards a relative and absolute increase in older adults requiring specialist treatment for illicit drug use in the future.

TREATMENT

Treatment of substance misuse is a multistage process involving the integrated use of physical, psychological and social interventions. These interventions should, where possible, run concurrently as opposed to consecutively and must be provided in a form that is acceptable to the individual and sensitive to the specific needs of the elderly⁴⁴. Among this client group, individuals rarely present complaining directly of a substance misuse disorder but may present with associated physical problems. The first step of treatment is the identification of cases. This requires clinical observation allied to sensitive yet persistent enquiry. The routine use of standardized screening tools may help to focus clinical impression more accurately. Once potential candidates for treatment have been identified, their attitude towards their substance misuse requires examination. Exploration of the risks and a discussion of potential avenues for change may help to establish or reinforce the motivation to change. Drugs that cause significant physical dependence may necessitate detoxification regimens, while co-morbid conditions such as depression that perpetuate the disorder need to be adequately treated. Social issues, such as housing and a social network that is comprised mainly of substance misusers, may perpetuate the problem and need to be examined for opportunities to change. The individual requires psychological rehabilitation to address the issues that may have contributed to the uncontrolled use of substances and to provide future coping strategies to prevent a relapse into substance misuse.

DETECTION

Self-presentation by elders may be limited by a number of factors^{45,46}. Practical issues, such as accessibility of treatment centres to disabled individuals, large-print information sources for the visually impaired and the availability of domiciliary treatment, are fundamental. Elders may not realize that they are ill, or may not realize that the medical profession identifies substance misuse as an illness and will offer help. Traditional forms of service promotion may fail to reach the elderly, while a service staffed by young professionals may seem intimidating or inappropriate for someone much older, particularly if his/her substance misuse is associated with a high degree of shame. If self-presentation is unlikely, then the number of professional caregiver contacts that the elderly have provides a further opportunity for education about the problem and

potential sources of help. This resource appears underdeveloped at present, with a need for better training for carers in identification of at-risk individuals and in appropriate actions once misusers are identified⁴⁷.

Currently, evidence suggests that carers are often unaware of sources of help and frequently are in collusion with alcohol misuse, citing reasons such as the elder 'has not got long to live' or that 'it's his only pleasure'⁴⁷. Studies have found that many agencies providing care for the elderly have no written policy to guide their employees when encountering a client with an alcohol problem. Greenwood⁴⁸ argues that substance misusers, and the elderly in particular, suffer as the result of stigmatization, as their disorder is perceived as self-inflicted. This stigma may be reflected in a clinician's reluctance to become involved by acknowledging the problem. For other carers, their own previous experiences with elderly substance misusers, both professional and personal, may lead to attempts to justify the behaviour, resulting in a similar loss of objectivity.

BENZODIAZEPINE USE DETECTION

Prevention and early recognition form the basis of management of benzodiazepine misuse. Appropriate prescribing of sedatives for time-limited periods should be accompanied with vigilance for drug-seeking behaviour. Such behaviour includes early requests for repeat prescriptions or requests for increased doses. The elderly may also receive medication from multiple sources, particularly where they are under the care of prescribing hospital specialists as well as their primary prescribers. Careful exchange of clinical information is vital in such settings. For those abusing over-the-counter medication, chance presentation or the intervention of a pharmacist presents the best hope of detection. The Severity of Dependence Scale has been validated as a screening tool for benzodiazepine dependence⁴⁹. It consists of five questions, referring to the past month:

1. Did you think your use of tranquillizers was out of control?
2. Did the prospect of missing a dose make you anxious or worried?
3. Did you worry about your use of tranquillizers?
4. Did you wish you could stop?
5. How difficult would you find it to stop or go without your tranquillizers?

Each of the items is scored on a four-point scale (Items 1–4: 0 = never/almost never, 1 = sometimes, 2 = often, 3 = always/nearly always. Item 5: 0 = not difficult, 1 = quite difficult, 2 = very difficult, 3 = impossible). A total score of 6 or more indicates problematic use, with a specificity of 94.2% and sensitivity of 97.9%⁴⁹.

Urine screening provides a reliable means of establishing the presence or absence of drug metabolites, but its clinical utility can be limited by the unacceptability of the test to many who may be offended by the suggestion that they have a substance misuse problem. In addition, urine screening is usually qualitative rather than quantitative. For those abusing a prescribed drug, the mere presence or absence of the drug is clinically uninformative. With these considerations in mind, the need for dependence-inducing drug prescriptions should be regularly reviewed and co-morbid contributory conditions, such as depression, should be actively treated. Changes in legislation on prescribing practice may reduce the opportunity for drug misuse³⁴.

INITIATING TREATMENT

There is no published data about the level of uptake of offers of help once elders abusing substances are identified. However, elders do achieve equivalent or better results than younger adults when they do enter treatment². Motivational interviewing and education as to the risks of alcohol use, along with the benefits of even a small reduction in levels of alcohol intake, may persuade some elders to change. Unfortunately, the pessimistic attitudes held by many professionals and carers towards the likelihood of successful resolution of the problem are frequently also held by the individual too. A fatalistic resignation to a life of substance misuse is often reported, particularly by long-term users, while more recent-onset users may express greater motivation for treatment⁵⁰.

Once long-term use of benzodiazepines is established, dose reduction can be difficult to achieve. Withdrawal insomnia and rebound anxiety make patient motivation difficult to achieve. Where abstinence is desired, a conversion to a longer-acting benzodiazepine and a gradual reduction in dosage over the course of months is advisable⁴³. Rapid detoxification is associated with breakthrough withdrawal symptoms and may be complicated by convulsions. If a rapid withdrawal is necessary, it is best conducted in an inpatient setting if severe dependency is suspected. As with alcohol, the withdrawal period for the elderly is more likely to be complicated by confusion than in younger adults. Longer term prescribing of benzodiazepines should adhere to the following general principles: clear indication of benzodiazepine dependence, clear intermediate treatment goals, regular review and methods to prevent diversion⁵¹.

Psychological techniques, such as relaxation training and educative initiatives in the areas of sleep hygiene and correct medication use, may also prove valuable. Cormack *et al.*⁵² demonstrated that writing to benzodiazepine users in primary care urging them to reduce their medication use resulted in a fall in total use by one third over the next six months. Treatment of other forms of drug misuse in the elderly is under-researched. Misuse of analgesics may require formal detoxification if opioids are involved or physical dependence has developed. More often the patient requires information to allow him/her to make an informed choice about drug use and an alternative form of treatment for his/her condition. Still less information is available on the treatment of illicit drug use in the elderly although several key publications argue for age-appropriate services to be formed^{2,44}. These services should pay particular attention to co-morbid health problems and should provide basic-level medical services². Severe or complex health problems should be identified and referred to appropriate specialist services.

PSYCHOLOGICAL INTERVENTIONS

Once a patient is detoxified, rehabilitation is necessary to address the issues behind his/her substance use and to foster coping strategies for the future. Few studies have examined the particular needs of the elderly in a rehabilitation setting and have mostly focused on alcohol. Janik and Dunham report on comparative outcomes for over 3 000 over-60-year-olds and younger entrants into alcohol treatment programmes⁵³. Outcomes after six months showed no differences between the groups.

Psychological programmes designed specifically with the elderly in mind may be more appropriate for consideration. Some success has been claimed for models encouraging the development of social networks with self-management skills⁵⁴. Kofoed *et al.*⁵⁵, in a small

study, reported that retention in outpatient treatment of older adults was greater in an age-specific treatment group that focused on socialization and minimal confrontation (a mainstay of many programmes), compared with older patients in a mixed-age treatment group. At one-year follow-up the effect was lost.

Variations of the Alcoholics Anonymous 12-step model tailored to the needs of elders have been reported in the USA, with varying degrees of success⁵⁶. Models low on confrontation, traditionally regarded as fundamental to overcoming denial on the part of the patient, appear to be supported by the work of Kashner *et al.*⁵⁷, who found that one-year follow-up of elders in a confrontational programme revealed half the levels of abstinence as compared with a group in a programme where self-esteem, tolerance and peer relationships were promoted.

Behavioural approaches, including cue identification and avoidance, have also been reported to be of clinical benefit⁵⁴. A programme focusing on cognitive techniques, such as cognitive restructuring, assertion training and self-monitoring of drinking, resulted in 75% of those completing the programme sticking to their treatment goals at one-year follow-up.

The evidence suggests that a range of therapeutic techniques may be beneficial for the elderly and that local provision may depend upon the skills available to the treating agency. It is suggested that even if an elders-only therapeutic programme is not available, a better therapeutic outcome may occur from a more homogeneous group, where the opportunity for identification and vicarious learning is enhanced.

Even fewer age-specific studies are available to guide the clinician in the provision of aftercare to the elderly non-alcoholic drug user. An avoidance of drugs that have a dependence potential is advisable if practical. Adequate rehabilitation and continuing support of the individual are indicated. This may be provided through generic old age psychiatry services or through specialist drug services, depending upon which service appears best able to cater for the specific needs of the user. The choice of service provider should reflect the lifestyle of the patient, as opposed to being a decision based solely on chronological as opposed to biological age. Further services may also be available in the form of mutual support groups similar to those available for alcohol. The adoption of a cognitively based programme low on confrontation and designed to foster strong social support appears optimal, as shown in work in the field of alcohol.

CONCLUSION

Substance misuse and old age psychiatry have long been unpopular choices for specialization. Both fields are known for providing challenging patients with differing priorities to those of the clinician. Research in either field is hampered by the difficulty in obtaining reliable clinical data on conditions for which few empirical measures exist. The field of old age substance misuse has suffered to some extent in clinical practice, where patients do not fit neatly into either service and are welcomed by neither. It is, however, clear that there exists a significant morbidity due to drug use in the elderly. The problem may be iatrogenic and autogenic in origin. Increased life expectancy and the cohort effect of generations of recreational drug users reaching old age are likely to intensify the problem. Adequate research to identify at-risk individuals and the provision of appropriate and accessible treatment services for the elderly drug misuser remain the major challenges to health care providers.

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Learning and Behavioural Studies

Old Age and Learning Disability

Oyepeju Raji and Asim Naeem

St George's University of London, London, UK

INTRODUCTION

In England and Wales approximately 2.5% of the population have learning disabilities, of which 1.2 million are at the mild end of the spectrum¹. While the mortality rate for people with learning disabilities is higher compared with the general population², improved standards of care, more positive lifestyles and attitudes to treatment for serious illnesses have contributed to increased longevity. Mean life expectancy is estimated to be 74 years, 67 years and 58 years for those with mild, moderate and severe learning disabilities, respectively³. This has made the issue of age-related illnesses within this population group highly relevant.

MENTAL ILLNESS IN OLDER ADULTS WITH LEARNING DISABILITIES

Mental illness is common among adults with learning disabilities. Cooper's epidemiological study⁴ comparing the prevalence rates of psychiatric disorder among older (≥ 65 years) and younger (20–65 years) adults with learning disabilities found significantly higher rates among the elderly cohort (68.7% compared with 47.9%). This was mainly accounted for by the higher point prevalence rates for dementia, generalized anxiety disorder and depression in the older cohort groups. While the ageing process can bring about a similar increased vulnerability to mental illness as seen in the general population, additional risk factors apply for people with learning disabilities. These include: the detrimental effect of pre-existing brain damage; co-morbid physical illnesses like epilepsy; specific psychiatric or behaviour disorders associated with genetic risk factors; low self-esteem which may be related to frequent placement breakdowns, past exploitation, neglect or abuse; and the complications of learned maladaptive behaviours such as self-injurious head injury.

Mental illness may go unrecognized due to a number of barriers in the pathways to health care. Service barriers can include the lack of specialist services or the lack of expertise in mainstream services, complex appointment systems that largely presume reading ability, and inaccessible health-care delivery. Problems with the doctor–user interface include communication difficulties, 'power imbalance' exacerbating the suggestibility of the person with learning disability, capacity issues and the complexities of atypical clinical presentations. Diagnostic overshadowing (assuming that any changes in behaviour or presentation are due to the learning

disability, rather than a co-morbid illness) remains one of the major barriers preventing people with learning disabilities from accessing adequate health care⁵. User–carer barriers include pre-existing cognitive impairments making it difficult to obtain an accurate timeline of symptoms, the effects of past negative experiences of health-care delivery and the failure of carers to recognize symptoms. Older people with learning disabilities from ethnic minority groups may have particular problems accessing appropriate services⁶.

DEMENTIA IN OLDER ADULTS WITH LEARNING DISABILITIES

The rates of dementia in older people with learning disabilities are four times higher than in the general population⁷. However, these high rates cannot be attributed just to those with Down syndrome and Alzheimer's disease. Strydom *et al.*'s epidemiological survey⁸ of dementia in older adults (aged ≥ 60 years) with learning disabilities, but without Down syndrome, has confirmed this. Alzheimer's disease was found to be the most common sub-type, but the prevalence rates (8.6%) were almost three times higher than expected. While vascular dementia is the second commonest sub-type in the general population, Lewy body and frontotemporal dementias were found to be commoner in the older learning disabled population. Vascular dementia had a prevalence rate of 2.7%. Explanations for these increased prevalence rates include the effects of poorly controlled epilepsy or other physical illnesses, the detrimental effects of brain damage during birth and early life, and genetic risk factors⁸.

Diagnosing dementia in people with learning disabilities can be difficult due to the wide range of pre-existing baseline cognitive, functional and behavioural impairments. Individuals are more likely to present with the behavioural and psychological symptoms of dementia, or with atypical symptoms such as unexplained seizures. Greater emphasis should be placed on personality and behavioural changes, in association with functional change, as diagnostic indicators⁹. Diagnostic difficulties can also result from altered social or communication skills making it difficult to identify subjective symptoms (psychosocial masking/intellectual distortion), and from diagnostic overshadowing¹⁰.

Good collateral information from the person's carers is essential. The exacerbation of pre-existing deficits ('baseline exaggeration') may only be detected in day-care environments, where the person has more demands placed upon them.

Table 109.1 Differential diagnoses of dementia: what are the causes of cognitive, behavioural or psychological decline in an older person with learning disability?

<i>Causes</i>	<i>Examples</i>
Medical	<i>Physical</i>
	Hypothyroidism
	Recurrent urinary/respiratory tract infections
	Deteriorating epilepsy
	Anaemia
	Persistent or intermittent constipation
	Visual impairments (e.g. cataracts)
	Hearing impairments (including ear wax)
	Medication side effects (e.g. beta-blockers, anticonvulsants)
	<i>Psychiatric</i>
	Dementia
	Normal age-related decline
	Depression
	Anxiety-related disorders (e.g. worsening obsessive-compulsive disorder or phobias)
Psychological	Psychotropic medication side effects
	Bereavement-like response to loss events (e.g. death of a family member/carer/friend; care staff/friends moving; day centre closure)
	Environmental re-triggering of past traumatic events
Social	Changes in staffing/layout/structure/routine at home/day activities, within the context of autism
	Physical/sexual/other abuse

A detailed history and clinical examination, incorporating the 'medical-psychological-social model' can help exclude 'pseudo-dementia' symptoms (Table 109.1). While the clinical domains affected in Alzheimer's disease in older adults with learning disabilities are similar to those in the general elderly population, their presentation can be different (Table 109.2).

The Mini Mental State Examination is not valid for use in people with learning disabilities, but there are a number of alternative observer-rated scales available. Examples include the Dementia Scale for Down Syndrome (DSDS), the Dementia Questionnaire for Persons with Mental Retardation (DMR), and the Modified Cambridge Examination for Mental Disorders of the Elderly informant interview¹¹.

Medical investigations should be focused on excluding the differential diagnoses of dementia. A full blood count, B12/folate levels, ESR or CRP, urea/electrolytes, blood glucose/calcium levels, liver function/thyroid function tests and urinalysis should be done. A baseline ECG (to exclude bradycardic conduction deficits) can be helpful if anticholinesterase treatment is being considered. Neuroimaging should be used to help support a clinical diagnosis, as people with learning disabilities can have baseline frontotemporal abnormalities. Within the context of dementia, people with Down syndrome may develop more significant atrophy in the frontal and temporal lobes¹², hippocampus and amygdala¹³.

Management should be based upon pharmacological and non-pharmacological interventions within the context of broad, multidisciplinary 'bio-psycho-social' approaches. Affected individuals

can often be maintained in their existing environment¹⁰ with additional support or adaptations. If the person needs to be moved into residential care, significant issues arise as to the suitability of mainstream dementia homes with significantly older people⁶.

A number of studies have reported on the efficacy and safety of using acetylcholinesterase inhibitors (especially donepezil) in older people with learning disabilities^{14,15}. Antidementia drug treatment can be initiated by the learning disabilities psychiatrist¹⁶. Associated behavioural and psychological symptoms that fail to respond to non-pharmacological measures may require treatment with an antidepressant, anxiolytic or antipsychotic medication. Persistent seizures may require anticonvulsant treatment. Non-pharmacological interventions such as reality orientation using a life-story photo book, art/music therapies and aromatherapy are of most use in people with learning disabilities.

As with the general population, the prognosis for dementia is generally poor, and the average duration of dementia is generally shorter.

ALZHEIMER'S DISEASE IN OLDER ADULTS WITH DOWN SYNDROME

While neuropathological studies have consistently revealed the evidence of neuritic plaques and intracellular neurofibrillary tangles in nearly all adults with Down syndrome over the age of 40 years¹⁷, not all develop Alzheimer's disease. However, there is a marked exponential rise of Alzheimer's disease in adults with Down syndrome from 30 to 59 years of age, with prevalence rates rising from 2.0% (30–39 years age) to 36.1% (50–59 years age)¹⁸. For adults with Down syndrome living beyond 60 years of age, approximately three in four will have Alzheimer's disease. The mean age range of onset of the clinical manifestations of Alzheimer's disease is 50–55 years, with the rate of deterioration increasing with age. There are no clear relationships between the level of learning disability and risk of dementia or age of onset of dementia¹⁹.

Neuropathological factors that may explain the increased risk of dementia include the over-expression of the amyloid precursor protein gene, the influence of apolipoprotein E alleles, genetic risk factors, the detrimental oxidative effect of increased superoxide dismutase activity in the brain, the earlier loss of the neuroprotective effects of oestrogen in women, and the effects of atypical karyotypes.

Compared to the general population, executive dysfunction (frontal lobe) symptoms such as social withdrawal, diminished initiative and pervasive slowness are common at an early stage of dementia in people with Down syndrome²⁰. Isolated impairments in verbal/long-term memory and visuospatial construction deficits, without significant impairment in other areas of functioning, are more likely to indicate normal age-related decline.

The Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID)²¹ is a reliable, observer-rated screening questionnaire for use in older people with Down syndrome. It allows the screening out of pre-morbid behaviours, with only changes in behaviour (or new behaviours) positively scored.

PHYSICAL ILLNESS IN OLDER ADULTS WITH LEARNING DISABILITIES

Older people with learning disabilities have health-care needs associated with ageing, and higher rates of respiratory disorders, arthritis, hypertension, urinary incontinence, immobility, hearing impairment and cerebrovascular disease²².

Table 109.2 Clinical presentation of Alzheimer's disease in older people with learning disabilities

<i>Clinical domain</i>	<i>Examples of symptoms and signs</i>
Memory	Forgetfulness of recent events, e.g. content of meals/day activities (episodic memory impairment) Forgetfulness of future planned outings/activities Forgetting location of recently placed objects (spatial memory impairment) Geographical disorientation (e.g. unable to find their way around their own home/neighbourhood) Forgetting names of/failing to recognize familiar people (semantic memory impairment) Loss of previously learned skills, e.g. making a cup of tea or dialling a phone (procedural memory impairment)
Abstract reasoning skills (judgement, planning and organization)	No longer selecting appropriate clothing for planned activities/routines, or putting on clothes back to front Decline in shopping skills Difficulty following more than one instruction at a time Decline in ability to dress/feed self, or brush teeth (apraxia) Decline in reading (alexia), writing (agraphia) or language skills (aphasia) Using common everyday objects inappropriately (agnosia), e.g. combing hair with toothbrush
Mood	Being unable to distinguish between day and night Low mood/decreased energy/loss of interest/apathy Emotional lability (e.g. unexplained tearfulness) Overactivity/restlessness/poor concentration Irritability/anxiety
Social behaviours	Sleep changes (insomnia or hypersomnia) Increased dependence on others Personality changes, e.g. aggression/disinhibition, pervasive slowness Obsessional slowness/repetitiveness in completing tasks Social isolation Fear of stairs, kerbs or uneven surfaces 'Covering up' of memory loss (e.g. saying 'sorry' to tasks they cannot do)
Perceptions	Auditory, visual or tactile hallucinations
Neurological	Gait disturbance/decreased mobility/falls Bradykinesia-like slowness in movements Seizures (early in Down syndrome) Dysphasia Dystonia/myoclonus/pathological reflexes Urinary incontinence

Hearing problems might further compound already poor communication skills and can be caused by structural abnormalities, neural damage or impacted earwax. People with learning disabilities also have a higher prevalence of sight problems, which may be acquired as they get older, or be as a result of brain damage or cerebral visual impairment²². The prevalence of ocular health problems ranges from 25% (in the mildly disabled) to 60% (in the profoundly disabled)²³.

Prevalence rates of epilepsy are considerably higher in people with learning disabilities compared to the general population (16.1% vs. 0.4–1%)². Individuals often have complex seizure types and patterns.

People with learning disabilities have higher levels of oesophageal, stomach and gall-bladder cancers, but lower rates of lung, prostate, breast and cervical cancers.

An increased risk of respiratory tract infections in people with learning disabilities can be caused by aspiration or reflux due to swallowing difficulties. Levels of obesity are higher in people with learning disabilities because of poor diet, lack of physical exercise and difficulty understanding health promotion information, which can

increase the likelihood of heart disease, stroke and type II diabetes mellitus. Many people with learning disabilities have high levels of *Helicobacter pylori* which may require testing and treatment throughout life²².

Certain syndromes that cause learning disabilities are particularly associated with an increased risk of specific morbidity. Down syndrome is associated with increased risks of congenital heart problems, respiratory disease, a poor immune system, eye disorders, lymphoblastic leukaemia, coeliac disease and hypothyroidism. People with fragile-X syndrome have increased connective tissue disease and cardiac abnormalities. Prader–Willi syndrome has an associated risk of obesity-related pathology.

AGEING AND SOCIAL NEEDS OF PEOPLE WITH LEARNING DISABILITIES

Most long-stay hospitals have now closed, with individuals moving to community residential provision motivated by the philosophy of

'normalization'. In England, national policy requires local authorities to offer person-centred planning to all people with learning disabilities, alongside regularly updated health action plans¹. Staff roles and training now focus on social inclusion, choice, independence and rights.

People with learning disabilities experience low employment and fewer meaningful relationships, as daily activities are usually only provided as part of a package of care. Placements often experience a high staff turnover resulting in carers having an incomplete knowledge of the individual. Many older adults may have been raised in institutions. Younger adults are more likely to have been raised within caring families in the wider community, with better lifestyles and opportunities that may have been denied to their seniors⁴.

With good planning, people may stay in their own home funded through the personalization agenda. Accommodation and support varies from minimal to total. People with milder learning disabilities might live by themselves or semi-independently with some structured support each day. Those who need greater levels of support may live in housing managed by private or voluntary organizations, or by health and social services.

SERVICES FOR OLDER ADULTS WITH LEARNING DISABILITIES

Being elderly and having learning disabilities can make people vulnerable to 'double discrimination', as services for both groups tend to be underfunded. Debate exists whether to use mainstream older people's psychiatric services (which may lack neurodevelopmental expertise), to continue with existing learning disability services, or to develop specific specialist services. National policies advocate that people with learning disabilities should be able to access mainstream health services where appropriate, and specialist community learning disability teams (CLDTs) can promote this by providing specialist advice and support to their mainstream colleagues. Some CLDTs operate a life-span approach, but the majority work with people from age 16 or 18 with no exit age. However, such teams need to develop additional skills with regard to age-associated disorders.

Older people with learning disabilities face additional difficulties in primary care settings. Primary care physicians list lack of awareness of conditions specific to learning disabilities as among the top five barriers to care²⁴. Strategic health facilitator posts tackle some of these issues by ensuring that people with learning disabilities are offered health screening, and that health promotion materials are accessible to them.

PALLIATIVE CARE ISSUES FOR PEOPLE WITH LEARNING DISABILITIES

Mainstream palliative care services need to be responsive to the needs of people with learning disabilities, as the combination of problems identifying symptoms and diagnostic overshadowing can result in the late presentation of illness at a stage when there is already advanced disease and severe symptomatology²⁵. Many people with learning disabilities can be surrounded by a 'conspiracy of silence', where information about the illness and impending death is not shared with them²⁶. Carers of people with learning disabilities may equate palliative care with hospice care, triggering unpleasant memories of largely institutional care. Educating well-meaning care staff and family members of the positive role of services in

supporting the dying person in the community (within their home) can help alleviate these fears.

Effective end-of-life care requires close collaboration between learning disability services, palliative care teams, carers (including family members, who may highlight important religious or cultural issues) and other medical services.

CONCLUSION

People with learning disabilities share the general experiences and difficulties of becoming old with the rest of the population. Their increasing life span brings about important challenges in view of additional risk factors, increased prevalence rates, co-morbidity and atypical presentations of mental and physical illnesses. There is need for more research, education and training, alongside collaboration between services, to inform service developments. Person-centred approaches take into account an individual's life experiences, clinical needs and the support mechanisms needed for their immediate carers and family. Psychiatrists can act as drivers of positive health outcomes by facilitating access to appropriate pathways to care. Commissioners of older people's and learning disability services need to take these factors into account for future planning.

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The Elderly Offender

Graeme A. Yorston

St Andrew's Hospital, Northampton, UK

The elderly are far more likely to be the victims of crime than the perpetrators, but a small number of older people do commit crimes, and this group is important for a number of reasons. First, the mental disorders of late life may lead previously law abiding people to act out of character and behave in a dangerous and distressing manner. Second, the criminal justice system is less sensitive to the ways in which mental disorders can present in older adults, with the result that they may go undetected, and, third, the needs of older mentally disordered offenders are often difficult to meet in existing prisons and secure hospitals, leaving them vulnerable, an easy target for physical aggression and with little chance of moving on because of inadequately developed risk management strategies and care pathways.

A question which most researchers in this field have posed is the age at which an offender should be deemed 'elderly'. Prison studies, particularly in the US, often include everyone over the age of 40! Others have used 45, 50 or 60 but relatively few the more traditional 65 cut-off. People who have had hard lives, no stable employment or relationships, several terms in prison, a history of drug or alcohol use, and patchy health care often appear much older than their peers who have led more conventionally prosocial lives, with the result that many are starting to look and feel old in their forties and fifties. There is a strong case, therefore, for using a lower age limit for research purposes, but all figures based on chronological age are arbitrary, and what is more important in the clinical assessment of an individual is *biological age*, as it is this that will largely determine their needs.

OFFENCE TYPES

Despite an ageing population, statistical data from the UK and US show the number of convictions of people over the age of 60 has been remarkably stable over the past 12 years^{1,2}. Broadly speaking, the elderly account for around 1% of recorded crime, though this figure varies considerably for the type of crime.

Sexual Offences

Sexually inappropriate behaviour in dementia is a familiar problem to all old age psychiatrists. Most of this behaviour is mild in severity and does not reach the attention of the police or criminal justice system. Older adults can and do commit more serious sex crimes, however, and account for approximately 1% of convictions for these offences in the UK, with broadly comparable figures from other countries.

The proportion of older adults is rather higher for those convicted of sexual offences against children, and a number of possible explanations for this have been proposed, including the greater ease by which children may be dominated by someone of declining physical strength, the degree of trust afforded grandparental figures, ready access to grandchildren, and regression to childhood fantasy objects. The proportion of older sex offenders with suspected or proven organic psychiatric diagnoses varies in published case series from 0% to 60%³⁻⁵. Other diagnoses reported in the literature include antisocial personality disorder, alcoholism, learning disability, depression and schizophrenia. Though research has consistently shown that older adults are capable of committing the most serious violent penetrative offences, there has been a tendency to minimize the seriousness of offending by this group in the past⁶. Several studies have shown lower rates of recidivism for older offenders⁷⁻⁹, but some of these failed to account for the reduced time at risk of re-offending of elderly men, and the fact that, as a group, older sex offenders tend to commit less serious offences which have lower recidivism rates. It should also be borne in mind that the lower recidivism rate is of little help in assessing risk in individual cases, which should be approached in a structured manner. The potential for serious harm should never be underestimated on the basis of age alone.

Homicide

There have been few psychiatric studies of elderly homicide offenders, though the individual case study literature is much richer. Rollin¹⁰ described a typical case of a 71-year-old man with a history of depressive illness who battered his wife to death after becoming convinced that she was beginning to fail in health and was too proud to allow herself to be looked after by anyone else should anything happen to him. Large homicide case series often include a small number of elderly cases: in Gillies' classic series of 400 homicides in Scotland¹¹, there were only three men over the age of 65 and the oldest woman was 54. Unlike the majority of people accused of homicide, who were considered mentally normal (82%), all three of the over-65s were psychotic at the time of the offence.

In a comparison of older and younger homicide and attempted homicide suspects in Canada¹², much lower rates of previous convictions and past hospitalization for mental illness were found in the elderly group. Half of the elderly group had psychotic diagnoses, with none found in those under the age of 30; 19% of the elderly group had an organic mental disorder, with none in the younger group;

50% had alcohol problems (31% in the younger group); and only 13% had antisocial personality disorder (compared to 68% of the younger group). Surprisingly, though, fewer of the elderly group were found not guilty by reason of insanity (19% compared to 30%). This finding contrasts with sentencing data from Scotland in the 1990s, which showed that elderly homicides were more likely to be given hospital disposals than younger offenders and far less likely to be given life sentences (F. Thorne, personal communication).

Forensic pathologist Bernard Knight¹³ coined the term *Darby and Joan syndrome* for elderly couple homicides which occurred in apparently close, loving relationships, in contrast to younger partner homicides which typically occurred against a background of infidelity, jealousy and money disputes, fuelled by alcohol or drugs. He cited the case of a woman in her seventies who killed her husband with repeated brutal blows to the back of his head with a heavy metal object while he was sitting watching television. No rational explanation for the act could be obtained. Knight commented on the extreme brutality used in elderly couple homicides and cited two cases of octogenarian men who killed their elderly wives with hammers – one of whom rained down 37 blows on his wife's head, resulting in multiple compound fractures of her skull. He also commented on the presence of *bizarre postmortem bondage* in many of the cases he was involved with, describing how a man trussed his wife up in a chair with twine and cord after killing her and then bound her face with towels and cloths secured by more twine.

Though the psychiatric literature emphasizes the differences between elderly homicide offenders and younger homicides, criminological data from US studies show that though elderly homicide rates vary between different US states, they are correlated with the non-elderly rates, which are themselves strongly correlated with urbanization and poverty, suggesting that the same societal pressures influence young and old alike¹⁴. Other US studies have shown that the elderly are more likely to kill family members, to use firearms and to carry out the offence in the home^{15,16}. The majority of elderly homicides are committed by men, but in a study of coroner's office and county prosecutor files of 179 homicides by the over-60s in Cincinnati and Detroit¹⁷ it was found that women accounted for 18% of cases. There have been no systematic studies of elderly women homicides, however, though there are a number of brief case descriptions^{18,19}.

Homicide–Suicide

A number of studies have demonstrated that homicide followed by suicide is commoner in older adults²⁰. It usually occurs in a spousal relationship, and depression and alcohol problems are common. One study showed a mean age difference of 18 years between perpetrators and victims along with prominent histories of discord, violence and separation. There are published case studies of homicide–suicides that have no history of conflict, however: for example, an 82-year-old man who shot his frail 84-year-old wife and then himself after becoming unable to provide care for her after he suffered a myocardial infarction²¹. In such cases it can be difficult to distinguish between homicide–suicide cases and suicide pacts.

Non-Fatal Violence

Minor aggression in elderly dementia sufferers is common, with up to 90% displaying some sort of aggression during the course of the illness²². Most is not serious and relatively easily managed, in

contrast to the type of behaviour described in an Australian case series of fourteen older adults accused of attempted homicide^{23,24}. The only one who succeeded in killing his victim in this series was a 68-year-old man who shot his neighbour with a shotgun.

Arson

There is no published literature on arson by the elderly. Clinical experience suggests that pyromaniacs, fascinated by fire and fire services, do not typically present in old age, but such individuals, many of whom have spent years in secure hospital or prison, may live on to old age and develop a neurodegenerative disorder. Such cases present extraordinary difficulties for psychiatric and social services, and the criminal justice system, which often struggle to balance the risk to others and individual vulnerability issues. It is not clear how risk to others from arson, or indeed sexual or violent offending, changes with the progression of a dementing illness, and so care generally has to be provided in an environment where risks can be managed through relational and procedural security measures. What appears to be more common in old age is the emergence of a pattern of setting small fires, often within residential homes. Though many of these fires cause little actual damage, because of the potentially devastating consequences, all fires in elderly care settings have to be taken seriously. As few old age psychiatrists have much experience of assessing fire setters, referral for a forensic psychiatric assessment is recommended. Arson in the elderly has been linked with personality disorder, psychosis, dementia and previously unrecognized learning disability.

Acquisitive Offending

Shoplifting is the commonest offence of late life, but most cases of acquisitive offending never come to the attention of old age psychiatrists. Anecdotally there is said to be an association with depressive illness, but there have been few studies on this topic. The shame of being arrested for shoplifting can have disastrous consequences for individuals with no previous criminal history, and the case of Lady Isobel Barnett, a British television personality who committed suicide four days after being convicted of stealing a can of tuna and carton of cream in 1980, is well known²⁵.

Drug- and Alcohol-Related Crime

For people born in the 1940s or before, drug use was uncommon when they were going through their period of highest risk; however, this is not the case for those born in the following decade, and old age psychiatry services are now beginning to see people with active drug problems, something that was almost unheard of previously. At present drugs do not present major problems in UK older adult secure hospital services, unlike services for younger patients, but this is likely to change over the coming years. Alcohol is being increasingly recognized as a problem in older adults²⁶ and alcohol problems are common among older men in prison in the US²⁷. When this is linked to offending behaviour it has serious implications for risk management. The assessment of older offenders with a history of alcohol abuse is further complicated by the possibility of alcohol-related cognitive impairment.

DIAGNOSTIC CONSIDERATIONS

All of the mental disorders that occur in late life can lead to criminal behaviour; for the overwhelming majority of individuals, changes in

behaviour as a result of mental disorder are recognized as such and dealt with by medical services. Sometimes, however, the behaviour can be so sudden and so severe that health services are not involved until after an offence has been committed. In these circumstances it is important that the individual receives an assessment by a clinician familiar with the psychiatry of old age.

Delirium

Metabolic and other causes of delirium, superimposed on the early stages of dementia or a pre-existing depressive illness, can lead to fatal aggression. Some of the bizarre, apparently motiveless homicides described above and many from my own experience have been the result of delirium, often occurring as a side effect of medication, including steroids, anti-parkinsonian medication and the anticholinergic effects of first-generation antidepressants.

Dementia

There are isolated case reports of crime associated with dementia, but given that it is so common, it is surprising that there are not more and that it has not been more systematically studied. Experience suggests that individuals with more than a mild degree of dementia are easily identified as such and not dealt with by the criminal justice system. This is not the case for those with very early dementia, or in cases of frontotemporal dementia with a well-preserved social façade. Dementia can present with a change in behaviour: either the emergence of new behaviours that were not present at all previously, or a change in the type, frequency and character of existing behaviour. Old age psychiatrists are familiar with the evaluation of such issues by taking careful histories from carers and relatives, but forensic psychiatrists are generally more used to assessing individuals through detailed mental state examinations, which may reveal little in early dementia. In a study of referrals to a regional medium secure unit in England, it was found that forensic psychiatrists did not routinely use standardized rating scales for the assessment of cognitive functioning²⁸. For these reasons individuals presenting with offending behaviour for the first time in old age ideally need assessment by clinicians with experience of both specialties, or if none are available, by clinicians from each specialty working closely together.

Psychosis

Unlike the psychosis of younger adults in which schizophrenia is the diagnosis most commonly associated with serious aggression and homicide²⁹, homicidal psychosis in the elderly is more commonly depressive in nature and characterized by nihilistic delusions, and it is often the spouse of the perpetrator who is the victim. The mindset is often that one or both of the couple are ill, leading to worries of how one would cope without the other, and the conclusion that they would both be better off dead. In such cases, the depression can be relatively mild on the surface and be missed by those looking for the entire gamut of symptoms, but careful enquiry about worries and preoccupations and changes in habit can be revealing. In a study of elderly men in English prisons in the 1990s³⁰, it was estimated that there were up to 50 older men in the UK prison system at any one time suffering from a depressive illness with psychotic symptoms severe enough to be in need of urgent transfer to hospital.

Developmental Disability

Asperger's syndrome, previously unrecognized, can present for the first time in late life and be associated with serious offending. This is commonly due to decompensation because of a change in routine by going into a residential home or through the loss of a supportive relationship, often a very old parent. Making developmental disability diagnoses in the absence of a reliable informant is difficult, however, and can be complicated further if a neurodegenerative disorder is suspected as well.

Personality Disorder

By definition, personality disorders cannot begin in old age, but what may happen is that a change in circumstances reveals a personality that has been disordered throughout life but compensated for by some means, often a spouse or other significant relationship. At retirement of one party or the other, or at the death of a partner, or entry into a care home, personality issues previously hidden within the family can emerge. These may simply cause annoyance or minor distress or be associated with criminal damage, fire setting or violence.

THE ELDERLY IN THE CRIMINAL JUSTICE SYSTEM

Arrest

Anecdotal evidence suggests the police may be reluctant to get involved in offences committed by elderly people with obvious mental health difficulties. This is particularly noticeable if either the perpetrator or victim suffers from dementia, presumably because of difficulties in obtaining evidence. This can lead to very serious offences being inadequately investigated, which then makes risk assessment almost impossible. A study of a special police project in one region in England in 1990³¹ showed that of 367 consecutive arrestees aged 60 or over, less than 10% were prosecuted. The remainder were cautioned if they admitted guilt, or were subject to no further action. Nearly two thirds of the arrests had been for shoplifting, in most cases of grocery items of small value. There were 15 arrests for violence, most of which was not serious, and 11 arrests for indecent assault. Police referred the arrestees to their primary care physician or to the police doctor more often than to any other agency. Though only 50 arrestees agreed to have research interviews, nearly one third of these were identified as 'psychiatric cases'.

Trial

All jurisdictions have rules on fitness to plead and fitness to stand trial. For older adults mental health issues must be considered along with physical health and perceptual issues. Is the defendant able to see and hear adequately? Do they need shorter court sessions because of fatigue? Do they need extra toilet breaks or different seating? All these questions need to be addressed when assessing an older adult. However, the main question to be answered in determining fitness to plead in the majority of cases is whether the defendant is able to follow the course of the proceedings in court. The answer to this can be very obvious for someone with severe dementia, or in someone with relatively mild or well-managed mental health problems, but in many cases of mild to moderate dementia, the issue is far from clear. Standard cognitive testing in such cases can be helpful but in serious cases fuller neuropsychological evaluation is recommended, which should include tests of malingering and suggestibility.

Prison

The number of older people in prison has risen sharply over the past 20 years: in England and Wales, there were 365 sentenced prisoners aged 60 and over in 1990³². By 2007, this figure had increased sixfold to 2 192, and older prisoners now make up 2.9% of the total prison population³³. In the US the number of older inmates showed a similar increase, tripling between 1990 and 2001, and their proportion in the total prison population doubled (from 4.0% to 8.2%)³⁴. These increases appear to be due largely to changes in sentencing by the courts. 'Three strikes and out' sentences were first introduced in the US in 1993, and in the UK in 1998, with the result that recidivist violent offenders in particular remain in prison well into old age, such that many US states have been obliged to develop nursing home wings for older prisoners and the UK prison service is having to take seriously the needs of older inmates.

In the UK, much of the prison estate is old and difficult to adapt to meet the needs of older adults. Prison regimes can appear harsh and inflexible, as they are primarily concerned with the maintenance of security and discipline, and not with meeting health care needs. The result is that older prisoners can be extremely vulnerable and they are not uncommonly on the receiving end of serious aggression, despite the often very caring attitude of the majority of younger prisoners. Special units for older prisoners began to appear in the US in the 1970s, and a body of qualitative research showed that older prisoners, generally, though not always, preferred being in these units away from the noise and aggression of younger inmates³⁵. In a study of sentenced older male prisoners in England and Wales high levels of psychiatric and physical morbidity were found^{30,36}. In total, 53% had a psychiatric diagnosis, most commonly personality disorder and depressive neurosis, but 5% had a psychotic illness. In contrast to studies of younger prisoners, in which schizophrenia is the commonest psychotic illness, depressive psychosis was found to be the most common in older prisoners, yet only 12% of those diagnosed with depression were on antidepressants. Somewhat surprisingly, only two cases of dementia were found, but the sample of prisons included in the study contained few lifer units, in which cases of dementia are more common.

It is known that younger prisoners have worse physical health than age-matched controls. There is also evidence that such ill health continues into old age, with the elderly having more physical health problems than younger inmates and age-matched community living elders. A recent US study²⁸ highlighted the importance of thorough physical evaluation of older men coming in to prison to ensure they benefited from secondary preventive treatment for cerebrovascular disease and other common physical health problems. The study also showed that sexually transmitted disease (STD) is common among older prisoners. Clinicians unfamiliar with working with the elderly often assume that older people are sexually inactive, and do not ask about the possibility of STDs. Older prisoners should have access to primary and secondary care physicians who are familiar with the latest research and guidance on health promotion in this age group.

Women

The number of older women in prison has risen sharply over the past ten years. Many of these are long-term prisoners, though there are some who have committed serious offences for the first time in late life. It is likely that they have at least the same prevalence of

mental health problems, if not greater, than their younger peers. But as numbers are small, little formal research has been carried out. In a sociological study of older women prisoners in the UK, it was found that there were a number of older women from ethnic minorities who suffered the double isolation of being different because of their age and different because of their culture³⁷.

Psychiatric Services

In the past it was very difficult for older patients to access specialist secure psychiatric services, particularly in the UK. Only 1% of those newly admitted to high and medium secure beds in England and Wales between 1988 and 1994 were over 60³⁸. The conclusion drawn was that this was because people of such age were regarded as unsuitable for existing UK forensic services, mainly because of concerns about their potential vulnerability to aggression from younger patients. A number of studies have shown that older adults make up between 1% and 3% of referrals to forensic mental health services in the UK and Sweden³⁹⁻⁴¹. There have been several descriptive studies of the elderly in high security, but these mainly focused on diagnostic issues⁴²⁻⁴⁴. In a more recent study at Broadmoor high security hospital in England the heterogeneity of older mentally disordered offenders in terms of diagnosis, assessed needs and expressed preferences was highlighted⁴⁵. Despite there being a ward specifically for older vulnerable patients, the 16 patients over the age of 65 identified in the study were spread across 9 different wards in the hospital. Some authors have proposed 'streamlining' older offenders to make their care more cost-effective²⁷, but if the findings of the Broadmoor study are replicated then it would appear that streamlining will be very difficult. Older patients have some similarities one with another, because of their age, but the range of problems they present and their needs appear to be just as diverse as those of younger patients. It would be wrong to confine them all together solely on grounds of chronological age. This important issue emerged in some of the earlier qualitative work in prisons when it was found that not all older inmates wanted to be housed together; some liked the hustle and bustle and felt they enjoyed a high status in mixed age units because of their age and life experience⁴⁶.

Care homes for older adults often cope with high levels of minor physical aggression and sexually disinhibited behaviour⁴⁷. However, they are not equipped to deal with more serious aggression or predatory sexual behaviour. The understanding of risk issues and how to assess and manage them is often highly sophisticated for the common behavioural problems of dementia, but for behaviour driven by antisocial personality traits it is usually lacking. This means there is a lack of suitable facilities for older offenders who have been assessed and require ongoing nursing care in an environment that is also able to manage their risky behaviour. In the UK specialist hospital units have been set up for those who require inpatient assessment and treatment, but a lack of suitable places to discharge patients to once they have been stabilized, though not necessarily to a state where the risks they pose to others have been substantially reduced, means that many remain in hospital for longer than would otherwise be necessary. Most offenders with established dementia will be unfit to plead or stand trial, and, if violence has been serious, will require further care and supervision in a hospital unit specially designed to meet their mental and physical health care needs with just sufficient security to ensure public protection.

TREATMENT ISSUES

The most important consideration in the treatment of the mental health problems of elderly offenders is location. For less serious offenders, normal treatment by their community mental health team in conjunction with their general practitioner is appropriate. For those in custody, treatment by a visiting psychiatrist and prison in-reach team may be sufficient, but for others assessment and treatment in hospital will be required. For some of these it may be appropriate for an old age psychiatrist to manage the case within their own service with advice from the local forensic psychiatric team, but in some cases the individual may need treatment in secure hospital. The ethos and treatment philosophy of specialist secure units for older adults should ideally be a synthesis of older adult and forensic psychiatric service models, modified and adapted to ensure that security is maintained without unnecessary levels of physical security. They should aim to be comfortable and homely without compromising safety. Staff training is paramount: a well-intentioned but infantilizing approach is likely to be robustly rejected by patients unused to *fluffy nurses* – a pejorative term used by patients to describe staff who are unfamiliar with forensic issues. Equally, a harsh and emotionless approach with an over-reliance on physical restraint is unlikely to meet the needs of individuals who may spend the rest of their lives on a particular ward and have no social contacts outside the ward team and co-patients. Pharmacological treatments are no different for elderly offenders with mental health problems than for their community peers, but the risk/benefit balance is tilted more towards drug treatment than would be the case in standard old age psychiatric practice. Despite all the safety concerns about using antipsychotic medication in dementia⁴⁸, there would be few who would argue against a trial of medication in an individual displaying thousands of aggressive acts per month in whom all other treatments have proved ineffective. Antipsychotics in schizophrenia tend to be used at doses more typical of working age adult services than old age services and occasionally there is justification for a trial of high dose antipsychotic medication providing safety guidelines are followed. Anti-libidinal medication can be useful in the treatment of sexual offenders with personality disorders and organic mental health problems though the evidence base for this is still very limited.

RISK ASSESSMENT

The unstructured clinical assessment that was the cornerstone of forensic psychiatric practice a generation ago has been largely replaced by a range of actuarial and structured clinical assessment tools backed up by a substantial body of research. The problem of using these tools is that none has been validated in the elderly, and many tend to focus on past behaviour or negative characteristics. There is a potential for misuse of actuarial tools that predict future risk as their positive predictive value depends on the base rate of offending in the population, which is of course much lower in the elderly than in younger adults on whom the instruments were developed. In the absence of instruments designed for the elderly, the use of structured clinical risk assessment tools such as the HCR-20⁴⁹ for physical violence and Risk of Sexual Violence Protocol (RSVP)⁵⁰ for sexual violence is recommended to ensure a systematic approach to the gathering of risk information.

PREVENTION

A number of studies in the US have shown that the elderly, being less physically able, make greater use of firearms than younger violent offenders^{15,16,27}. Access to guns is much more restricted in the UK, yet older homicide offenders still manage to find weapons of sufficient lethality without too much difficulty. The weapon of choice for such incidents is usually a blunt object, and I have dealt with homicide cases by older adults involving repeated blows to the head with a ceramic fruit bowl, a club hammer, a walking stick, a pair of long handled garden loppers, an antique flat iron, a stone in a sock and decapitation with a saw. Restricting access to conventional weapons is unlikely to affect the rate of these domestic homicides in the UK because the victims are generally of similar age and may be quite frail, and almost any household implement can be made into a lethal weapon given sufficient will and a little physical strength. A far better preventive strategy would be to focus efforts on delivering good quality psychiatric care to all older people with mental health problems, and increasing the skills of primary care physicians for early identification of depression. Other priorities will include persisting with efforts to help those with alcohol problems and routinely asking patients and carers about physical aggression and sexually inappropriate behaviour.

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Sleep and Ageing: Disorders and Management

Helen Chiu¹ and Joshua Tsoh²

¹*Department of Psychiatry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong*

²*Prince of Wales Hospital, Shatin, New Territories, Hong Kong*

INTRODUCTION

Sleep changes significantly across the human lifespan, and sleep disturbances are particularly prevalent in older populations^{1–12}. Epidemiological studies around the world have reported that the prevalence of insomnia symptoms increases with age and reaches around 50% in the elderly (readers can refer to Ohayon, 2002⁹, for a review). A representative study by Foley *et al.* on over 9000 participants aged 65 or older in three US communities reveals that over 54% of the subjects had one or more sleep complaints most of the time; the number of complaints rises with age, and the odds for women to have difficulty falling asleep are almost 50% higher than for men⁵. Upon longitudinal examination, insomnia emerges with an annual incidence rate of at least 5% among the seniors who did not have insomnia at baseline⁶.

Apart from being a major source of vexation to the elderly and their caregivers, persistent sleep disruptions are associated with poorer mental and physical health, elevated fall incidents, worse cognitive and functional performance, lower quality of life, earlier institutionalization and greater mortality over time¹².

To formulate evidence-based solutions to meet this public health challenge, clinicians should examine and understand the interplay of clinical factors, which include physiological changes in sleep architecture with ageing, sleep disorders that are more prevalent among the elderly (e.g. sleep disordered breathing (SDB), restless legs syndrome (RLS), rapid eye movement sleep behavioural disorder (RSBD)), and sleep modulating effects from physical and mental disorders, medications, undesirable sleep habits and environmental factors that are more common in later life.

INSOMNIA

Insomnia is the most common clinical sleep complaint; it can refer to difficulties initiating or maintaining sleep, waking up too early or an inability to obtain sleep that is of adequate duration or perceived as restorative. However, not all individuals with symptoms of insomnia are dissatisfied with their sleep or face daytime consequences⁹. A diagnosis of insomnia as a disorder according to the International Classification of Sleep Disorders (ICSD) criteria¹³ would require the concomitant presence of persistent sleep difficulty, daytime impairment and adequate sleep opportunity.

In a review of 13 representative epidemiological studies from around the world (involving 33 000 non-institutionalized elderly)⁹, Ohayon finds that the prevalence of insomnia symptoms varied vastly (9 to 65%) according to criteria differences, but the figures are consistently higher in females. Two studies have examined insomnia as a disorder (Chiu *et al.*, 1999¹⁴; Ohayon and Vecchierini, 2002¹⁵), in which cases the prevalence is comparable, and significantly more female than male elders suffer from insomnia (around 16 to 18% and 9 to 12%, respectively).

The high rate of insomnia in the elderly might be related to physiological ageing of the structures involved in homeostatic and circadian rhythm mechanisms, secondary to medical and psychosocial conditions that abound in late life, or a combination of these factors^{1–4,8–12}.

Sleep Architectural Changes with Physiological Ageing

The suprachiasmatic nucleus (SCN) in the hypothalamus is the biological 'master clock' that controls the circadian rhythms of physiological processes including sleep, body temperature and endocrine output in a roughly 24-hour cycle¹⁶. Its endogenous periodicity is entrained by external *zeitgebers* ('time-givers'), most notably environmental light, through the retinohypothalamic tract (RHT)¹⁶. Its rhythmicity is also affected by a number of interlocking feedback mechanisms, including pineal secretion of melatonin (a hormone causing drowsiness and lower body temperature), which peaks in the middle of the night¹⁶. Current evidence shows that sleep is initiated upon reciprocal inhibition of cholinergic, noradrenergic and serotonergic arousal systems in the brain stem by the ventral lateral preoptic (VLPO) area of the anterior hypothalamus, which is in turn influenced by circadian signals from the SCN. Once sleep begins, an ultradian oscillator in the mesopontine junction of the brain stem controls the regular alternation of non-rapid eye movement (NREM) and REM phases of sleep, which usually occur four to five times per night¹⁶. NREM sleep is divided into four progressively deeper stages (I, II, III and IV), is characterized by slow waves on an electroencephalogram (EEG), and predominates in the early part of sleep. REM sleep, on the other hand, is characterized by an active EEG pattern, REM clusters on the electrooculography (EOG), and muscle atonia. REM sleep is more pronounced in the latter cycles of sleep as NREM sleep becomes concomitantly shallower.

With ageing there is a physiological change in the circadian cycle at all levels; it has been observed that reduction in SCN cell numbers/neuronal activity³ and melatonin secretion occurs with advancing age¹⁷. The responsiveness of the circadian clock and pineal melatonin secretion to zeitgebers also diminishes, along with age-related decline in sensitivity to light in the visual structures³. The aged circadian system is also less adaptive to changes; difficulty adjusting to shift-work and jet lag are more common in middle-aged persons than in their younger counterparts³. Furthermore, along with other circadian physiological processes, phase-advances in sleep have consistently been observed³. Circadian amplitudes might also become less pronounced; the sleep of older individuals is often punctuated by periods of wakefulness, and they are also more easily aroused from sleep by environmental stimuli^{2,3,18}. Napping is generally more common; recent studies show that naps do not necessarily have a negative impact on the nocturnal sleep architecture^{1-3,18-20}.

In terms of sleep polysomnographical findings, Ohayon *et al.* reported, in a meta-analysis on 2400 healthy, non-institutionalized individuals aged 19 to 102 years from the US and Europe⁸, that there is a decrease in total sleep time (TST), sleep efficiency (SE), percentage of slow wave sleep (SWS; stages III and IV of NREM sleep) and REM sleep across the adult life span; on the other hand, an increase in stages I and II sleep, and wake after sleep onset (WASO) take place. Age-related differences in sleep and REM latencies are not pronounced; gender differences are modest.

It is, however, noteworthy that most of the stated age-related changes have taken place *already* in younger adulthood. When the sleep of older adults (aged 60 or older) in particular is examined, apart from the SE, which declines mildly, no clear changes in the sleep macroarchitecture are found with advancing age⁸.

These polysomnographical findings suggested that the normal sleep macrostructural changes with physiological ageing in later life are (probably with the exception of advanced sleep phase disorder) largely not accountable for the prevailing epidemiological findings of a rising rate of insomnia with age in the elderly, especially among older women.

Other Causes for Insomnia with Ageing

The Foley *et al.* cohort study of 9000 community-dwelling elders in the US found that advancing age was not associated with insomnia after adjusting for differences in health status⁵. Upon follow-up three years later, 93% of persons with incident insomnia in this interval were found to have risk factors including chronic physical disease, depressed mood, physical disability, poor perceived health, widowhood and use of sedatives, while improved self-perceived health was associated with remission of the 2000 survivors with chronic insomnia at baseline. The authors concluded that the incidence of insomnia in the elderly is not related to the ageing process *per se* but to other risk factors, a finding echoed by epidemiological studies on insomnia disorder subsequently conducted in populations from China and from France^{9,14,15}.

Recent studies have confirmed that incidences of secondary insomnia far outnumber those of primary insomnia disorder in the older population^{9,12,21}. Particularly common clinical conditions leading to secondary insomnia in late life include neuropsychiatric degeneration (e.g. Alzheimer's disease or Parkinson's disease), a number of age-related sleep disorders (SDB, RLS and RSBD), psychiatric illnesses (especially depressive and anxiety disorders, alcohol dependence) and other medical disorders (particularly those

affecting the musculoskeletal, cardiovascular, gastrointestinal, pulmonary and genitourinary systems, malignancies, painful conditions, and the drugs used to treat them)^{9,12,21}.

Interested readers can refer to Barcz and Juergens, 2006²¹ and Garcia, 2008²² for two extensive reviews on the relations between prevalent medical disorders and insomnia in the elderly. It should be noted that 'co-morbid insomnia' is the term currently preferred over 'secondary insomnia' when the causative relationships are not clearly proven²³. The specific conditions of SDB, RLS, RSBD and sleep disorders related to dementia will be discussed in separate sections in this chapter.

Evaluation of Insomnia Disorder

A carefully taken sleep history is important; Lichstein *et al.* recommend a multidimensional approach to exploring contributory factors to insomnia in the (i) circadian; (ii) psychiatric; (iii) pharmacologic; (iv) medical or neurological; and (v) psychophysiological reactivity (like subclinical anxiety and physiological tension) and negative conditioning (e.g. from poor sleep hygiene, or performance anxiety related to frequent insomnia) domains⁴. Along with a relevant physical examination, the primary condition(s) leading to insomnia should first be elucidated and treated where present. Routine investigation with polysomnography (PSG) is not recommended for insomnia disorder by the American Academy of Sleep Medicine except when there is diagnostic uncertainty (covert cases of RLS, SDB or RSBD are more common with advanced age) or prior treatment failure^{4,24}.

Non-Pharmacological Treatment of Insomnia Disorder

Psychological and behavioural interventions are effective in the treatment of insomnia in older adults, and in the treatment of insomnia among chronic hypnotic users²⁵. They are most commonly cognitive behavioural therapies that comprise a combination of relaxation exercises, stimulus control (e.g. limiting bedroom use for sleep), sleep restriction, sleep compression (gradual reduction of time in bed) and cognitive therapy that counters excessive worries about sleep, and education on sleep hygiene. The positive effects are most pronounced on measures of SE, WASO and sleep onset latency (SOL)⁴. Interested readers can refer to Lichstein *et al.*⁴ for a detailed review on the results from clinical trials of each cognitive behavioural therapy (CBT) technique. The role of light therapy in insomnia disorder needs to be further elucidated²⁶.

Pharmacological Treatment of Insomnia Disorder

In general, agents with a short half-life (thus less hangover/daytime sedation), a low dependence potential and a low propensity for disrupting normal sleep architecture are preferred. The newer benzodiazepine agonists including zolpidem, zopiclone, eszopiclone and zaleplon have all been found to be generally safe for short-term use in older adults. Zopiclone might be associated with a mild increase in SWS. For a comprehensive review, readers can refer to Salzman²⁷.

Complementary and Alternative Medicine for Insomnia Disorder

The use of complementary and alternative medicine approaches for sleep disturbances in older adults is widespread. Thus far there is

evidence of the efficacy of melatonin in treatment of circadian rhythm disorders, but its effect is less conclusive in primary and secondary insomnias. Mind–body exercises like meditation, yoga, and Tai Chi showed promising results in open trials; their roles require further evaluation²⁸.

RAPID EYE MOVEMENT SLEEP BEHAVIOUR DISORDER (RSBD OR RBD)

First described by Schenck *et al.* in 1986²⁹, RSBD is now understood to be a parasomnia characterized by abnormal behaviours during REM sleep that cause sleep disruption and/or injury. It is a male-predominant disorder that usually emerges after the fifth decade, although any age group can be affected¹³. The data concerning its prevalence are scant; it was estimated to be 0.5% among the UK general population by a phone survey³⁰ and determined to be around 0.4% in a two-phase study on community-dwelling Chinese elders³¹. It could take an acute form upon REM rebound state (like withdrawal from alcohol or hypnotics) or be precipitated by intake of different antidepressants (except bupropion)²⁹. More commonly, RSBD takes an idiopathic, chronic form which follows a progressively worsening course²⁹.

Patients with RSBD have dream-enactment behaviours during the REM stage of their sleep; they might talk, shout aloud, walk, kick or punch their bed partners, or fall out of bed^{13,32–35}; in clinical series studying US and Chinese populations, about 30 to 50% of patients injure themselves; about 60% hurt their bed partners^{32,34}. The patients often can recall their dreams, which are vivid and contain a high degree of violent/aggressive content that is usually out of keeping with the patient's normal behavioural patterns³⁶.

Moreover, features suggestive of early synucleinopathy including deficit pattern in brain perfusion scans³⁷ and abnormal cardiac autonomic regulation (likely from a loss of cardiac sympathetic terminals) on cardiac ¹²³I-metaiodobenzylguanidine (MIBG) scintigraphy^{38–40} have been reported in patients with idiopathic RSBD. In fact, RSBD also occurs with disproportionately greater frequency in synucleinopathies like multiple system atrophy, Parkinson's disease and dementia with Lewy bodies compared to other neurodegenerative disorders. RSBD has been conceptualized as a manifestation of evolving synucleinopathies⁴¹.

Diagnosis of RSBD is by clinical history, supplemented by video-polysomnographic study⁴². Electromyogram (EMG) during REM sleep reveals an excess of muscle tone or phasic EMG twitch activities¹³. Differential diagnoses include sleep-walking, night terrors, nightmares, nocturnal seizures, obstructive sleep apnoea, posttraumatic stress disorder, dissociative states and nocturnal confusional states³³.

High treatment efficacy (close to 90%) with clonazepam has been found in international studies. Protective measures against injuries during sleep might also be necessary, indicating the importance of the early recognition and management of RSBD^{32–35}.

SLEEP-RELATED MOVEMENT DISORDERS

Sleep-related movement disorders are characterized by stereotyped movements that disturb the sleep of the affected individual and, not uncommonly, their bed partners as well.

Restless legs syndrome (RLS) involves complex movements in the lower limbs to relieve the unpleasant local dysaesthesia (usually a deep-seated sensation described as 'creeping, crawling', 'pins and

needles', 'tearing' and even 'burning' or 'electric-current-like'), which usually take place at night, begin or worsen when the patient is restful and relaxed and are not better explained by another medical disorder^{12,13,43,44}. Low awareness and misdiagnosis of RLS are very common⁴⁴, which add to already significant distress and impairment from sleep disruption. Differential diagnoses include neuropathy, arthritic conditions, or vascular insufficiency in lower limbs, and leg cramps; RLS is distinguished by its high circadian rhythmicity (peak symptoms from midnight to 3 a.m.) and absence of local signs related to the mentioned disorder. Akathisia from antipsychotics is another differential diagnosis; apart from the drug history, features of akathisia are less focal than RLS⁴⁴.

The patho-mechanism for primary RLS is largely unknown. Sub-normal dopamine neurotransmission has been implicated. Currently the only FDA-approved medication for RLS is the dopamine agonist ropinirole⁴³ (although, in suitable cases, other dopamine agonists might be considered, according to the practice guidelines of the American Academy of Sleep Medicine⁴⁵). Low ferritin levels in adult RLS patients have also been reported in a number of studies involving blood tests, neuroimaging and cerebrospinal fluid examination, although the relationship in older individuals appeared less consistent⁴³. Secondary RLS has been recognized in uraemia and pregnancy¹³. Some argued that wandering behaviours in demented individuals might be related to unrecognized RLS⁴⁶. Therefore, drugs used to treat neuropsychiatric symptoms of dementia (e.g. antipsychotics and some antidepressants) might potentially aggravate the condition.

A related condition is *periodic limb movements in sleep (PLMS)* which involves clusters of stereotyped, repeated, non-epileptiform leg jerks (typically involving dorsiflexion of the anterior tibialis muscle, although the movement might involve the hip, or be confined to the toe) taking place at 20–40 second intervals over the course of sleep, with each jerk causing a brief awakening that could be captured on PSG; a diagnosis is made when there are at least five kicks per hour of sleep^{12,43}. The prevalence of PLMS in the elderly is estimated to be relatively high, at 45%¹². It is found in 80–90% of patients with RLS, and is also very common in other primary sleep disorders^{13,43}.

PLMS usually occurs in NREM sleep¹³. Typically, the patient is unaware of the limb movement or the frequent arousals, and might not report sleep dissatisfaction. Usually no treatment is required in such cases. The ICSD criteria require PLMS features occurring in conjunction with clinical sleep disturbance and/or complaint of daytime fatigue for a diagnosis of *periodic limb movement disorder (PLMD)* to be made¹³. Drug treatment with dopamine agonists might also be considered in such cases⁴⁵, along with judicious elimination of drugs (serotonin-specific re-uptake inhibitors (SSRIs), antipsychotics etc.) that might worsen the condition in applicable cases⁴³.

An epidemiological study involving 18 980 adult subjects who were 15 to 100 years old (representative of the general population of five European countries) revealed that the prevalence of RLS, but not PLMD, significantly increased with age. The prevalence of ICSD-based diagnoses of PLMD in older age groups (60 or over) was 3–4% and that of RLS was 8–9%. Risk factors for both disorders include female sex, musculoskeletal disease, heart disease, SDB, cataplexy, intense physical activity close to bedtime and the presence of a mental disorder. Factors solely associated with RLS are advanced age, obesity, hypertension, drinking at least three alcoholic beverages per day, smoking more than 20 cigarettes per day and the use of SSRIs. Factors specific to PLMD include shift-work, coffee intake, use of hypnotics and the presence of stress⁴⁷.

SLEEP-RELATED BREATHING DISORDERS

Sleep-disordered breathing (SDB) is characterized by apnoeas (complete cessation of airflow lasting 10 seconds or more), hypopnoeas (reduction of airflow of 10 seconds or longer, accompanied by an oxygen saturation decreased by 3–4% or more) on sleep PSG⁴⁸. The number of apnoeas and hypopnoeas per hour of sleep is called the *apnoea-hypopnoea index (AHI)*. Apnoeas and hypopnoeas during sleep leads to repeated arousals and hypoxaemia during sleep, and the *respiratory disturbance index (RDI)* refers to the number of apnoeas, hypopnoeas and the respiratory effort-related arousals per hour of sleep⁴⁹. In general, an AHI from 5 to 19 is referred to as mild obstructive sleep apnoea (OSA), an AHI from 20 to 29 as moderate, and 30 and above as severe OSA. When the AHI is 5 or greater and coupled with excessive daytime sleepiness (EDS) the patient is considered to have the OSA syndrome (OSAS)⁴⁹.

Symptomatically, OSAS manifests as loud snoring and daytime somnolence; associated features include headache, insomnia, apnoea and excessive movements observed during sleep, and nocturia and dry mouth on waking. In addition to sleep fragmentation, patients show decreased SWS and SE on PSG¹¹. Complications including elevated cardiovascular morbidities (hypertension, strokes, worsened cardiac functions) and mortalities, and cognitive impairments, especially in the domains of attention and vigilance, executive function, visuospatial learning and motor performance⁴⁹. There are two main types of sleep apnoea: obstructive and central; the former is more common.

The prevalence of SDB rises with age: in middle-aged adults (aged 30–60), the figures for OSA (with AHI 5 or over) are 9% for females and 24% for males; and those for OSAS are 2% and 4%, respectively. In adults aged over 60, the prevalence of OSA is reported to be around 38–62%; there is also a stepwise increase in the prevalence of SDB with each decade of life in old age, which might be due to an increase in central events (readers can refer to Norman and Loreda, 2008⁴⁹ for a review).

It remains unresolved, however, as to whether the clinical significance of SDB in the elderly diminishes as compared to that in their younger counterparts. The association between SDB and body mass index (BMI) and reports of snoring also decrease with ageing^{11,12}. Before further studies are available to cast light on the issue, elderly patients with symptomatic apnoeas or possible cardiovascular and cognitive complications should be treated as younger individuals would be treated. The mainstay of treatment is continuous positive airway pressure (CPAP) during sleep, which provides continuous air pressure, acting as a pneumatic splint to maintain patency of the upper airway. There is evidence that SDB complications might also reverse with this treatment⁴⁹. General measures including weight reduction, and the avoidance of alcohol and sedative medications should also be undertaken.

Compliance to CPAP could be a problem. Alternative options include oral appliance therapy (in elderly persons with full or nearly full dentition), and an array of surgeries designed to improve airflow in the upper airway. There is, however, scant evidence to support the clinical efficacy of these two alternatives in older adults⁴⁹.

SLEEP DISTURBANCES IN DEMENTIA

Sleep disturbances are common in patients with dementia¹²; among patients with Alzheimer's disease (AD) in clinic- and community-based samples, the prevalence varies between 24 and 44%^{50–52}, and is a major cause of caregiver distress and institutionalization^{12,53}.

Characteristic changes include significant sleep fragmentation, reduced SWS and REM sleep, decreased SE and TST, reversal of circadian rhythm, EDS and daytime napping, and 'sundowning' (a nocturnal exacerbation of disruptive behaviour or agitation)^{12,53}. Poor sleep in AD might, in turn, worsen cognitive function⁵³.

Causes of sleep disturbances in AD occur at multiple levels. Intrinsically, accelerated degeneration of the SCN and decreased pineal melatonin secretion might cause circadian rhythm disruptions. Degeneration of the cholinergic neurons in the nucleus basalis of Meynert and pedunculopontine tegmental and laterodorsal tegmental nuclei and noradrenergic neurons of the brainstem may account for decreased REM sleep in AD patients, and predispose them to RSD^{12,52–54}. Degeneration of the brainstem respiratory neurons and those in the supramedullary respiratory pathways may heighten risk for SDB in AD; in fact, the *APOE*4* genotype might be a predisposing factor for SDB in the general population⁵³.

Extrinsic factors might include reduced bright light, diminished daytime activities and increased noise in the environment, especially in group residential facilities. General medical conditions affecting the cardiovascular and respiratory systems and medications might also have negative effects on sleep; for example, cholinesterase inhibitors for dementia might cause vivid dreams and insomnia^{12,52–54}.

Treatment for sleep problems in dementia should likewise be multimodal. Techniques to counter circadian rhythm disturbances may include structured daytime social and physical activities, restriction of time in bed, and bright light, especially in the morning and evening^{12,52–55}. Hypnotics and antipsychotics are often used, although they are more commonly associated with adverse effects like sedation, parkinsonism or orthostatic hypotension and, for a number of antipsychotics, an elevated risk for stroke⁵⁶. Results from randomized controlled trials of melatonin are thus far conflicting⁵⁷. On the other hand, proper identification and treatment of SDB and depression in AD might improve sleep quality and reduce agitation^{53,58}.

CONCLUSIONS AND FUTURE DIRECTIONS

The management of sleep disorders in the elderly is a major public health challenge, given the rapid growth of the older population in most nations, the high prevalence of sleep complaints and variety of sleep disorders in this phase of life, the plethora of co-morbid clinical conditions and environmental factors that are associated with insomnia in seniors, and their greater susceptibility to the side effects of sedative medications in general.

As reviewed in this chapter, current evidence suggests that insomnia is not an inevitable effect of physiological ageing and the corresponding changes in sleep architecture. Given the fact that sleep disturbances are common in the elderly and that many of the underlying causes are reversible, sleep assessment should be a habitual part of their comprehensive clinical evaluation, with the sleep symptoms compared against a carefully taken history of physical and psychiatric conditions, medications, sleep habits and activity schedules, lifestyle changes and residential conditions. Standard sleep questionnaires in indicated cases (e.g. the Pittsburgh Sleep Quality Index) might facilitate the multidimensional evaluation of sleep quality and disturbances. Investigations should be arranged to rule out co-morbid medical conditions, and sleep polysomnography is indicated for cases in which specific sleep disorders like RLS, SDB, or RSD are suspected (readers can refer to Misra and Malow, 2008⁵⁹ for a review).

Future directions for sleep research on the elderly may include longitudinal outcome of insomnia and specific sleep disorders, and further elucidation of the roles of light therapy, enriched activity schedules, complementary medicine and other measures that might potentially enhance the quality of sleep.

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Sexual Disorders

Walter Pierre Bouman

Mental Health Services for Older People, University Hospital, Nottingham, UK

INTRODUCTION

Sexuality is an essential part of any person and expressing it is a basic human need and right of all individuals, including older people. Although sexual functioning and frequency decrease with age¹⁻³, a significant proportion of older people remain sexually active well into advanced old age and many older people continue to enjoy their sex lives. In fact, several cross-sectional studies have shown that sexual satisfaction does not decline with age^{4,5}, and the role and value of sexual activity and intimacy remain important quality of life issues to older people^{5,6}.

Older people can experience sexual problems for all the same reasons as their younger counterparts. Sex research in older women and men emphasizes the widespread prevalence of sexual difficulties⁷⁻⁹, which are strongly correlated with physical and mental health and with satisfaction in the intimate relationship¹⁰⁻¹².

Should a person or a couple wish to continue but experience sexual difficulties they deserve the same access to treatment as younger people. Furthermore, prevention of sexual difficulties in older people should be encouraged, including appropriate counselling before genital surgery¹³, during chronic medical care and after acute medical events such as a myocardial infarction or cerebrovascular accident¹⁴ and the provision of advice on safe sex practices.

HORMONAL CHANGES AND AGEING

In healthy men, testosterone production remains relatively stable until the fifth decade and then decreases slowly over the remainder of the man's life at a rate of about 1.0% per year¹⁵. It is probably mainly a result of testicular ageing, although a rise in sex hormone-binding globulin (SHBG) and testosterone-binding, a relative failure of the hypothalamo-pituitary axis to drive the testes, and a decline in the level of sensitivity of testosterone receptors in the brain also contribute. The decline in circulating testosterone occurring in older men is responsible for the decrease in desire, but not erectile function, although clinically it may be difficult to distinguish reliably between the two complaints¹⁶.

In women, the most prominent biochemical markers of sexual maturation and senescence are the age-related changes in the level of oestrogen and testosterone. The structural integrity of the female genitalia is predominantly maintained by oestrogen. Vaginal dryness and atrophy, dyspareunia and urinary tract symptoms suggest a lack of oestrogen which is more prevalent following the menopause¹⁷.

In healthy women testosterone levels decline markedly until the fourth decade with stable levels during the menopause transition. Testosterone levels then increase slowly over the rest of the life span¹⁸.

AGE-RELATED CHANGES AND SEXUAL RESPONSE

Master and Johnson's¹⁹ landmark research in the physiology of sexual responses have provided important information regarding sexuality and ageing, although their sample size was small. In both sexes, as one ages, the speed and intensity of the various vasocongestive responses to sexual stimulation tend to be reduced. In men all responses are slower and less intense from nipple and penile erection to rectal orgasmic contractions. An erection takes longer to develop and usually requires more direct tactile stimulation. The period of sustaining an erection gets shorter.

Ejaculation becomes less powerful with fewer contractions and seminal fluid volume is reduced. The point of ejaculatory inevitability becomes more difficult to recognize. Resolution following orgasm is rapid, with loss of erection occurring within seconds and the refractory period is markedly longer in comparison to younger men, sometimes extending to more than a day. In women the responses parallel those of the male. Increased time is required to become sexually aroused and vaginal lubrication is slower and less marked. Orgasms tend to be less intense and there is an increased need for stimulation to become orgasmic. There is no change in the ability to have orgasms, although multiple orgasms are less likely to occur. Resolution is more rapid.

Many older people are unaware of the normal age-related changes in sexual response that accompany ageing and are perplexed or put off by changes in their own or their partner's sexual response. If not appreciated, these changes are easily misinterpreted as sexual dysfunction. Explicit information about changes in sexual physiology with ageing can help eliminate false expectations and can permit modification in longstanding sexual practices that may have become counterproductive. Couples can be advised, for example, not to delay sexual exchange until late at night when tiredness or sleepiness may be great but, rather, to schedule their sexual encounters at a time of greater energy and alertness.

Similarly, increased manual or oral stimulation of the penis may be necessary to achieve an adequate erection for intercourse and may augment the effects of pharmacological therapy²⁰. The female

partner is often unaware of this important physiological change in her partner, and may misattribute his lack of erection to sexual disinterest or her loss of sexual attractiveness to her partner²¹.

Many older couples indicate they would enjoy greater sexual experimentation in their relationship, even though many have minimal experience of foreplay or non-intercourse forms of sexual stimulation²². While the overall decline of the sexual responses may seem gloomy and unpleasant, this process tends to develop extremely gradually, allowing an individual or a couple to adjust to a less intense, but not necessarily less enjoyable form of sexual activity.

EFFECTS OF ILLNESS AND MEDICATION ON SEXUALITY

One of the most frequent reasons given by older people for stopping sexual activity is the onset of illness; this may operate through a number of different mechanisms. Physical illness may generate unfounded anxieties about the risks of sexual activity (as in heart disease or stroke); it may make intercourse difficult, exhausting or painful (as in respiratory disease, arthritis and (sexually transmitted) infection); or it may impair responsiveness of the sexual organs (as in diabetes mellitus or peripheral vascular disease).

Illness may further undermine self-confidence and the feeling of attractiveness (as in mutilating operations such as mastectomy or colostomy), and it may have a direct effect in reducing sexual desire (as in depression, chronic renal or hepatic failure, and Parkinson's disease). Older people in general are more likely to suffer from a variety of chronic diseases which may impact on their sexual function²³. They also commonly undergo surgery, which may influence sexual function, either because of psychological sequelae or as a result of organic damage¹⁶.

If illness has reduced the capacity to respond to sexual stimulation, and this is something a couple cannot understand or discuss, then they cannot resolve this difficulty. In a relationship where the assumption was that the man always takes the active role in sexual exchange, his partner may be quite unused to stroking his penis as part of their preparation for intercourse, and may find it difficult to help him if this is what he requires. Similarly, if there is a transition from an equal partnership to one of caregiver and patient due to severe illness the latter may lose the self-esteem which reassures him that he is still contributing to the relationship; or the caring partner may think it unkind and selfish to make demands on the sexual responsiveness of the one who is ill. Particularly if there is a lack of communication around sexual issues, sexual relationship changes may never be adequately worked out. But even simple actions can have far-reaching effects, such as when a couple decide they should sleep apart so as to give the ill partner a better night's rest, resulting in a potential reduction of closeness and intimacy.

Furthermore, a substantial proportion of older people take medication, and often there is considerable polypharmacy. The list of drugs that can interfere with sexual function is extensive and the most widely prescribed drugs are mentioned^{24,25} (Table 112.1).

Where drug-induced sexual dysfunction is suspected, discontinuing the suspected medication or substituting with a different agent can usually resolve the question.

Occasionally medication can enhance (or overstimulate) sexual function, which has been described with trazodone^{26,27} and L-dopa²⁸.

Table 112.1 Drugs associated with sexual dysfunction^{24,25}

Anticonvulsants
Antidepressants
Antihypertensives
Antipsychotics
Benzodiazepines
Chemotherapeutic agents
Digoxin
Diuretics
H ₂ receptor blockers
Illegal substances ('street' drugs)
Lipid-lowering agents
Lithium
Opioids

SEXUAL PROBLEMS AND AGEING

Generally, the complaints in older people differ little from those of younger people who seek help for their sexual problems; they may have psychological or physical origins, or both. Fear of poor performance, lack of, or diminished sexual desire, difficulty becoming sexually aroused either physically or psychologically, difficulty maintaining an erection, difficulty achieving orgasm, and pain or discomfort with sexual activity, especially during intercourse, as well as a lack of opportunities for sexual encounters are among the most common of the complaints that older people present with^{21,29,30}.

Sexual dysfunction may also arise simply from a lack of information about the normal age-related changes in sexual physiology. A slower onset of erectile function, or a reduced need to ejaculate, may be interpreted by the man as the onset of impotence, or by the woman as a sign of declining interest in her; and their fearful or offended reactions may then aggravate the difficulty. Similarly, a reduced vaginal lubrication response may cause pain and discomfort during intercourse, leading the woman to avoid further sexual intimacy, which may be interpreted by the man as a rejection of the love he wants to express.

In addition to these problems, older people may mourn or regret changes in their body – its size, shape and firmness may differ significantly from the past. They may complain, as well, about the changing body of their partner, the reduction in, or loss of, passion and attention given to emotional and sexual intimacy, sexual boredom, jealousy of younger potential rivals and changes in sexual urgency or intensity. Menopause, surgery and various losses, both psychological and physical, can exacerbate these complaints.

Despite prevailing preconceptions, many older people are willing and open to address their sexual difficulties. Research suggests that if sex was a source of pleasure and gratification during early and middle adulthood, it will probably continue to be an important source of life satisfaction as one grows older³¹. On the other hand, it must be acknowledged that there remain many older people who grew up in fundamental and traditional households in which sexually proscriptive values and beliefs persist. For these individuals, sex is sanctioned primarily for procreation; sexual behaviours other than intercourse, such as oral–genital sex, are considered unnatural; sexual relations outside marriage are forbidden; and masturbation is sinful. For such individuals, the opportunity to 'retire' from an active sexual life may be ardently anticipated and easily accepted.

SEXUAL DISORDER IN OLDER MEN

Erectile Dysfunction

Erectile dysfunction is the persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection. It is the most common sexual disorder in older men and may be the first harbinger of cardiovascular disease³². The increase in the prevalence of erectile dysfunction in ageing men is well documented. The Massachusetts Male Aging Study surveyed 1290 men ranging in age from 40 to 70 years from the Boston area²⁸. A definite relationship was found between age and the probability of erectile dysfunction, such that the probability of severe erectile dysfunction tripled from 5.1% to 15% in men between 40 and 70 years, and the probability of moderate erectile dysfunction doubled from 17% to 34%.

The oral phosphodiesterase type 5 (PDE5) inhibitors, which include sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra), have significantly improved the treatment of erectile dysfunction³³. A concomitant essential part of first-line treatment for erectile dysfunction is the modification of risk factors, which include ischaemic heart disease, hypertension, diabetes mellitus, dyslipidaemia, depression, cigarette smoking, use of recreational or medically indicated drugs and alcohol misuse; this is vital in order to improve erectile function and the patient's response to treatment.

Despite the safety, efficacy and tolerability of PDE5 inhibitors, 30–35% of patients fail to respond³⁴. Educating patients on the correct use of these drugs can increase efficacy³⁵. Other treatment options include a vacuum constriction device³⁶, intracavernosal³⁷ and intraurethral³⁸ administration of alprostadil, psychosexual counselling, androgen replacement and penile prosthesis implantation. Despite the growing clinical evidence that combination treatment may be successful in men for whom monotherapy fails, research is lacking to establish the benefits, optimal dosage, possible adverse effects and acceptability to patients of these treatments.

Hypoactive Sexual Desire

Hypoactive sexual desire is described as a deficiency or absence of sexual fantasies and desire for sexual activity and can be caused by organic and psychosocial factors. It is considered a disorder if it causes significant distress or relationship problems. It is not an uncommon condition in older men although objective epidemiological data are lacking.

Schiavi¹⁶ found a prevalence as high as 17% in a highly selected sample of 236 men with a mean age of 65.7 years although the vast majority also had a diagnosis of erectile dysfunction. As sexual desire is androgen-dependent its loss can be caused by deficient androgenic stimulation. This may result from decreased testosterone secretion or increased production of sex hormone-binding proteins, causing decreased circulating free testosterone. The diagnosis of hypogonadism in older men can be difficult where there is a discrepancy between symptoms and endocrine assay results³⁹, so specialist advice is usually required.

Any therapeutic trial of androgen treatment must be preceded by exclusion of prostate cancer. A common psychosocial cause for loss of sexual desire in a long-term relationship is habituation and routine¹¹. Couples should be encouraged to bring variety into their sexual script to prevent or overcome this problem. Depression should also be considered as a cause for loss of sexual desire.

Ejaculation Disorders

Premature ejaculation can prompt an older man to seek treatment, but it is a rare presentation at this age compared to younger men⁴⁰. It may have been a life-long problem with the man presenting for consultation when he finds himself in a new sexual relationship. Alternatively, and more commonly premature ejaculation occurs for the first time as a reflection of the man's feeling of erectile insecurity – he ejaculates quickly before he loses his erection. Treatment should then focus on improving erectile function. Rarely, the onset of premature ejaculation may result from neurological or prostatic disease, and clinical examination is therefore necessary.

In the absence of controlled research data, clinical experience suggests that cognitive behavioural approaches to premature ejaculation such as the stop–start and squeeze techniques⁴¹ are usually ineffective in older men. Treatment with serotonergic antidepressants are highly effective⁴², but side effects can be troublesome. Currently these drugs are not licensed to treat premature ejaculation.

More frequent than premature ejaculation is delayed or failed ejaculation, which troubles many older men. This may be a reflection of ageing but can also result from inadequate stimulation. Reduced force of ejaculation, a decrease in the volume of ejaculate and decreased ejaculatory sensation are common age-related effects. Regular pelvic floor exercises may improve ejaculatory sensation.

SEXUAL DISORDER IN OLDER WOMEN

Hypoactive Sexual Desire

Desire problems are the most common sexual problem of older women. A recent nationally representative probability sample of community-dwelling persons 57–85 years of age from households across the United States yielded a prevalence rate of 43%, closely followed by 39% of the sample complaining of arousal difficulties³. The majority of studies investigating sexual desire in this population report similar findings⁴³ – a reduction in sexual thoughts or fantasy as well as a reduction in sexual intercourse. As in men, the age-related decrease in sexual desire is caused by a variety of factors including the age, health, sexual desire and sexual problems of both the woman and her partner, relationship satisfaction, the woman's past level of sexual satisfaction, sexual comfort and sexual interest, medication affecting sexual response that either she or her partner is taking, and finally, the effects of the hormonal changes following the menopause. Although a reduction or lack of desire is common in older women, it does not signal the end of sexual pleasure.

Sexual Arousal Disorder

As with reduced (hypoactive) sexual desire, changes in sexual arousal are also caused by many factors in addition to the postmenopausal hormonal changes. More than a decade ago Goldstein *et al.*⁴⁴ showed that arousal difficulties in older women may be exacerbated or caused by atherosclerotic vascular disease, which results in delayed vaginal engorgement, diminished vaginal lubrication, pain or discomfort with intercourse, and decreased vaginal and clitoral sensations and orgasm. Since then the use of vasoactive drugs has been evaluated by many pharmaceutical companies as a means of enhancing sexual arousal in women, but to date no treatment has been approved.

Dyspareunia

Dyspareunia is described as recurrent or persistent pain associated with sexual intercourse. It is probably one of the most common sexual

complaints of older women seeking gynaecological consultation⁴⁵. Pain that occurs in the absence of any infection or inflammation may indicate insufficient vaginal lubrication or incomplete arousal, so that the inner part of the vagina does not expand to make space for penetration. Lubricants and topical low-dose oestrogen treatment are available, if indicated. Alternatively, vulvodynia, which causes exquisite pain to the touch could be present, and this would require gynaecological assessment and possibly medication.

Orgasmic Difficulties

Some women experience changes in their orgasm with ageing, notably changes in the duration of orgasm, the ease and reliability of orgasm, and the number of uterine and vaginal contractions which accompany orgasm. Women who have lost their uterus and/or ovaries may have greater difficulty becoming sexually aroused and orgasmic because the uterus may contribute to arousal and orgasmic contractions. On the other hand the clitoris can be quite effective in providing erotic sensations and the ability to remain multi-orgasmic continues²¹.

COMMON SEXUAL PROBLEMS IN COUPLES

A number of common sexual difficulties may come up during consultation which can be helped by relatively simple advice and education. They include (i) when to restart sexual intercourse after a myocardial infarction or cerebrovascular accident; (ii) identifying different positions and different timing for analgesic medication for intercourse when arthritis or pain is a problem; and (iii) how long to wait before resuming sexual activity and how much activity to attempt after surgery. It should be pointed out that weakness may hinder usual sexual activity and 'going slow' may be the optimum approach. Concrete examples, such as 'if you can walk a flight of stairs without shortness of breath, you can resume intercourse' may be helpful.

With patients or partners who have undergone mutilative surgery, mastectomy or ostomies, it is important to address fears of causing pain and the need to respond to fears of rejection because of drastic changes in body image. The healthy partner may be reluctant to discuss feelings of revulsion or contagion⁴⁶.

If intercourse is no longer a possibility, masturbation should be discussed as another source of self-pleasuring and as an appropriate activity to enhance individual or couple-pleasuring activities. Depending upon the individual's religious and cultural background, masturbation may not be perceived as an appropriate or comfortable option. If this is not the case, discussing the subject, and giving implicit permission, may be all that is needed to enable the couple to begin engaging in sexual exchange again.

CONCLUSION

What are the implications for clinical practice of this chapter? Physicians and other health care staff are generally known to feel embarrassed and to lack confidence in their ability to take an appropriate sexual history. This is particularly so when the patients' personal characteristics (such as their gender, age and sexual orientation) differ from their own⁴⁷. This may especially disadvantage older people who are already assumed to be invisible and post sexual by society. Such people may be even less likely than most to approach health care staff with sexual problems and concerns, although research shows that most people hope that their physician will approach them⁴⁸.

Given that sex plays an increasingly important role in the lives of older women and men clinicians should ask – and be trained to ask – every patient, regardless of age, 'Are you experiencing any sexual problems or concerns?' The principles of taking a sexual history are not altered by the age of the patient⁴⁹. Clinical competency in discussing sexual issues in an open and non-judgemental manner, and the level of training received in dealing with sexuality, is a major factor in determining how sexual problems present or whether they are presented at all.

One can only speculate on the number of patients who set out to seek advice for their sexual difficulty, but fail because of the discouraging response from the clinician involved. Although clinicians may feel awkward and unskilled, the very willingness to discuss sexual problems offers the patient an opportunity that society rarely provides. Physicians in particular are not only well placed to normalize and affirm the value of fulfilling sexual relations for the well-being of the older patient, but also have a responsibility to ensure that their sexual concerns and problems are appropriately and adequately addressed and managed.

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Cultural Differences, Service Provision and Training in Old Age Psychiatry

Assessing Mental Health in Different Cultures

Rob Butler¹, Sati Sembhi¹ and Melanie Abas²

¹*Suffolk Mental Health Partnership NHS Trust, St Clement's Hospital, Ipswich, Suffolk, UK*

²*Institute of Psychiatry, Kings College London, London, UK*

INTRODUCTION

Assessing older people from different cultures requires a broad set of skills. Older people have acquired a wealth of life experience and knowledge. Clinicians need to understand how this and culture shapes their presentation and symptoms of mental disorders. Clinicians also need to be aware of their own cultural identity and to have some knowledge about customs and religions in different countries. Assessing older people includes asking about life history, social and family circumstances, and preferences for service delivery. This chapter offers an overview of how cultural competence can help with the clinical assessment. It includes some specific pointers for assessing depression, psychosis and dementia. It is worth noting that, due to a range of barriers, many older people from different cultures have poor access to psychiatric care and face a 'triple jeopardy' of disadvantage in terms of age, ethnicity and socioeconomic deprivation¹⁻³.

CULTURAL COMPETENCE

Culture is a network of knowledge, meanings, ideas and social rules shared by a group, often referred to as an ethnic group, who may also share geographical origins, religion and language. Culture will affect how illness is understood, the presentation of symptoms, and expectations regarding treatment and treatment choice⁴. The culture of the clinician will often differ to some extent from that of the patient⁵. The clinical setting in which treatment occurs has its own culture, which in turn influences the clinical relationship. Cultural competence means having an awareness of all three dimensions – that is, the culture of the older person, the culture of the clinician and the cultural setting – even when these are not obvious⁴. A culturally competent clinician can recognize the diversity of viewpoints, is willing to seek background cultural information from other members of the ethnic group or experts, and is flexible in approaching the doctor–patient relationship⁴. It should be appreciated that, in today's multicultural world, many people move between or within different cultures, and so it is important to avoid making assumptions about a patient's background which can lead to ethnic stereotyping⁶. Awareness of one's own culture and of potentially strong feelings about another's culture is important. Respectful enquiry and a desire

to learn about other lifestyles is the only way to engage with a patient's lived experience of ethnicity and its role in determining what is important for them. One consequence of cultural differences is that occasionally a patient may interpret a well-intentioned enquiry as intrusive or stigmatizing⁶. The Explanatory Models Approach is a method of understanding symptoms without making cultural assumptions⁶. The following questions form the basis of a discussion which explores the patient's experience and perception of illness:

What do you call this problem?
 What do you believe is the cause of this problem?
 What course do you expect it to take? How serious is it?
 What do you think this problem does inside your body?
 How does it affect your body and your mind?
 What do you fear most about this condition?
 What do you fear most about the treatment?

ASSESSMENT

The patient should be asked early on about his or her background and, for migrants, his or her place of origin, experience of migration and existence in the new setting. The clinician will sometimes need to work hard to develop rapport and trust. Within reasonable professional boundaries, the clinician should be willing to respond to any questions about him or herself. For example, with older Jamaican migrants, making 'a connection' with the doctor has been found to facilitate the assessment and acceptance of care⁷. The power imbalance in the patient–doctor relationship may evoke feelings of mistrust, particularly when the patient has been subject to discrimination. The clinician should be willing to discuss issues such as racism and social needs. It is helpful to show sensitivity, but not to neglect important areas on 'cultural' grounds (e.g. alcohol consumption in the case of Muslims). Ideas that appear persecutory must be explored and may reflect an appropriate response to injustice. History-taking should include use of traditional medicines and complementary treatments. Enquiries about spirituality may reveal deeply held views which are important for the patient to follow as part of recovery. Attitudes to death, widowhood and care homes may vary considerably. Consultation may be needed with a wide circle of people from the relevant culture.

FAMILY AND CARERS

Assessment will naturally include family and carers' roles and needs. The levels of caregiver stress, burden and depression vary across cultures. The use of prayer, faith or religion may be used as a coping mechanism. There may be a difference between generations in adapting to a new culture, for example because of fewer opportunities for older people to learn a new language or make social contacts at work. This may exaggerate differences between generations. Many groups, including refugees, may not have family support in their adopted country.

COMMUNICATION

Requiring patients to speak in a non-native language can distort the clinical picture. Language barriers can be reduced by employing an ethnically close bilingual worker. Alternatively, you can use a competent interpreting and advocacy service, preferably with individuals with experience in the mental health field. Some local services and national bodies, such as the Royal College of Psychiatrists in the UK, keep lists of psychiatrists who can speak different languages.

Using interpreters is a skill, and training is available for the effective use of such services. Before they begin, the clinician and interpreter should discuss their expectations of each other and of how the interview should proceed. It should be confirmed whether the interpreter's role will be confined to translating or will extend to advising on non-verbal communication and cultural appropriateness. The clinician should be aware that even though an interpreter may be from the same country as the patient, differences in class, gender, religion, tribal group and so on may limit their ability to accurately interpret their culture. Idioms and jokes should be avoided. The patient should be addressed in the second person. Clear, concise language should be used and interpreters given manageable chunks to translate. Sometimes, word-for-word translation will be needed rather than the interpreter's summary. The interpreter should be able to give an indication of language use and structure to aid assessment of formal thought disorder. The assessment will be more time-consuming and tiring for the patient, possibly requiring more than one session. Misunderstandings and miscommunications may occur even with trained clinical interpreters, often because information is skewed to fit the interpreter's or clinician's viewpoint⁸.

Aspects of non-verbal communication differ, such as avoidance of direct eye-to-eye contact in some Asian and Pacific cultures. Many cultures do not shake hands. There are differences in expression, gesticulation, speech patterns and communication styles. In some cultures, saying 'yes' may not indicate an affirmative response but be a mark of respect or deference to the doctor. There may be taboo subjects, such as the discussion of death in some Asian cultures.

CONFIDENTIALITY

In cultures with an individual focus, the expectation is that the patient is assessed alone and confidentiality between patient and clinician maintained. However, in cultures where the social group is more dominant, family members may expect to play a full role in the assessment, and have access to all information. Equally, the family might have strong views about topics they do not want disclosed to the older person. Taking the time to talk this through will usually help in finding a compromise. It is important to explain where the information you collect will be stored and who will have access to

it. Third-party information should be identified in case the privacy of the informant is infringed.

ASSESSMENT TOOLS

Most screening instruments, assessment tools and diagnostic schedules have been developed within a certain cultural setting. This means that they may lack validity if applied without modification to people from different cultures. The clinician is likely to need more time and perhaps a wider set of informants to assess psychiatric history and symptoms, in order to ensure diagnostic accuracy. Some specific examples of instruments for depression, functional psychosis and dementia are given below. A research tool developed for use in one culture will likely need to be adapted and translated, and then undergo reassessment for reliability and validity, before being used in a different culture^{9,10}.

DIFFERENT PRESENTATIONS OF EMOTIONAL DISTRESS

People from all cultures experience both somatic and psychological symptoms when emotionally distressed. One reason for a more somatic presentation may be that this is considered a more appropriate focus for medical consultation by some cultures. Secondly, there may be a continuum of experience and interpretation, with the more 'somatizing' culture at one end and the more 'psychologizing' at the other¹¹. Finally, a large number of 'somatic' complaints are actually metaphors for mental distress. Many of these relate to heart discomfort (e.g. a heart that is 'sinking' or 'uncomfortable') and to abdominal sensation¹². Culture-bound syndromes often represent cultural explanations for recognizable mental disorders¹³. For example, dhat, a belief that semen is leaking from the body in urine, is a complaint in India. It may be a presenting feature, and is used as an explanation for weakness due to depression or organic disease.

DEPRESSION

There has been much debate about the existence of depression as a universal cross-cultural category¹¹. However, it is reasonably well established that depressive disorders exist across cultures and are very strongly related to local constructs¹². While there are similarities in the cross-cultural expression and experience of depression, there are also differences. For example, depressed older Jamaicans and African Americans may describe feeling 'low', 'bad' or 'fed-up'⁷, or they may have multiple somatic symptoms, or they may present metaphors for psychological distress. Some cultures emphasize their explanation (e.g. social or spiritual) for their symptoms. Depression in old age may be more difficult to recognize because symptoms such as poor concentration or lack of interest can mimic dementia, and carers may perceive them as an inevitable part of ageing. The validity of screening scales may vary; for example, a lower cut-off point for the Geriatric Depression Scale has been recommended for older African Caribbeans¹⁴. The prevalence of depressive symptoms and probable depression in older people varies across Europe and appears not to simply reflect differences in age, gender, education or cognitive function¹⁵. Depression at community level also appears to be highly correlated with anxiety¹⁶. As a result, it is important to enquire about the *full* range of affective and other symptoms; and a wide definition of mood disorders is likely to be most useful in the clinical setting. Cultures vary in the acceptability of suicide,

ranging from a belief that it is an acceptable way to avoid dishonour to a belief that it is never acceptable and is always a sin. Islam forbids self-killing; the Muslim person who expresses the wish that God 'takes back' his life may be indicating he has suicidal thoughts which must be taken seriously.

PSYCHOSIS

Psychotic symptoms and signs are similar in form across a wide variety of settings¹⁷. However, the content of delusions and hallucinations will be influenced by culture. Also, the patient's and family's explanation for the illness will depend on their cultural framework¹⁸. For example, someone from Zambia who upholds traditional explanatory models may explain schizophrenia in the same way as they might explain a stroke, depression or a burglary – as being due to bewitchment or to having angered a spirit. An apparently unusual idea, such as believing oneself to be bewitched, is only a delusion if it is out of keeping with the beliefs of others in the same culture. This can be explored by asking someone with appropriate knowledge. If faced with the patient alone, the clinician should ask how he or she came to believe this, and if others close to him or her agree. If a traditional healer told him or her so, and his or her peers agree, then it is at least likely that this is a culturally sanctioned belief. Another error is to assume that a belief is culturally normal when it is actually abnormal.

DEMENTIA

The prevalence of dementia is increasing worldwide as populations grow and people live longer. New tools are being validated across countries^{10,19}. However, dementia is frequently unrecognized or misunderstood, and some languages lack wording for such impairment. Diagnostic criteria for dementia require the demonstration of cognitive impairment of sufficient severity to interfere with activities of daily living. Cultures vary in the extent to which they expect older people to take responsibility for aspects of daily living, such as domestic activities. Also, physical impairment is more common in socially disadvantaged people and will be difficult to distinguish from that due to dementia, requiring greater emphasis on physical examination and tests. Many cognitive tests include items affected by education and may have little relevance in certain cultures (e.g. 'take 7 from 100'). Bilingual immigrants often lose their adopted language quicker than their native one, leading to a possible overestimation of impairment. When testing those unfamiliar with such approaches, the clinician should be courteous and encouraging without 'helping', and give explicit instructions and some dummy tasks to allay anxiety. Rather than doggedly adhering to the original version of instruments, it is appropriate either to make rational adaptations or to develop new instruments. Novel adaptations will, of course, require translation, back-translation and retesting⁹. The Community Screening Instrument for Dementia⁹ combines culture-fair cognitive testing with a structured informant interview. Fully operationalized criteria appear to improve measurement of dementia in cross-cultural research¹⁹.

CONCLUSION

Training in cultural psychiatry needs to form an integral part of mental health training for clinicians²⁰. Rather than regarding the

acquisition of cultural competence as useful only in rare and exotic situations, it should be seen as an extension of good clinical skills. In the UK, the Royal College of Psychiatrists has developed a Race Equality Action Plan that emphasizes the importance of cultural capability in core training and education²¹. Clinicians are keen to acquire skills in the assessment and delivery of care to people from different cultures, and they should receive regular training in cultural capability, awareness, appropriateness and sensitivity to improve their knowledge, skills and attitudes²².

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The Cross-Cultural Epidemiology of Mental Illness in Old Age

Martin Prince

*Centre for Global Mental Health, Department of Health Service and Population Research,
Institute of Psychiatry, King's College London, UK*

BACKGROUND

Discussion of the mental health of 'older people' most often focuses on those aged 65 years and over – that is, above the most frequent, statutory retirement age in Western nations¹. This is arbitrary and culture-specific, and for research in low- and middle-income countries (LMIC) the cut-point is often set at 60 years. According to the Global Burden of Disease report, neuropsychiatric disorders account for 13.5% of the global burden of disease, and 27.5% of that attributable to non-communicable diseases (NCD)², while for those aged 60 years the proportion is smaller – 7.4% of the global burden of disease and 8.3% of that arising from non-communicable diseases. While the prevalence of dementia rises sharply in later life, doubling with every five-year increase of age, that of depression is, perhaps, a little lower than among younger adults. Many people with chronic severe psychosis do not survive into old age, and there is a small incidence of late-onset psychosis. However, mental ill health in later life poses particular challenges for public health. Health profiles among older people, particularly the oldest old, are somewhat distinct, with mental ill health often complicated by co-morbidity with chronic physical and cognitive disorders, a combination that is particularly strongly associated with disability and dependency. Beyond the challenges of living with chronic disease and disability, further obstacles to the maintenance of good mental health into late life include retirement (loss of occupational role, status and income) and a shrinking social network (loss of spouses, siblings and friends through bereavement)¹.

Older people, their health and social welfare, have for too long been under-prioritized in global public health policy. This is now changing with increasing recognition, over the past 20 years, of their growing importance in LMIC³. Demographic ageing is proceeding more rapidly than first anticipated in all world regions, particularly China, India and Latin America⁴. The proportion of older people increases as mortality falls and life expectancy increases. Population growth slows as fertility declines to replacement levels. In the 30 years up to 2020 the oldest sector of the population will have increased by 200% in LMIC as compared to 68% in the developed world⁵. By 2020, two-thirds of all those over 60 will be living in LMIC⁶, where, in the accompanying health transition, non-communicable diseases assume a progressively greater significance. NCDs are already the leading

cause of death in all world regions apart from sub-Saharan Africa. Of the 35 million deaths in 2005 from NCDs, 80% will have been in LMIC⁷. This is partly because most of the world's older people live in these regions. However, changing lifestyles and patterns of risk exposure also contribute. Among the NCDs, dementia and depression in older people have only fairly recently begun to be given the attention that they deserve in population-based research in LMIC. The purpose of this chapter is to describe the contribution of this research to our understanding of the epidemiology of these disorders, to contextualize these findings with what has been observed in high-income countries (HIC), and to describe some of the methodological challenges to be overcome in conducting this research in varied cultural settings.

DEPRESSION IN LATE-LIFE

'Depression', as a diagnosis applied in clinical settings, generally requires persistent and pervasive low mood and/or loss of pleasure, accompanied by other characteristic symptoms (including guilt, sleep and appetite disturbance), sufficient to cause significant distress and disability⁸. However, mood states do not fall naturally into discrete categories, but instead represent a spectrum from normality through increasing degrees of morbidity. As with any 'cut-off' applied to an underlying continuum (e.g. hypertension), the prevalence of the disorder depends substantially on the threshold that is selected. Severe depressive disorders have a high individual impact on those affected, but are rare. Milder syndromes have a lower individual impact but, given their higher prevalence, may have a substantially greater public health impact.

The Cross-Cultural Validity of the Assessment and Diagnosis of Late-Life Depression

There is reasonably strong evidence to support the cross-cultural validity of measurement of depression among older people. This has been most extensively studied with respect to the 12-item EURO-D depression symptom scale, which has been shown to have a similar factor structure in 14 European sites⁹, as well as in India, China and Latin America¹⁰. Measurement invariance was later formally

established for the EURO-D across 10 European countries in the SHARE study, using confirmatory factor analysis to confirm a common factor structure and Mokken analysis to confirm a common hierarchical relationship between items¹¹. The subsequent demonstration of higher levels of EURO-D depression symptoms among older people in three countries sharing a 'Latin' ethno-lingual heritage; France, Spain and Italy; after standardizing for age, sex, education and cognitive function suggested a possible role of culture in determining risk¹². In terms of clinical diagnostic assessments of depression, the strongest evidence for cross-cultural validity exists for the Geriatric Mental State and its AGE-CAT algorithm, probably the most widely used such assessment internationally¹³. The instrument has been validated against most major diagnostic systems, but primarily only in HIC settings¹³. As part of the 10/66 Dementia Research Group's pilot studies in 26 centres in Latin America, India, China, Nigeria and Russia, its Stage 1 AGE-CAT depression algorithm was found to have sensitivity varying between 89% and 100% by region against a criterion of MADRS score of 18¹⁰. Specificity was difficult to establish, since depression was not formally excluded from the control groups, whose main purpose was to validate the dementia component of the algorithm. Nevertheless, the prevalence of AGE-CAT depression was negligible in these groups other than in Latin American sites¹⁰. The AGE-CAT depression algorithm was subsequently validated in Hefei City, China, where there was a diagnostic agreement of 83.6% and a Kappa of 0.67 against Chinese psychiatrists' independent gold standard diagnostic evaluation¹⁴.

In the absence of qualitative research demonstrating the ecological validity of late-life depression as a pathological construct, the evidence for the cross-cultural validity of the commonly used ICD-10 and DSM-IV clinical diagnostic criteria among older people in LMIC is limited mainly to concurrent validation, that is from observations of cross-sectional associations with disability and impaired quality of life. In Nigeria¹⁵ and Brazil¹⁶, depression diagnosed was associated with high levels of social disability and impaired quality of life. In Mexico, Peru and Venezuela, high levels of disability were also identified in those with sub-syndromal depression identified with the EURO-D scale, suggesting a considerable prevalence (an additional 23–24%) of clinically significant disorder beyond the established diagnostic boundaries¹⁷. More research is needed to determine if these findings are typical of less developed regions in general.

The Prevalence of Late-Life Depression

The prevalence of late-life depression has been extensively studied in developed countries in the European, North America and Asia Pacific regions^{18,19}. The main influence on prevalence is the criterion used to make the diagnosis²⁰. According to rigorous research diagnostic criteria such as the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* major depression and the *International Classification of Diseases, Tenth Edition (ICD-10)* depressive episode late-life depression is uncommon with a weighted mean prevalence of only 1.8%; when all those with clinically relevant symptoms are included, the weighted mean prevalence rises to 13.3%¹⁸. The relative lack of epidemiological data from LMIC is particularly striking – in the two systematic reviews, all of the 34 publications covering the period 1989–96¹⁸ and the 122 papers covering the period 1993–2004¹⁹ described research carried out in high-income countries. Recently published prevalence studies from Nigeria, Brazil, Latin America and China have helped to redress this imbalance. Two publications report

an exceptionally high prevalence of DSM-IV major depression in Nigeria (7.1%)¹⁵ and of ICD-10 depressive episode in Brazil (19.2%)¹⁶. The 10/66 Dementia Research Group has also recently reported on the prevalence of ICD-10 and DSM-IV depression in three Latin American countries, Mexico, Peru and Venezuela, which in these settings was closer to that reported in HIC, the prevalence of DSM-IV depression varying between 1.3 and 2.8% and that of ICD-10 depression between 4.5 and 5.1%¹⁷. Conversely, the prevalence of GMS/AGE-CAT depression in Hefei City, China, was only 2.2%, roughly five times lower than in European studies using the same assessment and case definition¹⁴. The prevalence in a rural village in Anhui province was slightly higher, at 6.0%²¹.

In the few studies in LMIC to have examined this issue, treatment of clinically significant depression seems to be severely sub-optimal – in the 10/66 Latin American studies only 24.1% of those in urban Peru with a current ICD-10 depressive episode, 18.8% in rural Peru, 11.8% in urban Mexico, 4.4% in rural Mexico and 19.6% in Venezuela reported ever having received in-patient or out-patient treatment for depression¹⁷. In Nigeria, only 37% of lifetime cases had received any treatment¹⁵.

Sociodemographic Correlates of Late-Life Depression

The few studies to have assessed prevalence of depressive disorders across the adult age range suggest an increase from young to mid-adult age groups, followed by a fall in prevalence for older people within a decade of the retirement age^{22,23}. A striking trend in the opposite direction has been observed in Nigeria, the authors speculating that lack of social protection for older people may have contributed to their much higher prevalence of DSM-IV major depressive disorder.¹⁵ Studies from HIC that have focused upon depressive symptoms and broader depressive syndromes also indicate either an increase in their frequency²⁴ or stability with increasing age²⁵. The exclusion, in some diagnostic criteria, of symptoms thought to be attributable to bereavement and physical illness may account in part for the apparent lower prevalence of depressive disorders in older people. In European studies, the prevalence of late-life depression is consistently higher in women compared to men^{12,24}, but the gender difference tends to be smaller than that found in mid-life. In European studies, the effect of gender is consistently modified by marital status, with marriage being protective for men but associated with higher risk among women²⁴. A higher prevalence of late-life depressive disorder among women is also a consistent finding in studies in LMIC, replicated in Brazil¹⁶, Nigeria¹⁵ and the 10/66 Dementia Research Group Latin American studies¹⁷. However, in the 10/66 studies the association with female gender was entirely confounded by socioeconomic status and physical impairment, both of which were more common in women – a similar finding was reported in the SABE studies in six Latin American cities, although depression in that study was defined by a cutpoint on the Geriatric Depression Scale rather than a clinical diagnosis²⁶.

There have been many reports from cross-sectional community surveys, from a variety of cultures, of associations between late-life depression and socioeconomic disadvantage, for example with respect to educational level, occupational social class and income¹⁹. These are highly correlated variables, and it is difficult to determine the effect of one independent of the others. Reverse causality is possible – those whose adult life has been scarred by depression may experience lifelong occupational and economic disadvantage. Findings from LMIC are currently inconsistent – suggestive trends in the

direction of an association between socioeconomic disadvantage and depression were observed, rather inconsistently, in the five sites in the three 10/66 Latin American countries¹⁷. Level of education seemed to be more relevant than income or wealth. Food insecurity was strongly associated with depression in Mexico, with non-significant trends in Peru and Venezuela. Depression in Hefei City, China was also positively associated with economic disadvantage¹⁴. Unusually, in Nigeria, an association was observed in the opposite direction, with the highest prevalence of depression among older people with the highest economic status¹⁵.

The Aetiology of Late-Life Depression

To date there have been no prospective studies of potential aetiological factors for late-life depression in LMIC. There have, however, been a large number of well-designed cohort studies carried out in Europe and North America, the findings from which have been subject to systematic review^{19,27} and quantitative meta-analysis²⁷. There is strong and fairly consistent evidence to support an increased risk for incident depression associated with female gender, disability, prior depression, bereavement and sleep disturbance. Disability is probably the most salient of these factors. Prospective studies in older adults have consistently indicated a very strong association between disability at baseline and the subsequent onset of depression^{28–32}. In one of these studies³¹ the population attributable fraction was as high as 0.69. In general, the level of disability associated with a health condition, rather than the nature of the pathology mediates the risk for depression^{31,33,34}. Stroke may be an exception as some studies show persistence of associations with depression after adjustment for disability³⁵. Three population-based studies have suggested an interaction between disability and social support, with the strongest effect of disability in those with the least social support^{31,32,36}. However, there is also strong evidence for causal pathways leading from depression to the progression or emergence of disability^{37,38}. Cross-sectional data from the 10/66 studies in Mexico, Peru and Venezuela also support a strong association between limiting physical impairments and depression, with a past history of depression being the other consistently observed association¹⁷.

One of the more consistent findings from previous Western research is the apparent salience of contact with friends, in particular intimate, confiding relationships to mood and morale in older people. While older people typically receive instrumental support from spouses and relatives, they value friends for companionship and emotional support. In the longitudinal Gospel Oak study, no contact with friends was the only social support variable prospectively associated with the onset of depression³¹. The social environment for older people is affected by the ageing process. Social networks deteriorate with increasing age consequent upon bereavement. Social engagement, such as visiting friends, is impaired in those with disability. Women typically have more supportive and extensive networks of friends than men. Married older men cite their wife as their main confidant, whereas women more often cite a friend outside the home. There have been few such studies conducted in other cultural settings, but in a cross-sectional study in Cuba, social networks, mainly centred around children and extended families, were associated with fewer depressive symptoms in both older men and women³⁹.

DEMENTIA

Dementia is a syndrome due to disease of the brain, usually chronic and progressive, in which there is disturbance of multiple higher

cortical functions, including memory, learning, orientation, language, comprehension and judgement. Diagnosis is on the basis of decline in cognitive function and independent living skills. There are many underlying causes. Alzheimer's disease, vascular dementia, dementia with Lewy bodies and frontotemporal dementia are the commonest. Mixed pathologies may be the norm. Studies in developed countries have consistently reported Alzheimer's disease (AD) to be more prevalent than vascular dementia (VaD)⁴⁰. Early surveys from South-East and East Asian countries provided an exception with an equal distribution of AD and VaD⁴⁰. More recent research suggests this situation has now reversed^{41,42}. This may be due to increasing longevity and better physical health: AD, whose onset is in general later than VaD, increases as the number of very old people increases; while better physical health reduces the number of stroke sufferers and thus the number with VaD⁴¹. This change also affects the gender balance among dementia sufferers, increasing the number of females and reducing the number of males. Some rare causes of dementia (subdural haematoma, normal pressure hydrocephalus, hypercalcaemia and deficiencies of thyroid hormone, vitamin B12 and folic acid) may be treated effectively – these may, theoretically, be overrepresented in LMIC, but their contribution particularly in young onset cases has yet to be investigated.

The Validity of Dementia Diagnosis Across Cultures

The validity of the construct of dementia in less-developed settings is supported by three qualitative studies in India. The features of dementia were widely recognized, and named^{43–45}. However, there was no awareness of dementia as an organic brain syndrome, or medical condition. Rather, it was perceived as a normal, anticipated part of ageing. The consequences are little help seeking from formal medical care services⁴⁴, no structured training on the recognition and management of dementia at any level of the health service, and no constituency to advocate for more responsive dementia care services⁴⁵. Behavioural and psychological symptoms of dementia (BPSD) can lead to stigma and blame attaching to the carers as well as the person with dementia⁴⁶. In India, likely causes were cited as 'neglect by family members, abuse, tension and lack of love'⁴⁴, and carers tended to misinterpret BPSD as deliberate misbehaviour⁴⁵.

The validity of methods used in cross-cultural research is fundamental to the success of the enterprise. Without this, informative cross-cultural comparisons are impossible. Many potential obstacles needed to be overcome⁴⁷. Those with little or no education may appear to 'fail' on cognitive screening tests even in the absence of cognitive impairment or decline. The task may be unfamiliar to them, or the information requested irrelevant. Tasks involving literacy, numeracy or drawing are particularly problematic, but in practice any cognitive item for which the probability of a correct response is strongly influenced by education will tend to be biased. Culture, including language, may also influence the salience and feasibility of cognitive items, and their relative difficulty. Cultural influences, as we shall see, may also impact on the assessment of social or occupational disability, since the normal roles of older people may vary considerably between cultures.

The history of cross-cultural research in dementia is characterized by careful attention to the applicability and validity of the measures employed. In the 1990s, the National Institute of Aging funded US–Nigeria and US–India studies developed⁴⁸ or adapted^{49,50} cognitive tests to render them suitable and normed for the cultural setting, and also developed culture-specific assessments of

functional impairment⁵¹. In the wake of these efforts, the 10/66 Dementia Research Group carried out pilot studies in 26 centres from 16 LMIC in Latin America and the Caribbean, Africa, India, Russia, China and SE Asia, demonstrating the feasibility and validity of a one-phase culture and education-fair diagnostic protocol for population-based research⁵². The Geriatric Mental State (a structured clinical interview assessing dementia, depression and psychosis syndromes)⁵³, the Community Screening Instrument for Dementia (a cognitive test, and informant interview for evidence of intellectual and functional decline, used in the US–Nigeria study)⁴⁸ and the modified CERAD 10-word list-learning task (used in the US–India study) each independently predicted dementia diagnosis⁴⁹. A probabilistic algorithm derived in one-half of the sample from all four of these elements performed better than any of them individually; applied to the other half of the sample it identified 94% of dementia cases with false positive rates of 15%, 3% and 6% in the depression, high education and low education groups⁵². This algorithm (the 10/66 Dementia Diagnosis) was ‘education-fair’ in that the false positive rate among those with low levels of education was low, and ‘culture-fair’ in that equivalent validity was established for a wide variety of countries, languages and cultures. It therefore provides a sound basis for dementia diagnosis in clinical and population-based research.

The prevalence of DSM-IV dementia was strikingly low in the US–Nigeria and US–India studies^{54,55}. The validity of this criterion, developed in the USA, had not been established in LMIC settings. In the 10/66 Dementia Research Group studies, a computerized application of the DSM-IV criterion was devised and validated⁵⁶. The relative concurrent and predictive validity of the two diagnostic approaches, 10/66 Dementia and DSM-IV dementia, could thus be compared. In the Cuban 10/66 population-based study, the 10/66 dementia diagnosis agreed better with Cuban clinician diagnoses than did the DSM-IV computerized algorithm, which missed many recent onset and mild cases⁵⁶. An essential feature of the dementia syndrome is that it is a progressive neurodegenerative disorder; the principal rationale for an early diagnosis is that it alerts the person concerned and their family to the probability of future deterioration. The 10/66 Dementia Research Group confirmed the predictive validity of their diagnosis in the population-based study sample in Chennai, South India, identifying a high mortality rate, and greater cognitive and functional decline over three years among 10/66 dementia cases and those with cognitive impairment but no dementia⁵⁷. There was also clear evidence of clinical progression and increasing needs for care among the large majority of 10/66 dementia cases. The strong predictive validity of the 10/66 dementia diagnosis was consistent with a lack of sensitivity of the DSM-IV criterion to mild to moderate cases, and, thus, with the notion that it may underestimate prevalence in less developed regions⁵⁷.

The Prevalence and Incidence of Dementia

Dementia is largely a disease of older persons; only 2% of cases are to be found in those aged under 65 years. After this the prevalence doubles with every five-year increment in age. The EURODEM meta-analysis of European population-based studies from the 1990s used data from 11 studies carried out in eight European countries⁵⁸. Prevalence was consistent across sites; the pooled prevalence for males and females is shown in Table 114.1.

The annual incidence rates reported in the EURODEM meta-analysis⁵⁹ are roughly one-quarter of the point prevalence

Table 114.1 EURODEM meta-analysis of European population-based studies: pooled prevalence for males and females

	<i>Annual incidence per 100 (68)</i>		<i>Prevalence (%) (67)</i>	
	<i>Males</i>	<i>Females</i>	<i>Males</i>	<i>Females</i>
Age groups				
60–64	0.2	0.2	0.4	0.4
65–69	0.2	0.3	1.6	1.0
70–74	0.6	0.5	2.9	3.1
75–79	1.4	1.8	5.6	6.0
80–84	2.8	3.4	11.0	12.6
85–89	3.9	5.4	12.8	20.2
90+	4.0	8.2	22.1	30.8

(Table 114.1), suggesting an average disease duration (from onset to death) of four years. Clinical studies have suggested a duration of five to seven years from diagnosis. A recent meta-analysis⁶⁰ of the age-specific incidence of all dementias was based on data from 23 published studies. The incidence of both dementia and AD rose exponentially up to 90 years, with no sign of levelling off. The incidence rates for VaD varied greatly from study to study, but the trend was also for an exponential rise with age. While there was no sex difference in dementia incidence, for the oldest old the incidence of AD was higher in women, and for the younger old the incidence of VaD was higher in men.

In LMIC there is more uncertainty as to the frequency of dementia, with few studies and widely varying estimates⁴⁷. Early onset cases are again rare, although this may be changing in those world regions where HIV/AIDS is endemic. In 2004, Alzheimer’s Disease International convened a panel of international experts to review the global evidence on the prevalence of dementia, and to estimate the prevalence of dementia in each world region, the current numbers of people affected, and the projected increases over time (Lancet/ADI estimates). A tendency previously noted for age-specific prevalence to be lower in LMIC than in the developed north^{47,54,55} was supported by the consensus judgement of the expert panel⁶¹. Differences in survival could only be part of the explanation, as estimates of incidence in some studies^{62,63} were also much lower than those reported in the West. Differences in levels of exposure to environmental risk factors may also have contributed, with low levels of cardiovascular risk⁶⁴ and hypolipidaemia^{65,66} in some developing countries suggested as explanations. Other potential risk exposures will be more prevalent in LMIC, for example anaemia associated with AD in rural India⁶⁷. High infant mortality may contribute to population differences in dementia frequency; constitutional and genetic factors that confer survival advantage in early years may protect against neurodegeneration or delay its clinical manifestations. It seems plausible that as patterns of morbidity and mortality converge with those of the developed West, then dementia prevalence in LMIC will do likewise⁶⁸. While studies of secular trends in Sweden, 1947 to 1952⁶⁹ and in the US, 1975 to 1980⁷⁰, suggested no change in the prevalence of dementia over time, it is possible that age-specific prevalence of dementia in HIC might fall in the future because of reduced incidence linked to improvements in cardiovascular health or rise, due to reduction in mortality among those with dementia.

However, the Lancet/ADI estimates were described as ‘provisional’, given that prevalence data were lacking in many world regions, and patchy in others, with few studies and widely varying estimates⁶¹. Coverage was good in Europe, North America and

in developed Asia-Pacific countries: South Korea, Japan, Taiwan and Australia. Several studies have been published from India and China, but estimates were too few and/or too variable to provide a consistent overview for these huge countries. There was a particular dearth of published epidemiological studies in Latin America^{71–73}, Africa⁵⁴, Russia, the Middle East and Indonesia. Therefore, there was a strong reliance upon the consensus judgement of the international panel of experts for LMIC.

The 10/66 Dementia Research Group prevalence studies

The 10/66 Dementia Research Group subsequently completed its population-based surveys (2003–7) of dementia prevalence and impact in 12 sites in eight LMIC (India, China, Cuba, Dominican Republic, Brazil, Venezuela, Mexico and Peru)^{74–79}, with a second wave of surveys underway in Puerto Rico, Sri Lanka and South Africa. Cross-sectional comprehensive one-phase surveys were conducted of all residents aged 65 and over of geographically defined catchment areas in each site with a sample size of 2000–3000 in each country. The net result is a unique resource of directly comparable data on over 20 000 older adults from three continents. All studies used the same cross-culturally validated assessments (dementia diagnosis and subtypes, other mental and physical health, anthropometry, demographics, extensive non-communicable disease risk factor questionnaires, disability, health service utilization, care arrangements and caregiver strain). The prevalence of DSM-IV dementia varied widely, from less than 1% in the least developed sites (India and rural Peru) to 6.4% in Cuba⁷⁵. 10/66 dementia prevalence was higher than that of DSM-IV dementia, and more consistent across sites, varying between 5.6% and 11.7%⁷⁵. The discrepancy was explained by the observation that informants in the least developed sites, particularly India, were less likely to report cognitive decline and social impairment (an essential criterion for DSM-IV dementia diagnosis) even in the presence of objective memory impairment⁷⁵. Levels of disability were similar for 10/66 dementia cases regardless of whether or not they were confirmed by the DSM-IV dementia algorithm⁷⁵. After standardizing for age and sex, DSM-IV prevalence was similar in the urban Latin American sites to that in Europe, but in China the prevalence was only one-half, and in India and rural Latin America one-quarter or less of the European prevalence. The group concluded that the DSM-IV dementia criterion is likely to have underestimated dementia prevalence, particularly in regions with low awareness of this emerging public health problem. There are several possible explanations for the discrepancy between objective cognitive impairment and informant reports⁷⁵.

1. The high levels of instrumental support routinely provided to all older people may mean that objective cognitive impairment may be less likely to lead to noticeable impairment in the performance of normal social roles, particularly in the early stages of dementia. More attention may need to be given to developing culturally relevant assessments to detect the consequences of early intellectual decline.
2. A culture of respect to elders making it difficult for informants to disclose report decline (supported by the finding of lower informant report scores for heads of household and male participants⁷⁵).
3. Low awareness of dementia may mean that decline is attributed to 'normal ageing'^{44,45} and hence not worthy of mention given the implicit focus of the assessments upon abnormality.

The World Alzheimer Report – new estimates of global prevalence of dementia

Since the Lancet/ADI estimates were published, the global evidence base has expanded considerably. There have been new studies from Spain^{80,81}, Italy⁸² and the USA⁸³. The exciting development, however, has been an explosion of studies from LMIC, and other regions and groups previously underrepresented in the literature. These included 10/66 Dementia Research Group studies in Brazil, Cuba, Dominican Republic, Peru, Mexico, Venezuela, India and China^{75,76}, and further new prevalence studies from, Brazil⁸⁴, Peru⁸⁵, Cuba⁸⁶, Venezuela⁸⁷, China⁸⁸, Korea⁸⁹, India⁹⁰, Thailand⁹¹, Australia (indigenous people⁹²), Guam⁹³, Poland⁹⁴ and Turkey⁹⁵. The leaders of the Lancet/ADI review were commissioned in 2008 to assist the World Health Organization in updating the Global Burden of Disease (GBD) estimates, by conducting fully systematic reviews of the prevalence and incidence of dementia, and associated mortality, in 21 GBD world regions. This provided an ideal opportunity to revisit the literature, and to assess the extent to which it was possible, in some or all regions, to summarize the evidence on the prevalence of dementia by quantitative meta-analysis of the available data, rather than relying on expert consensus. Findings from this exercise were published in Alzheimer's Disease International's World Alzheimer Report⁹⁶.

The systematic review identified 147 prevalence studies worldwide since 1980. A recent marked increase in the number of studies from LMIC was accompanied by a sharp decline in research in high income countries. In many of these countries, the evidence base is fast becoming out of date. When compared with the earlier Lancet/ADI consensus, after age standardization to the Western European population structure, the new estimates of dementia prevalence for all those aged 60 years and over were higher for three regions – Western Europe (7.29% vs. 5.92%), South Asia (5.65% vs. 3.40%) and Latin America (8.50% vs. 7.25%). Those for East Asia were lower (4.98% vs. 6.46%). However, in comparison with the much greater heterogeneity seen in the Lancet/ADI estimates, regional estimates had generally converged (Figure 114.1). While there was a four-fold variation in prevalence overall, from 2.07% (sub-Saharan Africa, West) to 8.50% (Latin America), most of the standardized prevalences lay in a band between 5% and 7%. The major source of variation was clearly the very low estimated prevalence for the four sub-Saharan African regions.

When regional prevalence estimates were applied to population estimates, it was calculated that there were 35.6 million people with dementia worldwide in 2010, the numbers nearly doubling every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. These figures for global prevalence were approximately 10% higher than the earlier Lancet/ADI estimates. In 2010, 58% of all people with dementia worldwide lived in LMIC, rising to 71% by 2050. Proportionate increases over the next 20 years in the number of people with dementia will be much steeper in low- and middle- compared with high-income countries (see Figure 114.2). The World Alzheimer Report forecast a 40% increase in numbers in Europe, 63% in North America, 77% in the southern Latin American cone and 89% in the developed Asia-Pacific countries. These figures are to be compared with 117% growth in East Asia, 107% in South Asia, 134–146% in the rest of Latin America, and 125% in North Africa and the Middle East.

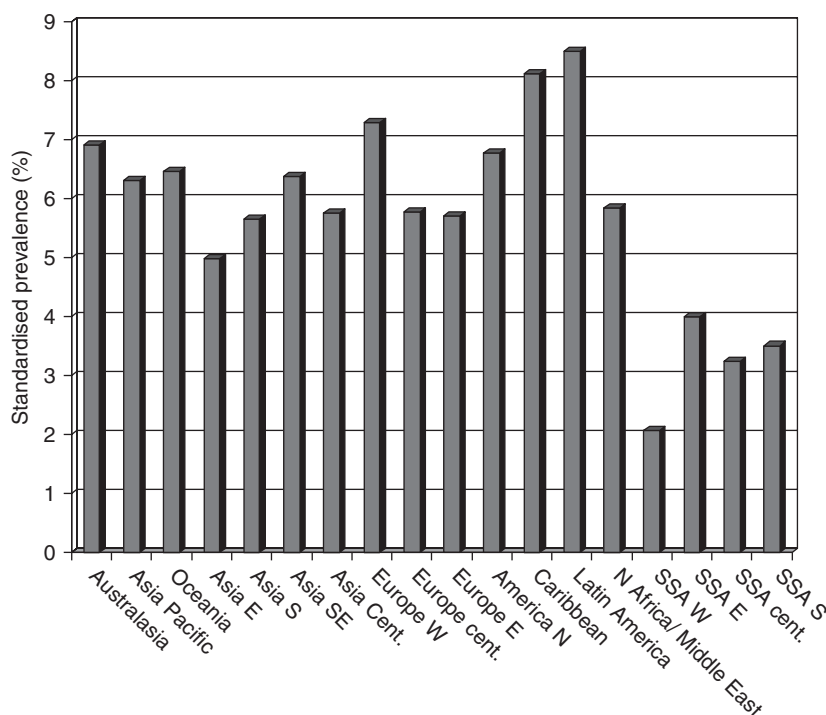


Figure 114.1 The prevalence of dementia in different Global Burden of Disease world regions, after standardizing for age (SSA = Sub-Saharan Africa)

Source: World Alzheimer Report 2009⁹⁶

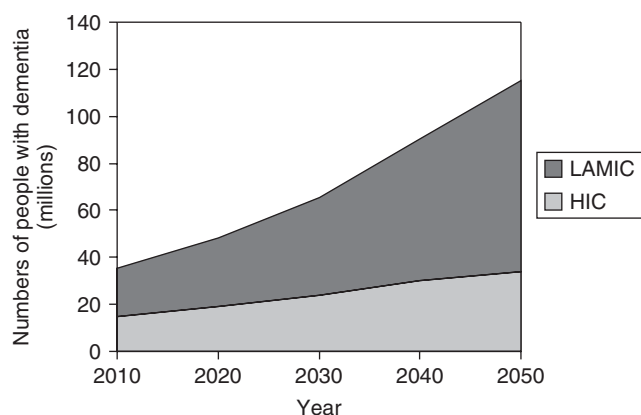


Figure 114.2 Projected increases (2010–50) in the number of people with dementia worldwide, broken down by country income status

Source: World Alzheimer Report 2009⁹⁶

The Impact of Dementia

Worldwide, surprisingly few epidemiological studies of dementia have gone beyond reporting on prevalence, incidence and aetiology of dementia. The impact of dementia upon the individual, the family and society has been little studied. In the Global Burden of Disease report, dementia was accorded a higher disability weight than almost any other condition and contributed 11.2% of all years lived with disability among people aged 60 and over; more than stroke (9.5%), musculoskeletal disorders (8.9%), cardiovascular disease (5.0%) and

all forms of cancer (2.4%). The global economic cost of dementia was recently estimated at US\$317 billion, 77% attributable to HIC where costly long-term care services are widely available⁹⁷. In HIC, as the disease progresses, formal sector care costs increase and institutionalization is the main cost driver. Informal (family) care is more important in resource poor countries, accounting for 56% of costs in LIC and 42% in MIC, compared with just 31% in HIC⁹⁷. According to the 10/66 Dementia Research Group pilot study in 26 LMIC centres, levels of carer strain were as high as those typically seen in European studies. In addition, care giving in LMIC often leads to substantial economic disadvantage⁹⁸. A high proportion of carers had to cut back on their paid work, and paid carers were also common⁹⁸. Compensatory benefits for carers and disability pensions for people with dementia were practically non-existent^{98,99}.

The 10/66 Dementia Research studied the relative contribution of chronic physical, mental and cognitive disorders (common physical impairments, depression, dementia, hypertension, diabetes, heart disease, stroke, chronic obstructive pulmonary disease and arthritis) to disability, in the baseline phase of its population-based studies in Latin America, China and India⁹⁹. Contrary to the Global Burden of Disease report, which cites blindness and deafness as the two leading contributors to years lived with disability among older people in LMIC, dementia made much the largest contribution to disability, with a median population attributable fraction of 25.5% (range across sites 19.3–43.5%). Other substantial contributors were limb impairment (11.7%, 5.6–34.0%), stroke (11.5%, 2–21.2%), arthritis (9.9%, 2.8–35.0%), depression (8.3%, 0.5–22.9%), eyesight (5.7%, 0–17.6%) and gastrointestinal impairments (5.1%, 0–23.2%). These findings suggest that chronic diseases of the brain and mind deserve greater prioritization. Aside from disability, they lead to dependency

and present stressful, complex long-term challenges to carers. Societal costs are enormous⁹⁷. Evidence from population-based research on ageing and dementia from LMIC should help to stimulate a wider debate about older people's health and social care needs, and how they should be met¹⁰⁰.

The Aetiology of Dementia

Currently most of the evidence from population-based studies on the aetiology of dementia comes from HIC, since the few incidence studies conducted in LMIC gathered data on a very limited range of potential risk exposures at baseline^{63,101}.

Genetic and environmental factors

The rare early-onset form of AD is highly heritable, and single-gene mutations at one of three loci (beta amyloid precursor protein, presenilin1 and presenilin2) account for the majority of cases. Late-onset AD is a multi-factorial disorder. The apolipoprotein E (*apoE*) gene polymorphisms account for up to 50% of the population attributable fraction, the e4 allele being enriched among AD cases^{102,103}. The association between APOE e4 and dementia has been observed in population-based^{102,103} studies in India, China and Latin America. However, the association seems to be attenuated among those with African ancestry^{104,105} and no association was observed among older Nigerians¹⁰⁶. Modest concordance rates among monozygotic twins for dementia diagnosis suggest a substantial environmental influence¹⁰⁷. Evidence from cross-sectional and case-control studies suggest associations between AD and limited education¹⁰⁸, and head injury^{109,120}, which, however, are only partly supported by prospective studies¹¹¹. Depression is a risk factor in short-term prospective studies, but this may be because depression is an early presenting symptom, rather than depression being a cause of dementia¹¹².

Dementia, cardiovascular risk factors and cardiovascular disease

The health transition currently underway in many LMIC will see an epidemic of cardiovascular disease (CVD). Latin America exemplifies the third stage of health transition. As life expectancy improves, and high fat diets, cigarette smoking and sedentary lifestyles become more common, so CVDs have maximum public health salience – more so than in stage 2 regions (China and India) where risk exposure is not yet so elevated, and than in stage 4 regions (Europe) where public health measures have led to reduced exposure to cardiovascular risk factors (CVRF)¹¹³. This is a matter of concern with respect to dementia in LMIC, given that recent research from developed countries suggests that vascular disease predisposes to AD as well as to vascular dementia¹¹⁴. While there has been no research to date on associations with dementia in LMIC, the INTERHEART cross-national case-control study suggests that risk factors for coronary heart disease operate equivalently in all world regions, including Latin America and China¹¹⁵. Despite occasional negative findings from large prospective studies^{116,117}, the accumulated evidence from HIC for a causal role for CVRF and CVD in the aetiology of dementia and AD is very strong. In short^{118–120} and longer latency^{121,122} incidence studies, smoking increases the risk for Alzheimer's disease. Diabetes

is also a risk factor¹²³, and in longer term cohort studies, midlife hypertension^{124,125} and hypercholesterolemia¹²⁵ are associated with AD onset in later life. Aggregated cardiovascular risk indices incorporating hypertension, diabetes, hypercholesterolaemia and smoking incrementally increase risk for dementia incidence whether exposure is measured in midlife¹²¹ or a few years before dementia onset¹²⁰. Recent studies report associations between metabolic syndrome and incident cognitive decline¹²⁶, and insulin resistance and impaired executive function¹²⁷. This has led to the hypothesis that atherosclerosis and AD are convergent disease processes¹²⁸, with some common pathophysiological and aetiological factors (APOE e4 polymorphism, hypercholesterolaemia, hypertension, hyperhomocysteinaemia, diabetes, metabolic syndrome, smoking, systemic inflammation, increased fat intake and obesity).

Nutritional factors

In LMIC, dietary deficiencies, particularly of micronutrients, are widespread and strongly linked to poverty. Deficiencies of folate and vitamin B₁₂ are of particular interest given their consequences; anaemia, neuropathy, hyperhomocysteinaemia¹²⁹, increased risk of stroke and IHD¹³⁰. Vitamin B₁₂ deficiency is strikingly prevalent (>40%) across Latin America^{131–133}, linked to gastrointestinal infections and diets deficient in meat and dairy produce¹³¹. Folate deficiency is endemic in those living in poverty¹³², and after economic crisis¹³³. Diets deficient in legumes may have contributed. Micronutrient deficiency is probably more prevalent in the elderly but there are few data on this age group¹³¹. Research on micronutrients and dementia in developed countries has focused upon antioxidants¹³⁴ with less attention towards deficiencies in vitamin B₁₂ and folate, which result in hyperhomocysteinaemia; only four small incidence studies^{135–138}, all underpowered and with inconsistent findings. Two out of three studies testing for an effect of folate were positive^{135,136}, in one case independent of homocysteine¹³⁵. B₁₂ was associated in only one out of four studies¹³⁶.

Iodine deficiency has also been a major public health problem in most Latin American countries¹³⁹. Iodized salt is now generally available but iodine content is poorly regulated¹³⁹. The prevalence of sub-clinical hypothyroidism was as high as 16.1% in post-menopausal Brazilian women¹⁴⁰. Overt hypothyroidism is a potentially reversible cause of dementia. Sub-clinical hypothyroidism (raised TSH levels with normal T4) is more prevalent, affecting up to 20% of older people in developed countries. It is associated with elevated total cholesterol and progression to overt hypothyroid disease, possibly also CVD¹⁴¹. It was strongly associated with risk for dementia in one cross-sectional study¹⁴². Conversely, a small incidence study reported a strong association with sub-clinical hypothyroidism (low TSH)¹⁴³.

Opportunities for prevention

Currently, efforts to prevent and control the coming epidemic of cardiovascular and other chronic non-communicable diseases in LMIC are in their infancy¹⁴⁴. Advocated measures include the implementation of tobacco-free policies, taxation of tobacco products, comprehensive bans on advertising of tobacco products, salt reduction through voluntary agreements with the food industry, and combination drug therapy for individuals at high risk of CVD¹⁴⁴. The detection and control of hypertension, hyperlipidaemia, diabetes and metabolic syndrome is poorly implemented by overstretched primary

care services that struggle to cope with the double burden of historic priorities (maternal, child and communicable diseases) and the rising tide of chronic disease in adults. Health systems are not trained, equipped or structured to deal with the latter. Given the strong evidence for CVD and CVRF as risk factors for dementia, the success or otherwise of these initiatives should in principle have an important effect on the future prevalence and incidence of dementia in LMIC⁶¹. Against this, is the disappointing evidence from prevention trials. One trial of antihypertensive agents has reported a protective effect on dementia¹⁴⁵, but four others did not find effects on cognitive function in primary analyses^{146–149}. Three large trials of cholesterol lowering agents have also failed to find effects on cognitive function^{150,151}. A randomized controlled trial of HRT in post-menopausal women indicated, against expectation, that women randomized to HRT had nearly double the risk of going on to develop dementia in the short follow-up period¹⁵².

CONCLUSION

Major advances have been made in our understanding of the cross-cultural validity of measurement and diagnosis of late-life depression and dementia. The prevalence of late-life depression meeting clinical diagnostic criteria has been found to be higher than the norm for developed Western countries in some but not all LMIC studies. Depression is consistently associated with high levels of disability and is considerably undertreated. Early indications are that patterns of risk association also seem to be somewhat different. With a large recent growth in the evidence base, the prevalence of dementia among older people living in LMIC, originally reported to be much lower than that in HIC, now seems to be quite similar worldwide. The possible exception is Sub-Saharan Africa, but the low prevalence of dementia seen in the one good quality study yet to have been conducted in that region⁵⁴ needs to be confirmed by more research. Possible similarities or differences in the risk factor profile for dementia across cultures, and between HIC and LMIC have attracted much attention¹⁰⁵, but very little is known due to the lack of informative incidence studies in LMIC. The incidence phase of the 10/66 Dementia Research group's population-based studies in Latin America and China, due to be completed in 2010, will go some of the way to redressing this imbalance⁷⁴. Aside from prevention of disease and promotion of healthy functioning, there is an urgent need to strengthen the ability of community health services to deliver evidence-based mental health care for older people. This should be done in an integrated way, within an overarching chronic disease management framework. More research is needed, into the epidemiology of late-life mental disorder (particularly their aetiology), into the effectiveness of high-risk prevention strategies for late-life depression and interventions for depression and dementia¹⁵³.

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Mental Illness in the Elderly in South Asia

Vikram Patel¹ and K. S. Shaji²

¹London School of Hygiene and Tropical Medicine (UK) and Sangath (India), Sangath Centre, Goa, India

²Government Medical College, Thrissur, Kerala, India

South Asia will house over 100 million older people by 2020¹. This chapter describes mental health problems that affect elders, focusing on the two commonest conditions: dementia and depression. The chapter will first review the epidemiology of these disorders and then consider the implications for care and policies in the region. While the scope of our chapter is intended to address the entire South Asian region, we note that as most of the research on mental illness in the elderly has been carried out in India, much of our discussion will pertain specifically to India.

DEMENTIA

Prevalence studies from the region have indicated a lower prevalence of dementia when compared to developed countries. However, there are wide variations in reported rates, ranging from 1.4% to 4.4%^{2–7}. One study reported an incidence of Alzheimer's disease (AD) of 3.24 per 1000 person-years for those aged 65 years⁸. Dementia incidence is predicted to increase in the developing world in tandem with the ageing population and the increasing burden of vascular risk factors⁹. It is estimated that there are already about 1.5 million people with dementia in India and this number is likely to increase dramatically in the next four decades¹. The major causes of dementia in the region are AD and vascular dementia. One study from Kerala reported that vascular dementia was more common than AD in a rural community sample⁶. A cross-national study compared *APOE*4*–AD epidemiological associations in India and the United States. Frequency of *APOE*4* was significantly lower ($p < 0.001$) in India. Correspondingly, the frequency of probable or possible AD was also lower in the Indian samples¹⁰. However, although there was a very low prevalence of AD in the Indian sample, the association of *APOE*4* with AD was of similar strength in Indian and US samples.

A challenge for the diagnosis of dementia, which relies heavily on interview-based examination, is the cultural and educational factors such as illiteracy. Several efforts have been made to improve the detection and diagnosis of dementia in this context. Screening questionnaires such as the Mini-Mental State Examination have been translated and validated for use in a North Indian population¹¹. A scale for activities of daily living has also been developed by the same investigators¹². In an epidemiological survey with a largely illiterate sample of 5126 individuals aged 55 and older in the rural community of Ballabgarh in northern India, the Hindi version of

the MMSE, a neuropsychological battery, and the Everyday Abilities Scale for India (EASI) had sensitivities of 81.3%, 81.3% and 62.5%, respectively, with specificities of 60.2%, 74.5% and 89.7%, respectively. The combination of all three was 93.8% sensitive and 41.8% specific¹³. An advantage of the EASI was that it could also be administered to informants of subjects who were cognitively not testable. In this largely illiterate community, with a low prevalence of dementia, the combination of cognitive tests and a functional ability questionnaire had substantial value for population screening.

The 10/66 Dementia Research Group interviewed 2885 persons aged 60 and over in 25 centres, including several in India, China and South East Asia. The sample included 729 people with dementia, and three groups free of dementia; 702 with depression, 694 normals with high education and 760 normals with low education. Experienced local clinicians diagnosed dementia and depression. The Geriatric Mental State, the Community Screening Instrument for Dementia and the modified CERAD 10 word list-learning task were then administered by an interviewer, masked to case status. Each measure independently predicted dementia diagnosis. An algorithm derived from all three performed better than any individually and identified 94% of dementia cases with false positive rates of 15%, 3% and 6% in the depression, high education and low education groups. The algorithm developed and tested in this study provides a sound basis for culture and education-fair dementia diagnosis in clinical and population-based research in India¹⁴.

Dementia remains a largely hidden problem in India. People do not differentiate between normal ageing and phenomena that are secondary to conditions like dementia¹⁵. Even when it is identified, it does not lead to caregivers receiving practical advice or longer-term support¹⁶. Given the low awareness about mental disorders in elders, there is a need to develop culturally sensitive methods for identification of probable cases. Shaji *et al.* have described a simple, cost-effective method of training community health workers to identify dementia in Kerala¹⁷. After two and a half hours of formal training, local community health workers in rural Kerala were asked to identify possible cases of dementia from the community they served. Diagnoses were then verified by a senior local psychiatrist with clinical and research interests in old age psychiatry. This method was found to have a positive predictive value of 64.7%. Later in this chapter, we will review the evidence on the burden of dementia, services for people with dementia, and innovative new strategies for addressing the needs of families affected by dementia.

DEPRESSION

There are a growing number of epidemiological studies of depression or common mental disorders (a broad diagnostic term which encompasses mood and anxiety disorders) in elders in the region, which have sampled general populations and clinical populations. Prevalence rates vary even more widely than those for dementia: rates in a community sample of elders vary from 6% in South India¹⁸ to over 50% in rural West Bengal¹⁹. Median prevalence rates tend to be higher in clinical populations^{20–23}. One of the largest recent population-based studies was carried out with 1000 participants aged over 65 years from Kaniyambadi block, Vellore, India²⁴. The prevalence of depression (ICD-10) within the previous one month was 12.7% (95% CI 10.64–14.76%).

The common presenting complaints are tiredness, sleep complaints, aches, tingling numbness in the hands, and palpitations²⁵. The hallmark cognitive feature is anhedonia or loss of interest. Suicidal feelings and agitation are also common¹⁸. The suicide rate is nearly twice as high in the 50+ age group (12/100 000) as compared to the national average (7/100 000). Co-morbidity with physical ill health is common; by some estimates, more than 90% of elders with a psychiatric disorder also have some physical disorder¹⁸. Risk factors for depression include female gender, low education, poverty, social isolation, chronic diseases such as diabetes, and family discord^{20,21,23–26}. Nuclear family structures, in particular, appear to be associated with a higher risk²⁰. The latter is on the rise as a result of the breakdown of traditional community structures as a result of the massive migration of younger productive members of families to urban areas and reduced economic activity in rural areas¹⁵. Older women face a triple jeopardy: that of being old, of being women, and of being poor. Elders living in rural areas may represent another risk group because rural areas lack resources, and with agriculture being the main occupation, there is neither income security nor any systematic provision for old age²⁷. One outcome study was carried out with a sample of patients attending psychiatry services of a tertiary care hospital in India. After 12 months, only 28% of patients had recovered. Factors predicting good outcomes were shorter duration of episode and living in a joint family system²⁸.

Help-seeking is not uncommon for somatic complaints associated with depression. However, the commonest treatments in primary care are symptomatic. Thus, benzodiazepines for insomnia and vitamins and 'tonics' for tiredness are among the commonest prescriptions for common mental disorders in general health care, while antidepressants or psychotherapy are rarely offered²⁹. Detection rates are very low, but there is good evidence that short screening questionnaires can considerably improve detection rates in primary care³⁰. One study evaluated the sensitivity and specificity of a two-question screen to identify depression and common mental disorders in the elderly, against the gold standard criterion of a structured diagnostic interview. The two-question screen has a sensitivity of 93.8% and specificity of 48.2%³¹. There are no specific treatment studies for older people with depression in the region, but it would be reasonable to expect that the considerable treatment evidence on the care of depression in general in developing countries would also apply to older people³².

CARE ARRANGEMENTS FOR THE ELDERLY WITH MENTAL DISORDERS

Ancient Indian scriptures advocate the preparation for old age by adopting the disengagement theory. Respect towards elders and the

concept of obligation towards parents forms part of the cultural value system³³. In contemporary Indian society, however, the position and status of the elderly and the care and protection they traditionally enjoyed have been undermined by several factors. Urbanization, migration, the break-up of the joint family system, growing individualism, the change in the role of women from being full-time carers, and increased dependency status of the elderly are some of the prominent factors. There have been changes in terms of education, aspirations and values, and the allocation of resources to different members of the family. Often the family has been unable to meet the financial, social, psychological, medical, recreational and welfare needs of the elderly²⁷. Care has often been conditional upon the child's expectation of inheriting the parent's property¹⁵. Care for those with dependency needs was almost entirely family based, with little or no formal services. Not surprisingly, fear for the future, and in particular 'dependency anxiety' was commonplace among older persons¹⁵.

Formal care arrangements for elders, for example in the public health sector, are scarce. Indeed, geriatric medicine as a special area of health care is not available in most medical colleges or hospitals in the region. The number of residential places for elders with severe mental disorders such as dementia is very low and inequitably distributed. There are no accurate estimates for the treatment gap for dementia in India in general, but a rough estimate is that this gap exceeds 90% in most parts of the country, with the exception of urban areas and the two southern states of Kerala and Tamil Nadu³⁴. Studies by the 10/66 Dementia Research Network in Goa and Chennai examined the impact of care giving for elders³⁵. Carers of people with dementia spent a significantly longer time providing care than did carers and co-residents of depressed persons and controls. The highest proportion of time was spent in communicating, supervising, and helping with eating and toileting. Levels of carer strain were notably higher among carers of people with dementia. They were 16-times more likely to have a common mental disorder than carers or co-residents of controls, and twice as likely as carers or co-residents of people with depression. Economic strain was indicated by the high proportion of caregivers of people with dementia who had given up work to provide care, coupled with the increased likelihood that the family had to meet relatively high health care costs. This was explained by the increased propensity for people with dementia to use expensive private medical care services rather than free or low cost government services.

There are several major barriers to closing this treatment gap, including the low levels of awareness about dementia and depression as medical disorders; however, the most significant barrier is the very low human resource capacity for the care of people with mental disorders. This scarcity of resources is true for all mental disorders across the continuum of life and has been systematically documented in the recent *Lancet* series on Global Mental Health³⁶. South Asia lacks the economic and human capital to achieve widespread coverage of specialist services; furthermore, specialist services tend to focus almost entirely on medical interventions, which have only a limited role in the long-term care of people with mental disorders, especially dementia. In view of the above, those responsible for service development for families of older people with mental disorders should keep in mind that the service should be home based, address the diverse medical and psychosocial health needs of the affected persons and their caregivers and be provided at a cost that the family can afford (and therefore use public and low-cost service providers).

Thus, the challenge for South Asia is to develop culturally appropriate interventions that can be delivered within existing resources, such as supporting families in their role as caregivers.

A randomized controlled trial has recently been completed in two talukas of Goa, evaluating the benefits of a low-cost, home-based intervention aimed at supporting families affected by dementia³⁷. The intervention was delivered by a community team and each team comprised two full-time Home Care Advisors (HCAs), a part-time local psychiatrist from the public health services and a part-time lay counsellor. The minimum requirements for being a HCA were knowledge of the local language, being literate, preferably having passed higher secondary school, and being motivated to be involved in the community care of older people. The specific components of the intervention carried out by the HCA were: basic education about dementia; education about common behaviour problems and how they can be managed; support to the caregiver, for example for an elderly caregiver living alone with the patient, in activities of daily living; referral to psychiatrists or the family doctor when behaviour problems are severe and warrant medication intervention; networking of families to enable the formation of support groups; and advice regarding existing government schemes for elders. The HCA applied a flexible home-care programme tailored to the needs of the individual and the family. The HCA were supported, and supervised, by the two part-time specialists. The intervention demonstrated a significant impact in reducing the caregiver burden, mental stress and distress due to the behavioural and psychological symptoms of dementia.

It is important to note that mental illness is seldom an isolated event among elderly people; thus, co-morbidity with other mental illnesses and physical health problems is typically the rule^{19,27}. The most common problems include deficits of vision and hearing, hypertension, diabetes mellitus, cardiovascular disorders and osteoarthritis. Thus, an ideal model of care for mental disorders in older people must fully address their physical health needs as well. There is a need to raise awareness about mental disorders in late life in the community and among health professionals, and to improve access to appropriate health care for the elderly with mental illness. Health education should aim to educate health workers and the community to recognize the common symptoms of mental disorders and, in particular, to stress that depression and dementia are real disorders and not just the natural consequences of ageing. Caregiver strain has not been acknowledged; instead, a near mythical strength is attributed to the abilities of families to cope. This distracts from the need for a rational debate regarding the future balance between informal family support and formal care services, and hinders evidence-based policymaking. We suggest prioritizing home-based support for elderly persons with dementia and their carers. Collaboration is required with non-governmental organizations (such as the Alzheimer's and Related Disorders Society of India) that are pioneering programmes to empower the elderly and support families with a mentally ill elder and provide health care sensitive to their needs. Working with the existing manpower and health and social service infrastructure is likely to be more successful in meeting the mental health needs of elders in South Asia than developing specialized psychogeriatric services throughout the country.

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Dementia and Depression in Africa

Olusegun Baiyewu

Department of Psychiatry, College of Medicine, University of Ibadan, Ibadan, Nigeria

INTRODUCTION

In 2001 it was projected that about 7% of Africans would be aged 60 years and over in the year 2002¹. Although the emphasis of health care in Africa is on preventable and communicable diseases in children and nursing mothers, as over 50% of the population is under 18 years of age, it has been estimated that the number of people aged 60 years and older in Africa will increase over the next few years. It thus becomes increasingly important that chronic illnesses associated with old age are considered. In this category are dementia and depression. In the last decade, a few studies have been carried out in Africa on dementia and depression; although the quantity of research on older person is small, significant advancements have been made.

Depression

One of the earliest community surveys on depression in the elderly in Africa was the study by Ben-Arie *et al.*², but since the 1990s there have been a number of research reports on old age depression in Africa^{3–6}. These studies were done in various locations, rural, urban and a combination of both and the prevalence rates varied depending on the methodology. For example, studies in which screening questionnaires alone are used tend to have higher rates, in the range of 20%, while those that have second-stage clinical diagnosis have rates ranging from 5 to 8%. A theme that emerges in all studies is that populations with high levels of depression correlate with low levels of education and low income.

Some hospital-based studies have looked at depression and other psychiatric disorders in clinic attendees⁷, and in patients admitted to non-psychiatric facilities^{8,9}. In these groups, high level of medical co-morbidity is a regular finding, though relationship between medical co-morbidity and depression is not often established. Another issue is that depression is often not recognized and neither is it treated⁵. Interaction between depression and chronic medical illnesses, such as heart failure, stroke and cancer, need further research. Intervention and outcome studies are also lacking.

Dementia

The flagship of dementia research in Africa is the Indianapolis–Ibadan Dementia Research Project, which has been ongoing since 1992. This group has reported prevalence and incidence rates for dementia and Alzheimer's disease in Ibadan and Indianapolis and found that

rates for both conditions were lower in Ibadan elders than in African Americans in Indianapolis^{10,11}. One important issue in assessment of cognitive functioning is that many questionnaires used in Western countries need modification when used in developing countries as the elders often have low education levels and have been involved in low occupational pursuits all their life. For example the Mini Mental State Examination (MMSE)¹² has both a ceiling and a floor effect due to education. In contrast, a screening questionnaire like the Community Screening Interview for Dementia (CSI-'D')¹³ has little education or culture effect and has been used in disparate populations. Another questionnaire developed by the group is Stick Design¹⁴, which resolves the graphomotor function difficulties experienced by people with little education when asked to carry out a constructional praxis test.

In this group of studies risk factors for poor cognitive functioning identified include age and female gender, but the most important risk factor for Alzheimer's disease, apolipoprotein E₄, is not related to either dementia or Alzheimer's disease in Nigerians^{15,16}. A similar report from East Africa also found that ApoE₄ is not related to Alzheimer's disease¹⁷.

A study from Egypt, however, reported a prevalence of 4.5% based on DSM-IV diagnosis¹⁸. This is close to the 5% often reported in Euro-American studies.

A study of mortality in the Indianapolis–Ibadan group showed increased mortality in Ibadan generally and a higher though non-significant rate in demented subjects when the two sites were compared¹⁹. While this might be a reflection of poor health delivery service to the residents of Ibadan, it is important to note that mortality associated with dementia is not significantly different. Studies on behavioural and psychological symptoms in dementia (BPSD) have shown that the pattern of presentation is probably not different from that observed in other regions of the world. BPSD is related to cognitive and functional impairment and in Western societies, BPSD is one of the most important reasons for nursing home placement. Even though nursing homes are unpopular in Africa, there is evidence that caregivers of demented subjects who have BPSD experience considerable distress²⁰. A small study of nursing home residents indicated that about 48% of the residents had dementia and 17% depression²¹, rates that are not too different from those reported in Western societies. Nursing homes, however, need further study.

There is some controversy about why prevalence of dementia reported in Africa and some developing countries is so low. One argument is that the elders in these countries are shielded from

activities of daily life in the multi-generational living arrangements they tend to have; it is possible that mild dementia may be missed²². While that is so, it is possible that prevalence of dementia may be truly different. Differential mortality rates may affect the prevalence of dementia. Elders in developing countries are generally likely to have shorter life spans because of the poor health care available; but factors such as the lower level of cholesterol and other cardiovascular risk factors may also affect the prevalence of dementia. In a community survey of elderly residents, cholesterol and triglycerides were higher in Indianapolis residents compared with those from Ibadan²³.

COGNITIVE IMPAIRMENT

The border area between normality and dementia is often referred to as mild cognitive impairment (MCI)²⁴ or cognitive impairment no dementia (CIND)²⁵. People with MCI or CIND have a higher rate of conversion to dementia compared with normal individuals. Although they have problems associated with memory which is about 1.5 standard deviation below the norm, they have little or no functional impairment.

Little or no information is available on MCI or CIND in Africans. Baiyewu *et al.*²⁶ reported a lower rate of conversion to dementia in Nigerians and it has been noted that conversion to dementia or Alzheimer's disease is not related to the presence of ApoE4, as is observed in many studies in Western society.

TREATMENT

Health care delivery in Africa is generally poor, this is more so for the elderly. There are very few specialized care facilities for the elderly. Elderly persons find it difficult to use general adult clinics in hospitals unless they have knowledgeable relatives or caregivers ready to take care of their needs. The situation is worse for mental health. Gureje *et al.*⁵ observed that many of the depressed elderly persons they studied in the community had never received treatment. Anti-dementia drugs are not available in many African countries. To the best of the knowledge of the present author there has been only one study in which patients from South Africa were included as part of a multicentre drug trial study on dementia covering five countries²⁷. Despite this, Ferri *et al.*²⁸ have estimated a 82% increase in the number of people with dementia in Africa between the years 2001 and 2020.

It could be argued that there are also non-pharmacological treatment options for dementia, but even these are not available in many African countries. The goal for the future is to raise awareness of these problems among policy makers so that they can be addressed.

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Dementia and Depression in China

Helen Chiu and Cindy Tam

The Chinese University of Hong Kong, Shantin, Hong Kong

According to data from the World Health Organization, 11% of China's 1.3 billion people were above the age of 60 in 2006. Life expectancy in China was 72 years for males and 75 years for females in 2006. The percentage of citizens over the age of 65 is projected to triple by 2050, from 8% of the population in 2006 to 24% in 2050, for a total of 322 million. China has 32 provinces and 2 special administrative regions (Hong Kong and Macau) and 56 ethnic groups. It has diverse geographic characteristics and demographic features, including dialects, customs and diet, which vary widely across the country.

DEMENTIA IN CHINA

Prevalence of Dementia

The number of people suffering from dementia in China was estimated to be 5 million in 2001, and it has been projected that there will be a more than 300% increase in this number by 2040¹.

Since 1980, a number of epidemiological surveys of dementia using standardized instruments and diagnostic criteria have been carried out. However, only a few of these studies have been published in international journals. Dementia prevalence estimates vary widely within China. This variation may be related to differences in population structure, genetics and lifestyle in the country's various regions, but it may also be due to different mortality rates of dementia and to methodological differences between studies. Chiu and Zhang reviewed 16 studies carried out between 1980 and 1999 and found the prevalence rates of dementia to range from 0.46% to 7.0%². Dong *et al.* performed a meta-analysis of 25 Chinese studies that were conducted between 1980 and 2004 and comprised a total population of more than 76 000. They estimated that the overall prevalence of dementia in China was 2.8% in people aged 60 or above³. Alzheimer's disease and vascular dementia were found to be the most common types of dementia, with the prevalence rate of the former reported to be 1.6% and that of the latter to be 0.8%. Both reviews^{2,3} found the rates of dementia, particularly that of Alzheimer's disease, to be lower than those reported in Western developed countries. In addition, Dong *et al.*³ found that the prevalence of Alzheimer's disease increased significantly from 1980 to 2004, and reported that the gap in the prevalence of dementia between China and Western countries has been decreasing.

Several epidemiological surveys that examined the prevalence of dementia in different regions of China using larger samples were published in international journals between 2004 and 2008^{4–8}. The initial screening for these surveys was usually performed using the Chinese version of the Mini-Mental State Examination, with diagnoses confirmed through neuropsychological assessment and clinical interviews. The results of some of these studies are presented in Table 117.1. A recent large-scale survey reported that the prevalence rates of Alzheimer's disease and vascular dementia were 3.5% and 1.1%, respectively. Greater prevalence of dementia was apparent in the northern regions compared with the south, but no difference was found between urban and rural Chinese residents^{4,9}. The burden of Alzheimer's disease and vascular dementia was not distributed equally among all regions and sociodemographic groups. Significant north–south variation was observed for both Alzheimer's disease and vascular dementia, but was more pronounced for the latter than the former. In both crude and age-adjusted associations, the prevalence odds of vascular dementia were approximately double in northern areas relative to southern areas. He *et al.* reported that the northern cities of China have a threefold higher incidence of stroke compared to southern cities, a fact that may be associated with different exposures to such risk factors as hypertension, a diet high in salt, and heavy alcohol and cigarette consumption¹⁰. In addition to this north–south variation, Zhang *et al.* also observed an east–west difference in the prevalence of dementia. Western China is less developed than the east, and life expectancy is also lower in the former. Thus, the lower prevalence rate of dementia in the western part of China may reflect a higher case fatality rate following Alzheimer's disease onset in the younger age groups or fewer persons at risk of Alzheimer's disease surviving until the period of onset⁹.

Incidence of Dementia

Studies on the incidence of dementia in China are scarce. Li *et al.* examined 1 090 elderly aged 60 or above in Beijing using the DSM-III criteria in a study that lasted from 1986 to 1989¹¹. The annual incidence rate of dementia was 0.6%. A similar cohort study was conducted in the same urban district of Beijing from 1997 to 1999⁶. In this study, 1 593 elderly aged 60 or above were examined using the DSM-IV criteria. The annual incidence rate was 0.9%, which was

Table 117.1 Prevalence of dementia in China

Study	Location	Urban/rural	Sample size	Age	Prevalence (%)
Zhang <i>et al.</i> ⁴	Beijing, Xi'an, Shanghai and Chengdu	Urban and rural	34 807 (aged ≥55)	≥65	3.5 (AD) 1.1 (VaD)
Zhou <i>et al.</i> ⁵	Linxin	Rural	16 095	≥50	1.83 (AD)
Li <i>et al.</i> ⁶	Beijing	Urban	1 593	≥60	2.5
Rodriguez <i>et al.</i> ⁷	Xicheng, Beijing	Urban	1 160	≥65	DSM-IV dementia: 3.1 (urban)
	Daxing	Rural	1 002		2.0 (rural) 10/66 dementia: 8.0 (urban) 4.8 (rural)
Lam <i>et al.</i> ⁸	Hong Kong	Urban	6 100	≥70	8.99 (mild dementia)

AD, Alzheimer's disease; VaD, vascular dementia.

significantly higher than that reported 10 years earlier. Zhang *et al.* examined 1 970 elderly aged 65 or above in Shanghai in 1987 and followed them up for five years¹². They reported an annual dementia incidence rate of 1.15%. Qu *et al.* surveyed 2 197 elderly in Xi'an in 1998 and 2001¹³. The annual incidence rate of dementia was found to be 0.89% among the elderly aged 65 or above. Of particular interest is the common finding that the incidence rate of dementia was higher in the illiterate groups in these studies.

Treatment

Guidelines for the treatment of dementia have been published recently. These guidelines cover the pharmacological and non-pharmacological treatment of cognitive and neuropsychiatric symptoms in dementia. In a section on potential drug treatments, acetylcholinesterase inhibitors (AChEIs) and memantine are listed along with other drugs, such as antioxidants and vasodilators. In clinical practice, huperzine A is used much more often in the treatment of dementia in China than other AChEIs, such as donepezil or rivastigmine, as it is covered by the National Drug Catalogue (China) and is inexpensive. It is an alkaloid isolated from the Chinese herb *Huperzia serrata*, and it is a reversible inhibitor of acetylcholinesterase. Randomized controlled trials in China have reported huperzine A to have some success in improving general cognitive functioning for patients with Alzheimer's disease¹⁴. The other cholinesterase inhibitors and memantine are not consistently covered by the National Drug Catalogue.

The drugs used in the treatment of neuropsychiatric symptoms include AChEIs, antipsychotics, antidepressants, anxiolytics and mood stabilizing agents. The US Food and Drug Administration (FDA) warning of increased adverse cardiovascular events with the use of atypical antipsychotics in dementia is mentioned in the Chinese guidelines. Such non-pharmacological treatments as reminiscence therapy, validation therapy, reality orientation and behavioural modification are also recommended. These guidelines emphasize the comprehensive assessment of the needs of both patients and their caregivers, as well as a multidisciplinary management approach.

Although not mentioned in the national treatment guidelines for dementia, numerous Chinese medicinal formulations have long been used for the treatment of insomnia and memory deficits. Some of the herbs used in these formulations, such as *Ginkgo biloba* and the

root of *Salvia miltiorrhiza* have been reported to exhibit cholinergic activities relevant to the treatment of Alzheimer's disease. In addition to these herbal agents, acupuncture has also been used in the treatment of dementia in China.

Access to Treatment

Zhang *et al.* found that about half of patients with dementia are classified as normally ageing and that only one fifth have adequate access to diagnostic assessment⁹. A low degree of public awareness, under-diagnosis and under-treatment are common hurdles to dementia care in China, which is similar to the case in other developing countries.

In general, patients with dementia are managed by traditional Chinese practitioners or primary care doctors, but their training may be inadequate. Those in urban areas may be managed by neurologists or psychiatrists, but there is no well-established referral system to specialist care yet in place. In Hong Kong, in contrast, psychogeriatric and geriatric services are well established, and these services play the main role in the medical care of patients with dementia.

Care of Dementia in China

The family has traditionally played a central role in support for the elderly in China. 'Filial piety' is a strongly held cultural norm that assumes that the care of older people with dementia will be provided primarily by the family. In recent years, however, the breakdown of the extended family, urbanization and the movement of young people to other cities for work have led to the weakening of family support for dementia sufferers. At the same time, community support and residential care facilities remain very limited in China and are particularly scarce in rural areas. All of these factors influence the pattern of care for dementia sufferers and create challenges for dementia care. In Hong Kong, in contrast, non-governmental organizations play a substantial role in providing community facilities and residential care for the elderly with dementia.

An organization called Alzheimer's Disease China was established in 2001 and is a member of Alzheimer's Disease International. In Hong Kong, the Alzheimer's Disease Association was set up in 1995, and the Hong Kong Psychogeriatric Association was established in 1998. Among their objectives are the facilitation of training, public awareness and advocacy for dementia.

DEPRESSION IN CHINA

Prevalence of Depression

Depression is one of the most common psychiatric disorders in the elderly population. Very few studies on the prevalence of this mood disorder have been carried out among the elderly in China. In 1999, Chen *et al.* conducted a meta-analysis of 10 epidemiological studies of the prevalence of geriatric depression in 13 565 subjects in China¹⁵. The pooled prevalence of depression was 3.86%, whereas that of depressive mood was 14.81%. The results reported in published Chinese studies vary, which may be due to methodological issues, non-standardized assessments and/or different definitions of depression.

The prevalence rates of geriatric depression in five recent epidemiological studies of major depression published in international journals from 2000 to 2008 are presented in Table 117.2. These studies adopted standardized instruments, and generally found lower rates than those reported in Western countries. The results of the Chinese studies can be interpreted in a number of ways. They may indicate a genuine rarity of depression. Indeed, some factors may protect the Chinese from depression, including such coping mechanisms as quiescence and stoicism, family and cultural support systems, and a traditional cultural belief in fatalism²¹. The lower prevalence rates may also be due to a lower level of reportage of depressive symptoms or the existence of 'depressive-equivalent' conditions. For instance, neurasthenia is a more generic label applied to wide-ranging symptoms, including somatic symptoms (such as insomnia, fatigue and dizziness), cognitive symptoms (such as poor memory and unpleasant thoughts) and emotional symptoms (such as excitability and nervousness), in addition to any depressive symptoms. Chinese patients and psychiatrists seem to prefer such a label to the psychiatric label of 'depression'²². Even in the 1990s, neurasthenia remained a more common diagnosis in Chinese patients than in other populations.

The elderly in rural areas seem more likely to suffer from depression than city dwellers^{15,20}. The relatively lower socioeconomic status of the rural elderly, as well as a poorer health care system and fewer social activities compared to their urban counterparts may increase the risk²⁰.

Treatment of Depression

Of the subjects with geriatric depression interviewed by Ma *et al.*, 25.2% received some type of treatment, with only 4.7% seeking

treatment from mental health professionals²⁰. This low rate of help-seeking behaviour may be explained by the following: (i) many Chinese people do not believe that depression is a treatable psychiatric disorder; (ii) stigmatization and discrimination prevent psychiatric patients from using mental health services in China; and (iii) the country offers inadequate access to community-based psychiatric services.

Treatment guidelines for depression have recently been published. Various types of antidepressants, including tricyclic antidepressants (TCA), selective serotonin re-uptake inhibitors (SSRI) and serotonin norepinephrine re-uptake inhibitors (SNRI), are available. The guidelines recommend the use of the newer antidepressants for geriatric depression, SSRI in particular, because they have less pronounced side effects and are safer for people with cardiovascular diseases. Modified electroconvulsive therapy was introduced to China only in recent years, and it is now recommended for the treatment of severe or treatment-resistant depression. Psychotherapy is briefly mentioned in these guidelines, but is not widely practised for depression. It is noteworthy that cognitive behavioural therapy training has only begun in recent years. Although not mentioned in the guidelines, acupuncture and traditional Chinese medicine have long been used to treat insomnia associated with depression.

ELDERLY SUICIDE IN CHINA

The suicide rate among the elderly is higher than that among the general population in China, which is similar to the pattern in many countries. What is unique in China is the fivefold difference between the urban and rural rates for suicide among the elderly²³. The rates of suicide among elderly rural residents of China, particularly for women, are among the highest reported in any country. Between 1995 and 1999, the suicide rates of elderly rural and urban residents aged 60–84 were 82.8 and 16.7 per 100 000, respectively²³. Wei *et al.*²⁴ studied 304 elderly suicides using psychological autopsy and found that 64.8% suffered from mental illness and 40.5% from depression. The most common method of suicide for this population is pesticide ingestion, followed by hanging²⁴. Insecticides are readily available in rural areas, and emergency medical care in these areas is relatively limited. Moreover, the elderly in rural areas have limited access to health care in general and are offered little social and financial assistance. These factors may contribute to the higher suicide rates of the rural elderly compared with their urban counterparts. However, it is interesting to note that the prevalence of depression in older Chinese

Table 117.2 Prevalence of geriatric depression in China

Study	Location	Sample/age	Diagnosis/instrument	Prevalence (%)
Chen <i>et al.</i> ¹⁶	Hefei (urban)	1 736 age ≥ 65	GMS-AGECAT	2.2 (point prevalence)
Chen <i>et al.</i> ¹⁷	Yingshang (rural)	1 600 age ≥ 60	GMS-AGECAT	6.0 (point prevalence)
Lee <i>et al.</i> ¹⁸	Beijing and Shanghai (urban)	547 age ≥ 65	DSM-IV/CIDI	2.6 (lifetime prevalence of major depressive disorder)
Lu <i>et al.</i> ¹⁹	Kunming (urban and rural)	(5 033 age ≥ 15 in the survey)	DSM-IV/CIDI	3.63 for those aged ≥ 65 (lifetime prevalence of major depressive disorder) 2.09 (12-month prevalence)
Ma <i>et al.</i> (2008) ²⁰	Beijing (urban and rural)	1 601 age ≥ 60	DSM-IV/CIDI	7.83 (lifetime prevalence of major depressive disorder) 4.33 (12-month prevalence) 8.42 (12-month prevalence in rural sample) 2.55 (12-month prevalence in urban sample)

residents of rural areas remains low, although the suicide rate is high. The exact reason for this discrepancy remains unclear.

In the special administrative region of Hong Kong, the suicide rate is also relatively high among the elderly, at 50 per 100 000/year for those aged 75 or above. Chiu *et al.* investigated suicide among elderly Chinese in Hong Kong using psychological autopsy²⁵. They found that 86% of those who had committed suicide had a psychiatric problem prior to doing so and that 53% had suffered from major depression, which is consistent with findings reported in Western countries.

CONCLUSION

Both dementia and depression are important and prevalent disorders in the elderly population. Although the reported prevalence rates of both syndromes are lower than those in Western countries, an enormous number of people are affected, given the sheer size of the population. As China's population is ageing rapidly, the country will face exponentially increasing demand for care for those elderly who suffer from these disorders. Mental health services for the elderly in China remain in the early stage of development. More epidemiological studies and clinical research are needed to guide the future development of such services and care.

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Spirituality and Mental Illness in Old Age

Susan Mary Benbow¹ and David Jolley²

¹*Centre for Ageing and Mental Health, Staffordshire University, Stafford, UK*

²*Personal Social Services Research Unit, Manchester University, Manchester, UK*

CONTEXT: SPIRITUALITY, FAITH AND RELIGION

Spirituality is an important concept and often regarded as intrinsic to mental health: the Health Education Authority includes it within its definition of mental health: 'the emotional and spiritual resilience which enables us to enjoy life and to survive pain, disappointment and sadness. It is a positive sense of well-being and an underlying belief in our own, and others', dignity and worth'¹.

Nevertheless spirituality is difficult to pin down, and its differentiation from (and relation to) religious faith is a matter of debate. The Church of England Archbishops' Council with the National Institute for Mental Health in England (NIMHE)² has defined it as: 'A quality that goes beyond religious affiliation: that strives for inspiration, reverence, awe, meaning and purpose, even in those who do not believe in God'. Thus spirituality can be independent of religious faith, or, as Paul Wilson³ writes, 'Spirituality is the searching for the meaning of life. Religion is one way of conducting the search'. Much of the literature relates health to religious belief and practice rather than spirituality as such and only now are we beginning to tease out how spirituality and faith interact.

As a concept, spirituality is sometimes criticized as free-floating and nebulous, although it has gained acceptability and respectability in Western societies, where adherence to faith or religion is sometimes regarded with suspicion, or as primitive, old-fashioned or outdated. On a global level there is massive commitment to religious faiths^{4,5}. Numbers of adherents to Islam continue to grow, and though there has been a decline in active belief and church going within the nominally Christian countries of the West, the number of Christians worldwide is sustained or growing⁶. Population movements mean that most countries are now home to communities of many faiths. Thus an understanding of the research evidence concerning the relationships between spirituality, religion and health is essential for health care practitioners. In addition, it is important to be aware of the influence of spiritual and religious beliefs on the perception and interpretation of symptoms by patients and their families. Beliefs will also modify views on the acceptability or appropriateness of interventions intended to be therapeutic.

Health is often divided into six dimensions: physical, mental, emotional, social, environmental and spiritual⁷. The first five are accepted routinely as significant in the understanding, aetiology and management of health/illness. Spirituality is the dimension that has been neglected in Western professional health care theory,

research and practice during the twentieth century, with health care staff taking little account of patients' perspectives regarding their experience of health/illness. Recent years have seen a return to interest in alternative views of life and a corresponding increase in study and research in this area. At a basic biological level, George *et al.*⁸ demonstrated an association between spiritual beliefs and enhanced immunity, while, within the realms of clinical psychiatry and behaviour, Strawbridge *et al.*⁹ found that strong spiritual beliefs were associated with a reduced risk of suicide. The Royal College of Psychiatrists has established a Special Interest Group on spirituality¹⁰. The evidence is such that the National Institute for Health and Clinical Excellence's (NICE) guidance on the supportive and palliative care of adults with cancer¹¹ recommends provision of spiritual support services, and the NIMHE *Guiding Statement on Recovery*¹² includes consideration of spirituality as intrinsic to holistic treatment.

Why should strong spiritual beliefs be associated with better health outcomes? Could it simply relate to the social support provided by membership of a faith community? Is it possible that interest in spirituality/membership of a faith community is independently linked with better health? Or are there specific aspects of a faith (such as prayer or worship) that carry additional advantages to health? Is it the case that, as Andrew Sims writes, 'one of the best kept secrets of modern epidemiological medicine is the effect that religious belief and practice have upon outcome from both physical and mental disorders'?¹³

Chronic illness (whether physical or mental) is likely to be an area where the relationship between spirituality and health assumes particular importance. How does spirituality impact on long-term illness and coping? What effect does long-term illness itself have on spirituality and faith? How does chronic illness affect membership of a faith community? What of the families and carers of those living with long-term physical and/or mental illness? As yet we cannot answer these questions, but there is evidence which hints at possible answers. The evidence divides into qualitative (often personal accounts of living with a chronic illness, e.g. Robert Davis's account of changes in his faith and understanding while living with Alzheimer's disease¹⁴) and quantitative. Researchers are exploring this area, measuring associations using instruments such as Hill and Hood's Measures of Religiosity¹⁵, which records 126 different measures of religion, faith, belief and spirituality, and the Royal Free Interviews for Religious and Spiritual Beliefs^{16,17}.

DEMENTIA AND SPIRITUALITY

Katsuno¹⁸ studied 23 people with mild dementia attending a day centre in the United States, using both qualitative and quantitative measures, and found a positive correlation between strength of spirituality and quality of life. Religion was reported to be important in the everyday lives of 19 of the group. One main theme, 'Faith in God', and six related categories were identified: beliefs, support from God, sense of meaning in life, private activities, public activities, and changes arising from dementia. Katsuno argues from her sample that it is an individual's intrinsic religiosity, rather than the social support they receive from a faith community, which influences their quality of life.

We used the Royal Free Interview for Religious and Spiritual Beliefs: self-report version¹⁹ in a memory clinic population in the West Midlands²⁰ to start to explore the following issues:

- How are spirituality and faith affected by dementia?
- How are spirituality and faith affected by caring for someone with dementia?
- How do religious communities view dementia and respond to its presence within their membership?
- How is the experience of dementia modified for patient and carer by their spirituality and faith?
- Are there opportunities for strengthening spirituality and faith and/or improving life for patients and carers in this situation?

A group of people attending a memory clinic in the West Midlands and their carers completed the Royal Free questionnaire and in additional semi-structured interviews were carried out with patients, carers and local faith leaders. The patients were mainly women living with Alzheimer's disease and they described themselves predominantly as Christian. They scored a mean of 24 on the Mini-Mental State Examination²¹. Our main conclusions were as follows: patients with dementia are interested in, and able to talk about, issues of faith and spirituality; the spectrum of their beliefs is similar to that of their main carers; the strength of their beliefs is at least as strong as their carers; and satisfaction with life and carer stress (as measured by the General Health Questionnaire²²) appear to be independent of strength of spiritual belief in this population. Both patients and carers ranked the personal components of spirituality most highly: for carers, coping came highest ('do you believe in a spiritual power which helps you cope with events which occur in your life?'), and for patients' strength of belief ('how strongly do you hold to your spiritual/religious view of life?'). Both patients and carers considered practices associated with their beliefs to be very important.

What of people with more advanced dementia? Some formulations argue that as dementia progresses and erodes the individual's abilities, memory traces and emotional repertoire, their spiritual identity is lost to a primitive chaotic biological base. Others say that if you know the person well, their spirit remains available for contact, and, indeed, that their spirituality becomes more evident and precious^{23,24}. Meeting spiritual needs is certainly accepted as part of supportive and palliative care in dementia as in other terminal conditions¹¹ and is anticipated in residential care, which pre-dates death for many people^{25,26}. Lawrence²⁷ argues that 'spiritual matters remain pervasively in the background' as dementia progresses and that staff need to employ non-verbal methods and devote time to connecting with the spiritual needs of people with dementia. Families and carers who have sustained intense involvement through this final stage will take time to adjust to the transition to life without their relative after the latter's death. Their experience of communication may continue and

the mode, manner and completeness of resolution will be influenced by their established beliefs^{28,29}.

DEPRESSIVE DISORDERS, PSYCHOSIS AND SPIRITUALITY

It is widely accepted that spiritual beliefs and religious practices can have positive effects on health and well-being in general. Lawler-Row and Elliott³⁰ reported an investigation of the role of religious activity and spirituality in the health and well-being of older adults and found that people with higher levels of existential well-being had lower scores on depression. It is said that people with a spiritual or religious affiliation are up to 40% less likely to get depressed than people who do not have such affiliation; an increased commitment to religion has been linked with lower levels of depression in medically ill hospital patients; and religious/spiritual commitment is associated with lower levels of substance abuse². Koenig³¹ studied older medical inpatients with major and minor depression and found that they were less religiously involved than non-depressed patients and that greater severity of depression was associated with lower intrinsic religiosity, less involvement in reading scripture and prayer, and lower religious attendance.

Ceramidas³² has described a qualitative study of depression and Christian faith in later life. Those participants who had what is described as a 'closer relationship with God' found comfort and strength in the practice of their faith but did not experience their churches as safe places to disclose their depression, fearing stigma and rejection.

Suicide has been regarded as a sin by most major religions, and attracted strong religious sanctions in the past, although views have moderated over recent years. Depression with suicidal ideation is therefore strongly influenced by spiritual/religious beliefs and different communities respond to it in different ways. This can be particularly challenging in large multi-ethnic multi-faith cities³³.

THE SPIRITUAL NEEDS OF SERVICE USERS

Kitwood and Bredin³⁴ introduced the term 'personhood' and defined it as 'a standing or status bestowed on one human being by others in the context of relationship and social being. It implies recognition, respect and trust.' They went on to describe the main psychological needs of a person with dementia as attachment, comfort, identity, occupation and inclusion. These ideas were developed in the context of Kitwood's work with people with dementia, particularly in institutional settings, but the concepts can be applied more widely. Kitwood came from a faith background, but later preferred a non-religious vision and interpretation of spiritual life which could be turned into operational therapeutic activities^{35,36}. In this he was a leader from whom followers are gaining strength and guidance in sensitizing services to the deeper needs of patients and families. This has additional benefits for care professionals, but makes additional demands on them.

There are practical ways in which staff can support the spiritual needs of service users³⁷. First, it is essential to take time to discover something about the personal beliefs and family culture that have informed the individual's life to this point. This may be achieved by a one-to-one interview, but may be more complete with the assistance of family and friends. Just to talk about things with a sympathetic, non-judgmental listener will be helpful. From this it may be possible to identify contacts, tracts, music or other resources that can be used

for spiritual nourishment within a care setting. Alternatively, outside settings may be identified whose ambience brings meaning and sustenance. Faith, hope and compassion are contributory components of clinical care³⁸ and inevitably impact on the two-way relationship between service user and care provider. This means that carers who are open to the dimension of spirituality and faith in their work with patients require some sophistication in understanding the origins and limits of their own spirituality and how this may be used to strengthen and support their work. It is important to be aware that their own beliefs may be threatened (or be threatening) when exposed to new and different views and value sets. Thus there is need for support and supervision with reflection and growth from experiences gained. 'Do-it-yourself' is not a safe option for carers or those they care for. Addressing this issue is a task for every organization offering care to dependent and vulnerable people, and a complex matter that is rarely approached comprehensively.

Wallace³⁹ has described the development of guidelines to support staff working with people with dementia, and recently Gilbert⁴⁰ has produced guidelines on spirituality for staff in acute mental health services.

Post and colleagues⁴¹ have addressed ethical aspects of attending to spiritual and religious aspects of a patient's experience. They consider the relationship between physician and patient, and the professional boundary between physician and chaplain, and note that patients' spiritual needs should be respected by those who aim to maximize therapeutic efficacy.

There are important ways in which faith communities can support people who have mental health problems². For individuals who have active membership of an organization, this will include maintaining the continuity of established social contacts and allowing them opportunities for shared prayer, worship and rituals as well as pastoral care. Others, who have known a faith but fallen out of regular contact, may find the experience of illness acts as a trigger to reconsider their thoughts and beliefs. Still others may have had little or no contact with a faith community, but begin to wonder from their disability or distress, whether there is more to be learned. These are situations when hospital or health care chaplains can be helpful, but the first approach may come via a friend or family member to a local church or other faith centre. It is possible that what begins as a challenge from the threats that illnesses carry can become a source of unplanned enlightenment and positive growth. Faith communities are known to provide support and comfort in times of illness, loss and bereavement – but there is the possibility of much more⁴².

THE SPIRITUAL NEEDS OF MENTAL HEALTH SERVICE STAFF

An area of potential difficulty is the possible dissonance between the spirituality and religious beliefs of service users and the staff who are supporting and treating them. The first step in dealing with this is to acknowledge it and then to provide information, education and support in reflective supervision so that unspoken fears and conflicts can be uncovered and examined.

Differences may be based, in part, on the generation gap between staff and the older people they are caring for. In all societies, older people are more taken up with spiritual/faith matters than younger people⁴³. Older people have a role in maintaining traditions that were operative in their earlier years and will carry the culture of those times into the present. In addition, maturation takes place with accumulating years and the eventual approach of the end of life,

bringing increased interest in matters of the mind and spirit, and less preoccupation with the pleasures of flesh.

But there are other factors, for paid carers are quite often drawn from a race, religion, country of origin, social stratum and language that set them apart from those they are caring for⁴⁴. Within a staff group, there may be wide variation of experience and belief. This may be spread unevenly between those providing hands-on care and those with management responsibilities, and there can be hazards associated with cliques and groupings.

Such differences are inescapable features of the fabric of care: awareness of their potential to impact adversely on the quality of care is essential and needs to be built into education, training and reflective practice. One useful tool in this work is Cecchin *et al.*'s concept of 'prejudice'⁴⁵. Prejudice is conceived as meaning 'any pre-existing thought that contributes to one's view, perceptions of, and actions in a therapeutic encounter'. Encouragingly, they argue that, when identified and confronted, prejudices can be construed creatively and usefully: 'any meeting of prejudices can create change'.

This change requires that, rather than one party attempting to impose the 'correct' view on any other, there is openness and negotiation between professional carers and those they care for. However, this runs counter to the power paradigm deemed usual within the staff–patient relationship. Involvement with, and respect for, family, friends and faith leader of the older person in discussions and care planning adds to complexity but also to the potential richness of care and health outcomes.

PAST, PRESENT AND FUTURE

There is evidence that people living with a mental disorder, including dementia, have spiritual needs which must be addressed in order to promote well-being and quality of life, that religious practices provide coping resources for people, and that their personal spirituality offers a source of comfort and strength for individuals⁴⁶. Newitt⁴⁷ argues that people without religious faith also benefit from approaches that address aspects of spirituality. This is a tricky area, for there is no easily accessible formula or accepted approach when seeking to engage spirituality outside the rites of a faith. The Royal Free studies have found that high spirituality outside a faith carries a poor prognosis for health outcomes (M. King, personal communication), which is an interesting insight, but considering how it might be dealt with in practice is challenging.

There is much to be learned, but we have made considerable progress in giving back respect to spiritual and faith dimensions of individuals, families and communities. Perhaps health and social care professionals will now recognize the need to join more closely with colleagues who have expertise in matters of the faith and spirituality of service users and their families in order to improve both health services and health for older people with mental health problems in the future.

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Development of Health and Social Services in the UK from the Twentieth Century Onwards

John P. Wattis

Centre for Health and Social Care Research, University of Huddersfield, Huddersfield, UK

IMPERIAL BEGINNINGS: THE POOR LAW AND THE ASYLUM

In Britain, the twentieth century dawned in a blaze of imperial glory. By the beginning of the twenty-first century, the world, including health and social services, had changed beyond recognition. In the year 1900, UK public health measures were rudimentary and confined largely to the establishment (in 1848) of sanitary authorities with medical officers of health to oversee sewers and water supplies. The poor law was still in force and poor law institutions were made deliberately unpleasant. This followed the principle of 'lesser eligibility', set out in 1834, which stated that those receiving poor law assistance should not be as 'eligible' (well provided for) as an 'independent labourer of the lowest class'¹. For the poor sick this had been ameliorated, to some extent, by the setting up of poor law infirmaries in 1868, but there was still a vast gulf between these institutions and the voluntary hospitals, which were supported by rich philanthropists. Retirement pensions, even retirement itself, were things of the future and there was an association between poverty, ill health and old age which was recognized by an 1895 Royal Commission on the aged poor. Despite over 50 years of the National Health Service (NHS), the association between poverty, ill health and old age is maintained to this day.

Until the middle of the twentieth century, mentally ill people were still incarcerated in large county asylums. In 1808, partly as a response to the appalling conditions in some private 'madhouses', local magistrates had been given the power to set up asylums, and in 1845 this provision had been made mandatory. In recent years we have seen a return to the private sector for some aspects of health and social care provision for people with mental health problems.

From 1900 onwards, developments have been influenced by major world events, political philosophy, public opinion and the power of pressure groups. The Boer War, starting in 1899, revealed the poor physical fitness and ill health of many young men. Improvements in midwifery and child care were soon legislated for, with school meals starting in 1906 and the notification of live births, health visiting and the school medical service soon following. In 1908 the first national scheme for old age pensions was set up to try to alleviate poverty among old people. It was non-contributory and means tested. Initially, recipients also had to be 'of good character'!

The Royal Commission on the Poor Laws and the Relief of Distress in 1909 considered most of the issues of domiciliary and hospital medical care. A minority report condemned the poor law institutions as a public scandal, with the infirmaries understaffed and lacking skilled medical input². Out of hospital, the poor law doctors had no contact with local authority public health services, the voluntary dispensaries were overcrowded and ineffective and the medical clubs, financed by workers' subscriptions, underpaid their doctors and did not cater for the chronic sick or dependants. The writers of this report dismissed the idea of a medical insurance system.

Yet, in 1911, the establishment of such a system marked an important development in the evolution of general practice in the UK. The medical profession fought for, and won, independence and capitation fees rather than a salaried service, and administration by insurance-based panels rather than local authorities³. Higher income groups, families and hospital care were excluded but the scheme was nevertheless a qualified success.

THE MINISTRY OF HEALTH: BETWEEN THE WARS

In 1918 the Ministry of Health for England and Wales was formed and the minister quickly appointed a consultative council, which in 1920 produced a report described by Pater² as 'nothing less than the outline of a national health service' (p. 7). Their scheme might well have avoided some of the split between general practitioners and hospital doctors that has been one of the problems of the NHS as it was eventually implemented.

Control of the workhouses passed to local authorities in 1930, the beginning of the end for the poor law. After a post-war cash crisis, the voluntary hospitals continued, becoming more specialized in acute care and leaving the chronic sick and infectious diseases to the local authorities. A number of reports pressed for a more coordinated hospital system and for universal health insurance. Knowledge was advancing. In 1935, Warren^{4,5} began her work in developing geriatric medicine and, a few years later, pioneers began to write of the issues concerning old people with mental illness⁶⁻⁸.

Before the Second World War, the Emergency Medical Service (EMS) was set up to cope with expected severe civilian casualties from the bombing of cities. On the declaration of war, 140 000

people, many of them elderly, were discharged from hospital over two days⁹. The EMS also coordinated the work of the voluntary and local authority hospitals, providing the framework for the future NHS Regional Hospital Boards. Physicians and surgeons from the elitist voluntary hospitals came face to face with the conditions of the former poor law institutions.

THE POST-WAR NATIONAL HEALTH SERVICE

The last of the series of British Medical Association (BMA) reports pressing for reform in 1942 coincided with the Beveridge report and was followed in 1944 by the NHS White Paper, enacted in 1946 and effective in 1948.

The National Health Service, as then set up, was tripartite. Primary care services – general practitioners, opticians, dentists and pharmacists – were answerable to local executive committees; maternity, child welfare, health visiting, health education, immunization and ambulances remained the responsibility of the local authority; and hospitals were administered by Regional Hospital Boards with teaching hospitals retaining boards of governors directly answerable to the Ministry of Health. One of the assumptions when the NHS was set up was that increasing health in the population would cause health expenditure to level off. It never did, and in 1956 the Guillebaud Committee, appointed to find ways of avoiding a rising charge upon the exchequer, concluded that there was no evidence of inefficiency or extravagance in the NHS. In fact, the committee was concerned about a lack of capital expenditure (a concern again of relevance more recently). In 1962, this problem was addressed in the Hospital Plan.

Meanwhile, in the mental health field, the idea of community care was gaining ground. Tinker¹⁰ attributed this to five factors. First, there was a general dissatisfaction with institutional care and a search for alternatives. Some of the experiments in the 'therapeutic community' work of the Second World War¹¹ had challenged the accepted authoritarian culture of the mental hospital. In addition, the advent of electroconvulsive therapy (ECT), antipsychotics and effective antidepressants facilitated the move away from custodial care to medical treatment at home or in ordinary hospitals. Next, there were beginning to be practical problems in running residential establishments, including staff recruitment. Then there was concern about the cost of institutional care and, finally, a recognition that mentally ill people were entitled to live in as normal a way as permitted by modern treatments. The 1959 Mental Health Act liberalized the treatment of mentally ill people and opened the way for a move away from the old psychiatric hospitals to the new concept of psychiatric units attached to the district general hospitals of the 1962 Hospital Plan.

The large institutions were, in any case, rocked by a series of scandals about the mistreatment of patients. This resulted in the establishment of the Hospital Advisory Service (later the Health Advisory Service), effectively an inspectorate to monitor standards and spread good practice.

In general practice, a financial allowance for practices in deprived areas combined with other factors to promote the rapid development of local health centres and group practices from the mid 1960s. Local authorities produced their own health and welfare plans but there was poor coordination with the hospital authorities and the general practitioners' executive committees. Within the local authorities, the Seeborn report (1968) was followed by the Social Services Act, which required the setting up of social services departments. The Department of Health and Social Security was created in 1968 by

the amalgamation of the Ministries of Health and Social Security, a merger that lasted for some 20 years.

REFORMS

In 1974, for the first time since its inception, the NHS itself was reorganized. The chief elements of this reorganization were the separation out of health and social services functions (now in the process of being reversed in children's services at least!), the integration of all health functions under one management and the establishment of area health authorities, generally coterminous with local authorities, to facilitate joint planning. Community Health Councils were also created to represent the views of consumers. Unfortunately, the reformed service did not work well. There were too many layers of responsibility, and taking decisions seemed to be delayed while information and responsibility were passed up and down the tree. There was an increase in clerical and administrative staff without a corresponding increase in managerial efficiency. During this period, important government reports were produced, including *Better Services for the Mentally Ill*¹² and *A Happier Old Age*¹³.

In 1982 the Area Health Authorities were abolished and new district health authorities combined the functions of the old areas and districts. In some areas, coterminosity with local government was lost. A new government was determined to cut public expenditure, and the rate of growth of the NHS slowed. Following the Griffiths report¹⁴, a general management structure was established within the NHS, and Family Practitioner Committees became independent. Government payment for continuing care was channelled to the private sector, and social services and hospital provision for this group of patients/residents was either reduced or failed to keep pace with demographic changes¹⁵.

Psychiatric services were coping with the implementation of the 1983 Mental Health Act (MHA), which set up time-consuming quasi-judicial procedures for reviewing patients who were detained in hospital under compulsory orders. The new Act also set up a Mental Health Act Commission to review treatment of detained patients and to advise on certain types of treatment. This Act was revised in 2007 to incorporate a number of changes, including broadening the categories of those who could apply for admission under the MHA and of those who could be responsible for their care under the Act. Generally, in combination with the Mental Capacity Act, the new legislation has improved patients' rights under law, but at the expense of increasing bureaucracy.

MARKET FORCES AND COMPETITION: A RADICAL DEPARTURE?

Then came the most radical reform of the NHS attempted to that date, a reform not just of the service but of the basic philosophy of 'service' underlying it. Some suspected that it was the beginning of the end for the National Health Service. The political theory was that nationalized industries were subject to 'producer capture' and that the workers tended to run the service in their own interest rather than that of the 'customers'. Competition and 'market forces' were seen as the remedy. The 1990 National Health Service and Community Care Act introduced the concept of an 'Internal Market'. The new health authorities became planners and purchasers of health care at 'arm's length' from the providers, which were initially directly managed units (DMUs), and became semi-independent Trusts. The health authorities were provided with a budget for the local population and

placed contracts for care with Trusts or the private and voluntary sector in order to obtain the best 'value for money'. Quality was, at least in theory, specified in the contract, and monitored.

Competition and other features of business life were 'introduced' into the NHS, not least by setting up groups of 'fundholding' general practitioners, who were enabled to make their own contracts for secondary care. In fact, doctors, health care workers, general practices and hospitals have always competed on reputation, but money was the new incentive. Some of the changes were potentially positive, such as the setting up of Trust Boards to manage local services and an emphasis on sound financial regulation through corporate governance. Unfortunately, the bottom line was very clearly financial and in many cases clinical services were sacrificed to balance the books.

These proposals were pushed through in the teeth of strong opposition from staff and groups representing the consumer. Honigsbaum¹⁶ analysed the situation in 1990 and concluded that if patient care suffered, then 'the nation may decide that the restraints imposed are not worth the savings they produce. Today, as in 1911 and 1948, it is the public interest that will predominate'. The medical profession were largely excluded from the plans for this reorganization. Klein concluded that, if a new political settlement were not reached between the government and the profession, it seemed unlikely that the NHS would survive long into the twenty-first century¹⁷.

A NEW NHS?

In fact, perhaps partly because of public dissatisfaction with what was happening to the NHS, the government was not re-elected, and a radical reforming Labour government came to power. From here, developments in the constituent parts of the UK became more dissociated. This account mainly follows what happened in England, since to follow all the differences following devolution would require more space than is available. The engines of privatization and the internal market were (temporarily) reversed and new reforms introduced. In December 1997 a White Paper, *The New NHS: Modern, Dependable*¹⁸ outlined a comprehensive new vision for the NHS. Two of the main planks of the new policy were the setting up of primary care groups (PCGs) to replace the fundholding/non-fundholding split, and the introduction of comprehensive quality controls to ensure high standards and equity in access across the country. PCGs were local groupings of general practices, involved in the commissioning of local community and secondary services. In a further reform, they became Primary Care Trusts (PCTs), providing community services and commissioning secondary services. More recently still, the concept was developed of 'Care Trusts' which could provide primary care and some secondary services, such as mental health services. The 'Quality Framework' involved a three-layer approach¹⁹. *Clear standards of service*, set by National Service Frameworks (NSFs), and a National Institute for Clinical Excellence (now National Institute for Health and Clinical Excellence, but still known by the acronym NICE), which evaluated new treatments in terms of cost-benefit as well as the safety and efficacy demanded for licensing. The NSF for Older People was published in 2001²⁰. The first of eight standards was 'rooting out age discrimination'. The seventh concerned mental health and included NICE guidelines for antidementia drugs (since revised to restrict use to those with moderate Alzheimer's disease). The new NSF made it clear that standards in the Mental Health NSF already published applied to older people. Local delivery of services was to be made dependable by a combination of lifelong

learning²¹ linked to professional self-regulation and clinical governance. *Clinical governance*²² placed obligations on chief executives of NHS Trusts to make arrangements to monitor and continuously improve the quality of health care their organizations provided. This was underpinned by the *national monitoring* of standards involving a National Performance Framework, an inspectorate (the Commission for Health Improvement, renamed the Healthcare Commission and renamed and reorganized again in April 2009 as the Care Quality Commission) and a National Patient and User Survey. This ambitious vision set a massive agenda for change and demanded radical shifts in the management and clinical cultures of the NHS²³. These well-intentioned reforms have been accompanied by a plethora of central guidance, much of it driven by a philosophy of competition and performance management that does not sit well with the complicated needs of patients and the real motivators of human behaviour. The emphasis on control and performance management clashes with the self-determination model that is rightly increasingly popular when it comes to service users and medical education²⁴.

PCGs initially resulted in a much greater influence for general practitioners and other primary care workers in the commissioning of secondary services. In the move to PCTs, PCGs were merged and grew, effectively to replace the former District Health Authorities (DHAs). They now have a board structure with executive and non-executive directors, analogous to the boards of existing secondary care Trusts. The strategic role of the former DHAs has been taken over by new Strategic Health Authorities (SHAs) covering areas even larger than the former Regional Health Authorities (RHAs). In England and Wales, 'standalone' Mental Health Trusts or Care Trusts have become the normal providers of mental health care. In smaller towns, a mixture of specialist Trusts covering wide geographical areas and of direct provision through PCTs remains. The provider Trusts have been encouraged to become 'Foundation' Trusts with yet another monitoring body (imaginatively called 'Monitor') overseeing the process. There was something of a scandal when a Trust preparing for Foundation status let its guard down on clinical quality and saw a significant increase in mortality rates. Shortly after Monitor cleared it to become a Foundation Trust, the Healthcare Commission was called in to investigate Mid Staffordshire NHS Foundation Trust and found serious failings. So far nobody at the Department of Health has publicly acknowledged that the pace of change and the New NHS structures might be causing damage.

The doctrine of 'commissioner-provider split', embodied in the new slogan 'World Class Commissioning', means that the mental health services as part of PCTs in England are unlikely to persist. For old age psychiatry, most current arrangements mean that the managerial separation between old age psychiatry and geriatric medicine continues. Unless imaginative and pragmatic solutions are found, this could result in many demarcation problems. However, a new culture of collaboration rather than competition could make all the difference (if not strangled at birth by political doctrine).

The *funding* of the NHS is probably even more important than its organization in determining the future of health care in the UK. It was the squeeze on NHS development in the 1980s that provoked the medical profession to campaign for more development money. In the light of international comparisons, both of spending on health care and the age structure of the population, this campaign seemed fully justified. Earlier reorganizations increased management costs and reduced the morale of many in the NHS. In the last 10 years there has been a marked increase in investment in the NHS. The controversial

Private Finance Initiative (PFI – rebadged as Public–Private Partnership, PPP) has continued to be a main strand of funding because it limits the Public Sector Borrowing Requirement. There is concern that PFI/PPP will result in a reduction in bed numbers and diversion of money away from services to support repayments to private providers in respect of capital developments; this is especially a risk if investment in the NHS slows down.

The government has recognized the need to train more doctors, nurses and other health care workers but, despite considerable investment, workforce planning is still problematic as demonstrated by the debacle in 2007/8 over the failed introduction of ‘run through’ training for doctors.

The direct reforms of the NHS were accompanied by a Royal Commission to review long-term care. The report of this Commission²⁵ controversially suggested that the personal care and residential elements of continuing care should be separately funded. It recommended that personal care should be paid for from general taxation, while living and housing expenses should continue to be means tested and subject to co-payment. The government did not make a positive response to this.

WHAT NEXT?

The ‘Next Stage Review’ of the NHS was commissioned in 2007 and published in 2008²⁶. There are many recommendations and supporting documents available on the Department of Health website (www.dh.gov.uk). The review incorporates visions from each of the new Strategic Health Authorities and combines an emphasis on preventative medicine (‘helping people lead healthy lives’) and quality with a vision of partnership and local clinical leadership. Already there are signs that some of the good ideas are being slowly strangled by bureaucracy. If there is anything to learn from the last 10 years it is that too much ill-considered change produces a churning of management staff that reduces efficiency, and that too many central targets distort provision towards that which is politically fashionable or easy to measure (e.g. surgical waiting lists). At the same time, the pace of change and emphasis on ‘top-down’ performance management reduces the responsible autonomy we need to encourage for staff and service users alike. As this chapter goes to press a new UK government has just been elected which professes support for the NHS and a strong distaste for excessive bureaucracy and central control. We can expect more change.

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The Pattern of Psychogeriatric Services

John P. Wattis

Centre for Health and Social Care Research, University of Huddersfield, Huddersfield, UK

HISTORICAL BACKGROUND

The roots of the National Health Service (NHS) and the development of psychogeriatric services in the UK are discussed in Chapter 119. The evolution of psychogeriatric services has been guided by professional knowledge and opinion, by the politics of the health and social services, by financial constraints and, occasionally, by public opinion. From the inception of the NHS, which effectively antedated the beginning of provision of specialist psychogeriatric services, until the 1990s there was a consensus about how developments in services should occur in response to changing demography and epidemiology as well as advances in medical knowledge. This consensus was shattered in the UK by the imposition of the ideology of 'market forces'. Much long-stay hospital accommodation was effectively 'privatized' by decisions to support patients in private nursing and residential homes from state funds and to close down as many long-stay NHS beds as possible. The ideology of market forces was also applied to local authority provision of community care. Since April 1991, psychiatric patients with social needs have been subject to a 'care-planning procedure' in which all parties, including social services, have to agree. In April 1993 the full implementation of the Community Care Act made local social services departments responsible for purchasing continuing nursing and residential home care, largely from the private sector and with a limited budget.

In the late 1990s, a government came to power that did not appear to share the vision of market forces as the best way to regulate the NHS. However, the internal market has crept back in England under the guise of 'world class commissioning' and 'contestability', and the NHS remains a 'political football'. Political devolution of health care arrangements has also resulted in different patterns of service development in England, Wales, Scotland and Northern Ireland. One can no longer write about 'UK' psychiatric services as a whole and this text mostly follows the situation in England. The professional consensus about how services should develop has been replaced by a centralized pattern of decision making and the important decisions, made at the inception of the specialty of old age psychiatry in the UK, about providing a comprehensive service for all severe mental illness in old age, whether organic or functional, have been disregarded in some areas.

THEORETICAL BASIS FOR PSYCHOGERIATRIC SERVICES

The pioneers of specialist psychiatric services for old people were motivated by the increasing need for psychiatric services for the age group, consequent upon increased life expectancy, the growing knowledge base about psychiatric disorders among old people, and the success of geriatric medicine. The special needs of older people were not always recognized by the generic services. Diagnostic problems included the differential diagnosis of dementia, the association of apparent cognitive impairment with some cases of depressive illness, and the non-specific presentation of disease in old people. The multiple pathology suffered by old people led to a need for new patterns of multidisciplinary working and for close liaison with physicians in geriatric medicine and social services¹⁻³. As in the early days of geriatric medicine, assessment and treatment in the community were emphasized not only because of 'blocked beds' but also because a more realistic picture of the patient's health problems usually emerged. More recently, advances in psychosocial care⁴, interest in the spiritual needs of old people⁵ and the advent of new classes of antidepressant, antipsychotic and antidementia drugs (discussed elsewhere in this volume) have all had their impact on the organization and delivery of psychiatric services.

CARE OR TREATMENT: PRIMARY OR SECONDARY?

One of the key theoretical issues for the future development of community services is likely to be the distinction between care and treatment. 'Care' is a word with many connotations. Some are positive but, in the medical world at least, some are negative. For example, 'care' is seen as what is provided when there is no possibility of effective treatment, as in the 'prescription' of 'tender loving care' for the terminally ill person. 'Care' tends to be relegated to untrained (although not necessarily unskilled) workers employed by social care agencies and commissioned by social services departments, whereas 'treatment' is the province of highly trained personnel employed by the Health Service. The move to 'Care in the Community' has served to reclassify older mentally ill people, especially those with dementia, as not needing medical treatment. Thus long-term care of people

with severe dementia, once shared by psychogeriatric and geriatric services within the NHS, is now provided in private institutions and is 'means tested', reducing the burden on the state but increasing the burden on afflicted families.

This situation is further complicated by the tendency of some health planners to equate primary care with *low cost and community care*, and secondary care with *high cost and hospital care*. Old age psychiatry services straddle the hospital–community divide and provide essentially secondary services, largely in a community setting. The new term, 'intermediate care', describes well some of these community services, but some who use the term believe that community psychiatric nursing services should be part of 'primary care', when in old age they work most effectively as part of secondary community care. Certainly, with the increasing prevalence of dementia, it is essential that primary care services and general hospital services become more proficient in recognizing and managing these conditions appropriately.

KEY COMPONENTS OF PSYCHOGERIATRIC SERVICES

Catchment Area and Comprehensiveness

Until recently, virtually all psychogeriatric services in the UK worked to a defined geographical catchment area, and the vast majority aimed to provide a comprehensive psychiatric service to all people over the age of 65 years^{6,7}. Many services are now also trying to provide for people with early-onset dementia, although often without any dedicated resources⁷. In some areas, managers are seeking to save money by closing specialist wards for old people with functional mental illness and diverting those who need inpatient care onto wards designed for working age adults. Some old age psychiatrists feel they are being pushed towards developing 'dementia only' services.

The Multidisciplinary Team

For some this is an outmoded concept, for others an ideal that cannot be obtained, but for many psychogeriatricians it is an essential context for all their endeavours. Most multidisciplinary teams for the elderly incorporate *community nurses*, a *social worker*, one or more *occupational therapists*, a *physiotherapist* and often a *psychologist*. Various patterns of working have evolved and been described but they have in common an attempt to involve all disciplines in formulating treatment plans for the patient. In parts of England, there continue to be problems in fully integrating social workers and psychologists into such teams.

Home Assessment

This lies at the heart of most psychogeriatric services. Until the last few years, around two-thirds of referrals were seen at home by a doctor, one-fifth by other members of the team and one-tenth in out-patient clinics^{6,7}. Just over 1 in 10 were seen as liaison referrals, although in some services this rose to a quarter or even one-third, perhaps partly depending on the admission policies of local geriatric services. Less than 1 in 20 were admitted direct without prior assessment. Patterns described as 'New Ways of Working' have now spread from working age adult psychiatry to old age. Generally this involves new referrals being assessed at home by various members of the team, and the senior medical staff tend to see people in the out-patient department after a preliminary assessment by another member of

the team (often a community psychiatric nurse). This has reduced the burden of new assessments falling on psychiatrists, and the impact on the quality of initial assessments has yet to be evaluated.

Community Treatment

Historically, the rate of acute admissions was only one-third of the rate of referrals, reflecting the fact that most home assessments do not result in admission but in treatment in the community. Home visits by community nurses are probably the commonest form of treatment in the community, although home visits by doctors and other members of the multidisciplinary team also play an important part. The rate of acute admission is probably reducing further as acute inpatient beds are closed.

Day Hospitals

In 1985, there were about 1.2 day hospital places per 1000 elderly people, and this had not changed significantly by the mid 1990s. Some services and Health Regions had relatively more and others less. The use of day hospitals varied from area to area, depending on the resource availability locally. The old government guidelines overestimated the need for dementia places. In many but not all cases of dementia, the need is for *care* rather than *treatment* and so a proportion of this day provision can be provided by social services or voluntary agencies. Here, however, issues will have to be addressed as to what kind of care is of most benefit to older people with dementia and their relatives, neighbours and friends. Elderly people with functional illness often have problems with psychiatric or psychological management that demand the *treatment* resources of a true day hospital or the more recently developed home treatment services. In the last five years there has been strong central pressure to close day treatment facilities, in some cases replacing them with home treatment teams.

Acute Inpatient Beds

The national rate of provision in 1985 was around 1 per 1000 elderly served, and again did not vary much over the next 10 years. In recent years there appears to have been a further reduction in acute beds. The reducing numbers may be insufficient to cope with the increasing demands caused by demographic changes and the loss of long-stay beds. Ultimately this depends on the community services available, since there is potential for considerable 'marginal shift' between community and inpatient resources. One study showed that around a quarter of acute psychiatric beds for all age groups were occupied by elderly people with depressive illness, and in many areas anecdotal evidence suggests that a greater proportion of acute psychiatric beds is being used for functional illness, principally depression. As with day hospital places, it appears that the old guidelines may have overestimated the needs for dementia assessment beds and underestimated the needs for patients with depressive illness and other functional illnesses. Because of the high prevalence of physical illnesses in mentally ill old people, it is recommended that acute beds should be on or adjacent to a general hospital site. Some services are now beginning to differentiate the assessment and management of behavioural problems in demented people, which can be carried out in the community or in community-based units, from the management of patients with depression, who often have major associated

physical illness or disability (and may need ECT) and are therefore better managed on an acute hospital site. The same may apply to atypical dementia patients requiring high levels of investigation or to patients with dementia and delirium. This last group may be best helped on geriatric medical wards.

Long-Stay Beds

The provision in 1985 was around 3.4 beds per 1000 elderly. Since then a large number of beds have been closed, with patients discharged to the private sector, where developments have been funded through the social security budget and means-tested contributions from patients and their families. In 1996 the number had reduced to around 1.1 beds per 1000 elderly. Since provision was largely (but not exclusively) for those with severe dementia, whose main need is for care rather than treatment, this development appears to demand a cautious welcome. Patients are generally being cared for in smaller units. However, there must be reservations. The smaller units are harder to inspect and they are not necessarily in the patients' communities of origin, since planning permission and housing costs enter into the commercial equation. They are subject to capricious changes in the market, including government refusal to pay the 'going rate'. They are not under specialist medical management and there is some evidence that this management may be one of the factors that reduces the rate of decline in demented elderly people (a factor which, if confirmed, might also have relevance in the day care setting). The switch to private care has been engineered for political reasons and its impact is yet to be fully assessed. Some psychogeriatric services have retained a proportion of their long-stay beds for rehabilitation and respite care. A survey of old age psychiatrists⁸ showed the majority in favour of around 1.5 long-stay (including respite) beds per 1000 elderly in community NHS units, with national rather than local eligibility criteria. The use of such beds for respite care to support carers in the community is now well established, and there is a potential for developing community units as centres of excellence for dementia care and education, as well as bases for multidisciplinary community teams.

GUIDELINES

The first guidelines for provision of psychiatric services for old people came in a Department of Health circular in 1972⁹. The government White Paper, *Better Services for the Mentally Ill*¹⁰, in 1975, suggested that services for old people should often be provided by a psychiatrist with 'a special interest', and incorporated guidelines for bed and day hospital provision for the 'elderly severely mentally infirm'. Subsequently, the Royal College of Psychiatrists produced guidelines intended to help College representatives reviewing job descriptions for new or replacement consultants. These were endorsed by the Health Advisory Service in its report, *The Rising Tide*¹¹, and by the joint Royal College of Physicians and Psychiatrists report, *Care of Elderly People with Mental Illness*¹². The second joint report¹³ adopted a more multidisciplinary approach and described the different types of mental illness in old age as well as appealing for equity and 'national reference frameworks', which corresponded closely to the concept of 'National Service Frameworks' introduced by the new government¹⁴. Since the turn of the century there has been a plethora of government guidance, especially on dementia, culminating in the National Dementia Strategy¹⁵. Unfortunately, despite their excellence in many respects, none come near to specifying resources

to be deployed even in the surrogate way of the old 'bed norms'. Further, many old age psychiatrists fear that the needs of older people with functional mental illness, especially depression, are being sidelined.

Reality and Guidelines

Although, in the UK, old age psychiatry has been recognized as a specialty by the Department of Health for many years, we are still awaiting the collection of routine statistics. Initial manpower statistics appeared to be grossly inaccurate. The most comprehensive data available are from the 1985 survey, updated by the 1996 survey, which unfortunately did not achieve such wide coverage. There are also now agreed international standards for old age psychiatry services¹⁶, and an international survey has established that basic levels of service exist in 12 countries worldwide¹⁷.

SPECIALIST SERVICES OR NOT?

In view of the documented rapid expansion of services over the years, this question may seem superfluous. However, it was possible, as a result of the 1985 survey, to compare services where psychogeriatricians worked half-time or more in the specialty, with those where the consultant commitment to the elderly was less than half-time¹⁸. Specialist services had generally higher staffing ratios (with the exception of non-consultant medical staff), a higher proportion of acute beds on general hospital sites and a greater proportion of long-stay beds within the area served. These last two could be regarded as surrogate indicators of quality of care. In addition, the specialist psychiatrists were more likely to look after all mental illness in old age (the pattern of service recommended by the Royal College Faculty for the Psychiatry of Old Age). They were also reported to be more likely to engage in teaching and to show an interest in research in the specialty.

CONCLUSION

Readers wishing to see a more comprehensive narrative of the early development of old age psychiatry in the UK are referred to a historical study hosted by the Glasgow University website: www.gla.ac.uk/media/media_107314_en.pdf. Psychogeriatrics has 'come of age' in the UK. Provision, although geographically patchy and relatively under-resourced, still provides one model for future developments. This model, fostered in the National Health Service with its principles of equality of access, payment from general taxation and central planning, survived the major changes of the 1990 'reforms'. However, centrally directed changes, under the regime of equity and quality proposed by the last UK government, appear to be sometimes having perverse effects and introducing greater (and perhaps inappropriate) variability. Old age psychiatrists need to show leadership in these times of rapid change, and governments need to furnish adequate resources and ensure national standards, both in terms of quality and quantity of provision.

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The Multidisciplinary Team and Day Care Provision

Martin Orrell¹ and Kunle Ashaye²

¹*Department of Mental Health Sciences, University College London, London, UK*

²*Mental Health Unit, Lister Hospital, Stevenage, Hertfordshire, UK*

THE MULTIDISCIPLINARY TEAM

The multidisciplinary team assessments and treatment of older people with mental health problems enables a holistic approach to care for and meet the complex health and social needs this group of patients may present with. The concept of the multidisciplinary team has been described as a group of members of different professions whose working skills, when combined for the needs of the patient, aim to exceed in quality the simple summation of their individual abilities¹. In describing features of a successful multidisciplinary team, Rosenvinge included communication within the team; high quality leadership; maintaining audit activities to help maintain and improve service delivery and management; and maintenance of morale of team members¹. Multidisciplinary team members may include psychiatrists, mental health nurses, occupational therapists, social workers, clinical psychologists, physiotherapists, speech and language therapists, pharmacists and support workers. Improving multidisciplinary assessments to promote health and social care of community-dwelling frail older people has become an important issue for policy makers throughout the developed world². In England, the introduction of the Single Assessment Process was to help multidisciplinary team members target the complex needs of older people, and may help identify appropriate team members or specialists to help meet those needs; however, in many areas it has not been effectively implemented³. It has, however, led to an increase in multidisciplinary assessments². Multidisciplinary teams are found in various settings in mental health services for older people, such as community mental health teams, day hospitals and day centres, along with newer services like the Assertive Outreach Teams and Crisis Assessment and Treatment Teams.

THE ROLE OF DAY HOSPITALS

Day services available to older people with mental health problems include day centres and day hospitals. Psychiatric day hospitals for older people tend to be managed and provided through health services and run by multidisciplinary teams consisting of the various mental health professionals. Day centres tend to be managed and funded through local authorities, social services or voluntary organizations with fewer or no health professionals. The first psychiatric day hospitals were opened in the Soviet Union in the 1930s, probably as a result of inpatient bed shortages, and by the early 1950s many

had been opened worldwide in developed psychiatric services⁴. In the United Kingdom, the first psychiatric day hospital was the Marlborough Day Hospital in London, opened in 1946⁵. Other psychiatric day care services for older people followed, with dramatic increases in the 1960s and 1970s⁶. The main factor in the growth of day hospitals was attributed to the development of new psychiatric treatments such as neuroleptics. They enabled the mentally ill to be treated in day hospitals, providing a high level of care during the day, but returning to their homes each evening.

The development of effective community support systems is essential for the successful shift from inpatient to community care for mental health services. The identified needs of severely mental ill individuals in the community include medication monitoring and therapy; psychosocial treatment, day and vocational activities; supported and supervised residential services⁷. Day hospitals with their various functions are ideally placed to play a significant role in assessment and community care.

The psychiatric day hospital provides short- and medium-term care to the mentally ill, with the option of receiving at times intensive psychiatric care without hospitalization. In the 1970s, a fully integrated psychiatric service for older people was described by Donovan *et al.* (1971) to include a day hospital serving four functions⁸. These functions were:

1. The outpatient investigation and treatment of older patients with physical and psychiatric disorders.
2. The continued observation of patients discharged from hospital.
3. To prevent deterioration from self neglect, loneliness or apathy.
4. To offer respite to carers, hence delaying or preventing inpatient admission.

Holloway (1988) described four main functions of day hospitals for mentally ill persons⁹. They are similar to those above and include:

1. An alternative to admission for people who are acutely ill and cannot be maintained as outpatients.
2. A service for support and monitoring in the often difficult transition between a stay in an inpatient ward and life at home.
3. A source of long-term structure and support for those with chronic handicaps, preferably in a friendly, low pressure environment.
4. A site for relatively brief, intensive therapy for people with personality difficulties, severe neurotic illnesses or in need of short-term focused rehabilitation.

In recognition of their important place in the care of older people, guidelines for current service provision for older people with mental health problems have included the provision of day hospital places^{10,11}.

For older people, Corcoran *et al.* (1994) described two objectives of the day hospitals established in Ireland as being¹²:

1. To provide acute psychiatric treatment, thereby functioning as an alternative to admission for patients of over 65 years with functional psychiatric illness.
2. To treat patients with behavioural disturbances associated with dementia.

These objectives are similar to those described above for generic psychiatric day hospitals, though the distribution of diagnoses is different^{8,9}. This is especially so in the case of persons with dementia, who are more likely to be found in a day hospital for older people than in a generic psychiatric day hospital. With such varied clientele, outcome and needs in various day hospitals will depend to a large extent on the type of patients being served, and available resources. One benefit of the above-listed functions taking place in day hospitals is that attenders are not taken away from home into hospital, but return home each day. This ensures that routines which may be difficult to re-establish after a long stay in hospital are less disrupted, other than due to illness, and so probably reduces the risk of institutionalization. Furthermore, reports obtained from home, by relatives and carers, give day hospital staff an extra tool in monitoring progress of attenders. For patients with cognitive impairment, maintaining them at home while attending the day hospital is likely to reduce problems of disorientation, resulting from movement into new environments like inpatient wards, as day hospital patients return to the familiar surroundings of their homes each day.

Shah and Ames (1994) described potential functions of an old age psychiatry day hospital as including: assessment, treatment, rehabilitation, long-term support, development of social networks and support of carers¹³. According to Rosenvinge (1994), characteristics of older patients' needs most likely to be met in a psychiatric day hospital can be grouped into functional and organic illnesses¹⁴. They include:

1. Assessment and management of acute functional illness.
2. Maintenance treatment of high-risk or vulnerable patients.
3. Continuation of treatment of discharged inpatients.
4. Assessment and management of patients suffering from dementia.
5. Provision of long-term support for those with severe dementia.
6. Treatment possibilities in dementia, such as advances in drug treatments requiring close supervision.

These characteristic needs are likely to be found in a wide variety of patients who are likely to benefit from day hospital care.

EVALUATION OF DAY SERVICES

Woods and Phanjo (1991), in a retrospective study of day hospital patients with dementia, observed the outcome of care after three years¹⁵. Circumstances of discharges were classified into planned and unplanned. Of the 145 discharges, 65 (45%) were unplanned, with reasons ranging from emergency admission in 14 (9%), to death or physical illness in 40 (28%) and refusal to attend in 11 (8%) patients. Of the planned discharges from the day hospital, only 11

(8%) were discharges to the community, with the remaining 69 (48%) transferred to long-term care in hospital or nursing/residential homes. Though not a randomized controlled study, the authors suggested that outside factors, such as the presence or absence of spouses or others who have taken on the role of carers affected outcome among day hospital attenders. Day hospital patients with spouses were observed to be less likely to be admitted to residential or nursing homes than those without spouses. Reasons that they proposed to account for the differences were that the patients with dementia remained longer with their spouses, and that when care was required, the severity of problems presented with at the time would require long-term hospital care rather than placement in residential or nursing homes. The findings of their study would suggest that it is essential that day hospital studies take into consideration such external factors as living spouses, carers and social support networks of patients.

In a study reviewing the impact of closure of a geriatric day hospital, following closure due to staff industrial action, Bhat-tacharyya *et al.* (1980) found few ill effects on patients over a six week period¹⁶. Ratings of mobility, self care, continence, mental state and need for services such as general practitioner, 'meals on wheels', day care or home help revealed minimal differences before and during the day hospital closure. Of the 55 patients in the study, most had cerebrovascular disorders, arthropathy and/or cardiovascular disorders, and only 9 patients had problems with dementia or depression.

In a similar study in older patients with mental health problems, Rolleston and Ball (1994) observed the impact of a two week closure of a psychiatric day hospital¹⁷. Data on well-being of patients and their carers were collected over eight weeks, to include three weeks prior to closure, two weeks of day hospital closure and three weeks following re-opening of the day hospital. They used two brief questionnaires, designed for patients and their main caregivers respectively, asking whether they felt the same, better or worse than usual, during the preceding week. They found a trend towards decline in well-being during the day hospital closure, which returned to pre-closure levels for both carers and patients on re-opening the day hospital. These findings would suggest that the day hospital was of benefit to both carers and patients. However, this study suffers from the arguments against many day hospital studies, in that they are not randomized controlled studies, hence no consideration is taken for confounding variables, such as the festive season during which closure took place, compliance with medication and/or the social network available to replace the day hospital over the same period.

Corcoran *et al.* (1994) noted that day hospital treatment enabled the older people with functional illnesses to be treated in the community with low usage of beds, and provided short/medium-term care for patients with dementia who had little support from statutory services¹². They reviewed all regular attenders of two day hospitals over a three-year period, in which 139 (59%) patients had an organic disorder, mainly dementia, and 98 (41%) patients had a functional disorder, with the most common diagnosis being depression. There was a low uptake of community services at the time of day hospital admission, despite the relatively high level of dependency, especially among patients with dementia. During the course of the study, the uptake in community services, such as meals on wheels, home help and day care, doubled. The average length of admission was five months for those with functional disorders and eight months for those with dementia. Of those patients with functional disorders, 71% were managed effectively through the day hospital and community psychiatric nursing visits, while 25% of them required inpatient care, of which two-thirds were for deterioration in physical health. In the

case of those patients with organic disorders, 88 (63%) entered into residential care, on average about eight months after initial referral to the day hospitals. In 20% of patients with dementia, the day hospitals served as a long-term supportive facility, with average attendance of 18 months among this group of patients with severe dementia. This study highlights the benefits of day hospital care in older persons with both functional and organic disorders, though it can be argued that the lack of a control group or comparison with any alternative form of care weakens its findings. The authors themselves acknowledge the importance of an increased range of support services in the community for day hospital attenders.

Johansson and Gustafson (1996) observed that the old age psychiatry day hospitals offered flexible and effective care, especially in supporting people with dementia at home¹⁸. The most frequent psychiatric symptoms that they observed among the day hospital attenders included delirium, anxiety, sleep disturbances and depressed mood.

Kitchen *et al.* (2002), in a study evaluating care provided through day hospitals, revealed insufficient clinical disciplines in terms of lack of psychiatrists, occupational therapists and psychologists in several day hospitals¹⁹. The physical environments were often unsuitable, highlighting the need for purpose-built or adapted day hospitals for older people.

COMPARING DAY HOSPITALS AND DAY CENTRES

Day hospitals, being a health resource, are often located on or close to hospital sites, whereas day centres run by local authorities are more community based, often closer to the clients they serve. Eagles and Warrington (2002) suggested that day centres could carry out similar roles to the day hospitals, as attendees had similar characteristics across both settings, such as severity of dementia, dependency and the range of behaviour problems²⁰. They further argued that unless the benefits of mental health staff in day care were demonstrated, resources would be focused on using cheaper untrained staff in day hospitals.

Furness *et al.* (2000) compared the characteristics and unmet needs of 129 older people attending day hospitals and day centres²¹. The day centres had a higher proportion of people with cognitive impairment, while day hospital attendees had increased behavioural problems and psychotic symptoms. There were similar high levels of high satisfaction expressed by carers of both groups. Collier and Baldwin (1999) found that day hospital patients presented with more behaviour problems than those attending day centres²². Though considerable research has been carried out comparing day centres and day hospitals, it has been suggested that they form part of a continuum. Day hospitals, with the various health professionals, can offer the short-term care required for patients with acute and increasing mental and physical health problems who need ongoing multidisciplinary team assessments, review of medication and psychological treatments. Day centres with more untrained staff should have the long-term goals of ongoing social care support and daytime respite for carers for relatively stable patients with enduring mental health problems.

DAY HOSPITAL VERSUS COMMUNITY MENTAL HEALTH TEAMS: THE DEBATE

The lack of adequate scientific data concerning the effectiveness of day hospitals has led to both an enthusiasm for newer service models

and, contrastingly, the more conservative approach of leaving the day hospitals as they are. According to Howard (1995), in favour of day hospitals for older people is the fact that carer support by day hospitals has been endorsed by the National Institute of Social Work²³. Most psychiatrists with access to day hospitals find that they can be used to prevent inpatient admission and facilitate early discharge from wards. Howard mentions that day hospitals may increase carer strain, caused by preparing patients to attend day hospitals and disruption of normal routines. Other arguments include that there is no evidence that day hospital attendance delays or prevents admission of patients with dementia to acute or continuing care placements.

Ball (1993) reviewed the future of day care in old age psychiatry, in which day hospitals undertook a wide range of activities, ranging from acute management of functionally ill to long-term management of patients with dementia²⁴. He noted that high levels of distress and depression were found among carers of patients with dementia and this could be relieved by attendance at a day hospital. Though claiming that models exist to examine the effectiveness and efficiency in day hospitals, he failed to give any examples, except to propose that their days may be limited with the coming of community teams working with small local units. To the present date, no randomized controlled trial of the two services in older people with mental health problems as been undertaken.

Day hospitals and day centres provide not only social contact for the elderly mentally ill, and support over crisis periods, but the former also provide treatment in the community. It is argued, however, that these are roles that community mental health teams could also be able to undertake. The community teams working with small local units would be able to target specialist care at groups of patients in need of support, and guidance to those carers providing for their ordinary needs²⁵.

The day hospital is no longer uniformly or unreservedly accepted as an essential service component in old age psychiatry²³. Despite the wide use of day hospitals in old age psychiatry, debates still continue over the effectiveness of day hospital care, as it has not been well researched^{6,26}. Fasey (1994), in arguing against day hospitals, highlighted the expenses, which included transport, capital investments and highly trained staff⁶. He questioned whether there could be a better and more cost-effective way of delivering the same service. An example he gave was the use of day centres with professional staff providing support and training to less skilled day centre staff. It was further noted that the stated aims of day care, such as delaying or preventing admission of persons with dementia and decreasing carer burden with daytime respite were not achieved^{15,27,28}. However, 10 of the 155 day hospital patients with dementia followed up by Woods and Phanjo (1991) were still attending after three years, indicating that day hospitals can serve long-term needs of patients and their carers¹⁵. Diesfeldt (1992) undertook a retrospective, longitudinal study of older people with dementia, involving a day care centre rather than a day hospital²⁷. Over the five-year period of the study, 150 (67%) of the 224 patients admitted to day care died. At time of admission, 148 lived in the community, but by the fifth year, only 9 (4%) patients still lived in the community and 65 were in long-term care residential/nursing homes. This study highlighted the well-known fact that dementia is associated with increasing dependency and mortality. However, the outcome of day care is difficult to identify, in light of the fact that it was a retrospective, longitudinal, descriptive study rather than a randomized controlled one.

Hassall *et al.* (1972) and Arie (1978) have highlighted problems with day hospitals, including the fact that a high proportion of day hospital attenders had been inpatients^{29,30}. This implies that the day

hospital failed to serve as an alternative to inpatient care, and is further supported by the findings of Greene and Timbury (1979) that significant numbers of day hospital attenders were admitted to long-stay care six months later³¹. In this latter study, most of these patients who went on to long-term care in a residential nursing home or hospital had dementia and had been admitted because of their families' inability to cope, and their admission to day hospital was for, on average, six months.

Despite doubts about the usefulness of day hospitals, Corcoran *et al.* (1994) indicated that 71% of patients with functional disorders were managed effectively in the community with a combination of day hospital care and visits by nurses¹². They also observed that day hospital attendance enabled thorough assessment and treatment, ensuring that only those with illnesses who could not manage in the community with maximum support were transferred into residential care.

The focus of shifting psychiatric care to the community, coupled with poor scientific evidence of day hospital care effectiveness, has resulted in support for community mental health teams in place of day hospitals²³. In evaluating the multidisciplinary approach of community mental health teams to psychiatric diagnoses in the elderly, Collighan *et al.* (1993) noted a high degree of accuracy when compared to independent formal assessments and consensus diagnoses by research psychiatrists³². A total of 378 new referrals to a community mental health team for older people were assessed independently by the team and research psychiatrists. The research assessment consisted of a structured psychiatric interview, full medical and psychiatric history, physical examination and routine blood investigations. Level of agreement between team and research diagnoses was between 90% and 99%. This finding suggests that community multidisciplinary team assessments are at least no worse than those done by psychiatrists, and possibly more likely to flag up problems in non-clinical areas like housing and social support.

Community mental health teams, like day hospitals, are staffed by nurses, occupational therapist, psychologists, psychiatrists and social workers³³. The teams are said to provide care that is less focused on a hospital or institution setting³⁴. However, it is uncertain whether they lead to benefit for seriously mentally ill people, their carers and society, with respect to how they function or behave³⁵. Lives of carers, especially relatives of persons with severe mental health problems, may be disrupted by the high degree of dependency and uncertainty that care involves. The profile of mental health is frequently raised in the media when there is an untoward event involving persons with mental health problems heightening the negative attitude and fear of the public at large. Some of the problems of community mental health teams, and possibly day hospitals too, emanate from this, in that people frequently do not want mental health resources near their homes, or make relocation and employment of persons with mental health problems more difficult.

A review of the literature on the use of community mental health teams in the care of older people does not indicate a marked difference in outcome from day hospital care. In a follow-up study of older people with mental health problems, referred to four community mental health teams, Bedford *et al.* (1996) reviewed outcome after six months of referral to the teams³⁶. They noted a poor outcome in patients with dementia, in that, over the six-month period, 22 of the 63 patients with dementia moved from living at home into institutional care settings and 11 (17%) had died. A recent systematic review of the literature by Hoe *et al.* (2005) found the evidence for the effectiveness of day hospital care for older people with mental

health problems increasing³⁷. It was observed that the day hospitals were effective in meeting the needs of patients.

THE FUTURE: INNOVATIVE DAY CARE AND DAY SERVICES

The National Service Framework for Older People is an essential component of the UK government's plan to develop health and social services^{38,39}. Key components include care of people with dementia and depression; range of community- and hospital-based services that should be made available; emphasis on the need for integrated, joined-up care and highlighting of the need for specialist mental health services to provide outreach. These requirements are likely to lead to more integrated day services, involving health authority, local authority and voluntary agency jointly run day services, with outreach day care available in the community rather than residing on hospital sites. It has been observed that, despite the introduction of the National Service Framework for Older People, there are substantial variations in service provisions⁴⁰. This may lead to the continued differences observed in day care provision as well.

Some recent innovative practices in day care have included the fast-track day hospitals providing rapid assessment and treatment of behavioural problems in dementia⁴¹, and Alzheimer's cafés, run jointly between statutory and voluntary services providing support to carers of patients with dementia. Crisis Intervention teams, more commonly placed in Adult Psychiatry, are becoming more accessible to older patients, and dementia care multidisciplinary teams offering intensive dementia care at home are being established, preventing hospital admissions. These developments may lead to less reliance on day care.

The Meeting Centres Support Program (MCSP) integrates different types of support for persons with dementia and their carers. The programme focuses on persons with mild or moderate dementia living in the community, and their carers. It is offered by a small professional staff (2 or 3 professionals for 15 people with dementia and 15 carers) in social cultural community centres in the neighbourhood, which is why it is called the Meeting Centre Support Program. Studies comparing MCSP to routine day care have found the programme to be more effective in influencing the feeling of competence of carers, and appeared to delay nursing home placement, along with a positive effect on behaviour and depressed mood^{42,43}. In a later study, aside from delay in institutionalization, MCSP proved more effective in decreasing psychological and psychosomatic symptoms in carers of people with dementia than routine day care⁴⁴.

In England, the drive towards creating more capable teams and new ways of working in multidisciplinary teams is leading to changing responsibilities and roles of various disciplines⁴⁵. Other team members are expected to carry out psychiatric assessments, prescribe and be the responsible clinician, which were once considered the traditional roles of the psychiatrists. This may lead to a different picture of staff and skill mix in multidisciplinary teams in various settings such as in day care services and community mental health teams.

With the expected rise in elderly population, governments are going to look more closely at various innovative cost-efficient means of delivering health care. It is likely to lead to even more demands to assess the effectiveness of day care services and the need to make day care more efficient and accessible. A comprehensive and flexible mental health service is likely to best serve and meet the changing

needs of older people with mental health problems. The delivery of such care through multidisciplinary teams available in such settings as community mental health services, day hospitals and day centres will ensure the adaptability to meet varying needs of this group of patients.

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NHS Continuing Care

Clive Ballard¹, Ramilgan Chitramohan², Zunera Khan¹ and Jean Beh¹

¹King's College London, London, UK

²Birmingham and Solihull Mental Health Foundation Trust, Heartlands Hospital, Birmingham, UK

BACKGROUND

All health and care systems have to address the difficult problem of providing appropriate treatment and care for people with severe dementia, who often have a complex combination of needs. This usually requires a variety of service provision options tailored to the needs of particular individuals and their families, which may include domiciliary support models, private care home and nursing home facilities and directly run National Health Service (NHS) nursing homes and NHS continuing care facilities. Within the UK system, services for people with dementia who have the highest level and greatest complexity of need are provided within the framework of 'NHS continuing care'. This has been technically defined as care for an individual whose treatment needs can only be met by NHS provision, usually meaning 24-hour specialist nurse input, with continuous overview supervision by an NHS specialist consultant. Depending on the needs of particular individuals and the service models in operation in different localities, this can be provided through intense NHS support for people in their own homes, through provision in private nursing homes with additional NHS support or through directly NHS-managed NHS continuing care units. Traditionally, these 'NHS units' were hospital wards, but the service provision has become more flexible, and the continuing care units are now more frequently stand-alone units, run by the NHS, but located in community settings.

This chapter is very much a personal view of the authors, highlighting the context of NHS continuing care and the key elements which the authors believe are essential to enable people to 'live well' with severe and complex dementia.

UK LEGAL STATUS OF NHS CONTINUING CARE

Various legal challenges have enabled refinement of the system and the models of care. Importantly, people who need NHS continuing care, whatever the setting in which that care is provided, receive the care free of charge. This is of course in complete contrast to care provision within the nursing homes, for which people contribute substantially to their financial cost using a means-tested formula¹. It has, however, been clarified that NHS hospital trusts are obliged to provide adequate NHS continuing care provision in some form. This has led to several major changes in practice:

1. A widespread review of continuing care provision within individual organizations, and an increased flexibility of that provision, which by and large has been helpful and appears to have reduced the widespread dismantling of NHS continuing care provision that was previously occurring as part of achieving 'cost efficiencies'.
2. Setting up of review panels to consider all individuals referred for NHS continuing care to ensure that those individuals have sufficiently complex needs to require NHS continuing care rather than an alternative form of care such as that provided by private sector nursing homes.
3. Ongoing review of people receiving NHS continuing care to ensure that their level of need continues to meet the criteria for this type of care provision. This is a marked departure from the traditional philosophy, which was that NHS care provision was a 'home for life', and a change to a model where the expectation is that most individuals will achieve a reduction in the complexity of their needs as part of the treatment and care that they receive, enabling their needs to then be met within a private sector care facility.

The Alzheimer's Society presented a comprehensive review of the definitions, framework and criteria for costings in 2007, and updated in 2008 to include new legal precedence¹.

CONTINUING CARE NHS MODELS

Traditionally, NHS continuing care has been provided in dedicated inpatient ward environments. These wards still exist in some NHS settings but are poorly designed for the provision of care for people with severe dementia and often concurrent behavioural and psychological symptoms of dementia (BPSD). There are usually a limited number of private rooms, with dormitory facilities that make it difficult to respect privacy and dignity and to meet the needs of individual patients. In addition, the environments are not designed specifically for people with dementia, are often in a poor state of repair, are rarely 'homely' and infrequently have access to outside space. As a result, many NHS organizations have now either built or leased smaller, purpose-built units in a community setting, or set up contracts with private sector providers to offer NHS continuing care beds with an agreed level of NHS support. Although the provision of

better designed, more homely facilities is likely to be an advantage, there has been limited evaluation of either model.

WHICH PATIENTS ARE PLACED IN NHS CONTINUING CARE

The proportion of people residing in care facilities who have dementia has consistently increased over the last 20 years, with most reports over the last decade indicating that at least two-thirds of care home residents have dementia, even though only a quarter of care home beds are registered specifically for people with this level of need^{2,3}. As a consequence, there has also been some blurring of boundaries between different types of care provision with respect to the needs of the individuals for whom they cater. For example, the proportion of people with dementia in nursing homes and specially register beds is not substantially different from that in 'ordinary care homes'²⁻⁴. There also appears to be a similar blurring of boundaries between the specialist nursing homes and NHS continuing care, with a similar proportion of people with a similar severity of dementia and comparable high levels of BPSD in both settings⁴. This possibly suggests that some people are being placed in private sector care homes when their level of need may require NHS continuing care, either within a dedicated unit or by providing much more substantial NHS support to enable the effective care of those individuals.

WHAT IS THE QUALITY OF CARE IN NHS CONTINUING CARE ENVIRONMENTS

There is an absence of published audit data or randomized controlled trials to provide a meaningful evaluation of usual NHS continuing care or novel models of care provision. An audit of 17 care facilities across the UK conducted in 2001 included 10 private sector residential or nursing homes and 7 NHS continuing care units⁵. Disappointingly, based upon daytime evaluation of well-being and activities, a similar pattern of impoverished daytime activities and poor overall well-being was evident in both care settings, and there was no evidence that NHS continuing care offered improved activities, well-being or quality of life for care recipients.

This does not reflect our anecdotal experience of clinical practice, and it will be increasingly important for more widespread evaluation of care using standardized approaches to measure overall quality of care provision, to enable benchmarking against the best care services and to enable continual improvement of professional practice and the quality of treatment and care provided.

Additional information is available from studies examining the transfer of people to different care environments when NHS continuing care facilities have closed. The primary outcome measure in these studies has tended to be mortality rates⁶ rather than wider health outcomes, and the effects of relocation on older people with dementia are not straightforward, with conflicting findings reported in different studies. For example, some authors such as Robertson *et al.*⁷ reported that disruption associated with the move was associated with higher mortality among residents after the move, while others found no increase in mortality or health problems⁸. However, two consistent findings did emerge from the literature relating to the relocation of older people with mental health needs. Firstly, that the moving of patients and staff together ('en bloc') minimizes disruption associated with the relocation. Secondly, that an individualized and comprehensive preparation programme is vital in maximizing the holistic outcome for the resident.

In a more recent report examining relocation of an NHS continuing care unit within the South London and Maudsley NHS trust, 23 residents from an NHS continuing care facility were relocated, 9 residents underwent individual transfers over a 12-month period and 14 were transferred 'en bloc' to a new unit⁹. The baseline assessments included an assessment of quality of life, which indicated 'adequate coping' and suggested considerably better quality of life than had previously been reported among people with complex mental health problems residing in long-term care¹⁰.

Importantly, the group of residents who were moved individually to new accommodation showed a significant decline in behavioural disturbance (as measured by the Neuropsychiatric Inventory), while the group who moved together to the new unit showed no change. This unexpected finding may be explained by the fact that considerable effort was taken to re-accommodate residents to locations of their and their relatives' choice. Those residents who moved away to new units were often situated much closer to their relatives, which may have provided greater opportunities for social interaction. This in turn may have had a positive impact on residents' behaviours. This does indicate that successful transfer of individual patients from NHS continuing care to other care environments can be achieved with careful planning and assessment⁹.

Several studies have evaluated more specific models of providing NHS continuing care, such as the *domus* model. 'Domus care' is provided in small units based in the community, operating with core 'person centred' principles and a 'rites-based philosophy' that the domus is the person's home. Evaluation of this model has demonstrated advantages over traditional NHS continuing care settings¹¹. In particular, BPSD and communication skills improved significantly among residents, although providing this type of care was twice as expensive as traditional models. While it is encouraging that good quality care can result in improvements in well-being and communication, it is unclear whether this is a specific feature of the domus model, related to better staffing ratios or an example of what can be achieved by motivated staff in a well designed environment. As a proof of concept it is, however, extremely important, as it demonstrates that it is possible to provide high quality care that meets the needs of these individuals.

The recent change in NHS continuing care to focus on 'rehabilitation' to reduce the level of need and enable transfer to other settings such as private nursing home facilities is contrary to the 'domus philosophy', and is likely to result in significant changes in care practice and the style of treatment and care. Further evaluations will be needed to determine whether this has a positive or negative impact on people with dementia living in these environments.

WHAT IS NEEDED TO PROVIDE TOP QUALITY NHS CARE

Provision of high-quality NHS continuing care for people with dementia requires a highly skilled group of staff, a well-designed, purpose-built environment and excellent links with other medical, social care and palliative care teams to provide a physical and social environment that can meet a broad range of need. Key areas include basic activities of daily living (ADLs), social needs, BPSD, transfer, mobility and reduction of falls risk, management of pain and concurrent physical health needs, feeding, skin care, other needs related to end-of-life issues, working with families and understanding the legal framework within which this care must operate.

UNDERSTANDING OF RELEVANT LEGAL FRAMEWORKS

The majority if not all of the people in NHS continuing care settings will lack capacity to make decisions regarding their medical treatment or long-term care. Many such individuals can be looked after in these settings under the general provisions of the Mental Capacity Act 2005 in the best interest of these individuals so long as their care regime is not considered to deprive them of their liberties¹². Those whose care regime is so restrictive as to amount to deprivation of liberty will come under the new Deprivation of Liberty safeguards which can authorise detention in the individual's best interests for up to 12 months after 6 assessments (the main issues are highlighted by Behan in a Department of Health Document, 2007)¹².

Some individuals may initially be admitted to an NHS continuing care unit under the auspices of the Mental Health Act (see¹³ for more detailed guidance on the 2007 Act), or such an order may be applied at some point during an individual's care. These are mainly patients who object to being looked after in such settings.

Specific decisions regarding resuscitation and other end-of-life treatment issues are complex and fall under various legal frameworks. Staff working within this sector therefore would need to understand a complex network of legal frameworks, and how to work within these frameworks to achieve a level of treatment and care that meets the best interests of the individual patient. At an organizational level this requires excellent training and processes, and at a unit management level requires excellent operationalization of these processes so that they contribute to, rather than hinder, good quality treatment and care.

SUPPORTING BASIC ACTIVITIES OF DAILY LIVING

Most people with dementia of a severity sufficient to require residence in a care home or NHS continuing care setting will require at least some assistance with basic self care, usually requiring help, prompting or supervision for washing, dressing and going to the toilet. The opportunities and skills to engage in other more complex activities such as cooking, making tea and activities outside the care facility such as shopping are likely to be limited by safety concerns, the organization of the care setting and the skills of the individual. With well-thought-through care plans and an appropriate level of assistance and supervision it is, however, possible to enable many individuals to take part in a limited number of more 'general' activities as part of supporting social needs (see subsequent section). In NHS continuing care settings this will vary hugely between different individuals depending upon the balance of complex needs. Some patients will have very severe dementia, while others may have dementia of moderate severity with additional BPSD and/or physical health care needs. A full assessment of every individual is therefore essential, working to the principle of maximizing people's abilities and competencies. Assessment tools like the Pool Activity Level¹⁴ and the person's life story work^{15,16} will inform the care planning process. As part of this assessment, detailed personalized care plans should be developed, outlining skills which it is important to enable people to continue using, self care activities which can be partly completed by the individual with appropriate prompting and help, and self care activities which need to be undertaken for the individual. In the latter circumstance it is also important to plan the support with self care in such a way as to maximize the opportunities it creates for normal social interaction, to minimize anxiety and distress, to make the assistance less challenging for the individual and

reduce the likelihood or impact of BPSD (see subsequent section). Supporting an individual's basic activities of daily living is vital and requires good care planning, but would not on its own constitute a level of need requiring NHS continuous care. When ADL needs are linked closely to other needs such as BPSD, skin care and feeding, the complexity of the 'need', and the skills needed to meet the 'need' effectively increase substantially.

Case Example

Mr Bell, a 65-year-old gentleman, was fully dependent on staff for all his needs. He was also bed bound. Whenever staff attended to his personal care, they would come out of his room exhausted and complaining that he was resistive and aggressive and it was 'a fight' caring for his needs.

But when Mary (staff member) attended to his personal care, she did not have the same experience. She would call him by his preferred name David, and explain to him step by step what she was going to do for him. She would inform him that she was going to wash his face before applying the wet flannel. She would also ask if he could relax his arm while she tried to take off the sleeve of his shirt. After much explanation and time taken with David in carrying out his personal care, Mary and her colleague would feel happy that they managed David's personal care without much struggle. David too looked comfortable sitting up in bed.

MEETING SOCIAL NEEDS

As part of statutory and regulatory frameworks and in developing care standards, the social needs of residents in care homes and NHS continuing care environments have been rather neglected. This is a major oversight as it is fundamental to everyone's well-being, and something which needs to be a key part of the care planning for every individual. People all have a large social need, which is frequently unmet in care settings. At a gross level, this is well evidenced by the fact that, based upon large studies of Dementia Care Mapping¹⁷, people spend less than 15% of their daytime period engaged in social interaction or any other positive or enjoyable activity⁵.

Often, the knee-jerk reflex to addressing social needs is to organize 'activities', usually games (e.g. bingo, a quiz), dancing/singing/music or an opportunity for reminiscence. In itself, if well planned, this type of activity can be very positive for residents who enjoy these types of event, but thought does need to be given to individual choice and to the development of more personalized care plans for every individual. It is rarely possible for 'Care home wide' activities to be undertaken more than a few times a week, and therefore, although a positive contribution to social need, they are generally a small contribution.

Talking to an individual, their families and friends to build up a life book, which includes details of their hobbies, interests, usual household activities and occupation, is an excellent way of learning more about each individual, developing material for reminiscence and for identifying specific individualized activities which may be beneficial or enjoyable for a particular person. A care plan can then be developed to create opportunities for specific activities that can be safely undertaken with the right level of support. Several excellent

research studies have shown the value of enhancing individualized care planning and individualized activities to improve well-being and reduce agitation^{18,19}.

Case Example

Ethel, an 80-year-old lady, would shout and scream every afternoon. The staff would play the same music (1950s songs); two of the residents would sing the songs, but Ethel would continue to shout loudly. Janet (staff) approached Ethel and asked her what was troubling her; Ethel just replied 'I am bored'. Janet asked her what she would like to do; Ethel replied 'push me around'. Ethel was chair bound and when she was well, she enjoyed going out for walks. Janet pushed Ethel's chair around the unit, into the garden and around the corridors of the unit. While Ethel was going round the unit and into the garden, Janet talked to her about the plants, flowers and pictures on the wall. Ethel would respond with 'that is lovely' or 'push the chair faster'. All the time Ethel was travelling around the unit, she stopped shouting and spoke quietly to Janet.

In addition, it is important to think about the environment: organizing chairs in a way that facilitates conversation; availability of 'coffee rooms'; providing a choice of television and radio programmes which is not over-loud or intrusive to other residents; providing interesting reading materials and objects for people to enjoy and which can facilitate conversation and reminiscence; providing adequate and interesting indoor and outdoor space to enable people to walk about in a safe and enjoyable way.

In people with very severe dementia, it is possible but more difficult to meet social needs. Again it relies on an individualized assessment, but often people may be more responsive to one-to-one interaction. Sometimes conversation or music may be perceived positively, but for many individuals touch is the most beneficial interaction – holding an individual's hand or an aromatherapy massage may, for example, give the greatest benefit.

Staff need to be encouraged to take steps toward positive risk taking when caring for a person with dementia. This will allow more creative approaches to care for people with dementia if staff are supported by management. Care that is collaboratively planned and managed by a multidisciplinary team after discussions with the person with dementia and their family will ensure that care provided is person centred.

Case Example: Individual Care Plan

John, a 70-year-old gentleman, used to be a dancing instructor. He would often walk up and down the corridor with his head bowed low. Staff had to listen very carefully to what he was saying, at times it was clear but, most times, his speech was muddled. But when staff offered to dance with him down the corridor, he would hold his head up a little, held good eye contact with the staff and, with a smile on his face, danced down the corridor.

MANAGEMENT AND PREVENTION OF BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD)

Approximately 80% of individuals in NHS continuing care experience BPSD at any one time⁵, and probably all individuals experience at least one of these symptoms longitudinally²⁰. BPSD are almost always present and severe at the point of admission to NHS continuing care, and are the usually part of the complex need for which NHS continuing care is considered necessary for a particular individual. Aggression and restlessness are the most frequent symptoms, occurring in 60% or more of residents⁵, but delusions and shouting are also frequent and problematic, while other less frequently occurring problems, such as sexual disinhibition and concurrent bipolar disorder, can be extremely challenging.

One of the advantages of working in a continuing care setting is that it affords a 'protected environment' with a skilled multidisciplinary work force, which allows time to conduct a detailed assessment and plan interventions carefully. A broad multidisciplinary clinical assessment can therefore be undertaken to inform any changes in treatment. As in any setting, the assessment includes screening for physical health problems such as infection, pain or dehydration, which are common, and often precipitate BPSD. A comprehensive review of pharmacological treatments may identify therapies exacerbating depression, other BPSD or confusion²¹. Visual and auditory impairment can also precipitate BPSD²², and should be treated when possible. These principles are outlined in more detail by Lyketsos and colleagues (2006)²³. A careful psychiatric assessment is also important, as specific psychiatric symptoms such as florid delusions or depression may be underlying or contributing to the presentation of other behavioural symptoms such as aggression or agitation. In parallel, a detailed assessment can be undertaken of the frequency and severity of any presenting BPSD and any associated risks to the individual, to other residents or to staff. An approach such as an Antecedent Behaviour Consequence diary can be used to clarify the pattern of occurrence and to identify triggers and re-inforcers.

The strength of this approach is that it provides an overall assessment of the situation, and allows medical, psychiatric and environmental precipitants to be targeted through specific treatments or care plans. It also provides an assessment of risk, which enables the team to carefully balance the risks and benefits of different treatment approaches, including the information to make a carefully weighted decision regarding whether pharmacological treatment is necessary. The assessment also provides the opportunity to get to know the individual and build up a 'life story' and develop a better understanding of the person's preferences by talking to the individual, their family and friends. This enables their needs to be met more effectively, improves communication and interpersonal relationships between the person and the staff, engages the family and provides important information for the development of care plans and for specific non-pharmacological interventions for BPSD. Again, an advantage of a continuing care environment in this situation is that the multi-skilled staff group and NHS medical/psychiatric support means that a less invasive option can often be implemented as a first-line strategy, as detrimental outcomes can be rapidly contained and management plans can be revised quickly. In practice, the most frequent practical management problem is physical aggression occurring when an individual is being assisted with personal care. In our experience, with a careful ABC (antecedent behaviour consequence) assessment, good interpersonal skills and a well-thought-through care plan, it is usually but not always possible to successfully manage and improve

the symptoms and the 'personal care experience' for the person and the staff without recourse to pharmacological intervention. If pharmacological interventions are necessary, best practice guidelines appropriate for all individuals with dementia should be applied²⁴. This is not discussed in detail here as the same principles apply to the management of dementia in general (for a review of evidence see²¹), but the principles should include limiting the use of atypical antipsychotics to short-term prescribing (up to 6–12 weeks) for serious management problems in most situations; the judicious use of other pharmacological interventions when appropriate, and the use of care and caution to limit multiple prescribing^{21,24,25}.

Case Example

Peter, a resident in a continuing care unit, was screaming whenever he was awake. The staff could see that he was distressed, but he was unable to communicate his reasons for his distress. The doctor prescribed antipsychotics to reduce his distress but the screaming continued. After much multidisciplinary discussion, it was decided to discontinue all medications except analgesia and to spend more individual time with Peter. The screaming stopped and Peter's distress was reduced to a minimum. To this day, we do not know whether the side effects of the medication were causing Peter's distress or the increased time spent with Peter alleviated his distress. The staff became more aware of the importance of observing for side effects of medication, especially for people who have difficulties in communicating verbally.

Paul, a resident in a continuing care unit, kept coming in to the staff office, especially at meeting times. This was disruptive to the staff as they had to stop their meeting to answer Paul's questions and requests for help. Reading through Paul's life story, the staff realized that he used to work as an administrator. The staff decided to make space for a table and chair in a corner of the dayroom. They left some paper and pens on the table. They informed Paul that the space was for him to do some work if he so wished to do. Paul sat at the table and wrote on the paper, occasionally he would go into the office but, most times, he would sit at his table writing or tidying up papers.

MAINTAINING MOBILITY AND MINIMIZING FALLS

Many individuals with moderately severe or severe dementia begin to lose independent mobility and even ability to mobilize with assistance. As mobility problems progress, even transferring from bed to a chair can be problematic. Mobility problems are likely to present even greater challenges in patients with motor disability related to vascular dementia and stroke or with other physical health problems impacting on the locomotor system, such as severe arthritis. Even in individuals who are able to mobilize, falls are a major clinical problem. Fifty percent of people with Alzheimer's disease fall over a three-year period, and fractures are extremely common^{26,27}.

There are, hence, a number of important challenges to maximize mobility and minimize fall risk. The importance of a multidisciplinary team is immediately evident. Good access to physiotherapy, consultation/liaison from Geriatric Medicine, robust assessment procedures and good quality person-centred care planning, focusing

specifically on mobility needs, are all essential components. The assessment and care planning procedures will need to determine the level of support needed to enable walking and transfer, such as appropriate walking aids, assistance from staff and a programme to maximize skills, for instance ensure adequate time spent walking to maintain strength, specific exercises to help maintain strength and balance. These types of programmes are clearly beneficial among older people without cognitive impairment²⁸, although the evidence is less clear in the context of dementia²⁹. Nevertheless, this probably is good practice, and will have concurrent benefits such as maintaining muscle strength and improving mood.

A careful assessment of fall risk needs to be undertaken for all individuals. Where possible, person-centred exercise and mobility programmes can then be developed which maximize benefits but reduce risk, for instance supervision needed when walking in outside spaces, or vigilance to ensure assistance during all walking. The assessment may also highlight the need for a more specific physiotherapy evaluation or a medical assessment of specific risks, for example syncope; or additional measures to reduce risk such as protective underwear, well-fitting footwear, good lighting, corrected vision with spectacles and clear pathways.

For individuals who are unable to mobilize, but can weight bear to transfer from bed to a chair, similar vigilance is required in completing an assessment, an evaluation of risk and a care plan to promote maintenance of skills using practice and exercises. Maintaining the ability to weight bear and avoiding the need for a hoist is a major factor in maintaining some independence and is therefore a very important clinical objective.

Given the severity and complexity of problems in these individuals, even with the best practice and care, disability is progressive and many individuals will eventually lose their ability to weight bear. Under such circumstances a hoist will be needed to transfer a person from a bed to a chair or from a wheelchair to a sitting chair, both important to enable social interaction and to protect skin. Being transferred using a hoist can, however, be a frightening experience. Safely operating different hoists appropriate to the needs of the individual requires practical skills, but excellent interpersonal verbal and non-verbal communications to prevent and reduce fear and anxiety are also critical.

ASSESSMENT AND TREATMENT OF PAIN

Pain can be very difficult to assess in people with severe dementia, but has a massive impact on the quality of life of an individual and contributes to the emergence of other problems such as BPSD. Jiska Cohen-Mansfield and colleagues³⁰ have recently reported a series of studies developing clinical instruments to assess pain, and demonstrating clear benefits in behaviour and mood with the implementation of appropriate analgesia based upon these assessments. In clinical practice these instruments are an excellent and practical tool. Assessing pain also relies on a detailed knowledge of the individual. As a rule of thumb, if there is a possible indication of pain, or a physical ailment which is likely to be causing pain, our usual practice is to err on the side of providing analgesia, but in the context of careful evaluation of benefits.

ADDRESSING PHYSICAL HEALTH NEEDS

Many individuals living in continuing care environments have vascular dementia, providing the additional challenges of managing disabilities and providing rehabilitation for stroke-related impairments,

and providing optimal medical management of related cardiovascular disease and vascular risk factors. For example, there is accumulating evidence that good control of blood pressure, lipids/cholesterol and diabetes significantly reduces the progression of disability and cognitive impairment (e.g. PROGRESS 2001³¹). This again emphasises the need for multidisciplinary working and the importance of open access to geriatric medicine expertise and specialist clinics as appropriate for specific individuals.

More generally, many individuals with dementia in NHS continuing care have concurrent physical illnesses as part of the complexity leading to their placement in this type of facility. High quality treatment and management of these conditions may be important in stabilizing cognitive decline, but is definitely critical in reducing additional disability, minimizing associated pain and discomfort and maximizing quality of life.

Many individuals are on multiple pharmacological treatments, many of which are not well tolerated in people with dementia or which may impact upon cognitive function. Ongoing review of medication is therefore also a key part of good management. The National Service Framework recommends three-monthly medication reviews³². For people in NHS continuing care settings, informal medication review should probably happen more frequently, but a more formal three-monthly review is also good practice.

NUTRITION AND FEEDING

Maintaining good nutrition is an important part of maintaining health and well-being. In particular, minimizing weight loss is a key objective, and good nutrition will help to prevent skin breakdown and the development of ulcers. In addition, food is a major source of pleasure to most people and it is a potential opportunity to provide people with some pleasure and enjoyment. Food tastes often change with advancing dementia, and a preference for sweet food types is common. Many people also, however, continue to appreciate food consistent with their own culture, and occasional 'themed' meals may give an opportunity for group participation and other related activities.

Poor appetite or reduced food intake are common problems which need careful assessment and specific personalized care plans. Reduced appetite may be related to depression, physical illness or altered food preferences, all of which can be addressed if identified. Some patients may develop marked restlessness, sometimes of a severity which makes it difficult to encourage people to sit and eat meals or to drink adequately. Again this needs careful assessment to exclude bipolar illness or other specific causes, and may require specific pharmacological or non-pharmacological interventions.

As dementia progresses, a substantial proportion of individuals lose the ability to feed themselves. With a good care plan that assesses level of ability, people can be enabled to continue feeding. For example, providing just one implement of cutlery if coordination of more than one item is challenging, or the provision of finger foods. If diet is changed in this way, it is important to still think about the nutritional value and taste of the food. The Alzheimer's Society has provided a series of booklets which addresses these issues comprehensively^{2,3}.

Either because of very severe dementia or as a result of concurrent cerebrovascular disease, some individuals will lose or partially lose their swallowing reflex or their ability to coordinate swallowing. Under these circumstances, aspiration of food is a major health risk. In individuals where there is any level of concern, it is important that a careful assessment of swallowing is carried out. Often a specific

care plan, such as having meals in a fully upright position, having a 'soft diet' and thickening drinks, will be sufficient to enable meals to be taken safely. In some circumstances, where even these measures are not sufficient to enable food to be taken orally, difficult decisions need to be made in conjunction with family members regarding alternative feeding methods and/or end-of-life care.

OPTIMAL SKIN CARE

Vulnerability of skin to 'break down', and the prevention and treatment of ulcers in pressure areas represent an enormous clinical challenge in the clinical care of people with severe dementia in continuing care settings, particularly in people with limited or no independent mobility, spending a substantial proportion of the day sitting or lying down. Nursing staff require expertise in prophylactic skin care, and access to specialist nurses when ulcers develop and need to be treated. Specialist beds and mattresses are needed for some individuals, together with a breadth of clinical expertise encompassing use of mattresses, management protocols and care plans and the use of appropriate dressings. In addition, the management of related pain/discomfort and infection is important.

END-OF-LIFE ISSUES

Although this may change to some extent as NHS continuing care evolves, and is no longer 'a home for life' for all residents, currently the majority of individuals receiving treatment and care in these settings will die within NHS continuing care facilities. There are many advantages to this, in particular that the staff know the individual and their family well, and understand the needs of the individual and the family members, and the person is cared for in a familiar and comfortable environment. End-of-life issues therefore need to be tackled proactively, so that the wishes of the individual and of the family can be met as far as possible with respect to resuscitation, other medical treatment issues and key care decisions. In addition, the staff group needs to be familiar with and have access to expert advice regarding best practice management protocols to manage pain, distress, discomfort and dehydration in terminal care situations, and to provide support as appropriate to family members.

Working with families: family members continue to be a vital part of people's lives even when they have severe dementia and are residing in NHS continuing care environments. As part of the initial assessment when people are first placed in NHS continuing care, the family can provide key information to confirm the past medical and past psychiatric history, and even more importantly are able to convey an understanding of an individual's personality, background, likes and dislikes, hobbies, occupation and other important considerations such as religious and cultural issues and how important they are as part of someone's life. This enables a 'life book' to be developed and enriches the opportunities to develop better, more personalized care plans that are better suited to meet people's social, cultural and spiritual needs.

Many family members feel disengaged when an individual moves into continuing care or a nursing home. It is important to break down those barriers and to enable people to play an ongoing and active part in the care and support of the individual with dementia, and to help the family, where appropriate, contribute to the implementation of care plans to meet social needs. It is also important to help the person with dementia to continue to feel that they are an important and contributing member of the family, for which links to all generations of the family can be very helpful.

Particularly when advanced directives are not in place, families also play a vital role in the best practice meetings to make key medical and care decisions.

CONCLUSIONS

Providing good quality care to people with complex needs and severe dementia is difficult and requires a multidisciplinary, multi-skilled team with excellent access to appropriate specialist services. Often NHS continuing care has been seen as a low priority, and investment in team development and skills has not always been at the forefront of service planning. As illustrated by specialist models and pockets of excellence, it is possible to meet the needs and enable a good quality of life for even the individuals with the most severe dementia and complex concurrent problems.

Applying the principles of the ten essential shared capabilities for the mental health work force in dementia care will promote care that is truly person centred³³.

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Overview of Law, Ethics and Mental Health in Old Age

Julian C. Hughes

*Northumbria Healthcare NHS Foundation Trust and Institute for Ageing and Health,
Newcastle University, UK*

INTRODUCTION

An overview should clarify how things fit together. Where there is a high degree of complexity, however, this might not be possible; or, at least, it might require some digging to unearth the connections. I am going to suggest that what we have to look for in law and ethics is coherence in terms of our patterns of practice. In addition, I wish to point to the notion of the person as being in some sense fundamental.

MORALS AND PRACTICE

Consequentialism and Deontology

Consequentialism suggests that whether an action is good or right depends on its consequences. The best-known consequentialist theory is utilitarianism, which states that actions are right insofar as they maximize happiness or pleasure and minimize the opposite¹. If, for instance, it seems likely that Mrs Jones will kill herself because of her depression and we have good grounds to believe that she will enjoy her life again if she were to receive appropriate treatment, then treating her would seem to be the ethically right thing to do, even against her wishes. But this depends upon a careful assessment, because although compulsory treatment would seem to maximize happiness, such treatment must not be so unpleasant or upsetting as to cause her permanent discontent.

We can see immediately, therefore, how complicated things might become in pushing forward this argument. What if, for instance, it could be known for certain that Mrs Jones would never be happy again? Should she then be left untreated or at least not treated against her will? A legal issue, about her ability to make decisions for herself, arises and reflects the Law's emphasis on the rights of competent persons to control what happens to their bodies under normal circumstances. Generally speaking, it is only when a person is not 'of sound mind' that others are allowed and required to make decisions on the person's behalf.

To return to the case of Mrs Jones, just as utilitarians might argue that it is best to have a rule that people like Mrs Jones should be treated because this is more likely to maximize happiness (i.e. rule utilitarianism, as opposed to a focus on particular and individual

acts, which is called act utilitarianism) so too we could more simply argue that we have a duty (*deon*) to treat Mrs Jones. We quite often speak of a duty of care, for instance, which carries with it the idea that this is something we must do – and the difference between this and utilitarianism is shown by the fact that we add 'whatever the outcome'. In deontology the consequences are not the main issue. What is at stake is how people should behave as rational agents in the world. Given some of our typical concerns as human beings – that we should have a basic level of certain sorts of good (warmth, clothing, food) – it can be argued in deontological mode that there is a duty, for those who are able, to provide these goods to people who lack them. Duties are sometimes thought of as being corollaries of rights. Hence, if a person has a right to be told the truth about his condition, we have a duty to be honest with him. A right to basic standards of care carries with it a duty to provide such care. A right to privacy entails a duty not to invade the person's privacy, to confidentiality a duty to maintain confidences.

Four Principles

In clinical ethics it has become commonplace, partly in order to avoid the complexity of the arguments that emerge in discussions of consequentialism and deontology, to use the four principles of medical ethics². These provide an easy way to access the relevant arguments in connection with health care decisions. Autonomy, often regarded as the main principle, stresses self-rule: the person with dementia should still be able to make decisions for him- or herself. But the second and third principles, beneficence and non-maleficence, stress the need for carers to seek to do good for those they care for and to avoid them coming to harm. So, at some point, doing good for the person with dementia may involve taking over certain decisions in order to avoid harm. Perhaps, because of cognitive impairment, the person's money now needs to be controlled by someone else to avoid financial abuse. Finally, the principle of justice stresses the need to treat people fairly. So resources to help people with dementia should be distributed evenly, or at least in a fair manner (albeit what is considered fair in one political system may not be considered fair elsewhere).

The principles of medical ethics give us a framework within which to discuss moral dilemmas. One of the complaints about these

principles, however, is that they do not give us a way to decide between them. Perhaps someone thinks Mrs Jones should be left to make her own decisions about whether or not she commits suicide (i.e. her autonomy should be respected), while someone else feels that compulsory treatment would do her good (i.e. beneficence) and avoid her coming to unnecessary harm (i.e. non-maleficence). The difficulty of deciding between principles seems intractable.

Ethics of Care

In response to the messiness of moral decision-making in the real world, a new approach to ethics has emerged from practice³. Whereas the more traditional theories stress calculations of pleasure, rules and principles (they also seem to hold out the possibility of *definitive* answers), the newer approach stresses context and the nature of our relationships within contexts of care. The move from rules to relationships has been regarded as a key feature of feminist ethics. But there have been several such approaches – communicative ethics, narrative ethics, hermeneutic ethics, situation ethics – all of which stress the importance of person-to-person interactions and the nature of our interdependency^{1,3}. For any given situation the key elements in deciding the right thing to do will be the nature of the communication, the way in which the stories of those concerned (the actors) interact, the meaning of the events viewed from different perspectives with different interpretations, and so forth. This can lead to the conclusion that there are no definite answers in ethics, because (for any given case) we shall always be told that it depends on the details of the context and the perspective. But, to my mind, this is too relativist, as if anything goes and nothing can be called right or wrong. Rather than say that no ‘definite’ answers can be given, I should rather say that the answers are not ‘definitive’ in the sense that they are not final and unconditional. They are revisable and open to new interpretation.

Casuistry

Being open to appeal in the light of new evidence is the approach of casuistry, which considers matters case by case, where the factual details of the case must be understood and those making decisions must immerse themselves in them, but where cases are then compared to sentinel or paradigm cases, where decisions have already been made⁴. Appeal is then made to appropriate moral principles to explain the important moral distinctions between cases, but it is always left open that decisions might be revised in the light of alternative information. Thus, the casuistic process underpins law, allowing a development of legal thought in response to new cases, but with reference to established principles. The same holds for clinical decisions, which tend to be (at one and the same time) both practical and ethical. As with other types of care ethics, casuistry pays attention to the fine-grained details of individual circumstances, which will have a determining effect on our judgements about what might seem either right or wrong in a given case.

Virtue Theory

Virtue ethics draws on a long tradition going back to Aristotle and is based on the idea that the right or good thing is that which the virtuous person would do⁵. Hence, in the case of Mrs Jones, it would be appropriate to look towards those we consider to be good (in the sense of virtuous) in order to decide matters. Although virtue ethics

is a well-established ethical theory, it has much in common with the ideas that come from the ethics of care. This is partly because the very notion of ‘care’ reflects important virtues – compassion or charity – that lie at the heart of clinical practice. In addition, it would not be a virtuous thing to make an ethical decision in a particular instance without being aware of the details of the case.

Some people complain that making a decision about who is virtuous is just too subjective: we might differ in our opinions. This is true, but the fundamental claim of virtue theory is that there are features of the world on which we can agree, even if there is potential disagreement about how these considerations apply in particular cases. Thus, we can agree that we do well as human beings, we ‘flourish’, if we are brave, compassionate, honest, trustworthy, just and so on. We would not, after all, usually seek advice from someone whom we regarded as cowardly, malicious, dishonest or untrustworthy. In particular, we would want them to be prudent or to show practical wisdom, one of the other virtues highlighted by Aristotle, so that they had a good grasp of the ends at which we should be aiming in our clinical decisions and of how to achieve those ends. We might want to argue about whether a particular decision is just and compassionate, and we need practical wisdom to decide when, for example, to be brave; but in all such cases we are then arguing about the virtues and about what it might be to flourish as a human being. In a sense, then, virtue ethics stresses neither consequences, nor rules or duties, but what we *become* by what we do.

We shall do the right thing for Mrs Jones if we approach her with compassion, with empathic understanding; but we may be required to show steadfastness, to insist she is treated against her wishes on the grounds of our experience (or practical knowledge), which suggests that people with even severe depressions can be helped and that it is certainly worth trying to do so. Similarly, the person with dementia may require a good deal of honesty and integrity to be shown towards him in order that he might comply with decisions being made about his care. It may be that the manner of our dealings with those we care for is crucial and this also falls under the description of the virtues: we can do things in a way that shows basic human charity, or we can behave crassly.

Patterns of Practice

How does all of this come together in terms of our day-to-day actions and decisions? We do not, after all, routinely consider ourselves to be making ethical decisions. The emphasis on care and virtue ethics, however, helps to underscore the important point that clinical decisions are by their nature ethical: we cannot escape the reach of values in what we do, even in the case of making a diagnosis. An especially good example of this is making a diagnosis of mild cognitive impairment (MCI), which might seem like a benign activity, but is underpinned by a raft of value judgements and ethical concerns⁶. Hence, we should look at our normal patterns of practice since these provide evidence of our values and presumptions^{3,7}.

Does this mean, however, that just any old patterns of practice will do? On my view the clear imperative is that our patterns of practice should show both internal and external coherence⁷. Internal coherence relies on casuistry: does this decision in these particular circumstances cohere with similar decisions I have made in the past and, if not, what are the morally different aspects of the case that allow me to make the different decision? External coherence is based on acknowledgement of the virtues: does this decision square with the virtues? In other words, can I demonstrate that this is the sort

of decision someone would have to make in order to flourish or do well as a human being? In the next section, we shall gesture at how this might work in particular cases.

ETHICS AND THE PERSON

There is, however, one final plank to put into place, which concerns our notion of personhood.

Person-Centred Ethics

Since the seminal work of Tom Kitwood⁸, the notion of person-centredness has become ubiquitous in dementia care. This is a broad notion that is, in fact, co-terminous with a number of other types of care: patient-, family-, relationship- and client-centred care all share a number of characterizing themes. They all emphasize: respect for individuality and values, attention to meaning, social context and relationships, an inclusive model of health and well-being, the importance of lay knowledge, the idea of shared responsibility, communication, respect for autonomy and the notion of the professional as a person⁹. Person-centred care, therefore, suggests a broad conception of the person, one that allows and encourages a holistic view, that sees the person as situated in a variety of fields (biological, psychological, social, spiritual, legal, cultural, historical and so forth) and also as an embodied agent: neither simply a disembodied spirit, nor just physical matter¹⁰. This is the broad view of the person that should underpin our thoughts about our patterns of practice. In occupying this place, it underpins the notion of person-centred ethics too; that is, an approach to ethics that places decisions and actions in the context of the person, where this context is drawn broadly. Some examples should help to make this plain.

Case Study 1

Mr Phipps lives alone and develops the delusion that he is being watched because a neighbour thinks he is a paedophile. He believes there is a conspiracy to kill him by poisoning his food. So he'll only eat food if he can be absolutely sure of its source. He becomes socially withdrawn and gradually loses weight. A decision will have to be made about when to intervene because he will not comply with medication or outside help, although he does not object to seeing health professionals.

The broad notion of person-centred ethics supports the view that Mr Phipps should be taken seriously. He needs to feel he has the support of those who want to help him. They must try to understand how he acquired his odd beliefs. It might be there is a way to pacify his concerns, partly by understanding his social and cultural background. But carers must take seriously his physical and mental health needs too. They will have to be aware that at some stage his physical health will be compromised by his behaviour and so compulsory treatment may become an option. In judging their practices with respect to Mr Phipps, health care workers should be considering the need to approach him with compassion, honesty and integrity. Without these virtues, their practice will not demonstrate external coherence. They might consider, too, how their

management of Mr Phipps coheres with their management of similar cases. Why have they not yet used compulsory powers to enforce treatment as they have done before? Well, perhaps it is because Mr Phipps continues to eat so that his physical condition is not yet as precarious. Or perhaps they feel that they are slowly but surely establishing rapport—not achieved in former cases—which might negate the need for compulsory treatment. Thus, person-centredness and an approach that considers practice in terms of internal and external coherence provides room for a thorough account of the ethical justification for the actions taken, but always against the background possibility that things might need to be re-evaluated, either because of a change in Mr Phipps's state, or because of an alteration in the context that surrounds him.

In many places risk assessment has become the preoccupation of health care managers to the detriment of overall clinical care.

Case Study 2

Mrs Hayward has a moderate to severe Alzheimer's dementia and her family has taken the unhappy decision that she needs to be looked after in a private nursing home. She settles into the home quite quickly and soon becomes very friendly with a man, who also has dementia, whom she refers to as her husband (who had died six years previously). She frequently directs him into her bedroom and one day the staff find him there in a state of undress. A risk assessment concludes that she is at risk of being sexually assaulted by the man, so – since he does not have family whereas Mrs Hayward's have complained – he is moved to a different wing of the home.

This might seem like a perfectly reasonable solution to a potentially difficult situation and one that many health care professionals might endorse. However, it is important that we know the details of the case before we can make this judgement. From the mere outline of the story we do not yet know the thoughts of the main actors in this narrative. Even in the moderate to severe stages we know that people with dementia are able to convey meaning and present them-selves precisely as persons¹¹. We need to take this person-centred view. On the same ground, we need to consider the value of the relationship for both Mrs Hayward and her friend. Even when people with dementia cannot make choices based on full recollection of their past values or wishes, they can still be valuers¹². But this potentially sexual relationship is not the only relationship in which Mrs Hayward is situated, for the feelings of her family are not completely irrelevant to our estimation of what is right and wrong. They know more of her history, of her previous beliefs and wishes, all of which must be relevant. It is noteworthy that all of this takes us a long way from mere 'risk assessment', which should now be seen in the context of a fuller approach to the person as a whole.

Having taken a broad and detailed view of Mrs Hayward's standing as a person in this particular context, we can then attempt to judge the decision to move her friend against both

similar decisions we might have made in the past and against the broader canvas of the virtues. We need, at least (even if the answer will be negative), to ask whether there might have been a more compassionate or prudent way to deal with the problem. The legal framework for such a decision would be to assess the capacity or competence of those involved to make this particular decision and, if it is deemed they lack capacity, a decision should be made in the person's best interests. But the point has to be made repeatedly that this does not mean assessing her best *medical* interests, it means taking a broad view, which reflects the broad nature of our standing as persons in worldly contexts.

ETHICS AND RESEARCH

Making decisions for others and doing what is best for them are issues that come to the fore in connection with research. Many people lack capacity to consent to participate in research and research is often unlikely to benefit the person individually. This has led, therefore, to a good deal of consideration of the use of surrogates to make decisions for people who are incompetent. Some have also argued that advance directives might be useful as a way to record a person's competent wishes. A surrogate is usually approached to find out what the person is likely to have thought about entering research. And it is usually regarded as good practice to try to seek the person's assent even if they cannot give full consent¹³.

For people who lack capacity to consent, research should only be on the condition that affects them. This reflects the principle derived from the philosopher Kant, that people should always be treated as 'ends in themselves' and never as mere means. If the person cannot consent, there should either be some likelihood of benefit, or any harm should be (according to the Mental Capacity Act that covers these matters in England and Wales) 'negligible'. Once again, however, judgements will need to be made about what is appropriate and in keeping with standard and acceptable patterns of practice. The requirement that ethical approval should be sought from an established research ethics committee is one way in which patterns of good practice can be assured.

CONCLUSION

This brief overview has attempted to show the connections that hold together ethics and law in connection with mental health care for older people. What we see are patterns of practice that derive their strength from their coherence. In one direction this points towards the internal coherence of our decisions and actions one with another, where differences need to be justified in terms of established moral precepts. In the other direction we are impelled towards the virtues, where our actions must cohere with those inner dispositions (the virtues) that help to define what would constitute a flourishing human life. Underpinning our understanding of our practices, however, is a broad and complex notion of personhood, which provides the context in which we make decisions.

This framework, it can be argued, forms the basis of a moral and legal approach to health care. It is especially pertinent to the health care of older people, where mental ill health increases the person's vulnerability.

This is most distinctly seen, perhaps, as the person approaches death. When palliative care becomes appropriate, our patterns of practice must tend towards an acceptance of the concrete realities of the situation and life should not be prolonged; but neither should it be shortened. For this would rock the basis of our established social and legal practices, predicated on respect for the dignity of the human person broadly conceived, which prohibit the taking of innocent human lives.

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The US System of Geriatric Mental Health Care: Financing and Future Challenges

Stephen J. Bartels

Dartmouth Centers for Health and Aging, Dartmouth Medical School, Lebanon, NH, USA

INTRODUCTION

The ageing of the 'baby boomer' generation will result in nearly 15 million older adults with mental illness by 2030, dramatically challenging the nation's capacity to adequately serve this population¹. Further compounding this challenge is a fragmented mental health service delivery system for older adults, a paucity of providers trained in geriatrics and insufficient financing of mental health services under Medicare and Medicaid^{2,3}. Major financing and regulatory policy reforms are necessary to provide older adults with the array of services they need.

This overview of the US mental health services delivery system for older adults reflects the assumption that 'form follows finance'. In this chapter, we provide an analysis of the major issues pertaining to mental health policy and ageing, with a focus on: (a) financing geriatric mental health services and (b) future policy directions and challenges.

FINANCING GERIATRIC MENTAL HEALTH SERVICES

Medicare and Medicaid are the primary financiers of the US system of geriatric mental health services. Structured into the delivery of Medicare and Medicaid services are several key components including: (a) Medicare beneficiaries and expenditures; (b) Medicare's benefit design including fee-for-service and managed care arrangements; (c) the emergence of managed Medicare, the Balanced Budget Act of 1997 and Medicare Part C; (d) Medicare Part D prescription drug coverage; (e) dually eligible Medicaid and Medicare beneficiaries; and (f) Medicaid beneficiaries and expenditures. The following sections provide an overview of each area including historical context and current issues.

Medicare Beneficiaries and Expenditures

Medicare is a federally funded health insurance programme. It was enacted in 1965 under President Johnson to cover health care for the elderly. Medicare benefits expanded in 1972 to include coverage of the disabled and individuals with chronic renal failure. Approximately 95% of older Americans receive Medicare health insurance⁴. Medicare comprises the second largest social insurance programme

in the United States after social security⁵. In 2008 Medicare expenditures amounted to \$468 billion and covered 45.2 million Americans, including 37.8 million individuals aged 65 years and older⁶.

Medicare's Benefit Design for Mental Health Services: Fee-for-Service and Managed Care Arrangements

Medicare consists of four components (Parts A, B, C and D). This section reviews the four components of Medicare along with legislation enacted to restore parity in the administration of Medicare mental health benefits.

The fee-for-service (FFS) Medicare insurance programme covering health services is composed of two components (Part A and B). Part A, typically referred to as Hospital Insurance, covers inpatient psychiatric hospital care (up to 190 days lifetime maximum) and partial hospitalization⁷. Part A also covers hospice and home health-care services. Part B, or Medical Insurance, covers medically necessary physician and related ancillary services.

Medicare reimbursement policies have historically posed challenges for older adults and disabled persons seeking outpatient mental health services. Prior to the mid-1980s, Medicare payment policies supported reimbursement for acute inpatient care while restricting payments for outpatient services⁸. Restrictions on outpatient services included a \$500 annual cap for outpatient psychotherapy, in conjunction with requiring a 50% co-payment. The Omnibus Budget Reconciliation Act of 1987 (OBRA-87) increased the \$500 cap for psychotherapy reimbursement to \$2200, yet retained the 50% co-payment. OBRA-87 also exempted medical evaluation and management of psychotropic medications from an annual cap. Subsequently, the Omnibus Budget Reconciliation Act of 1989 (OBRA-89) eliminated the annual cap on psychotherapy, yet retained the 50% co-payment⁹. Sustaining the discriminatory policy of a 50% co-payment for psychotherapy services set the stage for the Stark–Wellstone Medicare Mental Health Modernization Act of 2001 aimed at achieving mental health parity. This act was essential to the future development and enactment of legislation that restored parity in the delivery of mental health services.

In honor of the late Senator Paul Wellstone, the Wellstone–Domenici Mental Health Parity and Addiction Act (MHPAEA) was enacted in October 2008. MHPAEA required equal coverage for

mental health and physical health care in group health plans by 2010. According to MHPAEA, equal coverage includes annual and lifetime limits, deductibles, co-payments, number of visits and other similar coverage requirements¹⁰. Although MHPAEA does not apply to Medicare beneficiaries, it does apply to Medicaid managed care health plans. Medicaid beneficiaries have access to mental health and substance abuse services at parity with other medical benefits¹¹.

Enactment of the Medicare Improvements for Patients and Providers Act (MIPPA) of 2008 restored parity in the delivery of mental health services to Medicare beneficiaries. Prior to MIPPA, Medicare beneficiaries were subject to a 50% co-payment for outpatient mental health services (but only 20% for medical services). Following enactment of MIPPA, co-payments for mental health services will be reduced to 45% in 2010, 40% in 2012, 35% in 2013, finally reaching parity with medical co-payments of 20% in 2014¹¹. This legislation represents a major step towards eliminating the barriers that older adults face in accessing mental health services.

The Emergence of Managed Medicare, The Balanced Budget Act of 1997 and Medicare Part C

Managed care programmes were developed to control the escalating costs of delivering quality care to Medicare beneficiaries. This section provides an overview of managed care and legislation aimed at controlling Medicare expenditures. This section also includes a review of Medicare Part C.

The Balanced Budget Act (BBA-97) of 1997 made significant changes in the payment methodology to Medicare Risk Contracting (MRC) plans. Medicare Part C also introduced managed care alternatives to fee-for-service Medicare. In addition, Medicare Part C, or 'Medicare + Choice', expanded Medicare to health maintenance organizations, preferred provider organizations, provider sponsored organizations, religious fraternal benefit plans, private fee-for-service plans, point-of-service plans, PACE (Programs of All-Inclusive Care for the Elderly) and medical savings plans¹². However, due to the Plans' inability to manage payments to providers, in addition to modest increases in Medicare plan payments, many providers left the programme. The result spurred an increase in premiums with a reduction in benefits¹³. New legislation became necessary to restore Medicare Part C and patient choice.

In 2003, President Bush signed into law the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Pub. L. 108-173). MMA expanded the role of private health plans through prescription drug plans and renamed Medicare + Choice to 'Medicare Advantage'¹³. The enactment of MMA enabled Medicare beneficiaries to choose from a variety of health plan options, including regional preferred provider organizations (PPO), health maintenance organizations (HMO), Medicare Special Needs Plans, Medical Savings Accounts (MSAs) and traditional fee-for-service (FFS) Medicare. The legislation also included a prescription drug benefit that allowed beneficiaries to choose among competing prescription drug plans. Although many Medicare Advantage plans offer mental health coverage to beneficiaries (coverage typically consists of a maximum of 20 outpatient visits and 30 hospital days per calendar year), most plans do not cover chronic mental illness in their standard benefit package. Despite the original intent of containing costs through competition by private insurance plans, Medicare Advantage has been characterized as government subsidization of health insurance companies at higher than average costs. In 2009, Medicare Advantage Plans have come under scrutiny by the Obama Administration as a potential source of savings¹⁴.

Medicare Part D Prescription Drug Coverage

The major impact of MMA was the introduction of Medicare Part D and the provision of a prescription drug benefit under fee-for-service Medicare. The implementation of Medicare Part D was meant to protect beneficiaries from the increasing cost of drug expenditures and to reduce costs associated with the underuse of medications¹⁵. In this section the implementation of Medicare Part D is reviewed along with suggested strategies to improve the delivery of prescription coverage to beneficiaries.

The introduction of Medicare Part D was largely welcomed as a means to address a longstanding lack of coverage for prescribed medications, yet presented specific challenges in covering psychiatric medications. Approximately 25% of Medicare beneficiaries are treated with psychiatric medications¹⁶ that are prescribed on a long-term basis. Some insurers, in an attempt to manage costs, initially provided Part D formularies with restrictions to discourage individuals with psychiatric disorders from enrolling in plans. Despite Part D guidelines intended to ensure patient access to prescribed medications, administrative tactics prohibited some beneficiaries from obtaining medication. Tactics included limited formularies, extensive use of prior authorization and step therapy requirements. Part D plans also included the preferred use of less costly medications, although many were inappropriate for older adults according to Beer's criteria¹⁷.

Despite the welcome coverage of medication prescriptions, clinical providers experienced significant administrative burden with the implementation of Medicare Part D. For example, with some plans, every hour of direct patient care resulted in approximately an hour of administrative time¹⁸. Additionally, some psychiatrists reported making medication decisions based on whether exceptions or appeals would need to be pursued. Some also avoided patients whose care would entail higher administrative costs. These unintended consequences associated with the administrative burden of Medicare Part D have been cited as potential sources of compromised quality of care for some patients with psychiatric illness, an already vulnerable group¹⁸.

Recent changes have been implemented to improve the administration of Part D. According to a 2009 Medpac-funded report the minimum cost for specialty tiered drugs was raised to \$600 a month. Since long-term users of specialty tiered drugs reach the maximum relatively quickly, they also qualify for catastrophic coverage. Federal reinsurance limits the beneficiary's expense by paying 80% of costs once they qualify for catastrophic coverage¹⁹. Finally, the recently passed health-care reform legislation will result in removing the "donut hole" gap for covering costs of medications in excess of \$2,830 and up to \$4,550 by the year 2020.

Dually Eligible Medicaid and Medicare Beneficiaries

Some older adults are eligible for both Medicare and Medicaid benefits. This population of individuals is referred to as 'dually eligible'. This section provides an overview of the dually eligible population including estimates of expenditures for individuals with serious mental illness (SMI) (including schizophrenia, bipolar disorder and treatment refractory depression).

Many dually eligible beneficiaries are over the age of 65, have significant disabilities and often have fewer financial resources than the average Medicare beneficiary. According to a 2008 report by MedPac, dually eligible beneficiaries account for a disproportionate amount of Medicare spending. Dually eligible beneficiaries account

for 16% of Medicare beneficiaries and 25% of Medicare spending. Medicare spends 1.8 times more on dually eligible beneficiaries as compared to non-dually eligible beneficiaries. According to MedPac, \$6212 is spent per non-dually eligible beneficiary while \$10994 is spent per dually eligible beneficiary. An assessment of total spending (including Medicare, Medicaid, supplemental insurance, and out of pocket spending) on dually eligible beneficiaries averaged about \$23 554 per person in 2005. This amount is more than twice the amount of other Medicare beneficiaries²⁰. Similarly, the dually eligible beneficiaries comprise a major portion (42%) of Medicaid spending²¹.

A 2003 study of Medicaid and Medicare dually eligible expenditures indicated that the highest per capita spending was on older beneficiaries with schizophrenia. According to this report, dually eligible beneficiaries age 65 and older with depression cost roughly \$27 850, while beneficiaries with dementia and schizophrenia cost \$39 154. Conversely, beneficiaries in this age cohort without mental illness generated a per capita cost of \$10 898. Per capita spending by diagnosis increases with age. This study indicates a greater service need and cost for dually eligible older adults (age 65 and older) with mental illness²².

Medicaid Beneficiaries and Expenditures

While Medicare covers a portion of health-care expenditures for the elderly, the Medicaid programme also provides additional benefits and services to some older adults. This section provides an overview of this joint federal–state Medicaid programme which represents one of the largest public health-care insurers in the United States. Medicaid delivers health-care services to poor, blind or disabled individuals, including individuals with serious mental illness. People with SMI may also be covered by Medicaid. Total Medicaid expenditures in 2007 were \$333.2 billion. In 2007 57% of Medicaid expenditures were federally financed (190.6 billion), while 43% (142.6 billion) were financed by state funding²³. By mid-2007, 61.9 million people (one in every five people in the US) were enrolled in Medicaid. Spending on individual beneficiaries averaged an estimated \$6120 in 2007. Although older adults and disabled people represent less than a third of Medicaid enrollees, almost three-quarters of the Medicaid budget is expended on this population of beneficiaries²¹. Adults 65 and older covered by Medicaid averaged \$14 058 per beneficiary, while disabled persons averaged \$14 858 per beneficiary²³.

A considerable amount of Medicaid spending is dedicated to long-term care services in a variety of settings. In 2006, approximately one-third of Medicaid expenditures were for long-term care, including care in nursing homes, as well as home and community-based services (HCBS)²⁴. Although nursing home care for adults is an area that Medicaid is required to cover, states may choose whether or not to cover alternative models of community-based long-term care services such as PACE or services for older adults in mental institutions²¹. Medicaid is also accountable for a significant share of the cost of mental health services. In 2001 Medicaid payments comprised more than one-quarter of all mental health expenditures, including both private and public payers. No other payer, including Medicare, spent more on mental health services²⁵.

Variability in the structure and design of the Medicaid programme limits generalizations that apply to the entire system of care. Many states differ with respect to eligibility criteria (particularly with the dually eligible Medicare–Medicaid population), breadth of coverage for inpatient and outpatient mental health services, prescription coverage, arrangement of co-payments, pre-authorization guidelines for

inpatient and outpatient services, and managed care options. A common attribute of most Medicaid programmes, however, is a 20–30% reduction in reimbursement rates for procedures and services relative to the standard fee-for-service charges²⁶.

Each state is provided the opportunity to administer Medicaid benefits in novel ways through the implementation of 1115(a) waivers or demonstration projects. The Secretary of Health and Human Services, via Section 1115(a), may approve demonstration projects that are time limited to test and evaluate entrepreneurial approaches to delivering and financing health care. According to the Centers for Medicaid and Medicare Services (CMS), many states use Section 1115(a) waivers to implement Medicaid. Various project areas include designing state-based models for eligibility determination, administration, delivery systems, coverage and benefits, quality assurance, access, systems support, financing issues, implementation time frames and evaluation. Demonstration projects typically last for five years and may be renewed for an additional period of time. Also, demonstration projects must remain ‘budget neutral’, meaning projects cannot cost the federal government more to implement the project than it would cost without the waiver²⁷.

FUTURE CHALLENGES IN MENTAL HEALTH POLICY AND AGEING

Over the past three decades policy and legislative endeavours have shaped the current financing and delivery system for older adults with mental illness. There are numerous future challenges in mental health policy that will require targeted efforts to meet the needs of an ageing America. Among the most pressing include: (a) Medicare’s impending insolvency and health-care reform; (b) implementing integrated mental and physical health care and a true ‘medical home’; (c) the changing landscape of long-term care on the increasing need for home and community-based options; (d) the ageing of the population with serious mental illness (SMI); (e) addressing the workforce gap in geriatric providers; and (f) bridging the gap between research, practice and policy.

Medicare’s Impending Insolvency and Health Care Reform

According to a 2009 federal report, Medicare will be insolvent by 2017⁶. At the current growth in expenditures, Medicare and Medicaid are predicted to consume 15% of the gross domestic product (GDP) by 2040²⁸. Part of the challenge of financing Medicare is directly associated with the demographic realities of an ageing US population.

Older age is associated with increasing episodes of acute medical care (including hospitalizations, surgical procedures and home health care). Older adults constitute a group that have a high risk for needing intensive and expensive services, resulting in ‘adverse selection’ for individuals with high insurance premium costs. For example, insurance plans (such as Medicare) that primarily target older adults are much more likely to selectively attract patients who present a higher financial risk, and less likely to have the capacity to spread the risk over healthier beneficiaries who are less costly. In addition, older adults disproportionately represent beneficiaries with low incomes. Approximately one-quarter of older adults are at or near the poverty level, including 16% living in poverty and an additional 9% living between poverty and 125% of the poverty level²⁹. Finally, the shifting demographic profile associated with the ‘greying of America’ is resulting in growing numbers of adults reaching retirement age, at the

same time that there are proportionately fewer younger adults paying into the Medicare trust fund through employment contributions. When Medicare was enacted in 1965, there were approximately 18.2 older adults for every 100 working age adults. This 'old-age dependency ratio' is projected to climb to 20.9 in 2010, 27.0 in 2020, 34.9 in 2030 and potentially increase to 42.1 older dependents for every 100 workers in 2080³⁰.

In addition to demographic realities, the predicted insolvency of Medicare is also due to escalating health-care expenditures. Current reform efforts identify regional variations in spending that account for higher costs without better health outcomes. For example, from 1992 to 2006 Medicare spending (adjusted for inflation) grew 3.5% annually. By comparison, spending in Miami, Florida rose by 5%, contrasted with a 2.3% increase in Medicare spending in Salem, Oregon. Similarly, 2007 per capita Medicare spending averaged \$12 100 in Manhattan, New York, compared to \$6 700 in Minneapolis, Minnesota (31). Higher cost regions are generally associated with fewer primary care physicians, greater numbers of specialists, more spending on discretionary procedures, greater use of intensive care units in the last six months of life and poorer health outcomes³². *The Dartmouth Atlas of Healthcare* estimates that reducing annual per capita growth in spending from the current national average of 3.5% to 2.4% would result in a savings of \$1.42 trillion, leaving Medicare with a positive balance of \$758 billion in 2023 in contrast to the predicted \$660 billion deficit³¹.

Accountable Care Organizations (health-care systems that are rewarded for high-quality care and lower expenditures) have been proposed in the recently passed health-care reform legislation as one example of a potential model for achieving savings and improving care. However, the structure, financing and role of mental health care in plans for health-care reform will need to be identified to ensure compliance and the delivery of effective care.

Integrated Mental and Physical Health Care and the 'Medical Home'

Conventional mental health services have been organized and financed by 'carving out' care into separate settings, providers and financing that is distinct from general medical care. This separation has been promoted as a means to support the integrity and financing of specialty mental health care. However, it also has been identified as a potential barrier to holistic care that incorporates the interaction of physical and mental health in overall outcomes. Collaborative models of physical and mental health treatment have been proven to result in improved outcomes in primary care³³, home health care³⁴ and long-term care³⁵. Older adults with depression who receive integrated care not only have lower aggregate health-care costs over several years of follow-up³⁶, but also indicate signs of improved survival, quality of life and patient satisfaction². Studies have also shown that patients with substance abuse related medical conditions who receive integrated care have reduced hospitalizations, inpatient stays, emergency room use and medical costs³⁷.

A historical barrier to integrating mental and physical healthcare has been the lack of appropriate financing mechanisms. Prior to 1 January 2008, only physicians were permitted to use Current Procedural Terminology (CPT) billing codes that indicated time spent conferring with providers from other disciplines regarding patient care. New CPT codes permit psychologists and other non-physician providers to bill for integrated team conferences¹¹. The next step needed in reforming billing is to allow for same-day billing of mental and

physical health services 'incident to' a single primary care provider. This change will enable individuals to access physical and mental health care that is integrated, concurrent, co-located and simultaneously addresses the needs and preferences of the whole person.

'Medical home' is a term first coined by the American Academy of Pediatrics in 1967. In a medical home responsibility for care and the coordination of services is in the hands of the patient, family members, a personal medical provider and a medical team. The teams are formed according to patient needs and may include specialists, nurses, social workers, care managers, dietitians, pharmacists, occupational therapists and the community³⁸. Key attributes of the medical home include: (a) the use of evidence-based practice and clinical outcome tools to guide joint decision making; (b) an organized process of care coordinated under a single primary care provider that incorporates principles of the Chronic Care Model (CCM); (c) development of an integrated plan of care that connects patients and families to a team of support; and (d) delivery of advanced care through multiple venues including face-to-face, email and telephone communications³⁸. Research suggests that medical homes have a significant impact on societal health as they improve medical standards, patient experiences and outcomes³⁸. The use of medical homes in the delivery of integrated care may further improve outcomes for older adults with SMI. Policy makers will need to promote greater integration of mental health in primary health care and inclusion of mental health providers in the development of primary care delivery modelled on the concept of a 'medical home'.

The Changing Landscape of Long-Term Care: Home and Community-Based Options

The Olmstead decision enacted by the Supreme Court in 1999 regulated federal policy regarding the inappropriate and unnecessary placement of individuals with disabilities into institutions³⁹. States were required to assess thousands of individuals living in psychiatric institutions and nursing homes to conclude whether they could receive care in a community-based setting⁴⁰. However, the lack of community-based residential options for older adults with serious mental disorders is a barrier to complying with the Olmstead mandate⁴¹.

The increasing demand for alternatives to nursing homes is demonstrated by the development of continuing care communities, assisted living facilities, home health-care options and community-based ageing network services. Despite the growing demand for home and community-based services (HCBS), occupancy rates at nursing home facilities have remained constant between 2002–7, and 73% of long-term care Medicaid dollars went to nursing home facilities in 2007⁴². Medicaid spending on HCBS was reported at \$17 billion for older and disabled persons while nursing home spending totaled \$47 billion. However, the proportion of Medicaid expenditures for HCBS versus nursing homes varies considerably by state. For example, in 2007 New Mexico spent 61% of its Medicaid long-term care budget on HCBS. In contrast Tennessee spent only 1% of the Medicaid long-term care budget on HCBS⁴². Overall, Medicaid spending on HCBS has increased by 68% over the past five years as the number of older and disabled individuals receiving HCBS services has increased to 1.4 million in 2005⁴². The growing demand for HCBS substantially exceeds budgeted resources for home and community-based long-term care alternatives. For example, an estimated 90 000 people were on waitlists for HCBS waiver programmes in 2007⁴².

To accommodate the future needs and preferences of older adults, health-care reform will need to shift financial incentives away from supporting nursing homes as preferred long-term care settings to provide incentives for developing an array of HCBS options. In order to be successful these policy initiatives will also need to include financing for integrated mental health services within home and community-based services.

The Ageing of the Population with Serious Mental Illness

The ageing of the population of persons with SMI is challenging state-supported services across the nation to develop and finance an array of services aimed at older adults with schizophrenia, schizoaffective disorder, bipolar disorder and treatment refractory depression. Per capita combined Medicaid and Medicare expenditures for disorders such as schizophrenia in older adults (age 65–74) are over 3.5 times greater than expenditures for dually eligible Medicaid and Medicare beneficiaries receiving services for a medical diagnosis only (without a co-occurring psychiatric disorder)⁴³. One of the primary drivers of higher expenditures is the association of SMI with higher rates of institution-based long-term care. Nearly two-thirds of older adults with SMI are hospitalized or admitted to a nursing home annually. Middle-aged and older adults with schizophrenia are three times more likely to be admitted to a nursing home than adults without SMI⁴⁴. Medicaid beneficiaries with schizophrenia are admitted to nursing homes nearly 13 years earlier than other Medicaid beneficiaries (age 65 versus age 78)⁴⁵. Finally, adults with SMI have a 25–30-year shorter lifespan than the general population, presenting a dramatic health disparity associated with the need for improved health care and attention to prevention and health promotion as a core component of quality mental health services⁴⁶.

Effective interventions exist for older adults with SMI⁴⁷. A reorganization of the mental health services system must take into account the leading factors attributed to high rates of institutionalization among the SMI population including: poor social skills and supports; high medical co-morbidity; and inadequate independent living skills. Mental health services that include age-appropriate psychosocial rehabilitation combined with physical care are likely to reduce health disparities and address the needs of older adults with SMI⁴⁸. New integrated models of care for older adults with SMI will need to be developed and implemented that attend to the combined need for psychosocial rehabilitation and health care addressing the needs of the ‘whole person’^{47,49}.

Addressing the Workforce Gap in Geriatric Providers

As the population ages, current demographic projections for the number of older adults with mental health problems or cognitive impairment indicate that the system of health care will become increasingly unable to deliver effective services to this population⁵⁰. Conversely, projected declines in health-care providers with expertise in geriatrics will pose a serious challenge. For instance, over half of geriatric psychiatry fellowship slots went unfilled in 2006⁵¹. Recently, the Institute of Medicine (IOM) released a report that underscores the issue of a serious shortfall in the geriatric health-care provider workforce². The American Association of Geriatric Psychiatry (AAGP) has suggested a follow-up study to advocate for loan forgiveness legislation, funding for the Geriatric Health Professions Program, and reform of Medicare to enhance mental health coverage⁵⁰.

Several legislative initiatives have been proposed to begin to address the shortfall in the workforce of geriatric health providers. In March 2009, the ‘Geriatricians Loan Forgiveness Act’ (H.R. 1457) was referred to the House Committee for review⁵². The Act would classify each year a person is enrolled in a geriatric training programme as a year of obligated service under the National Health Service Corp Loan Repayment Program guidelines. Individuals are entitled to repayment of \$35 000 in educational loans. Another loan repayment bill, the ‘Caring for an Aging America Act of 2008’ (S. 2708) would include loan forgiveness as well as other incentives to attract and retain geriatric care providers into the workforce. At the time of this update both bills are under review.

Bridging the Gap Between Research, Practice and Policy

The gap between what we know regarding effective mental health treatment and the services currently offered by health-care providers constitutes a major challenge in improving the effectiveness and efficiency of health care^{53,54}. Although a significant array of evidence-based practices (EBPs) are effective in the prevention and treatment of mental disorders^{55,56}, research has shown that it takes more than a decade to implement findings into the delivery of care⁵⁷.

Current initiatives from the National Institute of Mental Health (NIMH), the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Administration on Aging (AoA) are focused on multiplying the availability and use of EBPs⁵⁸. NIMH and SAMHSA have partnered to promote and support the use of evidence-based services in state mental health systems. These strategies and others must continue to expand in order to reduce barriers to implementing EBPs for older adults. Possible areas of focus include increased emphasis on interventions that are designed for use in real-world settings by real-world providers, development of financing options and incentives, improved educational opportunities for health and social service providers and improved understanding of effective dissemination and implementation strategies.

SUMMARY AND CONCLUSION

This chapter summarizes the major components of the Medicare and Medicaid programmes for older adults in the United States with attention to the delivery of mental health services. The most substantial changes to improving the delivery of mental health care to older adults have occurred through the implementation of recent legislation and programming including: (a) the Wellstone–Domenici Mental Health Parity and Addiction Act of 2008; (b) the Balanced Budget Act of 1997, and the Medicare Prescription Drug, Improvement and Modernization Act of 2003; (c) the implementation of Medicare Part D and the provision of prescription drug coverage to older adults; (d) the provision of coverage to beneficiaries dually eligible for Medicaid and Medicare benefits; and (e) the provision of long-term care to older adults through Medicaid, and 1115(a) waivers and demonstration projects aimed at encouraging novel home and community-based Medicaid services.

While the enactment of legislation and programmes have enhanced Medicare and Medicaid services for older adults with SMI, the system still faces many challenges. In order to improve the mental health services that older adults receive, attention must be paid to addressing: (a) Medicare’s impending insolvency; (b) integrated care and the ‘medical home’; (c) the changing landscape of long-term care with attention to home and community-based options; (d) the ageing of

older adults with SMI; (e) the workforce gap in geriatric providers; and (f) the gap between research, practice and policy. Timely and thoughtful attention to each of these issues will not only improve the delivery of mental health care that older adults receive, but may also reduce the current administrative and economic burdens associated with the delivery care. Addressing the future challenges of an ageing America will require innovative approaches to organizing, delivering and financing mental health services as a core component of general health care for older adults.

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Geriatric Psychiatric Outpatient Care: The Private Practice Model in the USA

Elliott M. Stein¹ and Gary S. Moak²

¹*Jewish Home of San Francisco San Francisco, CA, USA*

²*University of Massachusetts Medical School, Worcester, MA, USA*

In the USA, ambulatory or outpatient psychiatric care of individuals in later life is provided in a variety of public and private office settings. These include publicly financed community mental health centres, hospital-sponsored or university-sponsored outpatient clinics or services, the offices of psychiatrists (and other mental health professionals) in private practice, health maintenance organizations (HMOs, both privately and government-funded; the governmentally sponsored ones are now called Medicare Advantage plans) and others. This chapter will focus on practical aspects of providing psychiatric treatment to older Americans in office-based psychiatric private practices. We will not discuss the details of treatment in these settings, but rather the 'mechanics' of the process.

An important focus of community-based psychiatric ambulatory care is the need to create relationships with other community services and providers of care and assistance. This provides both a framework and a means by which many of the services are provided. Some of the barriers and obstacles to care will also be reviewed.

In providing community-based ambulatory care, the psychiatrists must have a comprehensive and patient-centred focus, following the patient to provide whatever psychiatric treatments are needed in whatever setting. While there are some geriatric psychiatrists who limit their activities to specific treatment locations, such as in offices or in-hospital programmes, this type of care may require the patient to be seen and treated sequentially in many places and circumstances.

INFLUENCES ON PRIVATE PRACTICE

For the purposes of this chapter, we will define private practitioners as independently employed or self-employed psychiatrists who work alone or in small groups. These practitioners provide treatment to patients who individually seek their help, and who pay for services received, primarily with Medicare health insurance benefits. Notwithstanding the current and ongoing, large-scale reorganization occurring in the American health care system, private practice remains a widespread model of medical practice in the USA. In many ways it has served as a starting point for the pattern of care provided in the other settings mentioned above. Many of the techniques discussed below are applicable to other models of treatment. Older patients

seek care from private practitioners or other mental health providers with varying degrees of utilization and satisfaction^{1,2}.

Private practices are essentially private businesses, typically started, owned and operated by the individuals providing and/or supervising the clinical services provided. They may be small businesses, comprised of a single individual or several associated people, or they may be larger groupings of multiple people joined together to provide psychiatric/psychological treatment, or be part of a large medical multi-specialty affiliation. Such groups may grow to include dozens, or even hundreds of providers, becoming large businesses in the process. This chapter will focus on the smaller entities which are more typical and more common, although there are market forces which are encouraging practitioners to join together in larger groups to achieve both economies of scale, and to better negotiate with third-party payers of services, and other caregiving entities.

The private practice of medicine in the USA has evolved as a cottage industry within a historically unsystematized, free-enterprise, fee-for-service climate. Changing lifestyle preferences and demographics among young physicians are having some impact on this pattern. From its inception in 1965, the Medicare system had a built-in prejudice against the provision of outpatient psychiatric services. There was a discriminatory 50% patient co-payment requirement for all psychiatric treatment services delivered outside of an acute care hospital setting (unlike all other covered medical services, for which the patient co-payment is 20%)³. In 2008, this co-payment requirement was addressed by a new law which will gradually phase out the discrimination over a several year period until 2014, when there will be parity between payments for physical and psychiatric treatment⁴. This limitation on Medicare insurance coverage had constrained provision of these services to the elderly. Over the past 10–15 years, however, much greater influence has been felt from a multitude of other outside forces, at times impeding geriatric psychiatry practice^{3,5}, but in some cases expanding it. These forces (to list a few) include: efforts by the federal government to rein in Medicare spending^{6,7}; the penetration of health maintenance organizations (HMOs) into Medicare; the advent of federal nursing home reform regulations; the growing presence of health care agency accrediting

bodies, such as the Joint Commission for the Accreditation of Health-care Organizations (JCAHO) and the National Council of Quality Assurance (NCQA); the creation by the American Board of Psychiatry and Neurology of subspecialty board examinations in geriatric psychiatry; social attitudes (e.g. public attitudes about medical care and doctors, as well as about mental illness and psychiatric care); the influences of physician attitudes⁸ and medical malpractice litigation⁹; the availability of newer psychopharmacologic agents (including their increased acceptance by the public and their increased utilization by primary care physicians); patient finances; and folklore and 'common sense' of both the professional and the general population. Geography also is a factor, as there is significant regional variation among practitioners and communities in different areas of the country, as well as variations in payment rates and public (Medicare/Medicaid) and private (HMOs and other managed care companies) monitoring and regulation. Some geriatric psychiatry practices have adopted the use of physician extenders, such as nurse practitioners or physician assistants, to enhance the scope of treatment options. Adaptation of geriatric assessment and treatment principles has been slow, for the most part, in private general and psychiatric medical practice. Nevertheless, successful practitioners need a working knowledge of these forces in order to function. As a field which is now well into its adolescence in the USA, there are a growing number of examples of psychogeriatric care models that have proven generally applicable. In fact, the fee-for-service system in the USA has thus far been a relative failure in geriatrics, since it has not incorporated many of the accepted principles of geriatric care¹⁰. Some varying approaches have been tried by practitioners, but most still follow the above-noted model. The incursion of managed care HMOs into the Medicare system held out promise to change this state of affairs. HMOs, in theory, employ methodologies such as integrated delivery systems, screening, prevention and case management that are ideally suited to geriatrics¹¹. Their track record has been disappointing, however, and their approach to managing mental health care has been largely ineffective for the elderly. Managed care companies often 'carve out' the management of mental health services by subcontracting it to managed behavioural health care companies with specialized expertise in mental health benefits management¹². Such companies rarely have any expertise in geriatrics, and do not appreciate its differences from general adult psychiatry¹³. These companies have often ageist attitudes built into their coverage utilization guidelines, and inappropriately limit treatment or completely deny it, especially involving members with Alzheimer's disease, which they do not view as a covered psychiatric disorder. To the extent that managed care has penetrated Medicare, this practice has made the practice of geriatric psychiatry more difficult, as the seniors enrolled in these plans typically may only receive services from health care providers who are contracted with them. This limits their access to care which might otherwise be available.

PRIVATE PRACTICE AS A BUSINESS

Another important factor in discussing this type of psychiatric practice is the previously mentioned idea that geriatric psychiatry is a business. As such, the patients are to be considered as customers. Furthermore, at times, other physicians, and additional referring sources, may also be regarded as customers. As such, it behoves the psychiatrist to organize the practice and to provide services in ways that answer the needs of these customers. The psychiatrist may help the patient to define these needs, provide information about them, alter

them or aid them in various ways. The psychiatrist may need to refuse patients' requests when professional judgment dictates this. American consumers, especially the adult children of geriatric patients, are becoming more and more concerned about the availability of health care, its costs, its efficacy and its risks. At the same time they are becoming more educated and aware of health care issues and, due in large measure to the availability of health-related information from the internet, and other mass media sources, more knowledgeable about treatment options and risks, although this knowledge may be of variable accuracy. If the psychiatrist does not do a good job or does not adequately address at least some of the patient's needs (and/or their adult child's needs), the psychiatrist may lose that patient's business. The interaction between them, therefore, has aspects of an exchange of service for payment. Providing a comprehensive service, as mentioned above, is often very satisfying and helpful to patients. At the same time, the business opportunities for income are maximized. In a community-based private practice, people are often referred to the individual doctor, rather than to a hospital, a university or a public clinic where they may be assigned a doctor. Patients may be referred because of the doctor's quality of service, reputation or relationships with the referring party. These qualities therefore become significant aspects of the psychiatrist's success in business as well as clinical practice.

Important factors in satisfying the patient/customer include:

1. Cost: reasonable fees and/or helpfulness and knowledgeability in filling out insurance claims. Acceptance of the patient's insurance coverage in payment for the services.
2. Accessibility: convenient and comfortable office location and surroundings. The psychiatrist may decide to provide more services in more locations.
3. Availability: the availability of the psychiatrist to go to the patient if needed (e.g. to consult at a medical hospital if the patient is admitted by another physician for a physical ailment, or to see the patient at home, in a nursing home, or an assisted living facility) is very important. The convenience of the geriatric psychiatrist going to where the patient lives, rather than the patient coming to the doctor's office, is very attractive to family or caregivers responsible for transportation. Because of the time and effort, as well as the distraction from other activities, the viability of this form of practice, in private practice, depends upon the numbers of people who may need services in that area or location; sometimes arrangements can be made with facilities that ensure an adequate volume of patient visits for each trip to the facility.
4. Scheduling: flexibility to see patients at convenient times without excessively long delays in scheduling appointments. This is crucial, since many frail patients are brought by their adult children, who may work.
5. Communications: the ability to contact the psychiatrist quickly and easily at need (e.g. by telephone by the patient and, when appropriate, by the patient's family). This includes the willingness of the psychiatrist to return such phone calls quickly, and the friendliness and accuracy of the psychiatrist's secretary or answering service. It also includes the ability and willingness of the psychiatrist to speak to the patient (and family) about his/her symptoms, illnesses and treatments in a clear and patient manner.
6. Concern: the feeling that the therapist has a genuine interest and concern for the patient. This feeling of concern extends to the patient's interactions with the office staff. This is an especially vital factor for the older population¹⁴.

7. Confidence: patients and involved family members need to feel that the psychiatrist knows what the patient's problem is and has an idea about what can be done. The doctor does not need to provide definite answers, but must indicate a grasp of the situation and some ideas for an approach to it. This helps to provide a structure to what is often a strange and frightening experience. Empathy with the patient's distress is very helpful in this, as is reassurance to the patient that his/hers is not the worst case the doctor has ever seen (a common fantasy).
8. Understanding: A related skill is being aware of and addressing, when needed, those concerns, preconceptions, prejudices, fears, needs, worries and expectations which may interfere with the provision of services to the identified patient; these can be the patient's feelings or those of the family member(s) involved. They may include fears of being controlled, a bias against doctors, psychiatrists, medications or hospitals, belief that the patient's problematic behaviour is wilful, concerns of financial worries, caregiver stress or the feeling that coming for help is a sign of weakness or failure, the presence of partial information, such as information gleaned from pharmaceutical advertising, news reports about medications, or the neighbour's experience with a particular drug, or the expectation that the doctor has an easy answer to the problem.

There are only limited data available on income and workload for geriatric psychiatrists as a group. For all psychiatrists, 1998 median annual gross income was \$171 490 (a 3.5% increase from 1997), and annual net income was \$118 630 (a 4.33% increase from 1997). This was the second lowest income of the 20 largest specialties (above general practitioners) surveyed by Medical Economics that year. The rate of inflation in the year 1997–1998 was 1.6%. Comparable 1998 income data for all US physicians show an annual gross income of \$256 290 (down 0.7% from 1997) and a net income of \$163 940 (up 2.2%); for non-surgical specialties, the gross income was \$227 300 (up 1.7%) and the net income was \$147 140 (up 2.4%)¹⁵. When these data are compared to the median annual net income for psychiatrists in the USA in 1989, which was \$103 570 (the fourth lowest of 15 office-based specialties surveyed that year; the only doctors who made less were general practitioners, family physicians and paediatricians)¹⁶, we find that the income of psychiatrists had risen 14.5% in that period. The median net income for all fields of medicine rose just under 25% during the same period, while the cumulative inflation rate added up to 35%.

Although most American psychiatrists see few or no geriatric patients, this trend is changing somewhat. There were over 5400 out of the over 36 000 members of the American Psychiatric Association who expressed an interest in geriatrics during their 1997–1998 Professional Activities (Biographical) Survey (unpublished data, courtesy of the American Psychiatric Association, 2000). The membership of the American Association for Geriatric Psychiatry has grown to over 2000 (unpublished data, courtesy of the American Association for Geriatric Psychiatry, 2009), and interest among general psychiatrists continues to increase. In 1991, the American Board of Psychiatry and Neurology first administered a Board Certifying subspecialty examination in geriatric psychiatry. As of December, 2008, there were 2953 individuals who have passed this examination (data courtesy of the American Board of Psychiatry and Neurology, www.abpn.com/cert_statistics.htm, 2009).

In 1996, 18% of American general psychiatrists had geriatric caseloads exceeding 20% of their practices¹⁷. Overall, in this 1996 survey of 970 responders, an average of 14.0–17.7% of their

psychiatric patients were aged 65+, compared to 8.4% found in a 1987 study¹⁸. When psychiatrists who provide a higher proportion of geriatric services (more than 20% of their case load – HGP) were compared to those who were low-volume providers with the elderly (less than 20% of their workload – LGPs), it was found that the HGPs spent proportionately less time in their offices (although still spending most of their time there), more time in hospitals and significantly more time in nursing homes, than LGPs¹⁷.

In 2002, the National Survey of Psychiatric Practice¹⁹ found the proportion of HGPs had increased to 26.0% of respondents, and 28.1% of respondent members of the American Psychiatric Association (a 55% increase from the 1996 survey). Of the HGPs, 31% were Board Certified in Geriatric Psychiatry. These geriatric psychiatrists saw approximately three-times as many geriatric patients and five-times as many patients with dementia as the non-HGP generalist psychiatrists. Nonetheless, most did not have exclusive geriatric practices. Of note is the finding of a wide range of annual incomes among the respondents.

The 2008 report of the Institute of Medicine highlighted the existing and future shortfall of geriatric medical care providers, including geriatric psychiatrists^{19,20}. At that time there was calculated to be one Board certified geriatric psychiatrist for every 11 372 older Americans, and that, by 2030, if training programmes continued at their current rates, there would be only one for every 20 195 older Americans²¹.

A significant impediment to the collection of data on the work done by geriatric psychiatrists and the income generated by this work has been the inability to differentiate those individuals who provide services to the older population from the work of other psychiatrists. The Medicare system has not differentiated general psychiatrists from geriatric specialists. In May, 2009, the Centers for Medicare and Medicaid Services (CMS), the United States federal agency which administers the Medicare programme, approved the creation of a specialty identification code for Geriatric Psychiatry (personal communication, American Association for Geriatric Psychiatry, 2009), as a recognized specialty, beginning in April, 2010. Individuals who choose to do so, may register with Medicare as having a subspecialty in this area. This will allow information to be collected as to the work load, diagnosis and treatment provision and income generated by these practitioners.

There may be changes in the future, but currently there are relatively low numbers of psychiatrists with a specific interest in treating the elderly. When the medical and general communities know that a particular psychiatrist is a geriatric specialist, there is usually no shortage of patients needing these services. However, at the time of this writing, the economic downturn in the United States along with the projections of future medical costs, together with the current governmental motivation to make changes in the nation's health care system, make uncertain the nature and form that medical care, and specifically geriatric psychiatry care, will take.

OFFICE PLANNING AND DESIGN^{22,23}

Establishing a practice to treat older patients requires some attention be paid to the setting in which such treatment will occur and to factors that might act as barriers to treatment. Offices that can only be reached by climbing stairs, or those with varying levels into which one must step up or down, are difficult and potentially hazardous. Long corridors that must be traversed are similarly problematic. Chairs should be available that are sturdy and have armrests

and firm seats, high enough for ease in sitting or rising. They should be upholstered with waterproof and stain-resistant fabrics. Adequate lighting, readable signs and patient information literature should be planned with poor vision in mind. Interesting, recent magazines and a television in the waiting areas should be available for patients, and those who accompany and wait for them. Area carpets, spring-hinged doors and other possible hazards should also be considered. Toilet facilities and drinking water should be in reasonable proximity.

Mobility and transportation problems are another potential obstacle to treatment. Selection of an office location in a rural community, or in an area with poor public transportation or poor handicapped access may be factors. Convenient parking, especially in crowded urban areas, is necessary. Treatment may be interrupted during the winter months if the cold interferes with the patients' ability to get to the office. Some communities have senior transportation services, which will take people with limited mobility to physicians if reservations are made 24–48 hours in advance. Some hospitals may transport patients to and from the hospital or to physicians' offices located in adjoined buildings. Offices may also be located in senior retirement buildings or communities. Some senior living facilities will bring people to doctor's offices or medical centres. Clear signage on the exterior of the building and in the lobby areas and corridors will help the older patient find you.

THE BEGINNING OF THE RELATIONSHIP

Older patients seek out, are referred to or are brought to the psychiatrist's office for care. An initial 'gatekeeper' function may occur by means of enquiries (usually by telephone) into the reasons for the request to be seen, the age of the prospective patient, the referring source, the status of insurance coverage or other financial information. Such enquiries may lead a particular practitioner who prefers to specialize in geriatrics to decline to accept an adolescent as a patient, or to suggest that a patient being seen by another psychiatrist first discusses the idea of transferring with the current therapist, or to refer the patient to a geriatric psychiatrist in a geographically more convenient location.

A prospective patient, once given an appointment, should be told about additional information the psychiatrist would like to have available at the time of the first visit (e.g. the names of the patient's other treating physicians, current medications being taken, information about past psychiatrists, psychiatric medications, hospitalizations, past and current medical conditions). If the referring source is a physician, family member or a member of the staff of a senior-living facility, information from them as to the nature of the problem may be requested.

THE RANGE OF SERVICES

Among the most important services a psychogeriatric specialist can provide are diagnostic services. Too often, inadequate or erroneous evaluation leads to inadequate or erroneous treatment. A knowledge of physiology, psychology and the illnesses of late life, a comprehensive approach to history taking, assessment and testing and the ability to formulate an appropriate treatment plan form the basis of a unique contribution by geriatric specialists^{24,25}. In fact, the ability to provide such a comprehensive evaluation and treatment perspective may be a primary reason why patients and referral sources seek the assistance of a geriatric psychiatrist.

An important aspect of the coordinated treatment plan is the collection of past information. With the patient's permission,

contact is established with the patient's family, other physicians and therapists. To the extent possible, past records, diagnoses, psychological testing reports, doctors' treatments, psychotherapy records, laboratory and radiological reports are requested and reviewed. While not revealing confidential information, these contacts also benefit the patient by making the patient's other physician(s) and support system aware of your activities with the patient. This increases the likelihood that you will be notified of future problems that may occur and that other medical treatments will be coordinated with you by other physicians. In the absence of such relationships, physicians may call a different psychiatrist to provide treatment, due to lack of awareness of your involvement.

As has been reviewed elsewhere^{23,26,27}, including sections of this volume, older individuals can be suitable candidates for many of the therapeutic modalities provided to younger patients, including individual, group and family psychotherapies, which utilize insight-orientated, cognitive, behavioural and other techniques. Some approaches, such as reminiscence or life-review therapy²⁸, have more specific applicability to the ageing person. Modification of family therapy may be necessary, for example to address the role of adult children in assisting in the care of a demented or otherwise impaired parent.

Psychopharmacologic treatment of the elderly often requires alteration in the selection, dosing and scheduling of medication because of changes in absorption, distribution, metabolism, receptor sensitivity and excretion^{29,30}. Once again, the geriatric psychiatrist may be sought out in recognition of this expertise by the patient and others involved in the patient's care. Pharmacoeconomic trends in the USA create additional conflicts for geriatric psychiatrists in private practice. Pharmaceutical costs are escalating rapidly in the USA compared to many other countries. Patients may have coverage under a Medicare Part D prescription drug plan, a voluntary federal programme begun in 2006. These plans are designed and administered by a number of private corporate entities. There are limitations and restrictions in expenditures and available drugs under these plans^{31,32}. For example, benzodiazepines and barbiturates were not covered under the plans. The exclusion of these medications was changed in the 2008 Medicare legislation and will be available for prescription beginning in 2013. Treatment options may be limited by restrictive formularies designed with cost containment in mind, but often with limited consideration of the greater sensitivity of elderly plan members to medication side effects. Nursing homes have also adopted formularies to contain their costs, even in the absence of significant managed care penetration. Consultant pharmacists are employed by the homes to monitor physician prescribing, with respect not only to federal regulations but also to formulary requirements. Psychiatrists in private practice are thus often under pressure to prescribe less costly drugs or to run the risk of receiving fewer referrals from primary care physicians or nursing homes.

Sometimes assistance provided may be primarily educational, such as telling the patient or his/her family about the nature of the ageing process or the symptoms, prognosis and treatment of an illness. Treatment may be primarily informational, directing patients and carers to appropriate senior housing, services for the blind or hearing-impaired, continuing education programmes or volunteer work. At times treatment may be directive, for instance telling a patient to get a physical examination, buy a hearing aid or give up driving, or telling a family member to seek the assistance of respite services to provide some relief in caring for a cognitively impaired person, or to advise that the parent or sibling should no longer live alone. The community-based psychiatrist must develop expert knowledge of the available

community resources, as well as relationships with the providers of them.

The initial psychiatric diagnostic evaluation of the patient also is the time of the patient's actual evaluation of the doctor. The practitioner must address the overt and covert concerns, the anxieties and fantasies about the nature of geriatric psychiatry, the reasons why the patient is there and the treatments that will be instituted. Although these anxieties are not unique to this model, the need to address them is. Unlike treatment limited to one location or modality or situation, this relationship will be multifactorial and ongoing. Furthermore, a privately operating care provider is likely to represent an entry contact point into mental health care. If the patient and the associated significant family members are not put at ease, their questions answered and concerns addressed, the contact may quickly end.

Older patients are often novices regarding mental illness and its treatment. They are often fearful of being thought 'crazy' or of being 'put away'. Structuring the beginning of the initial interview can help relieve their anxiety. You may start with 5–10 minutes of specific questions, such as address, age, date of birth, concrete information on marriages, children, parents, siblings, education, employment, interests and so on. This can also give you a lot of information in a short time, helping to give a more complete picture of the patient. Simultaneously, you are assessing aspects of mental status and memory.

Treatment of the older patient includes the time when the patient is away from the office. The patient is helped when assured of the doctor's continued interest and care. This can often be achieved using relatively simple techniques: (i) providing specific information tells the patient that you know what is going to happen, for example 'This medicine is going to take two to three weeks to build up in your system. You may experience some side effects during that period but you will not experience the benefit for two to three weeks. You need to be patient during that time'; (ii) assuring access and inviting communication, for instance 'My telephone number is a 24-hour number. If you have any problems or need to reach me, you can call any time'. Patients rarely do call outside of office hours after being told this, but they feel very reassured; (iii) specific instructions for behaviour and for contacts; for instance, instead of saying, 'Call me if you have any problems', saying 'Call me next Tuesday' assures the patient that you want to hear from him/her. It also reduces the number of calls he/she might otherwise make before next Tuesday.

FAMILY INVOLVEMENT

Families are often interested and involved in the psychiatric care of elders. Relatives and friends can be important sources of information to the doctor. Interactions may include mediation and other interventions into the family system, reinterpretation and re-framing of past and present events, support, reassurance and education. Attention to family issues is especially important in treatment of patients with dementing disorders^{33,34}.

Because of the increased interrelationships and involvements some families have in an older patient's status and treatment, it is often vital to maintain contact and a positive rapport with the family. Also, patients will often request this. Conversely, when family members feel unnecessarily excluded or denied access to information, they can influence or disrupt the treatment entirely. This is not to imply that therapeutic confidentiality is not maintained; families generally understand this. They do, however, want to know that appropriate help is being provided. Such reassurance can have a positive therapeutic effect on the patient, as a reflection of the family's confidence in the doctor. It can also have the practical influence/effect of helping

to keep the patient in treatment. Differing opinions among relatives may also be a source of potential disruption of the treatment. Patients will often give permission, or even request the doctor to speak to family members. Sometimes family involvement is necessary, such as in ensuring compliance with medications or appointments, or in providing observations of behaviour or of problems which the patient may not report.

In situations where there are no immediate relatives, non-kinship support networks become increasingly important³⁵. The therapist may at times utilize the assistance of family surrogates in gathering information and in helping the patient. Where such networks are weak or absent, assisting the patient in their creation can be of great benefit.

RELATIONSHIPS WITH OTHER PHYSICIANS

In the absence of the formalized organization of a university environment or the planned hierarchy of a hospital or corporate structure, the geriatric psychiatrist in private practice must create or seek out relationships with other practitioners. This can be done through involvement in professional societies, participation in the activities of the community's hospitals and through non-medical social contacts. Eventually, further relationships will also be created by patients who seek psychiatric services and request that contact be established with their other treating physicians. Collegial relationships thus created can provide advice and assistance, help in monitoring the status of patients between visits to the psychiatrist and provide sources of referrals for new patients.

As noted previously, private practitioners may also consider other physicians as customers. They are often the ones who initiate, refer or make the appointments for their patients. They do this in the expectation that their patient's needs will be met. They may also feel that, by doing so, they relieve themselves of the burden of caring for that aspect of the patient's condition, therefore making their jobs a little easier.

RELATIONSHIPS WITH OTHER PSYCHIATRISTS

As with other physicians in general, private practitioners must create a network of relationships with other psychiatrists in the area, both near and far. Those at some distance, or whose special areas of interest or expertise differ, can be sources of referrals. Other psychiatrists may receive enquiries or have patients referred to them whom they are unable to treat; they may then direct them to you. Psychiatrists who practice in closer proximity may also be sources of new patient referrals, especially when their treatment interests vary from yours. Furthermore, a certain percentage of patients, especially those with chronic or recurring illness, may be 'doctor-shoppers' and spontaneously, or by referral, change from one practitioner to another over a period of time. Developing good rapport with other local psychiatrists helps in providing better care to these patients by sharing understanding of their needs, pathology and past successful treatments and by helping to avoid duplication of previously attempted unsuccessful treatments.

Formal or informal groupings of private psychiatrists may gather for continuing education and study, to help with supervision, second opinions or 'risk-management' of difficult cases, or to share tasks, such as psychiatric coverage for a local hospital's emergency room. When a private practitioner takes a break, to go on vacation or to a conference, it may be one or more of these local psychiatrists who

may help to provide coverage for patient care, who is asked to be available to take care of emergencies or to provide ongoing services to patients who are hospitalized at the time. Such coverage may be done reciprocally as a courtesy for mutual benefit, or may be by formal arrangement.

RELATIONSHIPS WITH OTHER PROFESSIONALS

Other professional care providers with whom privately practicing geriatric psychiatrists and their patients come into contact include psychologists, social workers, nurses, speech therapists, occupational therapists, private care managers, hospital administrators and the operators of day treatment programmes, and senior activity centres, nursing homes, assisted-living and independent living facilities, and other residential settings where seniors reside. Knowledge of these and other community resources is essential for the geriatric psychiatrist. At times the best treatment offered to a patient may be a referral to one of them. Needless to say, each of these can provide valuable services. As they get to know the geriatric psychiatrist, they can also be valuable resources; for example, they can be excellent sources of information about a patient's status and functioning when the patient is not in the doctor's office. They may allow the psychiatrist to provide more and better service to patients by helping to monitor, care for and carry out treatments with the patient. They can alert the doctor when problems are developing, often earlier than the patient might have, and can assist in the management of a crisis by supporting and reassuring the patient. These individuals are sources of referral to the practitioner. They will also speak to others in the community of their experiences and contacts with the practitioner. This is an important facet of how a professional reputation is made.

PROFESSIONAL ORGANIZATIONS

Working alone or in small group practices can be isolating. Involvement in local, regional, national and international professional organizations is yet another important aspect of private practice. These may be specific psychogeriatric, or psychiatric societies, or they may be medical or interdisciplinary. These associations provide mutual support, education and professional validation, and well as being additional avenues for networking and encouraging referrals of new patients.

RELATIONS WITH HOSPITALS

Each psychiatric programme within a hospital can have its own rules, regulations, standards, patterns of practice and pattern of relations with community-based practitioners. Some hospital facilities employ psychiatrists on staff; others may not. Some programmes are organized more in accord with the direction given by the hospital and the hospital-based staff. Others encourage more involvement in programme planning by the community staff physicians. Some facilities are sites for training programmes and have psychiatric residents and Fellows who provide services. There are some geriatric facilities within free-standing psychiatric hospitals and others that are geriatric units within medical hospitals; some are located in private, for-profit hospitals, or in non-profit or public or charitably funded institutions, or in university-affiliated programmes. While the rules, staffing patterns and required paper forms may vary from hospital to hospital, these variations are, for the most part, not so onerous as to be unworkable or impossible to deal with for the community-based

practitioner. In some of these settings, the community-based practitioner may be able to influence the nature of the hospital's policies and treatment programme by participation in psychiatric departmental meetings and activities.

The differences among hospitals require some flexibility on the part of the doctor, but also may allow the possibility of tailoring referrals to the hospital most appropriate to the patient. For a variety of reasons, different hospital units acquire different patient populations and characteristics. Some programmes are age segregated, with specifically designated geriatric psychiatry wards. Others are age integrated, with younger and older patients sharing and participating in the treatment programme together. Some programmes may be more suitable for cognitively intact, physically healthy older people suffering from affective or anxiety disorders or relationship dysfunctions. Others may be more focused on evaluation and treatment of problems associated with dementia or delirium.

THE POSSIBILITY OF INPATIENT HOSPITAL TREATMENT³⁶

At the time of the initial visit or at some subsequent time in the course of the treatment of an older patient, the psychiatrist may recommend inpatient hospital treatment. The process begins with an assessment of whether the hospitalization is something that would be beneficial and therapeutic but non-emergent, or is an urgently needed admission due to imminent danger to the patient or others. Immediately after this decision, the psychiatrist must decide whether the patient is capable of consenting to this plan. Depending upon the hospitals and resources available in the community, these assessments may lead to a decision to use a particular inpatient facility. For example, there may be one that can admit people on an involuntary basis, or care for people who are potentially suicidal or aggressive. Similar choices may result from the ability of a specific hospital's psychiatric ward to care for elderly patients who have concurrent severe medical problems, or who are wanderers, or who need the hospital's specific therapeutic approach. Other factors that affect the choice of inpatient service include locations of past hospitalizations, the hospitals used by the patient's other treating physicians, proximity to the patient and the patient's family to allow for visitation and, importantly, whether a particular hospital has a room available for the patient at the time it is needed, and whether the admission can or cannot be delayed until a bed becomes available. In some cases, where room is not available locally or at the time needed or where local facilities are not appropriate, referral for hospitalization may have to be made to a psychiatrist or facility elsewhere.

In the United States, at this time, there are multiple providers of health care insurance for the elderly. These include the Federal and State governments and a variety of private health insurance companies and managed care organizations (MCOs). Some health plans, especially the MCOs, may have contractual agreements with particular hospitals to provide care; this may dictate which hospital may be used for the individual's inpatient care.

ADMISSION TO HOSPITALS

Various hospitals and psychiatric facilities within hospitals may have different procedures for arranging admissions. Typically, the psychiatrist or his staff communicate with a designated person or office to make the reservation for admission. Information that must be provided at this point varies, but usually consists of the patient's

name, age, insurance information and admitting diagnosis. Some facilities may also wish to have information regarding the geriatric patient's ability to function in activities of daily living, mobility, signs and symptoms of the patient that warrant admission, a preliminary treatment plan, or the likelihood of the patient being a danger to self or others.

When the patient is admitted, each hospital's usual procedure begins. Administrators and nurses fill out forms. The patient is shown to a room, belongings are put away and the staff make the patient acquainted with the facility and programme of activities. At about the same time, the private psychiatrist is notified that the patient has arrived. If not already given, initial orders are requested. When the psychiatrist is not available to come to the hospital immediately, orders might be given by telephone to the ward nurse, addressing such needs as diet, monitoring of vital signs, laboratory tests, ward therapies and medications to be started and so on.

IN-HOSPITAL TREATMENT^{36,37}

In-hospital treatments for the elderly can include the full spectrum of therapeutic approaches devised for psychiatric patients in general, although these might vary depending upon the resources and philosophy of the facility and the specific instructions of the doctor. The psychiatrist may personally provide individual psychotherapy, family therapy, psychotherapeutic medication management, electroconvulsive therapy, or other treatments, as well as ongoing diagnostic evaluation. At times the community psychiatrist may not provide all of the therapeutic services, and may seek the assistance of other professionals, such as utilizing a psychologist to provide psychotherapies. Many older patients also benefit from group, occupational, recreational and ward milieu therapies, physical therapy, speech therapy or reality-orientation/memory-stimulating techniques. The community psychiatrist may not be directly involved in these treatments; the hospital's staff members provide them as part of the hospital's programme and report back to the doctor regarding the patient's progress. Nurses, social workers and other staff members also inform the psychiatrist about the patient's status, symptoms, behaviour and reactions to treatment as observed during the day. Coordination, mutual understanding of achievable goals, cooperation and respect between the psychiatrist and the hospital administration and staff facilitate the psychiatrist's functioning and the treatment of the patient. It is vital that a good working relationship be achieved. If it is not, the doctor and the treatment can be undermined in numerous ways.

Working in the hospital requires flexibility on the part of doctors and staff. The staff must accommodate to various physicians and their styles of treatment. The doctors must adapt to the hospital and its programme, including its staffing pattern, its treatment approach and its physical plant. Patients may be seen at times under less than ideal conditions, including differing circumstances, locations, times and schedules (e.g. seeing a patient in a semiprivate room, planning hospital rounds to not conflict with group therapy programmes, visiting patients only to find that they are in physical therapy or getting X-rays).

POST-HOSPITAL TREATMENT

Planning for hospital follow-up begins during the hospital stay. The physician can direct the social service worker regarding possible directions and options for such problems as living situation changes, needs for at-home services, assistance or care, possible

adult congregate-living facility or nursing home placement³⁸. The social worker can investigate these and coordinate planning with the physician, patient and patient's family. Other post-discharge options the doctor can order include visiting nurses, physical therapy and other home health treatments or referral to a senior day centre or a partial hospitalization day programme^{39,40}. The patient's needs, desires, finances and therapeutic considerations (including the options for follow-up treatment with the psychiatrist) are important factors in these choices. Similarly, the available, involved members of the family may have opinions or suggestions. They may also direct the psychiatrist's attention towards additional problems or issues they feel are significant.

An important part of discharge planning is the re-engagement of the patient in outpatient treatment in the psychiatrist's office. An appointment can be given at the time of discharge, or the patient may be instructed to make an appointment within a specified period of time. The psychiatrist makes certain that needed hospital records, including discharge summary, list of discharge medications, copies of laboratory and radiograph reports and medical consultation reports, are sent to the office. This enhances completeness and continuity of care. Use of electronic or computerized medical records, where available, can enhance this process.

In addition to other usual psychotherapeutic issues that can be discussed in the post-hospital treatment, it is important to include a review of the patient's reactions to the hospital, the symptoms that necessitated the admission and the patient's progress there. Also, it is important to watch for post-hospital regressions and symptom recurrences, as the patient returns to his/her usual surroundings or to a new environment. Medication compliance and monitoring is another post-discharge task that requires attention, especially if the medication is new, if it is causing some side effects or if it requires special care in its use (e.g. special diet or times of administration).

POST-HOSPITAL TREATMENT IN OTHER SETTINGS

As the American health care system has evolved, many patients who in years past were treated in hospitals for longer periods of time are now felt to have improved sufficiently as to no longer warrant an inpatient level of care, and are therefore discharged back in to the community or to facilities while still in need of some ongoing treatment. Others may be in need of treatment but are deemed suitable for the sub-acute level of care provided in a skilled or long-term nursing facility. This may also be done in an out-patient hospital or partial hospital programme, where the person receives some therapeutic services during the day and returns to his or her usual residence at night.

CONCLUSION

Community-based ambulatory psychiatric care is an evolving treatment area in the USA. Economic, political, medical and demographic forces are all having an impact on the provision of care. While aspects of the treatment of younger adults in the community are being applied to the care of seniors, modifications are important in order to more fully address the special problems and needs of this population.

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The Medical Psychiatry Inpatient Unit

Maria I. Lapid and Teresa A. Rumman

Mayo Clinic College of Medicine, Mayo Clinic Rochester, Rochester, USA

Medical psychiatry inpatient units are specialized units designed to provide care to patients with concurrently active psychiatric and medical illnesses. These units focus on the integration of medical and psychiatric care and emphasize a disease model of psychopathology¹. Two important distinctions of medical psychiatry units from traditional inpatient psychiatric units are: (i) the patient population; and (ii) the capacity to safely manage concurrent medical and psychiatric illnesses that cannot be safely handled on a homogeneous unit alone.

The patient population in a medical psychiatric unit by definition has both active psychiatric and medical illnesses. These co-morbid conditions can co-exist independently, result from a medical illness that causes or contributes to a psychiatric disorder, result from a psychiatric illness that causes or contributes to a medical disorder, or result from a psychiatric illness that requires psychotropic medication with potential to produce medical illnesses².

The clinical focus and the organization of medical psychiatry units across the country vary widely. Operations of the units occur either primarily in psychiatric departments or in medical departments, and rarely are they units with combined administrative ownership³. However, the existence of a medical psychiatry unit, along with its structural organization and model of care, is based on several factors. Overall institutional need is one factor. Access to medical beds in a general hospital can be impaired by length of stay if patients have co-morbid psychiatric conditions. Transferring these patients to a different specialized environment improves the access for medical patients who do not have psychiatric co-morbidity. Another factor is improving the overall clinical care of patients in the hospital. Patients with acute and/or severe psychiatric conditions can be managed better on a combined unit, rather than leaving patients on medical floors or transferring them to traditional psychiatric units, as medical psychiatry units have greater capability for handling both problems concurrently rather than sequentially. Additionally, many of the medical psychiatry units are more capable of dealing with geriatric issues since there is a growing number of geriatric patients with combined medical illness who also require special environments. As a result, medical psychiatry units that focus on geriatric care will become increasingly important as the United States population ages. This chapter will review the general administrative, clinical, educational and research aspects of medical psychiatry inpatient units. Much of the material is based on our own institutional model of a medical psychiatry inpatient unit within a psychiatric hospital, as empirical published data regarding these units are limited.

ADMINISTRATION

Some medical psychiatry units are based in academic medical centres with full-time faculty, while others are found in private hospitals available to physicians of any specialty (psychiatry, family practice, internal medicine and neurology) with admitting privileges. There are also medical psychiatry units in state hospitals for patients with chronic mental illnesses⁴. There are four types of medical psychiatry units based on level of acuity of medical and psychiatric illness⁵. Type I units primarily provide psychiatric care with a low level of medical acuity. Type II units include general medicine or medical subspecialty units associated with a psychiatric liaison service and provide low levels of psychiatric care to those admitted to the general medical setting. Type III and Type IV units provide care for patients with concurrent and more severe medical and psychiatric problems in a unified setting. Type III units provide care to patients with low to high psychiatric acuity, and medium medical acuity (e.g. a non-compliant, poorly controlled diabetic with borderline personality disorder; a hyponatraemic, agitated schizophrenic patient with primary polydipsia; or a depressed renal failure patient refusing dialysis). Type IV provides care to patients with low to high psychiatric acuity, and medium to high medical acuity (e.g. a patient with chronic factitious disorder/borderline personality disorder who injected him/herself with stool water and is septic; or a delirious patient with a pulmonary embolus; or a ketoacidotic borderline/anorectic/bulimic diabetic patient)⁶.

Physical Structure/Layout

The physical environment of a medical psychiatry unit is designed to accommodate patients with medical needs, cognitive impairment, functional impairment and sensory deficits such as hearing or visual impairments. It should also provide safety for those with severe behavioural disturbances in the context of delirium, dementia or other psychiatric illness. Ideally, a medical psychiatry unit is a locked unit, with restricted and secure access for safety and to prevent wandering or elopement. Each bedroom and bathroom should have wall oxygen, an emergency cord and call light. For fall precautions, every bed should have a bed alarm and thin, soft padded strips on the floor to minimize impact of fall and fall-related injuries (these are commercially available). All doors, hallways and the entire unit should be handicap and wheelchair accessible,

with handrails, grab bars and safe flooring. A special tub or shower room is designed to keep patients warm, comfortable and safe while showering or bathing. Transfer equipment such as Hoyer lifts enable safe patient transfers with less risk of injury to patients (i.e. falls) and staff (i.e. back injury).

Medical psychiatry units have the capability to access and obtain essential diagnostic work-up required in evaluation of organic causes, including imaging, electroencephalography, electrocardiogram and other laboratories, procedures and tests. Other important distinctions of a medical psychiatry unit from other general psychiatry units include the capability to provide intravenous fluids and drug therapy, nutritional support such as total parenteral nutrition and feeding tubes, surgical wound and drain care, intravenous access and care of peripheral and central lines, oxygen support, dialysis and isolation¹. Medical complications arising from electroconvulsive therapy (ECT) can also be managed on a medical psychiatry unit.

Overall, a medical psychiatry unit provides an environment that is pleasant and accommodating to a patient population with high levels of psychiatric and medical acuity, but at the same time has the essential elements that facilitate the rendering of appropriate medical and surgical services.

Admission Criteria

The focus of care of each medical psychiatry unit across the country is diverse, including elderly, neuropsychiatric or behaviourally disturbed patients, substance abuse, eating disorders, chronic pain, schizophrenia and even patients as young as 13 years old^{4,7,8}. Similarly, there is a wide variation in sources of referral, including the general hospital, long-term care facilities (nursing homes, assisted living facilities, memory care units), emergency rooms, outpatient clinics, direct referral from community providers, and tertiary referrals.

Medical psychiatry units maintain a distinctive patient population by virtue of admission criteria⁹. Admission criteria are necessary to ensure that the specialty of the medical psychiatry unit best matches the medical psychiatric problems that require treatment. Criteria for admission specify age, acuity of psychiatric and medical illness, acuity of nursing care, skilled care needs, and other factors. Patients without any concurrent medical illness, or with medical illnesses that are chronic and stable and do not require active intervention, are commonly excluded. Those whose high acuity level of medical illness that exceed the capacity of a medical psychiatry unit to safely manage them on the unit are best admitted to medical surgical services, with the consultation liaison service providing psychiatric care appropriately. Patients with severe behavioural problems should be excluded if there is no available staffing or if the physical environment is inadequate to handle the behaviours. Admissions for psychosocial reasons, in particular severe dispositional problems unlikely to be resolved even with effective psychiatric treatment, should not be accepted¹. A waiting list for admission to the unit should be maintained, and priority given to patients from other psychiatric units within the facility, and those from medical and surgical units in the general hospital.

Despite implementation of admission criteria or a priority system, some admission decisions can still be difficult. It is helpful to have a team (typically a physician and/or an advanced level nurse) review all referrals for admission to ensure compliance to admission criteria and to make gatekeeping decisions. Hospital administration should support the medical director's authority to decline

inappropriate admissions. Inappropriate admissions are not unexpected, even with admission criteria in place. One study that examined admissions to a medical psychiatry unit that required transfer to medical-surgical units within 48 hours of admission due to acute changes in medical conditions noted that the acute changes occurred after admission and were not foreseeable, although more vigilant screening for pulmonary, cardiovascular, electrolyte and infectious disorders was recommended¹⁰. When inappropriate admissions do occur, mechanisms should be in place to correct the problem, such as facilitating transfers to a more appropriate unit.

The Multidisciplinary Treatment Team

A medical model of diagnosis and treatment is practised in a medical psychiatry unit, because the patients are not only psychiatrically but also medically ill. A multidisciplinary treatment team is necessary in order to address the complex needs of this patient population. Similar to other psychiatric inpatient settings, a medical psychiatry unit utilizes a multidisciplinary treatment team to directly provide comprehensive care to patients in a biopsychosocial model. However, medical psychiatric treatment teams have more experience and expertise in providing care for medically compromised and elderly patients with psychiatric problems. One possible model would comprise a physician trained in medicine and psychiatry, or another would be two physicians, one being a psychiatrist and one being an internist. If the model is a single physician, this person should be trained with subspecialty in psychosomatic medicine, geriatric psychiatry, neuropsychiatry, or combined internal medicine and psychiatry. If the model involves a second physician, preferably an internist with specialty training in geriatric medicine, that physician is dedicated to the medical psychiatry unit daily to provide initial and follow-up consultations, to help evaluate and manage acute and chronic medical conditions, urgent or emergent situations, and to conduct medical examinations for clearance for ECT or other procedures.

Psychiatrists commonly lead the multidisciplinary treatment team. It is important for the psychiatrist team leader to have sound medical knowledge of the various aspects of psychiatric interventions (psychotherapy, pharmacotherapy, ECT, behaviour modification etc.), efficiently coordinate patients' care, communicate effectively, and successfully handle or resolve conflicts within or outside the team.

The other core members of the treatment team include nurses, social workers, pharmacists, therapists and chaplains. The nursing staff is one of the most important factors in the successful operation of a high-level acuity medical psychiatry unit³. Medical psychiatry nurses should have particularly strong medical/surgical nursing skills. In fact, hiring medical/surgical nurses and training them in the care of psychiatric patients is often preferable. Social workers coordinate placement and liaison with community agencies, meet and provide support to family members, conduct family therapy, and perform a thorough psychosocial assessment. Pharmacists assist with proper medication administration, advising the treatment team of drug interactions, monitoring drug levels and medication reconciliation. Recreational therapists organize and coordinate aspects of the clinical programming related to leisure and recreational activities. Physical therapists are available to provide gait assessment, manage deconditioning, conduct exercise regimens for strengthening, and help improve deconditioning and mobility of patients. Occupational therapists serve many functions. They provide relaxation training and stress management training to reduce anxiety. They conduct safety and cognitive evaluations to help determine disposition planning.

They evaluate patients for activities of daily living (ADLs) and help with improvement of ADLs. Chaplains help assess spiritual needs and concerns, provide spiritual support to patients and lead spirituality groups.

While the psychiatric treatment team is the team that provides the primary care, other services and disciplines are consulted as appropriate. Psychologists provide consultation with personality assessment, neurocognitive assessment and recommendations for behavioural therapy. Other medical or surgical services readily provide consultation and assist management of specific problems.

Unit Operations

Teamwork between a physician medical director and nurse manager is essential in successfully operating a medical psychiatry unit. A medical director in a medical psychiatry unit balances the unit's need to fill beds with the need to screen for appropriate admissions, integrates medical psychiatric care, advocates for high quality of care, addresses financial and regulatory issues, and respects psychosocial and biomedical dimensions of care¹¹. Both the medical director and the nurse manager lead a multidisciplinary service committee, comprised of representatives from other disciplines in the unit (nurse, social worker, recreational therapist, other allied health staff), which meets regularly to review operations and clinical issues, hear staff input or concerns, review new rules and regulations or systems changes, resolve conflicts between staff, review unit performance and satisfaction surveys, and discuss other administrative and clinical issues pertinent to the unit.

The costs of operating a medical psychiatry unit are high, and financial issues are significant. There are constant pressures to reduce costs and shorten hospital stays, but at the same time taking care of more medically ill patients increases costs and the amount of staffing requirements and nursing time. This in turn has led to patients with more psychiatric and medical acuity that paradoxically increases the cost, making many medical psychiatry units less viable long-term. Therefore, partnerships must exist to underwrite the up-front costs of care of these patients. This will be beneficial in the long term as it will reduce re-admission rates to medical-surgical hospitals and overall

expense of care for patients with co-morbid medical and psychiatric problems. Additionally, medical psychiatry units can decrease the cost of care by shortening hospital stays in the medical-surgical hospital, reducing disability in patients by having the psychiatric comorbidity in medical patients addressed, delivering better aftercare, and ultimately helping patients become more functional.

Clinical Programming

While medical psychiatry patients receive psychopharmacologic and somatic/biological treatment for their psychiatric illnesses, psychotherapeutic interventions are equally important and should be structured and tailored to the needs of the medical psychiatry patient. An example of how clinical programming can be structured during the day in a medical psychiatry unit is shown in Figure 126.1. Group activities are led by non-physicians, typically nursing or allied health staff. All aspects of the clinical programming are flexible to accommodate various levels of cognitive functioning as well as the physical limitations that are common among medical psychiatry patients.

Different types of group therapy are available, including psychotherapeutic (grief, support, problem solving, cognitive behavioural, reminiscence, spirituality) and psychoeducational (mood disorders in particular depression and anxiety, chemical dependence, coping skills, ECT, proper use of medications), as well as other kinds of therapy (occupational therapy: relaxation, stress management, time management, optimization of ADLs; physical therapy: gait assessment, conditioning, strengthening, mobility, transfers; and recreational therapy: crafts, games, socialization, and other recreational or leisure activities). Family members can be included in some activities. Individual therapy or counselling is available as needed. Community organizations such as a National Alliance for the Mentally Ill (NAMI) family group may be available for families to attend within the psychiatric hospital. Other forms of intervention include modified exercise, music therapy, pet therapy, and other sensory activities such as a sensory room available for use for those who need de-stimulation in a quiet and relaxing environment.

DAILY SCHEDULE—MEDICAL PSYCHIATRIC PROGRAM

Time	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
8:00 am	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast
8:00–10:00 am	Daily Planning Morning Cares Team Rounds	Daily Planning Morning Cares Team Rounds	Daily Planning Morning Cares Team Rounds	Daily Planning Morning Cares Team Rounds	Daily Planning Morning Cares Team Rounds	Daily Planning Morning Cares Team Rounds	Daily Planning Morning Cares Team Rounds
10:00–11:00 am	RT*	Leisure Discussion	RT	Leisure Discussion	RT	Free time of Family Time	Church
11:30–12:00 pm	Free Time	Music Therapy	Free Time	Music Therapy	Free Time	Sittercize	Free Time
12:00–1:15 pm	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch
1:15–2:15 pm	Support Group	Support Group	Support Group	Support Group	Support Group	Support Group	Family Support Group
2:30–3:30 pm	RT/Sensory	Sensory	RT/Sensory	Spirituality	RT/Sensory	Sensory	Sensory
3:30–4:30 pm	Walk/Rest	Walk/Rest	Walk/Rest	Walk/Rest	Walk/Rest	Walk/Rest	Walk/Rest
4:30–5:15 pm	Free Time/Rest	Free Time/Rest	Free Time/Rest	Free Time/Rest	Free Time/Rest	Free Time/Rest	Free Time/Rest
5:15–6:00 pm	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner
6:00–7:00 pm	Education Group	Education Group	Education Group	Education Group	Education Group	Education Group	Education Group
7:00–7:30 pm	Social Group	Social Group	Social Group	Social Group	Social Group	Social Group	Social Group
7:30–8:30 pm	Provide Relaxing Environment	Provide Relaxing Environment	Provide Relaxing Environment	Provide Relaxing Environment	Provide Relaxing Environment	Movie and Popcorn	Movie and Snack

* RT - Recreational Therapy

Figure 126.1 Daily clinical programming

Factors that Influence Length of Stay and Re-admissions

Many important factors influence the length of hospital stay and re-admission to a medical psychiatry unit. One study examined factors associated with frequent admissions to a university-based acute geriatric psychiatric inpatient unit by dichotomizing patients into single versus multiple admissions, and found that the majority of re-admissions occurred within the first three months following discharge; and that being single, male and having bipolar disorder were significant predictors of rehospitalization¹². Another study looking at predictors of psychiatric rehospitalization specifically among elderly patients found that re-admission was more likely for diagnoses of schizophrenia, bipolar disorder, depression and substance abuse¹³. The same study found re-admission to be different for mood disorders and non-mood disorders, with very short hospitalizations being associated with increased risk of rehospitalization among persons with a mood disorder. Often treatments can adversely impact length of stay and re-admission. ECT and many psychopharmacological agents are risk factors for falls in a psychogeriatric unit, increasing the length of stay. A similar but more recent study found several factors associated with longer lengths of stay among geriatric psychiatric units¹⁴. These factors include ECT and its unavailability on weekends; higher positive symptom scores on brief psychiatric rating scales following psychopharmacology complications; multiple prior psychiatric hospitalizations; court proceedings; consultation delays; and placement issues.

CLINICAL ISSUES

Overlap among the geropsychiatric, general medical psychiatry and neuropsychiatric patient population is more common than not. Geriatric psychiatry inpatient units are dedicated to serving patients who are 65 years and older, who have severe psychiatric illnesses that require psychiatric hospitalization. They may or may not have concurrent medical illnesses or high acuity. General medical psychiatry inpatients are adults of any age who require psychiatric hospitalization for acute psychiatric problems, with concurrent active medical problem or problems that need intensive medical care that cannot be safely managed on a general psychiatric inpatient unit. Neuropsychiatry inpatient units provide acute psychiatric care primarily to patients with dementia or active neurological problems that directly contribute to the psychiatric problem. Patients in a medical psychiatry unit are typically geriatric in age and have both co-morbid medical and neurological conditions (see Figure 126.2).

Common Conditions Treated in a Medical Psychiatry Unit

The conditions common to all three patient populations (i.e. geropsychiatric, neuropsychiatric and medical psychiatric) are organic mental disorders (delirium, dementia), mood disorders (depressive and bipolar disorders) and common chronic medical problems. Psychiatrically, depression is the most common condition seen in a medical psychiatry unit. Depression often complicates medical illnesses through medication interactions, side effects or non-compliance. Often, symptoms of depression mimic medical illness and pose diagnostic challenges. Sorting out these issues is a benefit on a medical psychiatric inpatient treatment unit. Untreated depression results in increasing rates of suicide, which is already a significant problem for the geriatric medically ill population. A study of psychogeriatric inpatient suicides in Australia found that

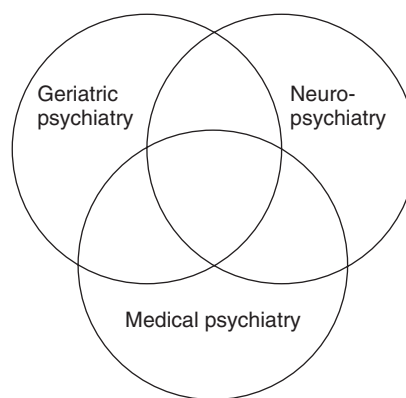


Figure 126.2 Overlap between geriatric psychiatry, medical psychiatry and neuropsychiatry patient populations

compared to younger inpatient suicides, they are more likely to have depression and more alcohol misuse in pre-admission and intra-admissions suicidal ideation¹⁵.

A survey of 11 academic medical psychiatry units reported that mood disorders and organic mental disorders were the most common conditions seen¹⁶. Other psychiatric diagnoses include schizophrenia, personality disorders, anxiety disorders, somatoform disorders, pain syndromes, drug and alcohol abuse/detoxification and eating disorders. These diagnoses are similar to those in traditional psychiatric units. The most common medical concerns were neurological and cardiovascular. However, most medical psychiatry units that treat older patients have a high prevalence of cardiovascular and respiratory issues.

Other medical psychiatry problems managed on medical psychiatry units include delirium, dementia and behavioural complications; psychiatric manifestations of neurological disorders such as stroke, epilepsy, Parkinson's disease and head trauma; medically complicated eating disorders; chronic pain; paroxysmal behavioural disorders of unknown aetiology; factitious illness; somatoform disorders; and physical illness combined with a complex family of psychosocial problems that interfere with the patient's ability to cooperate with necessary medical treatment¹.

Inpatient Evaluation and Management in a Medical Psychiatry Unit

A comprehensive and thorough evaluation of all active psychiatric and medical problems is the goal in the inpatient medical psychiatry setting, which leads to a similarly comprehensive treatment and management of concurrent psychiatric and medical issues in a unified setting. A multidisciplinary approach is essential in order to meet the complex needs of medical psychiatry patients. The highly supervised and structured environment in an inpatient setting allows care providers to closely assess and monitor a person's psychiatric and medical status, including mood, behaviour, thought process, appetite, sleep patterns, level of physical functioning, vitals signs and other physical parameters. It is possible to see fluctuations in any of these areas in such a closely monitored environment. Members of the treatment team have more time to obtain collateral information regarding a patient's history and recent events leading to hospitalization from family members, friends, local physicians or other care providers.

Diagnostic evaluation is efficiently completed, including laboratories, imaging and other appropriate medical and surgical tests. Because of medical co-morbidities in this psychiatric population, baseline electrocardiogram, complete blood count, electrolytes, glucose, liver function tests, renal function tests and thyroid stimulating hormone should be standard. Other tests should be ordered according to a patient's active symptoms. Medical consultations from dedicated internists (details above under 'Multidisciplinary Treatment Team') are standard, and other consultations from medical and surgical specialties are also easily available and accessible. Care conferences, treatment planning and discharge planning are held in the inpatient unit in a coordinated manner with input from all sides, including patients, families and treatment team.

All modalities of psychiatric treatment are available in the inpatient unit, including psychopharmacologic agents, biologic treatments such as ECT and psychotherapeutic interventions. Because of the frequently more complex discharge needs of medical psychiatric and geriatric patients as dictated by their clinical and psychosocial needs, intensive social work involvement is essential for effective discharge and aftercare planning. Family support throughout hospitalization, and even immediately post-discharge, is commonly provided.

EDUCATION

The medical psychiatry unit is a rich training ground for medical students, residents, fellows and students of other specialties and disciplines. From a medical student perspective, rotations in the medical psychiatry unit allow them to grasp the concepts of mind-body connection and also realize that psychiatry is indeed a medical specialty. Psychiatric residents gain competence in the management of patients who are very ill and have very complicated medical and psychiatric co-morbidities. Other students who rotate on medical psychiatry units include fellows in geriatric psychiatry, psychosomatic medicine and geriatric medicine; residents in neurology or internal medicine; and students from other disciplines, such as nursing, pharmacy, chaplain services and recreation therapy.

RESEARCH

Many issues can be explored more comprehensively on a medical psychiatry inpatient unit to allow us to provide a better value of care for such patients with these co-morbid conditions. The three most pressing issues that should be explored on a medical psychiatry inpatient unit are: (i) research on the interface among medicine and psychiatry, neurology and psychiatry, and geriatrics; (ii) research on treatment outcomes in this patient population to determine which treatments work well and which do not; and (iii) research on the cost effectiveness of providing dual treatment concurrent care rather than separate, fragmented sequential care.

SUMMARY

Medical psychiatry units serve a unique role in the care of the complicated patients who have both psychiatric and medical problems. In addition to clinical care, medical psychiatry units educate medical students to recognize the common interactions between these

problems and geriatric patients. Residents and other physicians learn to integrate, rather than fragment, care in order to provide the best patient outcomes. Determining how the medical psychiatry unit can improve value and the overall cost of care is essential for viability.

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Psychiatric Services in Long-Term Care

Marc E. Agronin¹, Stephen M. Scheinthal² and Ashok J. Bharucha³

¹*Miami Jewish Health Systems, Miami, and University of Miami Miller School of Medicine, Miami, FL, USA*

²*Geriatric Behavioral Health, New Jersey Institute for Successful Aging, University of Medicine and Dentistry of New Jersey – School of Osteopathic Medicine, Stratford, NJ, USA*

³*Robert Young Center, Iowa Health System Moline, IL, USA*

As the percentage of individuals living into their 70s and older continues to increase dramatically across most developed countries in the world, there has been a corresponding increase in the number of individuals living in long-term care (LTC) facilities. In the United States alone there are approximately 1.43 million residents living in nearly 16 000 nursing homes, and over 1 million residents in over 35 000 assisted living facilities (ALFs)¹. Psychiatric illness represents one major reason for individuals needing the structure and assistance of an LTC facility. Epidemiological surveys indicate that at least two-thirds of all residents suffer from one or more psychiatric conditions, usually dementia, depression, delirium and/or behavioural disturbances². A survey of LTC nursing directors in six states identified not only a pressing need for psychiatric services in general, but also highlighted the need for specific help with non-pharmacological approaches to resident management³. All of these figures suggest that competent, skilled provision of mental health services is fundamental to the well-being of these residents. As a result, there is a critical need for geriatric-trained psychiatrists and other mental health specialists to work in these settings. In addition, the myriad regulations that the psychiatrist must understand in caring for patients in a facility is constantly expanding. This chapter will review the potential roles of the geriatric psychiatrist, key clinical issues and the important regulations that guide practice in LTC. Although the regulations cited are specific to the United States, they represent approaches to quality of care that are relevant to international LTC settings.

ROLES

The main role of the geriatric-trained psychiatrist in any LTC setting is to provide psychiatric consultations and follow-up care for residents. These consultations are warranted by the presence of psychiatric illness, by regulations that stipulate routine psychiatric surveillance of residents and monitoring of psychotropic medications, and by the need for risk management for situations in which potentially dangerous behaviours present. In addition, the psychiatrist may play roles in administration, education, clinical oversight and research. A summary of all potential roles can be found in Table 127.1.

Although it is rare for a psychiatrist to serve as the actual medical director of a facility, it should be clear from Table 127.1 that his or

Table 127.1 The roles of the psychiatrist in LTC settings

- Provide psychiatric evaluation and follow-up for residents
- Provide crisis management for residents (e.g. for suicidal, assaultive, abusive and homicidal behaviours)
- Initiate and oversee voluntary and involuntary hospitalizations
- Provide liaison for relevant mental health issues to administrators, social workers, MDS coordinators, risk managers, and other caregiving staff
- Communicate with family and other caregivers regarding resident mental health issues
- Conduct forensic evaluations of decision-making capacity
- Provide oversight for the use of psychotropic medications
- Maintain adherence to state/federal/national regulations
- Educate staff about psychiatric issues
- Administer or lead a mental health team
- Supervise ancillary mental health trainees and staff
- Participate in facility committees: medical staff, pharmacy and therapeutics, ethics etc.
- Assist the primary medical team in facilitating communication of complex medical, psychosocial, and safety issues with clients and their families
- Assist with end-of-life care decisions
- Conduct research studies
- Manage mental health programmes (group therapy, intensive outpatient programmes, memory centres etc.)

her multifaceted roles go well beyond being merely a consultant. In fact, the psychiatrist's deep immersion in the LTC milieu is critical to his or her understanding of the day-to-day dynamics of institutional care that impinge upon the well-being of residents.

The psychiatric consultant is also a key player in risk management. From the perspective of any facility, many situations that involve potential threats of harm to residents or that have the potential to incur substantial liability inevitably involve psychiatric conditions or the effects of psychotropic medications. Several of these circumstances are listed in Table 127.2.

One of the most critical roles of the consultant is to provide oversight for the use of psychotropic medications. As will be discussed

Table 127.2 Psychiatric issues that increase the risk of harm and liability

- Poor safety awareness (wandering off from units, handling inappropriate objects, walking with unsteady gait)
- Suicidal threats, gestures or attempts
- Indirect life-threatening behaviours (e.g. refusing to eat, take medications or submit to life-sustaining tests or treatments)
- Physically aggressive/assaultive behaviours towards other residents and/or staff
- Sexually abusive behaviours
- Homicidal threats
- Risk of falling due to psychotropic medications (e.g. benzodiazepines, antipsychotics, sedative-hypnotics)
- Risk of severe psychotropic medication side effects, especially those related to antipsychotics (e.g. diabetes, severe weight gain, tardive dyskinesia, stroke, cardiac conduction delays and death)

later in the chapter, the use of nearly all psychotropic medications requires clear documentation of the diagnostic indication, implementation of concomitant behavioural strategies, judicious dosing and mandatory attempts at dose reductions for conditions that naturally have symptomatic remission.

Another important role for the psychiatrist is to educate LTC staff about common psychiatric symptoms and diagnoses, and how to initiate referrals and provide clinical data, recognize medication side effects and deal with behavioural disturbances. Any employee of an LTC facility has the potential to recognize psychiatric illness, ranging from nurses, aides, dieticians, therapists and social workers who provide hands-on care, to administrators who deal with complaints and crises, to kitchen and custodial staff who may form bonds with residents and notice early changes in behaviour. Thus, all of these individuals need access to the psychiatrist as well as training in the recognition and management of common psychiatric symptoms.

Communication with family members and other caregivers is one of the most critical and yet often neglected roles of the psychiatric consultant. Not only can these caregivers provide some of the most detailed and accurate clinical information, but they often aide the implementation of treatment plans, from encouraging residents to take medications and participate in activities, to simply providing essential care and companionship⁴. Working in partnership with caregivers helps to reduce caregiver burden that otherwise takes a toll in terms of their mental and physical health⁵, and makes the LTC facility feel more like a community and less like an institution⁶. Ideal doctor–caregiver communication also serves a primary role in risk management for the facility, since it can mitigate feelings of anger, alienation and confusion when unfortunate events such as injuries occur – ultimately reducing litigiousness. In fact, such communication can engender realistic expectations of care in the LTC setting and even anticipate certain problems before they erupt. Several ways to optimize education and communication between the psychiatrist, staff and caregivers are listed in Table 127.3.

CLINICAL ISSUES

The entire spectrum of psychiatric diagnoses seen in geriatric patients is present in LTC settings, and requires the same approaches to diagnosis and treatment as in any other setting. One challenge for the psychiatric consultant is that there does tend to be greater medical and psychiatric co-morbidity in residents suffering from either

Table 127.3 Optimizing education and communication

- Staff in-services on Alzheimer's disease and other dementia types, depression and suicidality, anxiety disorders, behavioural disturbances, sexuality, sleep disorders, psychotropic medications and non-pharmacological management techniques
- Lectures to family and friends of residents on mental health issues
- Routine phone contact with caregivers regarding resident status
- Write educational articles for LTC facility publications and websites, and for local media
- Speak to community organizations that interface with the facility (e.g. guardianship associations, Alzheimer's Association)
- Sponsor memory and depression screenings at the facility or in the community

Table 127.4 Epidemiology of major psychiatric conditions in nursing homes^a

<i>Diagnosis</i>	<i>Community prevalence (%)</i>	<i>Nursing home prevalence (%)</i>
Major depression	2–4	15
Depressive disorders	10–15	30–47
Anxiety disorders	11	20
Anxiety symptoms	20	40
Dementia (all types, ages 65+)	25	50–67
Schizophrenia	< 1	6

^aNote: these figures are rounded off and based on approximate ranges from four sources^{8–11}.

acute delirium or chronic dementia – or both. There is also a greater concentration of psychiatric disorders including depression, dementia, anxiety disorders and schizophrenia compared to the community (see Table 127.4). Many of the same stigmas that limit adequate psychiatric care for elderly in the community will also apply in LTC, such as viewing depression or cognitive impairment as 'normal' in late life, or assuming that older personalities are more rigid, stubborn and treatment resistant⁷. All of these assumptions are incorrect and can prove discriminatory. Complicating the effects of these ageist views is the shortage of geriatric psychiatrists to consult in LTC settings, and the discriminatory reimbursement rates that have historically penalized psychiatric diagnosis (now being reversed by recent US federal legislation).

On the other hand, individuals with psychiatric impairment living in LTC settings have a much greater chance of being evaluated in a timely manner due to mandated regulations. Medication adherence can be better monitored, and supportive staff and therapeutic activities are all on site. Thus, many of the barriers to treatment in the community, such as lack of transportation or timely access to mental health clinicians, do not exist in LTC settings.

The first and most fundamental trigger of psychiatric decompensation in LTC is the transfer to the facility itself. Whether they are coming from a long-standing home or an inpatient ward at a hospital, most new admissions have faced a recent medical or psychiatric stress or crisis and are no longer able to live alone. The psychological impact of the reason for admission and the unfamiliarity of the setting and its rules can be upsetting, especially for individuals who do not like living with others or have set routines that are now being disrupted. The psychiatric consultant must be attuned to the symptomatic manifestations of this stress, found in anxious and depressed moods, anger, agitation, resistance to care, disruptions in sleep and

Table 127.5 Recognition and treatment of adjustment reactions to LTC placement

STEP 1	Review profile and history of resident prior to arrival to anticipate unique needs and challenges (e.g. resident has complicated psychotropic regimen that should be reviewed and monitored from the moment of arrival)
STEP 2	Educate staff to recognize manifestations of difficult adjustment: nervousness, anger, sadness, social withdrawal, agitation, insomnia, anorexia, exaggerated physical complaints, resistance to care, poor rehabilitation
STEP 3	Develop admission procedures for social workers and nursing staff to collect basic psychiatric history as well as to screen for cognitive impairment and depression in order to identify individuals who need early intervention. Staff should be proactive about talking to primary care physicians or the medical director to write orders for psychiatric consultations
STEP 4	Obtain information about residents' interests and needs in order to best provide care and therapeutic activities. Ask family members to provide photos, room decorations, radios, televisions etc. in order to make the new room feel familiar and comfortable
STEP 5	Provide individual and group counselling for adjustment issues
STEP 6	Promote early and aggressive intervention for new psychiatric symptoms or the exacerbation of previous disorders

appetite, exaggerated somatic complaints, poor rehabilitation, and even failure to thrive. Although previous psychiatric history may be a key guide to diagnosis and treatment, the adjustment reaction itself must be addressed. Several ways to recognize and ameliorate this adjustment are listed in Table 127.5.

In general, the diagnosis and treatment of psychiatric disorders in older patients will be similar regardless of whether they live in the community or in an LTC setting. There are, however, a number of clinical features that are unique to LTC settings, summarized in Table 127.6.

The psychiatric consultant often has to work with family members and other caregivers who may be dealing with their own emotional issues over having a loved one in the facility. Strong feelings of guilt, grief and anger are sometimes displaced onto staff members, resulting in conflicts over care issues. Often these conflicts stem from unrealistic expectations of what institutions can provide and how quickly they can do it. In other situations the family or caregivers themselves suffer from psychiatric disorders that limit or distort their interactions with staff. A general rule of thumb is for the consultant to identify the next-of-kin or legally authorized representative of the patient and then communicate early on in order to obtain history and discuss the diagnosis and treatment plan. A team approach can help to optimize care and provide a consistent approach with difficult caregivers. Consultants need to avoid engaging in defensive or passive-aggressive approaches with these caregivers, such as not answering phone calls or arguing over treatment issues, since they will only worsen the situation and lead to further conflict.

In thinking about the provision of psychiatric services in LTC, an obvious question is: what is known about the models of mental health services delivery and the relative effectiveness of such models? A

seminal review of the literature by Bartels, Moak and Dums (2002)¹² identified three relatively distinct models that merit mention: (i) a psychiatrist-centred model, (ii) a psychiatric-nurse-centred model, and (iii) a multidisciplinary team-based approach. The approximately 20 reports that examined these three models, however, were noted to suffer from serious methodological limitations, including (in the vast majority of cases) non-experimental designs, small sample sizes, lack of control groups and outcome measures that may not have been ideally situated to capture the model's effectiveness. Nonetheless, a few broad pragmatic themes emerged that appear to be relevant to clinical practice in LTC settings. Firstly, preliminary evidence indicates that nursing home personnel prefer regularly scheduled psychiatric visits with timely (and medically necessary) maintenance treatment follow-up³. Secondly, interdisciplinary, multidimensional approaches appear to be favoured over solo consultations. And finally, innovative approaches that integrate education and training with consultation, and offer hands-on advice about behavioural management in addition to neuropsychiatric diagnostic work-up and treatment planning are considered optimal.

REGULATIONS

For the last two decades, psychiatric care in LTC settings has been under increasing scrutiny from US state and federal governments. This scrutiny began in the 1980s when concern about the inappropriate use of psychotropic medications and physical restraints resulted in the adoption of Nursing Home Reform Amendments in the 1987 US Federal Budget Act, known as the Omnibus Budget Reconciliation Act of 1987 or OBRA '87. Final OBRA regulations came into effect in 1991¹³. OBRA '87 represented the biggest change in Medicare regulations since the programme was created in 1965. One mandate was the reduction and/or elimination of both physical and chemical restraints in nursing homes. Much of the drive to reduce the use of psychotropic medications came from the realization that many of them have potentially serious adverse effects, particularly extrapyramidal symptoms, tardive dyskinesia and neuroleptic malignant syndrome associated with antipsychotic agents.

The philosophy of OBRA is that judicious dosing and frequent attempts at dose reduction will prevent unnecessary use, reduce the frequency and intensity of adverse effects, and promote better surveillance and safety in LTC settings. The implementation of OBRA guidelines and their enforcement through routine surveys has resulted over time in up to a 50% overall decrease in chemical and physical restraints accompanied by a significant increase in the use of behavioural interventions^{14,15}. Despite the enactment of these guidelines, however, documented physical restraint usage remains as high as 61% in some facilities¹⁶. Psychiatrists who work in LTC settings in the USA must understand OBRA guidelines in their entirety and be able to ensure their maintenance in order to optimize psychiatric care and avoid citations from routine surveys. A summary of these responsibilities can be found in Table 127.7.

Prior to an admission to a nursing home in the United States, state licensing agencies (under the authority of the OBRA regulations) must conduct a Preadmission Screening and Annual Resident Reviews or PASARR in order to prevent admission of people with developmental disabilities or severe, chronic mental illness. The PASARR regulation was set in motion in January of 1993. The PASARR screen needs to be conducted independently of a facility, and should be completed annually. To date, however, outcome studies of the PASARR programme have documented poor compliance

Table 127.6 Common psychiatric diagnoses and issues relevant to LTC settings

<i>Diagnosis</i>	<i>Relevant issues</i>
Major depression and depressive disorders	• Suicidal behaviours (may be indirect life-threatening behaviours) • Apathy that interferes with daily functioning • Failure to thrive (with weight loss, malnutrition, dehydration, and complication of co-morbid medical issues)
Alzheimer's disease and other dementias	• Disruptive and/or dangerous behaviours • Psychosis (delusions, hallucinations) • Postural and gait instability and risk of falls • Bladder and bowel incontinence • Risk of aspiration and pneumonia • Sensitivity to centrally active medications
Anxiety disorders	• Phobia of falling may limit ambulation and participation in physical therapy • Compulsive behaviours are frustrated by institutional schedules and lack of privacy • Panic attacks may involve physical and verbal agitation
Schizophrenia and other psychotic disorders	• Disruptive and/or dangerous behaviours based on paranoid, grandiose or bizarre delusions • Suicidality • Risks of antipsychotic side effects • Health and safety risks from excess tobacco use • Lack of appropriately structured therapeutic activities
Personality disorders	• Staff and family burnout due to excess demands and emotional and behavioural crises • Suicidal and homicidal behaviours • Loss of functioning and deconditioning due to excess dependency needs • Non-adherence with institutional rules, medications, and other treatments • Litigiousness

Table 127.7 A summary of the psychiatrist's responsibilities under OBRA '87 Interpretive Guidelines (USA only)

- Become familiar with OBRA Guidelines, including the use of the MDS and RAPs
- Be familiar with Beers criteria which list medications to be avoided since they involve a high potential for adverse outcomes
- Promptly provide comprehensive psychiatric evaluation for requested individuals in order to document: (i) current symptoms, (ii) diagnosis, (iii) potential causes, (iv) use of behavioural interventions, (v) justification for psychotropic and/or physical restraint usage
- Document required diagnoses and stay within OBRA designated dosing ranges when prescribing benzodiazepines, other sedative-hypnotics and antipsychotic agents (unless the rationale for higher doses is documented)
- For sleeping pills, daily use should be for less than 10 days unless a gradual dose reduction has been unsuccessful (and attempted at least 3 times within a 6-month period)
- For antipsychotics, benzodiazepines and sedative-hypnotics, consider and document a gradual dose reduction at least twice within a year (approximately every 6 months)
- For antidepressant medications, document appropriate diagnosis and attempts at gradual dose reduction if there is complete lack of efficacy or long-term symptomatic stability
- Attend regular psychotropic medication meetings at the facility with nursing staff and the consulting pharmacist to review psychotropic drug use and adherence to OBRA guidelines

with recommendations for alternative placement as well as with the implementation of new mental health services^{15,17}. These findings highlight yet again the critical role of the psychiatrist in identifying residents in need of mental health services, as well as investigating (both from a clinical as well as research standpoint) care processes that may facilitate implementation of the PASARR mandate.

Upon admission, nursing homes must conduct a comprehensive assessment of each resident's needs and functional capacity and then

repeat this yearly using a standardized instrument called the Resident Assessment Instrument (RAI). Two major parts of the RAI include the minimum data set (MDS), which collects a spectrum of relevant resident-specific information on needs and function, and resident assessment protocols (RAPs) which are triggered by certain MDS data, and help clinical staff conduct more detailed evaluations of problems such as mood and behavioural disturbances. Quality indicators (QIs) and Quality measures (QMs) are derived from MDS

data and used as rough grading measures for the nursing home (and are even posted for public review on the website of the Center for Medicare and Medicaid Services or CMS). QIs specific to psychiatric care include items that report the prevalence of behavioural symptoms affecting others, symptoms of depression (especially without antidepressant therapy), cognitive impairment, the use of other psychotropic medications, and restraint usage. It is worth noting that the greatest unresolved controversies regarding the validity of the MDS items centres upon the behavioural symptoms, suggesting a need for expert psychiatric evaluation, rather than relying upon clinical assessment by routine staff alone¹⁸.

Psychiatric Consultation

The psychiatric consultant needs to be acutely aware when practicing in LTC facilities (and to a lesser extent in ALFs) that these are highly regulated environments with regular surveys by state, federal and other accreditation organizations. In his or her varied roles, the consultant contributes critical services and oversight that can maintain adherence to key regulations, such as OBRA, and prevent citations for not meeting state regulations. In addition, the consultant must be able to work closely with the medical director, administrator, director of nursing, risk manager, social workers and unit managers to ensure that everyone is 'on the same page' and functioning as a team. These interactions become particularly critical when working with residents

with severe behavioural disturbances that pose a risk of harm to self or others, and help to ensure that proper channels of communication are maintained with distressed families.

CMS regulations are very strict as to who may provide psychiatric care in a nursing home. In addition to psychiatrists, clinical nurse specialists with psychiatric training are also allowed to use psychiatric consultative codes and psychotherapy codes, but the regulations for geriatric nurse practitioners are more restrictive. A consult must have a signed order by a physician, typically the primary provider, and the need should be supported by nursing notes. The order should then reflect the specific reason and not simply state 'psychiatric consult requested'. Pre-printed orders and family requests are not sufficient for a consultation because they do not necessarily support medical necessity. Verbal orders are permitted but should be the exception and not the rule. In addition, there should be documentation in the physician's notes as to why a consult is required. The bottom line is that a psychiatric consultation is neither automatic nor at the discretion of non-clinical staff, but must have a specific, documented justification and order.

Psychotropic Drug Reviews

As noted above and in Table 127.1, a primary role of the psychiatrist in LTC facilities is to prescribe and monitor psychotropic medications. The need for clear documentation on diagnosis, rationale for

Table 127.8 OBRA Interpretive Guidelines for specific psychotropics¹³

Short and long-acting benzodiazepines and other anxiolytic/sedative drugs

- Other possible reasons for resident's distress have been considered and ruled out
- The resident meets criteria for one of the following DSM-IV diagnoses: generalized anxiety disorder, organic mental syndrome (delirium, dementia, or amnesic and other cognitive disorders), panic disorder, symptomatic anxiety due to another disorder
- Use is equal to or less than the maximum recommended daily dose
- Daily use at any dose is less than 4 consecutive months, unless an attempt at gradual dose reduction is unsuccessful
- A gradual dose reduction should be attempted at least twice within 1 year
- Long-acting benzodiazepines should only used after an attempt to use a short-acting agent has failed
- Exceptions to the rule for long-acting benzodiazepines: withdrawal from short-acting agent, diazepam for neuromuscular syndromes, clonazepam for bipolar disorder, tardive dyskinesia, nocturnal myoclonus, or seizure disorders

Drugs used for sleep induction

- Other possible reasons for resident's insomnia have been considered and ruled out
- Use is equal to or less than the maximum recommended daily dose
- Daily use at any dose is less than 10 consecutive days, unless an attempt at dose reduction is unsuccessful
- A gradual dose reduction should be attempted at least 3 times within a 6-month period

Antipsychotic drugs

- The resident meets criteria for one of the following DSM-IV diagnoses: schizophrenia or other acute or chronic psychotic disorder, Tourette's disorder, Huntington's disease, organic mental syndromes (delirium and dementia) with associated psychotic and/or agitated behaviours that are documented and that pose a risk of harm to self or others or interfere with staff's ability to provide care
- Use is equal to or less than the maximum recommended daily dose
- prn use discouraged unless a quick taper is being conducted
- A gradual dose reduction should be attempted at least twice within 1 year
- Close monitoring for tardive dyskinesia, postural hypotension, cognitive and behavioural impairment, akathisia, parkinsonism and metabolic disturbances (weight gain, hyperlipidaemia, hyperglycaemia)
- Inappropriate indications: wandering, fidgeting/restlessness/nervousness, insomnia, anxiety, uncooperativeness, unsociability, impaired memory, depression, poor self-care and agitation that does not pose a danger to self and others
- Exceptions to the rule for attempted dose reductions are for chronic psychotic disorders and bipolar disorder

Table 127.9 Drugs and drug–diagnosis combinations with high potential for adverse outcomes based on Beers criteria

- Tricyclic antidepressants (amitriptyline and doxepin)
- Use of tricyclic antidepressants in residents with cardiac arrhythmias
- Use of sedative-hypnotics in residents with chronic obstructive pulmonary disease
- Use of antidepressants with anticholinergic properties in residents with benign prostatic hypertrophy

use, appropriate dosing, behavioural management and attempts at gradual dose reduction has been emphasized. The failure to provide this documentation can not only lead to citations for the facility, but on a broader level can create jeopardy for the psychiatrist in terms of reimbursement for services. Lack of compliance with CMS regulation in terms of medical necessity of the visit and the use of the correct procedural code can lead to hefty fines.

In terms of actual prescribing, OBRA guidelines provide specific lists of regulated medications, conditions that justify their use, and maximum recommended daily doses. Although all of these details are too numerous to list, a condensed list can be found in Table 127.8.

Original OBRA '87 guidelines covered benzodiazepines, other sedative-hypnotic medications and antipsychotic agents. More recent revisions by CMS under Guideline F-329 consider *any* drug as unnecessary if it is being given under any of the following conditions: (i) excessive dose, (ii) duplicate therapy, (iii) a prolonged period of time without justification, (iv) without adequate monitoring, (v) without adequate indications, or (vi) in the presence of adverse consequences. Although each of these requirements seems rooted in common sense and is associated with good clinical practice, their implications are perhaps greatest with respect to the widespread use of antidepressants, antipsychotics, and mood stabilizers in LTC. Whereas in the past a psychiatrist might have routinely considered antipsychotic tapers while maintaining long-standing use of antidepressants, now both classes of medication might be in line for gradual dose reductions (GDRs) if the clinical need for prolonged use is not documented and justified.

Another important set of regulations first promulgated by the geriatrician Mark Beers, and later incorporated into OBRA guidelines, is known as the *Beers criteria*, and is composed of a list of drugs and drug–diagnosis combinations that incur a high risk of adverse outcomes in individuals over the age of 65 years^{19,20}. In general, these high-risk situations should be avoided or only used with explicit justification and close monitoring. Beers criteria most relevant to psychiatric practice are listed in Table 127.9.

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Geriatric Psychiatry Care in the Private Psychiatric Hospital Setting

Brent P. Forester¹, Robert Kohn², Susan Kim¹ and Thomas Idiculla¹

¹*McLean Hospital, Harvard University Belmont, MA, USA*

²*The Miriam Hospital, Brown University Providence, RI, USA*

INTRODUCTION

The private psychiatric hospital offers an opportunity to deliver specialized treatment to geriatric patients across a continuum of care. The types of psychiatric services offered in these hospitals vary, but may include a dedicated geriatric psychiatry inpatient unit, partial hospital programmes that can accommodate the needs of older patients transitioning out of the acute psychiatric setting or requiring more intensive outpatient treatment, and outpatient services that include memory diagnostic clinics. Private psychiatric hospitals offer unique challenges to providing the appropriate medical care often needed for older adults with complex neuropsychiatric disorders. Most private psychiatric hospitals are not geographically proximate or integrated into the general medical hospital setting. Consequently, they are more limited in the acuity of medical care provided. This chapter will review models of geriatric psychiatry care in the private psychiatric hospital setting, examine the limited literature available on this topic, and describe an analysis of diagnosis and treatment trends over the past 15 years in two private psychiatric hospitals: McLean Hospital and Butler Hospital.

INPATIENT GERIATRIC PSYCHIATRY TREATMENT IN THE PRIVATE PSYCHIATRIC HOSPITAL

Most of the literature describing inpatient geriatric psychiatric treatment does not specifically examine inpatient units in private psychiatric hospitals. However, a review of what we know about inpatient geriatric psychiatry treatment will help provide a useful background for more specific diagnosis and treatment trends in the private hospital setting. Research conducted in New Zealand has shown that treatment in an acute geriatric psychiatry inpatient unit is effective and beneficial. This outcome study found that those with 'functional disorders' showed improvement in behaviour and symptoms, while those with 'organic disorders' had improvement in functional impairment, behaviour and symptoms¹. Furthermore, there are clinical advantages to having a sub-specialized geriatric psychiatry unit. A retrospective chart review revealed that the specialized geriatric psychiatry unit offered more thorough and dedicated care to their geriatric patients compared to the general psychiatry unit². This study revealed that significantly greater percentages of older inpatients

treated on the geriatric psychiatry unit received 'complete organic medical workups, structured cognitive assessment, ageing-sensitive aftercare referral, and monitoring of psychopharmacological side effects and blood levels' than patients on a general psychiatry unit.

Physical Structure of the Inpatient Unit

The physical structure of the geriatric unit is designed to accommodate both the emotional and physical needs of the patients. These units are designed to provide a therapeutic milieu that limits restrictions on the geriatric patient. Adaptations that may not be appropriate or considered safe for a general psychiatric unit (e.g. handrails and grab bars) are made for a specialized geriatric psychiatric unit. Other adaptations include: low beds and over-bed tables, walk out showers, whirlpool tubs, enlarged signs and posters, appropriate furniture (such as seating with arms that enhances independent standing), call lights, personal alarms, non-slip and cushioned flooring, large day rooms with space to wander safely, a designated area for those who yell to limit the disruption of the rest of the unit, wheelchair and walker accessibility, bright lighting, calendars in rooms, and large clocks in rooms. These units may even have fish tanks and other visually stimulating additions. Light and pet therapy, which has been shown to improve 'psychopathological status' and 'perception of quality of life' in cognitively unimpaired elderly subjects³, may be readily available.

Sub-specialized geriatric units might offer amenities that are specific to the unique needs of geriatric patients such as large signs, colour coordination and enlarged room numbers which aid patients in confronting problems with loss of orientation⁴. Private geriatric psychiatry units may create a home-like ambiance which is associated with 'improved intellectual and emotional well-being, enhanced social interaction, reduced agitation, reduced trespassing and exit seeking and improved functionality of older adults with dementia and other mental illnesses'⁴.

Specialized Dementia Units

Private psychiatric hospitals that do offer designated dementia units are able to address needs specific to patients with dementia. For

example, such units may utilize decreased auditory and visual stimulation, which has been shown to reduce agitation and aggression levels among demented patients⁵. A number of studies support the efficacy of environmental interventions to successfully manage the prevalent behavioural complications of dementia⁴. Factors to consider include providing patients with dementia-appropriate sensory stimulation and safety measures. Sensory overstimulation may exacerbate problems with distraction, agitation, concentration and confusion⁴. Alternatively, deprivation of sensory stimulation may have negative effects on patients with dementia⁴.

Designing a separate unit for patients with dementia may also afford the opportunity to create group treatment programming that is more specific to the needs of cognitively impaired individuals. Although some hospitals may offer a distinct dementia unit for those who are cognitively intact, many units include both those with cognitive disorders and primary affective or psychotic disorders. This requires that the treatment team be versatile in addressing the needs of the unit as the population mix changes.

The Multidisciplinary Team

The inpatient geriatric psychiatry unit utilizes a multidisciplinary team that focuses on respecting the patient and their culture. This team includes the geriatric psychiatrist, the nurses, mental health workers or clinical nurse assistants, an internist preferably specialized in geriatric medicine, a clinical pharmacist, neuropsychologist, social worker, occupational and physical therapists and activity support staff. The geriatric psychiatrist is often the treatment team leader and the medical director, with administrative responsibilities that may include screening admission referrals, managing length of stay and handling personnel training and supervision. The geriatric psychiatrist initiates the appropriate neuropsychiatric work-up, including referral to subspecialists in neurology, geriatric medicine, neuropsychology, physical medicine and rehabilitation, and physical and occupational therapy. The geriatric psychiatry inpatient unit nurse must be comfortable with patients who may require total ADL (activity of daily living) care. The nurse needs to demonstrate flexible skills that enable her to assume the role of a medical nurse while providing traditional psychiatric nursing interventions, including supportive therapy for those who are cognitively intact. The neuropsychologist conducts neurocognitive testing to assist with differential diagnosis of cognitive disorders for patients referred by the geriatric psychiatrist. In addition, the neuropsychologist may assist in developing behavioural treatment recommendations, including implementation of individualized behavioural plans.

Managing Medical Co-morbidity in the Free-Standing, Private Psychiatric Hospital

Any inpatient unit in a private psychiatry hospital (and non-general medical hospital) setting is limited in the management of individuals who are severely medically compromised. Many of these units have a dedicated internal medicine specialist who is an integral member of the treatment team and will round daily and monitor individual medical issues including hydration status, treatment of co-morbid infectious disease (pneumonia, UTI, diarrhoea) and management of chronic medical issues such as diabetes and hypertension. Daily laboratory monitoring or the use of intravenous fluids or antibiotics may be required. The coordination of care with the medical team is essential to allow for a rapid and appropriate assessment of the patient

with a suspected delirium. One of the most challenging aspects of this coordination of care is being able to differentiate the medical issues that can be effectively managed on-site and those that require a transfer-out to a local general medical hospital setting for diagnosis and management. In general, the development of a diagnosis of delirium in a hospitalized older adult is a medical emergency, and underlying causes need to be determined and treated in a timely manner. If the aetiology of the delirium is unknown or if there are changes in an individual's vital signs or EKG, a referral to a general medical hospital setting is initiated for further acute medical work-up and treatment.

The Role of the Social Worker

The social worker on a geriatric psychiatry unit has an expanded, multilayered role, but primarily serves to educate families and coordinate post-discharge care with families and community referral sources. The social worker often provides supportive therapy directly to the patient or family. Focused interventions include helping families recognize and manage caregiver stress, feelings of grief related to illness in loved ones, and guilty preoccupation regarding decisions of long-term care placement. Some of the social worker's responsibilities include: advocating for the family while planning for assisted living or nursing home placements, assisting families in arranging financial planning, and managing legal issues related to substituted decision making and guardianship. Social workers will also advocate for and coordinate hospice care after discharge when medically appropriate. The social worker must also be intimately familiar and liaise with community agencies, homecare and nursing agencies and protective services, as well as guardians and attorneys. Although the primary goal of the social worker on the geriatric psychiatry unit is to ascertain that each patient is placed at the appropriate level of care, this must be completed under increasingly time-pressured circumstances in which hospital administration goals and family wishes are often in direct conflict.

The Occupational Therapist

The occupational therapist works with patients on the unit to continuously assess physical and cognitive needs. The occupational therapist examines gait, mobility, motor skills, use of adaptive equipment, and independence with activities of daily living (ADLs), including transfers. These assessments are performed throughout the hospitalization, as medications and inactivity may adversely affect gait. Functional independence may be assessed with the structured Occupational Therapy Evaluation of Performance and Support (OTEPS)⁶ or the Kohlman Evaluation of Living Skills (KELS)⁷, which evaluate mobility, self-care, instrumental ADLs, safety, medication management, financial management, and meal planning and preparation. The occupational therapist functional assessment assists in providing an appropriate disposition for the patients based on their level of function. Furthermore, the occupational therapist will try to create an atmosphere on the inpatient unit that permits inclusiveness of all patients, adjusted for their cognitive level.

The Clinical Neuropsychologist

Neuropsychologists also play a critical role on the geriatric psychiatry inpatient unit, assisting with cognitive assessment, diagnosis and

coordinated treatment planning. Examining the relative degree of change in cognitive performance from previous visits can be a very useful guide in understanding the aetiology of cognitive dysfunction and developing discharge planning options. Neuropsychologists may help guide implementation of appropriate group therapy activities with the cognitively impaired patient, and assist caregivers with decisions regarding the level of restriction that should be allotted to a patient. Decisions may also involve matters regarding administration of medication and discharge location⁸.

Inpatient Group Therapy Interventions

The daily schedule on the geriatric psychiatry unit is structured with activities planned throughout the day. Patients will be evaluated individually with the psychiatrist and may receive individualized and family therapy with the psychiatrist, nursing staff and/or social worker. Patients are encouraged to participate in group activities regardless of cognitive capacity. Examples of group activities include task-oriented groups or craft activity groups involving patient-centred tasks, groups focusing on spiritual needs of patients, and sensory-oriented groups designed to examine gross motor activities in an environment to help calm patients (e.g. music). An end-of-the-day focus group may include relaxation exercises designed to teach the more cognitively intact patients about sleep hygiene, muscle relaxation and deep breathing.

The geriatric inpatient unit may also have distinct groups modified to address certain needs that are specific to patients with dementia. Memory groups are not only effective in addressing cognitive issues, but also the agitation and aggressive behavioural components that accompany memory loss in dementia. An individual inpatient treatment programme for geriatric patients with dementia and dysfunctional behaviours was found to be effective in improving the agitation and aggressive behaviours of patients with dementia while 'preserving or enhancing cognitive and functional abilities'⁵. Distinct dementia groups may provide therapies, such as morning bright light therapy, which has been shown to be effective in normalizing irregular sleeping behaviours among demented patients by increasing total nocturnal sleep and reducing sleep time in the afternoon⁹.

Multi-sensory Behavioural Therapy

'Snoezelen' units, originating in the Netherlands in the 1970s, were developed to provide a multi-sensory experience that promotes the stimulation of all senses and does not rely on verbal interaction. Individuals may choose specific aromas, sounds, colours, tactile experiences and tastes, all of which promote relaxation. 'Snoezelen' units can be large enough to permit sufficient space for individuals who like to wander, thereby reducing intrusion into another patient's personal space. Some units promote stimulation of the senses by being connected to an outdoor area where patients may freely walk within a fenced-in space when the season is appropriate.

Multi-sensory behavioural therapy in single-blinded studies showed a modest reduction in agitation and apathy, and improved ADLs compared with standard psychiatric inpatient treatment alone¹⁰. Other studies with dementia patients carried out in nursing homes have been negative^{11,12}, or showed modest improvement in mood and well-being.

The Geriatric Neuropsychiatry Unit at McLean Hospital works exclusively with the dementia population. The unit has a dedicated

sensory stimulation room with equipment such as a sound machine, a soft-toned lamp, a weighted blanket, a sand tray and a lighted ball which may be used with supervision in an effort to reduce levels of stress and agitation. A recent pilot study demonstrated the efficacy of a sensory-based intervention for individuals with dementia and associated behavioural disturbances. Interestingly, psychotropic drug administration did not improve the response to this intervention¹³.

The Patient Population

Data from Medicare inpatient hospitalizations from 1990 to 1991 found that 19% of patients with a primary psychiatric diagnosis were treated in the psychiatric hospital compared to general hospital psychiatric units or general hospital non-psychiatric units¹⁴. Those with schizophrenia, bipolar disorder and major depression were most likely to receive inpatient treatment in a psychiatric hospital, while those with anxiety and substance-related disorders were less likely to be treated in a psychiatric hospital. However, the population mix in geriatric psychiatric inpatient units has been changing over the past several decades. One study examining admissions data from 1988 through 1998 found that recent admissions were more likely to have a primary diagnosis of dementia and to present with agitation or psychosis¹⁵. In 1988, over 60% of admissions had a diagnosis of affective disorder, which was reduced to 34% by 1998. Over this 10-year time period, the admitted patients were older, took more medications on discharge, had shorter lengths of stay, and were less likely to be discharged home.

Several studies have examined factors that result in re-hospitalization among elderly psychiatric patients. These studies have suggested that co-morbid depression and dementia, substance dependence, short lengths of stays, social isolation, maladaptive family systems, being single, co-morbid physical and mental health problems, male gender and bipolar disorder are all potential factors that may increase the risk of re-hospitalization¹⁶.

Length of Stay

Length of stay (LOS) is frequently longer for geriatric patients compared to younger hospitalized individuals. A study conducted at the Institute of Living, where the average length of stay in 2001 was 14.1 days, revealed that 12% of the patients had a length of stay of over 26 days¹⁷. Factors contributing to an increased length of stay included receiving electroconvulsive therapy (ECT), not performing electroconvulsive therapy on weekends, being more impaired based on the Brief Psychiatric Rating Scale positive symptom scale, falling, pharmacological complications, multiple prior psychiatric hospitalizations, requiring court proceedings to continue treatment, and delays in consultations. Diagnosis and demographic factors did not appear to play a role in length of stay.

In a review of the determinants of LOS on the Geriatric Neuropsychiatry Inpatient Unit at McLean Hospital in 2007, factors associated with an increased length of stay included older age, aggressive or sexual behaviour, need for guardianship and ECT treatment. Furthermore, neither diagnosis on admission nor discharge location contributed to LOS.

The length of stay is longer in the private psychiatric hospital setting, as compared to the general hospital psychiatric unit for elderly patients¹⁴. Interestingly, the cost for care in the private psychiatric hospital may be lower possibly due to less medical co-morbidity¹⁴.

GERIATRIC PSYCHIATRY INPATIENT ADMISSION PATTERNS: BUTLER HOSPITAL AND MCLEAN HOSPITAL, 1994–2008

We examined admission patterns for 1994–2008 to geriatric psychiatry inpatient units at two private psychiatric hospitals, Butler Hospital in Providence, Rhode Island and McLean Hospital in Belmont, Massachusetts. Butler and McLean Hospitals had a similar age distribution of patients: ages 65–75 (45.1%, 38.9%), 76–85 (39.9%, 44.6%), and over the age of 85 (15.0%, 16.5%). Since 1995 there has been a decline in admitting individuals between the ages of 65 and 75 years, and a steady rise in the other two age groups (Figure 128.1). The decline in those aged 65–75 was more dramatic for Butler Hospital, possibly due to McLean Hospital also having a dedicated dementia unit. Overall, more women than men are hospitalized: 67.8% and 64.4% were females, for Butler Hospital and McLean Hospital, respectively. The female-to-male ratio increased with age for both hospitals, with the 65–75 age group averaging 64.8% and 63.4% women; the 75–85 group averaging 69.7% and 63.0%, and the over 85 group averaging 71.7% and 70.4%. The most common discharge diagnosis for Butler Hospital across all age groups was dementia, followed by substance use disorder and depressive disorders; while for McLean Hospital the most common discharge diagnoses across all groups were dementia, depressive disorders and bipolar disorder. However, diagnosis varied by age group (Table 128.1).

The average length of stay from 1994 to 2008 was 13.4 days; 13.7 days for females and 12.8 days for males for Butler Hospital. McLean Hospital had a longer length of stay: 20.1 days; 20.6 days for females and 19.3 days for males. For Butler Hospital there was little evidence of a significant decrease in length of stay over time. At McLean Hospital there was an overall decrease in length of stay. However, this decrease in the length of stay was not dramatic. For instance, in 1994 the length of stay was 19.4 days and in 2008 it was 17.7 days; there was a peak in 2000 of 25.7 days.

Overall, 37.5% of patients at Butler Hospital and 33.7% of patients at McLean Hospital are discharged from the inpatient unit to a nursing facility, with increasing age related to more frequent nursing home placement. A quarter (24.1% and 25.5%) of those aged 65–75 are discharged to a nursing facility; while 44.6% and 36.3% of those aged 76–85, and 58.8% and 45.8% of those over 85 are sent to a

nursing home from Butler Hospital's and McLean Hospital's geriatric psychiatry units, respectively.

GERIATRIC PARTIAL HOSPITAL PROGRAMMES

The private psychiatric hospital offers an opportunity to have a continuum of care for elderly patients from the inpatient programme to partial or day hospital and outpatient services. One goal for providing geriatric patients with intensive outpatient services is to reduce readmission rates, thereby reducing total costs incurred for the patient and the hospital. Whether such programmes achieve such fiscal savings remains unknown. Private psychiatric hospitals struggle with the conflicting tension between keeping the inpatient census full while also making efforts to reduce inpatient LOS. Older adults with mood and psychotic disorders generally experience recurrent acute exacerbations, which require more intensive interventions. The partial hospital programme may serve to avoid or delay inpatient admission and allow for a more successful transition back to independent community living. Partial hospital programmes may be designed specifically for the geriatric patient or have tracks within the adult partial programme that would be appropriate for the older patient depending on their cognitive capabilities. These programmes typically are Monday through Friday for one or two weeks, and act as a bridge to outpatient care.

Such a programme would have geriatric patients with limited cognitive impairment participating in a general programme that may emphasize cognitive therapy, group therapy, problem-solving therapy and psychoeducation. Problem-solving therapy has demonstrated effectiveness in reducing severity of depression in older patients as measured by the Geriatric Depression Scale and the Hamilton Rating Scale for Depression¹⁸.

However, those who cannot benefit from groups that demand a greater degree of cognitive functioning are best served in a more support-oriented track. Such a track typically has a shorter day and consists of smaller groups, less detailed psychoeducation and more concrete activities such as art therapy, an occupation therapy task group and nutrition teaching. Group therapy in the cognitively compromised track would focus more on daily goals and planning pleasurable activities.

The elderly patient who is cognitively intact would participate in higher-functioning groups such as cognitive behavioural therapy, mindfulness, assertiveness, psychoeducation and behavioural

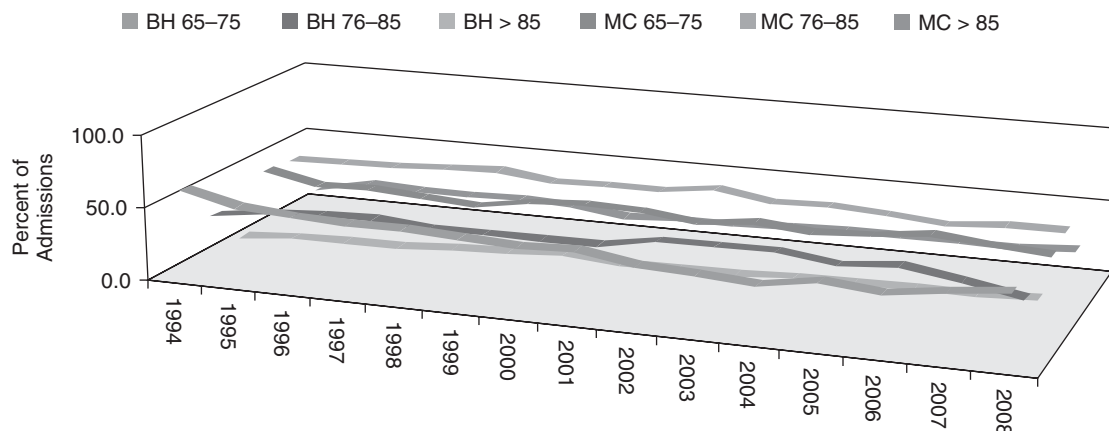


Figure 128.1 Inpatient admissions from Butler Hospital (BH) and McLean Hospital (MC) by age group from 1994 to 2008

Table 128.1 Discharge diagnosis (as % of all discharges) by age group for Butler Hospital and McLean Hospital from 1994 to 2008 (based on Butler Hospital ($N = 7213$) and McLean Hospital ($N = 7896$) discharge diagnosis)

	<i>Butler Hospital</i>				<i>McLean Hospital</i>			
	<i>1994–1998</i>	<i>1999–2003</i>	<i>2004–2008</i>	<i>Total</i>	<i>1994–1998</i>	<i>1999–2003</i>	<i>2004–2008</i>	<i>Total</i>
Age 65–75								
Adjustment disorders	1.6	0.8	0.6	0.9	0.7	0.1	0.3	0.4
Anxiety disorders	12.5	10.8	7.0	9.3	1.5	0.9	1.0	1.1
Bipolar disorders	7.2	2.4	1.7	3.0	15.7	18.3	21.3	18.3
Dementia	23.7	29.4	19.2	23.2	26.4	24.7	20.5	23.9
Depressive disorders	20.4	13.7	13.0	14.7	28.0	35.9	35.6	33.0
Non-affective psychosis	4.6	4.3	4.6	4.5	18.2	16.6	17.3	17.4
Substance use disorders	19.3	29.4	36.5	30.8	1.9	2.0	1.6	1.8
Other disorders	12.8	9.5	17.6	13.6	7.8	1.4	2.5	4.0
Age 76–85								
Adjustment disorders	1.4	0.2	0.3	0.4	0.5	0.4	0.2	0.4
Anxiety disorders	11.0	7.7	7.1	8.0	0.4	1.1	0.7	0.7
Bipolar disorders	3.4	2.0	3.3	2.9	6.0	11.2	9.1	8.6
Dementia	31.6	47.8	49.2	45.5	53.2	48.2	46.7	49.6
Depressive disorders	20.3	20.0	11.4	15.7	25.9	29.4	29.6	28.1
Non-affective psychosis	4.8	5.2	3.7	4.4	7.2	5.6	8.0	6.9
Substance use disorders	14.4	9.9	13.0	12.3	1.6	1.5	0.5	1.2
Other disorders	13.0	7.2	12.0	10.7	5.3	2.6	5.2	4.3
Age > 85								
Adjustment disorders	1.7	1.6	0.6	1.1	0.4	1.2	0.2	0.5
Anxiety disorders	6.8	5.5	6.5	6.2	0.2	0.0	0.7	0.3
Bipolar disorders	8.5	1.1	1.9	2.3	2.4	2.9	3.6	2.9
Dementia	33.9	47.3	62.0	54.3	67.2	65.2	65.1	65.9
Depressive disorders	28.8	20.3	11.7	16.3	22.7	25.5	24.0	23.9
Non-affective psychosis	0.0	4.4	4.0	3.7	1.8	3.2	1.8	2.2
Substance use disorders	8.5	8.2	2.2	4.8	1.4	0.3	0.0	0.6
Other disorders	11.9	11.5	11.1	11.3	3.8	1.8	4.7	3.6
Age > 65								
Adjustment disorders	1.5	0.7	0.5	0.7	0.6	0.4	0.2	0.4
Anxiety disorders	11.5	8.9	7.0	8.4	0.8	0.8	0.8	0.8
Bipolar disorders	5.9	2.1	2.3	2.9	9.0	12.8	13.0	11.5
Dementia	27.4	38.8	36.7	35.7	45.4	41.4	39.5	42.3
Depressive disorders	21.0	17.0	12.2	15.3	26.1	31.4	31.0	29.3
Non-affective psychosis	4.4	4.7	4.2	4.4	10.4	9.6	10.6	10.2
Substance use disorders	16.6	19.0	22.6	20.4	1.7	1.5	0.9	1.4
Other disorders	11.6	8.9	14.5	12.3	5.9	1.9	4.0	4.2

activation groups. Table 128.2 illustrates a typical partial hospital schedule using various tracts depending on the level of functioning of the patient. A cognitively impaired partial hospital track may be appropriate for those with mild cognitive impairment or dementia, but adult day care in the community setting may be more helpful for individuals with moderate to severe dementia.

There are a number of financial issues specific to the United States that must be considered when developing a partial hospital programme for the elderly. Medicare requires careful documentation of medical necessity for the initiation and continuation of group therapy interventions in partial hospital programmes. In addition, medications are not covered in partial hospital programmes under Medicare; therefore, the patient is responsible for purchasing and bringing daytime medication to the programme. Importantly, transportation is not covered by insurance and may be a limiting factor.

The partial hospital programme is appropriate for those who can benefit from structure and support. The programme allows for family education and interventions for dealing with conflicts, while also providing support and an opportunity for intensive psychopharmacological management. The partial hospital programme also permits the staff to observe an individual's daily functioning and diurnal changes in behaviour.

Examining data from Butler Hospital and McLean Hospital provides an illustration of the types of patients treated in a partial hospital programme. Between the years 1994 and 2008, the Butler Hospital partial hospital programme had 887 admissions for patients aged 65 and older. The McLean partial hospital programme is considerably larger and had 2702 admissions during that period of time. The majority (77.6% Butler Hospital; 58.0% McLean Hospital) of individuals were between the ages of 65 and 75, while

Table 128.2 An example of a partial hospital schedule for geriatric patients who cognitively cannot participate in a traditional cognitive behavioural therapy-focused programme

<i>Time</i>	<i>Monday</i>	<i>Tuesday</i>	<i>Wednesday</i>	<i>Thursday</i>	<i>Friday</i>
9:30 a.m. ^a	Arrival and individual appointments	Arrival and individual appointments	Arrival and individual appointments	Arrival and individual appointments	Arrival and individual appointments
10:00 a.m.	Goal setting	Goal setting	Goal setting	Goal setting	Goal setting
11:00 a.m.	Focus group	Focus group	Focus group	Focus group	Focus group
11:45 a.m.	Lunch	Lunch	Lunch	Lunch	Lunch
1:00 p.m.	Medication education	Wellness group	Anger management	Spirituality or substance support or task group	Mindfulness or task group
2:00 p.m.	Nutrition or task group	Behavioural activation or task group	Relapse prevention	Sleep education	Leisure skills
3:00 p.m.	End of the day check in	End of the day check in	End of the day check in	End of the day check in	End of the day check in
3:15 p.m.	Medication distribution	Medication distribution	Medication distribution	Medication distribution	Medication distribution

^aGeriatric patients in this track arrive later at the partial hospital programme than those in the traditional cognitive behavioural tracks. For those who are not cognitively able to manage specific groups, as noted in the schedule task groups are provided as an alternative.

only 2.1% and 6.0% of the admissions were over the age of 85, respectively. The majority of those in the partial hospital programme were females: 62.5% Butler Hospital and 74.8% McLean Hospital. The most common discharge diagnoses for Butler Hospital were depressive disorders, 23.6%; anxiety disorders, 22.8%; substance use disorders, 17.6%; and dementia, 12.2%; whereas McLean Hospital's programme was more focused on depressive disorders, specifically, accounting for 81.9% of discharge diagnoses compared with only 5.7% for bipolar disorder, 8.2% for non-affective psychosis, 8.3% for mild cognitive impairment and 2.7% for dementia.

A cross between the time-limited partial hospital and the outpatient geriatric psychiatry clinic where patients are seen for 15 minutes to an hour on an as-needed basis, is the enhanced outpatient treatment programme. McLean Hospital provides an example of such a programme that was initiated in 2008. The SAGE (or Seniors Aging Gracefully Everyday) programme is now utilized as a step down from inpatient care, or used to prevent the need for hospitalization. The SAGE programme is geared toward those with major depression, bipolar disorder, anxiety disorders and psychotic disorders. Patients attend the programme two to five days weekly for about four hours per day. Individual and group psychotherapy along with psychopharmacological assessment and management are available services. Such a programme typically offers cognitive behavioural therapy, illness education, coping skills, family counselling and community-resource need assessment.

SPECIALTY GERIATRIC PSYCHIATRY PROGRAMMES

The private psychiatric hospitals often have substance abuse treatment programmes, which may offer an opportunity to provide treatment specific for the geriatric population. For instance, Butler Hospital has a weekly group therapy session open to the elderly population. The rationale for this group is that a number of geriatric patients feel intimidated among younger substance users in Alcoholics

Anonymous, and an age-specific group provides them with a more secure environment to promote abstinence.

Memory disorders clinics, directed by either a geriatric psychiatrist or a behavioural neurologist, are also common in the private psychiatric hospital setting. These clinics often are multidisciplinary and include neuropsychology and occupational therapy. The memory clinic primarily focuses on providing diagnostic services and consultation to referring medical professionals. The clinic also provides treatment and follow-up services including the use of medications, counselling for patients and families, and assistance with locating and using community-based resources. Most of these clinics also actively conduct research and may offer patients an opportunity to participate in trials with commercially unavailable medications.

CONCLUSION

There are both challenges and opportunities for the care of older adults with neuropsychiatric disorders in the private psychiatric hospital setting. Foremost among the opportunities is a vertical system of care that integrates traditional inpatient geriatric psychiatry treatment with a range of outpatient services including partial hospital programming and specialty mood and memory disorders clinics. Multidisciplinary teams help provide inpatients with a full range of specialty medical and psychiatric, neurological, neuropsychological, physical and occupational therapy and social work services. Over the past 15 years, trends at two prominent private psychiatric hospitals indicate a shorter inpatient length of stay for both centres, and varying prevalence rates of dementia, affective and psychotic disorders. In addition to the financial hurdles associated with providing geriatric psychiatry care in the private psychiatric hospital setting, are the challenges of managing medically complex inpatients with both neuropsychiatric conditions and medical co-morbidities. Nevertheless, private psychiatric hospitals in the United States remain an important resource for older individuals and their families struggling with

mood disturbances, psychosis, behavioural disinhibition syndromes and cognitive impairment.

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Liaison with Medical and Surgical Teams

David N. Anderson

*Mersey Care NHS Trust, Older People's Mental Health Services, Sir Douglas Crawford Unit,
Mossley Hill Hospital, Liverpool, UK*

'My own experience suggests that the proportion of geriatric referrals is growing and that a liaison psychiatrist increasingly acts as a part-time geropsychiatrist, yet one without the benefit of appropriate training and expertise'¹.

This was said by one of the founding fathers of liaison (general hospital) psychiatry. It demonstrates how the mental health needs of older people admitted to general hospitals is increasing and has been for some time. Global demographic change is becoming a major challenge for all nations of the world. Because ageing is associated with increased health problems and multi-morbidity², this will be reflected in hospital populations. Because physical morbidity increases the chance of psychiatric morbidity, this will be reflected in greater need for liaison psychiatry services with expertise in older people's problems.

In most parts of the world, mental health of older people is not a distinct speciality. In the UK, where older people's mental health has become a separate speciality, there had been no consideration of the needs of older people admitted to general hospitals until the Royal College of Psychiatrists published the first national guideline on the development of specialist older people's liaison services³. This has stimulated great interest, and these services are now recommended in national guidance from government and professional bodies^{4–6}.

In the UK, two-thirds of National Health Service beds are occupied by people over the age of 64 years⁷, and up to 60% of this age group admitted to general hospitals may have or acquire a mental disorder during an admission³. Furthermore, this mental disorder will be an independent predictor of poor outcome by increasing mortality, length of hospital stay and loss of independent function, and reducing the prospect of a return to independent living³. This morbidity has been shown to increase subsequent health care utilization and cost⁸ and readmission to hospital⁹.

This adverse effect remains apparent some time after hospital discharge, with increased mortality being evident two years later¹⁰, nine years later for depression¹¹ and still doubled three years later with delirium¹².

In the UK, liaison psychiatry has been a developed speciality for adults under age 65, but older people received mental health attention by the inferior process of consultation¹³. Consultation is a reactive process where patients are seen on a case-by-case basis, frequently by inexperienced medical staff working independently of the general care team; a single opinion is given and the patient referred again if problems fail to resolve. Liaison is proactive, integrated with general

hospital care and based on collaborative working (Table 129.1). The superiority of liaison has been shown in controlled trials and by systematic review (Table 129.2).

The desire by clinicians to move to a liaison approach is clear¹⁴. This change is supported by accumulating evidence that addressing older people's mental health in general hospitals improves the outcome for patients and the efficiency and effectiveness of general hospitals. How this can be achieved for the more common conditions is briefly discussed in this chapter.

PREVALENCE AND INCIDENCE

Systematic review of the literature finds that the most common disorders are dementia, delirium and depression, which together will account for about 80% of the psychiatric morbidity (Table 129.3). All three are substantially more common in general hospitals than found in the community, and all conditions combined are 3–4-times more common. Rates vary with hospital departments, being particularly high in medical and orthopaedics. There is very little known about rates in emergency departments.

Each of the three major disorders creates different problems and a different focus of approach, discussed later.

DETECTION

Despite mental disorder being so common, detection by general care teams is poor. The diagnosis of delirium is missed in 32–67% of cases¹⁵, and cognitive impairment in over half¹⁶. A meta-analysis of older medical admissions reported a median detection rate for depression of 10%¹⁷. In England, a national report found that only 41% of people with dementia had any form of mental assessment recorded¹⁸.

General care teams have difficulty understanding the concept of syndromes, and their response to mental disturbance is, predominantly, a reaction to symptoms. Consequently, crying, not eating, and thoughts of death are synonymous with depression, and any cognitive errors with dementia. Jackson and Baldwin¹⁹ reported how nurses on medical wards recognize symptoms of depression rather than the syndrome. A small qualitative study in the USA found that 75% of general nurses could not distinguish dementia from delirium, despite 75% saying that they had received formal education on the subject or had attended a conference about confusion in the elderly²⁰.

Table 129.1 Characteristics of liaison and consultation services

<i>Consultation</i>	<i>Liaison</i>
Reactive	Proactive
Limited resources	More labour intensive
Isolated input	Collaborative
Low priority	High priority
Little impact	Developmental
	Education and training
Slow response	Rapid response
Little review	Frequent review
	Improve quality of referrals
	Improve adherence of recommendations
	Change practice and attitudes
Mental health separate from general services	Mental health integrated with general services
Mental health physically distant from acute care	Mental health physically part of acute care

Table 129.2 Benefits of liaison compared to consultation

Quicker response
Increase referrals and quality of referral
Increased specialist assessments
Improved diagnostic concordance between referrer and assessment
Better adherence with treatment recommendations
Reduced length of admission
More return to independent living
Reduced readmission
Reduced health care utilization
Reduced cost
High patient satisfaction

Table 129.3 Average period prevalence of psychiatric morbidity (%)

Dementia	31
Depression	29
Delirium	20 (50% incident)
Cognitive impairment	22
Anxiety	8
Schizophrenia	0.4
Alcoholism	3

A further example, and one which emphasizes the importance of syndrome diagnosis, is a report on older people referred to a liaison service with depression when 40% were found to be suffering from delirium²¹. Depressive symptoms were as common in the delirious patients as those diagnosed with depression, 50% expressing a wish to die, 25% suicidal thoughts and the majority thoughts of worthlessness and guilt.

But, detection in an acute hospital with serious physical comorbidity can be difficult. Particularly so for depression, when key biological symptoms like fatigue, loss of appetite, weight and sleep can arise from physical or psychological illness, and evaluating loss of motivation and worry in people seriously physically ill is difficult.

A diagnostic approach to depression based on DSM-III-R²² criteria, counting all symptoms regardless of their origin (inclusive)

or excluding any symptom that could arise from physical illness (exclusive), produces a variation in prevalence of 27 to 46%²³. The exclusive approach had high specificity for severe and persistent major depression, but missed 49% of major depressions identified by the high-sensitivity inclusive approach, almost 60% of whom continued to experience symptoms of depression weeks after discharge. Furthermore, these findings are based on structured psychiatric interviews, and unstructured clinical impressions are less reliable.

Interpreting cognitive function can be similarly difficult. Is a person's cognitive performance poor simply because they feel ill or too tired to attend? What is the significance of disorientation to day and date when a person has spent weeks or months in hospital or has been very ill?

It is partly for these reasons that mental health liaison teams are needed to develop expertise working in this environment. Assessment and diagnostic instruments do not solve this problem as they also need to be interpreted and few are validated for use with physically ill people. In untrained hands these tools can be dangerous, lead to false conclusions and the mistaken belief that a quick tick-box approach can replace the history and mental state examination.

Routine screening for cognitive impairment and depression has been suggested, but the benefit and method remain uncertain. A screening instrument would need high sensitivity (like the inclusive approach for depression described above) but would yield false positives, while a diagnostic instrument would require high specificity (like the exclusive approach for depression above), but risks missing many people with the disorder who would benefit from treatment.

A systematic review of screening for depression and anxiety in non-psychiatric settings concluded that the routine administration of psychiatric questionnaires with feedback to clinicians does not improve the detection of emotional disorders or patient outcome; although, those with high scores may benefit²⁴. Studies of the systematic detection and multidisciplinary treatment of delirium or depression in medical inpatients have, so far, been unable to demonstrate superiority over usual medical care^{25,26}. The systematic detection and treatment of delirium has shown small benefits for older surgical patients²⁷.

The exception is the use of clinical prediction rules to identify older people at risk of developing delirium, and this is discussed later under delirium.

EDUCATION AND TRAINING

The limitations of general care teams discussed above highlights the need for education and training, and suggest that whatever training is currently employed seems to have little effect. Teaching and training is core business for liaison teams and there is evidence that the introduction of liaison services into general hospitals is associated with changes in referral that might be taken to indicate a more informed change of behaviour²⁸. And so, it is likely that their presence, in itself and by clinical contacts, has an educative effect.

However, the best way to deliver more formal training to general care teams remains uncertain. Principles of adult learning which may be usefully incorporated into educational programmes include timely and relevant information based on participant identification of learning needs and integration of new information into existing knowledge base(s) with time for consolidation and appropriate non-judgemental feedback to the individual²⁹.

Case-based discussions that bring immediate relevance, supervision that reinforces knowledge and skills, and audit to evaluate

change will be important to effective education. Care pathways can be helpful. This might suggest that an approach which focuses on the needs of specific departments and specialities involving complete clinical teams could be more effective than random teaching sessions for hospital staff and particular professional groups. The circumstances and subject matter should dictate the approach.

Whatever the approach, training time must be built into job plans and the resourcing of liaison teams. The time needed is always underestimated, and when clinical staff are under pressure, training will be relegated to low priority. In one audit of a nurse-led liaison service, 7.5% of time was spent directly on formal education and 33% giving guidance, advice and making recommendations to ward staff³⁰.

Delivery to large hospitals, including night staff, with staff who move through in training, is difficult and a perpetual process. Incorporating mental health into established teaching programmes will give it credence and importance. The presence of liaison teams in general hospitals offers the prospect of mental health being absorbed into the culture of the hospital and not seen as a separate activity just provided by mental health services. The importance of improving the mental health knowledge and skills of general care teams cannot be overestimated because the vast majority of older people admitted to general hospitals with mental health needs will not be seen by specialist liaison teams. The management of non-referred cases will be the ultimate measure of how successfully liaison services have changed the general hospital's response to mental health.

INTERVENTIONS

Delirium

Delirium is the most common non-specific presentation of physical illness among older people and the most common new condition in the hospitalized elderly. It will complicate 5–10% of routine surgery. Delirium present at the time of admission is referred to as prevalent delirium, and that beginning in hospital as incident delirium. The distinction is important when discussing prevention, as 30–40% of incident delirium may be hospital acquired and preventable. Rates of delirium will vary between hospital departments, being highest with the most ill patients (Intensive Care), higher with emergency than elective surgery and higher with more complex conditions.

It is a cause of death, prolonged admission, loss of independent function, high cost and is associated with an increased risk of hospital-acquired complications including incontinence, falls, pressure sores and infection. Estimates from the USA suggest that it affects more than 2.3 million older people each year, is responsible for more than 17.5 million inpatient days and costs over \$4 billion (1994 dollars) each year³¹.

Furthermore, it is now clear that not all delirium resolves, and cognitive impairment persists 12 months after a medical admission when 15% still meet the diagnostic criteria for delirium³². Patients developing delirium during a medical admission are twice as likely to have died, and six-times more likely to have acquired a diagnosis of dementia three years later¹². Reversibility seems crucial for outcome. A prospective study of older medical patients found that the 6 and 12 month outcome for delirious people who survive and recover was no different to no-delirium groups in relation to cognition, function or institutional status³³.

Once established, the treatment is that of the underlying condition, with supportive care and management of behavioural and psychotic symptoms³⁴. There is a theoretical basis to developing pharmacological prophylaxis and treatment with cholinesterase inhibitors^{35,36} and

manipulation of the immune system³⁷, but small controlled trials of the former have failed to demonstrate efficacy.

There is compelling evidence for interventions which prevent incident delirium that is closely linked to processes of care. Clinical prediction rules have been described for medical, non-cardiac thoracic surgery and elective orthopaedic populations^{38–40}. These enable people at risk to be identified on admission to hospital and preventative care strategies employed to reduce delirium risk. Because delirium mostly develops within the first seven days of admission or surgery, this approach can concentrate on that period⁴¹.

The most developed prevention approach arose from studies of older medical patients, identifying the strongest independent predisposing and precipitating factors that predict incident delirium^{42,43}. These large studies found the relative risk was 9.5-times greater for people with a high-risk predisposing profile, and 8.9-times greater for those with a high-risk precipitant profile, than those with low risk.

This formed the basis of a controlled trial of a preventative intervention involving 852 older medical inpatients, employing a multi-component intervention strategy (The Elder Life Program). The subjects were identified on admission as being intermediate or high risk, and in the intervention arm the incidence of delirium was 34% lower than usual care. The intervention group experienced significantly lower total days with delirium, lower total number of episodes, improved cognitive function in those already cognitively impaired and lower use of sleep medications⁴⁴.

This intervention was shown to be cost effective for intermediate risk (72% of subjects) but not high risk. Cost of the intervention was offset by savings accrued from treatment intensity, including nursing and diagnostic procedures³¹.

A randomized controlled trial of 126 older people admitted with hip fracture employed a similar structured prevention strategy of proactive geriatric consultation and protocol of care. The incidence of delirium was 36% lower in the intervention group, with 58% less severe delirium. Number needed to treat was 5.6⁴⁵. Reducing the severity of delirium is important, as increased severity is associated with increased mortality, loss of function and institutionalization^{46,47}. Sub-syndromal delirium is also associated with worse outcome compared to no delirium, and equivalent to mild delirium⁴⁷.

Though the protocols were different in the medical and surgical studies, they were essentially proactive high-quality medical and nursing care. It has been said that incident delirium is a sign of hospitals failing older people⁴⁸.

Dementia

Dementia increases the risk of delirium five-fold, and recognizing delirium superimposed on dementia is particularly difficult²⁰. It is, however, very important because delirium is a common presentation of acute physical illness in people with dementia, with no localizing signs. As a general rule, any person with dementia in hospital who shows a sudden change of behaviour, function or mental state should trigger the possibility of delirium. There is no evidence, at present, to indicate any particular approach to the treatment of delirium in those with chronic cognitive impairment, and standard protocols of care apply⁴⁹.

People with dementia are highly susceptible to environmental change. Lying in bed, not given the opportunity to maintain their personal care skills, and disruption of familiar routines exposes them to a loss of independent function quickly. They take longer to recover, and cognitive impairment hampers their ability to benefit from rehabilitation.

A cross-sectional regional audit in England found that people with dementia were more likely to be in acute hospitals than any other health care beds, and 68% of those no longer required acute hospital care¹⁸. In a study of elderly hip fractures, over 70% of cases had not been diagnosed before admission⁵⁰.

Consequently, there are multiple reasons why the presence of dementia has to be identified at the time of admission, and general care teams need to recognize the significance this has for management and eventual discharge. Care plans have to take account of the effect of their cognitive impairment and the added risks it creates. All too often, it is only when a person is considered medically fit for discharge that any thought is given to their cognitive function and planning that should have occurred much earlier. A person with dementia is five-times more likely to develop delirium and then suffer the consequential effects on outcome²⁷.

A randomized, controlled trial of intensive multidisciplinary rehabilitation after hip fracture surgery achieved a reduced length of stay for those with mild or moderate dementia in the intervention arm. Those with mild dementia were as successful returning to independent living as those without dementia⁵¹. There was no benefit for length of stay or independent living for people with severe dementia, and the mild or moderate group from the intervention arm were more likely to be living independently three months after discharge.

The National Institute for Health and Clinical Excellence⁵ recommend that every suspected case of dementia in general hospitals has a specialist assessment and there should be specialist older people's liaison teams available for treatment and training.

Depression

All forms of depression are seen in a general hospital, where presentations are more varied and more difficult to diagnose. Preoperative anxiety and depression are associated with an increased risk of post-operative complications, and usually linked to worries about surgery or the disease. These often resolve following successful surgery. Unfortunately, depression accompanying a medical admission has a poor prognosis¹⁷.

Physical illness and disability increase the risk of depression greatly. Depression in older age increases mortality from natural causes⁵² and independently increases six-month readmission after discharge⁹. Up to 50% of people with depression in the general hospital have a disorder present before admission. The course of depression after discharge from a medical admission remains very stable, and a 12-month prospective study of older medical patients failed to find any effect of antidepressants⁵³. The more severe course was predicted by higher initial Hamilton Depression Rating Scale score, depressive core symptoms lasting six months, and female sex.

The evidence base for effective treatment is poor in general, and with important co-morbidities. Antidepressants, in general, are better than placebo or usual care in the presence of physical illness, with very respectable number needed to treat or harm; although, this Cochrane review included all adult ages⁵⁴. Antidepressants are also effective for depression in older people, but this Cochrane review comments on how few trials include people with physical illness⁵⁵.

Large, placebo-controlled trials have shown the superiority of selective serotonin re-uptake inhibitors after myocardial infarction for severe or recurrent depression, and confirm their safety⁵⁶. This class of antidepressant may reduce the risk of further fatal and non-fatal ischaemic events, possibly by virtue of an effect on platelet coagulability⁵⁷.

The evidence for treatment effectiveness in Parkinson's disease, stroke or with chronic obstructive pulmonary disease (COPD) is largely absent^{58–61}. There is emerging evidence that older people with COPD may be particularly difficult to engage in antidepressant treatment, but case management with a problem-solving behavioural approach is promising⁶⁰. The differing nature of presentation and outcome of depression with these co-morbidities creates challenging questions about the very nature of these disorders and whether they represent the same condition.

The only randomized, placebo-controlled trial of antidepressants in older people in a general hospital involved medical patients who were quite seriously ill⁶². The protocol purposefully kept exclusion criteria to a minimum, but the study was underpowered. Fluoxetine was superior to placebo, though not a statistically significant difference, and side effects no more likely with active treatment. Despite evidence supporting the safety of selective serotonin re-uptake inhibitors, and some benefit, less than 50% of depressed medical patients and 25% of depressed older hip fracture patients receive antidepressants^{17,45}.

One controlled study has shown the superiority of interpersonal counselling for older people with mild depression six months after a medical admission⁶³. Two prospective randomized controlled trials of older people depressed during a medical admission employed the intervention of an older people's liaison nurse. Though improvement was not statistically significant, possibly due to being underpowered, both showed more symptom improvement with intervention than usual care^{64,65}, and improved quality of life⁶⁵.

Self Harm

Self harm is much more common among younger adults and only 2–3% of cases presenting to general hospitals will involve older people. However, with older people the risk of completed suicide is higher; older people show greater suicidal intent than younger people, and the profile of older people who self harm is similar to that of older people who die by suicide, with 60–90% depressed^{66,67}. In a small study of consecutive older medical admissions, 36% expressed suicidal ideas, with 19% still having these thoughts six months later⁶⁸. About one-third of older people with self harm presenting to a general hospital will have a history of previous self harm⁶⁹.

Following self harm there is a 66-fold increased risk of suicide in the first year, which increases with age⁶⁷, and over 20 years a 49-fold increase of suicide and 33-times increase of open verdicts with older people⁷⁰.

Suicide in people with dementia is relatively uncommon, but risk may be difficult to detect. A study of nine years of recorded suicides to the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness found only 1% associated with dementia⁷¹. This only reports suicides occurring within 12 months of contact with mental health services in England and Wales. It found younger people with dementia over represented (over 20%) and fewer of the typical risk factors for suicide; particularly: history of self harm, psychiatric admissions or noted psychiatric symptoms, and more likely to have a diagnosis in excess of 12 months.

All older people presenting with self harm or suicidal thinking must be assessed by a specialist service.

Somatoform Disorder

This includes somatization and hypochondriasis and is now often referred to as medically unexplained symptoms. These presentations

of physical symptoms thought to have psychological origins are common in medical and surgical departments, though much less common with older people. In addition, the development of a mental disorder, particularly depression in later life, may cause exacerbation of symptoms from a long-term condition. If late onset, this last is more common, and most patients will have physical illness or disability even when attribution of the physical symptoms to the known disorders may be difficult.

There is little information about these conditions in general hospital populations and only a limited amount from studies in other health care settings. These conditions can lead to costly investigations and interventions and impair quality of life⁷².

In a prospective study of elderly primary care attenders, somatization was found in 5% and associated with depression, physical illness and low perceived social support⁷³. It was commonly transient, even though 13.6% had a somatizing attributional style which was quite stable. Frequent attenders were characterized by high rates of depression (28.3%), psychological distress associated with physical symptoms and perceived lack of social support (40%).

Antidepressants and cognitive behaviour therapy have been shown to be effective⁷⁴. Improving perceived social support is likely to be helpful. Treatment should only follow thorough medical investigation.

LIAISON SERVICES

Working in a general hospital environment creates different problems and questions for mental health practitioners than outpatient or community practice. Mental health practitioners will need greater knowledge of acute physical illness and how this changes the meaning of mental disturbance. General hospitals are not designed to cater for mental disorder, and the environment can contribute to the problem and will limit the way in which mental health is both assessed and managed. To acquire the necessary expertise requires that the liaison specialist's time is committed to working in this field. This is discussed by Anderson and Ooman⁷⁵.

Though the development of these services for older people is relatively new, there is accumulating evidence of their value and effectiveness. The principle functions are to work collaboratively with general care teams, provide a rapid response, manage complex conditions, improve the detection and understanding of mental health, and deliver training to general care teams that will improve their skills in mental health assessment and management³.

By improving the treatment of mental disorder they contribute to greater efficiency of general hospitals. A systematic review has shown that the introduction of a specialist liaison service has a significant benefit on health savings⁷⁶. A summary of benefits reported from controlled trials is shown in Table 129.2.

It also seems to be the case that admission to a general hospital is a common first presentation of mental disorder for older people. Holmes⁵⁰ found that over 70% of older people with dementia admitted with hip fracture were not previously diagnosed. An analysis of 2760 referrals to a specialist liaison service for older people in the UK showed that 68.2% were not under the care of mental health services, though 20% had been, and 62% of mood disorder cases represented a new-onset disorder (unpublished data: Anderson D, Nortcliffe M, Dechenne S *et al.* Characteristics of a nurse-led liaison mental health service for older people: the Liverpool Dataset Project).

Several models of service delivery have been described³ but the essential elements for a service to be most effective are:

- multidisciplinary team
- based in the general hospital
- dedicated to hospital liaison
- strong links with mental health services
- good information system.

Psychiatric morbidity varies between departments, being generally higher in medical and orthopaedic wards. Complex medical co-morbidity, the acute presentation of physical illness and the strong association between cognitive impairment and falls characterise these populations. A liaison service would expect 70% of referrals to come from medical specialties and the referral rate per admitted case is higher from medicine than surgery. The composition of the hospital and presence of very specialist departments will impact on the work of liaison services. Surprisingly little is known about the morbidity in accident and emergency departments. There is evidence that the rate of referral of older people and the average age of those referred has been increasing for at least three decades.

A large series of referrals over a five-year period found the most common reasons for referral to be cognitive assessment (42.8%), depression or anxiety (19.3%) and behaviour disorder (6%) (unpublished data: Anderson D, Nortcliffe M, Dechenne S *et al.* Characteristics of a nurse-led liaison mental health service for older people: the Liverpool Dataset Project). This generally accords with findings from smaller studies. The most common diagnoses from this series, as expected, were dementia (35%), mood disorder (17%) and delirium (11%). Dementia was more likely to be of vascular type than reported in community services, and 43% of delirium occurred in the context of dementia.

About half the referrals only required a single assessment, and the most common recommendations were for behaviour management (30%), further investigation or assessment (27.1%), medication prescribing (14%) and discharge planning (12.6%). In this series, 66.3% were discharged to their original place of residence and 19.4% to care homes; 8.4% required transfer to a mental health inpatient unit and 8.6% to a community outpatient mental health service.

CONCLUSION

The psychiatric co-morbidity of older people admitted to general hospitals is high, and admission is a common means by which mental disorder of older people comes to the attention of the health care system. General care teams have serious limitations in their ability to detect, diagnose and manage mental disorder. Two-thirds of this morbidity is mild and uncomplicated and will need to be recognized and managed more effectively by general care teams.

The development of specialist liaison services for older people brings an opportunity to improve the outcome for patients and the efficiency of general hospitals. These teams bring the skill and expertise necessary to manage complex co-morbidity, and provide training and education that general care teams require. This developing subspeciality will become increasingly important in ageing populations and is a vehicle for improving the quality of care.

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Rehabilitation

Rob Jones

*Mental Health Services for Older People Directorate and Nottingham University Section of Old Age Psychiatry,
Queen's Medical Centre, Nottingham, UK*

INTRODUCTION

In one sense the broad principles of rehabilitation seem well and securely established. But in another sense they seem to be rediscovered anew by succeeding generations, with sometimes wise old concepts seeming to come newly dressed as fresh approaches. In England up to 70% of acute hospital beds are occupied by older people, a theme familiar to most ageing societies, focusing attention on how to promote recovery more rapidly and ensure it can be sustained, not least with older people with mental health problems.

Rehabilitation of the older person with psychiatric disorder means restoring and maintaining the highest possible level of psychological, physical and social function despite the disabling effects of illness. More broadly it also means preventing unnecessary handicap associated with illness, preventing unnecessary handicap secondary to maladaptive responses to illness and combating the deadening effects of low expectations for older people among professionals, patients, families and society in general. Managing chronic disease and disability is the greatest challenge to modern medicine. Within this, rehabilitation of many older people with psychiatric disorder looms large – although, of course, many old people with psychiatric disorder respond well to ‘curative’ therapy and require little rehabilitation.

In fact, rehabilitation has always been a fundamental and inseparable part of old age psychiatry (as of all psychiatry). Perhaps for this reason, as with rehabilitation in geriatric medicine^{1,2}, little writing in the way of conclusive evaluation or substantial trials has addressed the topic specifically. Some particular techniques, such as psychological approaches with the cognitively impaired, have been well described^{3,4}, but little evaluated⁵, and evaluative research is much needed here.

SPECIAL PROBLEMS WITH PSYCHIATRIC DISORDER IN THE OLDER PERSON

‘Old age’ may span 40 years or more, posing quite different rehabilitation problems; but the most major challenge is the very frail, the old old. In this group multiple disability is prominent, easily complicated by polypharmacy, and physical and mental ill health interact in complex ways. With this vulnerable population, disentangling the respective influences of ageing, previous personality and current ill

health can be exacting. Two thirds of the UK’s disabled population are older people and the true extent of handicap due to psychiatric disorder is probably still not established.

With depression especially there may be restriction of physical activity, threatening physical capacity and health. Depression associated with stroke disorder⁶ or with Parkinson’s disease⁷ particularly illustrates both the connection between physical and psychiatric problems and the importance of physiotherapy and occupational therapy in psychiatric rehabilitation.

Physical factors are frequently of great importance in dementia. A quiescent individual may become delirious and disturbed at night through heart failure, obstructive airways disease or even the uncomfortable effects of severe constipation. Settling such problems may transform the reality of care for a carer and seeking out such therapeutic opportunities is an important part of rehabilitation. Similarly, in dementia physiotherapy and occupational therapy to promote and maintain the best possible physical capacity are key elements. Advice and practical aid to carers, such as with lifting and handling the physically disabled person with dementia, can be crucial.

A judicious mixture of the ‘therapeutic’ (curative) and the ‘prosthetic’ (supportive) approaches, sagely described over two decades ago by an eminent wise voice in geriatric medicine^{8,9}, is very necessary in old age psychiatry. While much functional psychiatric disorder and delirium can be ‘cured’, and this must be the aim, most older people with dementia need some degree of supportive care at some stage. The poor financial and housing state of many older people, together with the lack of children or spouses to help as carers for many of the old old, are further complicating factors. Maximizing ‘participation’ despite psychiatric disorder needs to be a major goal: maintaining as far as possible a role in the family, social contact, a range of activities and minimization of loss of autonomy or institutionalization. This requires an approach which embraces psychiatric, medical, rehabilitation, nursing and social perspectives. Vigorously pursuing active prevention of disability or of reduced participation as a consequence of psychiatric disorder is a vital part of rehabilitation.

SPECIAL PRINCIPLES IN REHABILITATION OF THE OLDER PERSON WITH PSYCHIATRIC DISORDER

Table 130.1 summarizes the principles. The home must be the focus of attention. This is where problems have arisen and where they

Table 130.1 Principles of rehabilitation for the older person with psychiatric disorder

Focus on the home
Ensure comprehensive assessment
Encourage normal function
Treat the treatable
Analyse disabilities and chart progress
Clarify team goals with patient and carers early
Clarify team goals with support workers early
Teach what can be relearned
Adapt the adaptable
Coordinate support and follow-up
Promote flexibility and ingenuity
Promote realistic optimism
Promote participation and autonomy

will need to be overcome. Planning for rehabilitation should begin at the earliest moment; an initial assessment at home by a senior psychiatrist, or other experienced team member, is invaluable – even if ‘home’ by now is an institution in the community. Home is also where the carers, and often any social services support staff involved, may readily be found. It is where they will need to work with solutions. This contrasts with standard medical rehabilitation where traditionally often no such opportunities for outreach have existed.

Frequently, further assessment by, say, an occupational therapist, physiotherapist or another specialist team member may be necessary – and this can perhaps also be arranged at home. But avoiding disruptive admission should not be at the cost of really meeting assessment needs. The day hospital or a community-based therapy resource centre and their teams may often be useful to complete such assessments. They (or a day centre specially supported with outreach expertise) may be settings where important rehabilitation efforts can be made.

Effectively supporting the carers with people at home is essential for rehabilitation. In the UK, Admiral Nurses are a good example – specially trained mental health nurses who work all the time in the community with people with dementia and their carers.

Poor function or morbidity should never be accepted as immutable, and, still less, as normal. Assessment should aim at a thorough understanding of social, physical and psychological function as well as the previous pattern of personality and lifestyle. From this, diagnoses and specific treatment for the treatable should follow. But also analysis should show the extent of disability, how it is mediated and how it may be overcome. Problems should be clearly recorded, with proposed solutions and with regular review of progress, and with this it is useful to use standardized assessments, such as the Bristol Activities of Daily Living Scale (BADL)¹⁰, and a standardized framework, such as the International Classification of Functioning, Disability and Health (ICF)¹¹. From the earliest moment, independent function and improvement should be sensitively encouraged, especially with hospitalized patients.

As early as possible, the agreed goals of rehabilitative efforts need to be clarified with the patient, with the relatives/carers, with the whole rehabilitation team and with any support workers needed in the community. Education, guidance and a rehabilitative ‘demonstration’ may well be necessary to resolve conflicting views on the prospects for progress. Carers may need therapy or rehabilitation in their own right. Almost always the support of carers is essential, though some stoutly independent patients manage well without this.

A prognosis-based plan is useful. This means assessing: what are the problems and what are their causes? Prognostication will follow: will these get better or worse? To what degree? Over how long a period? From this a plan can flow consistent with what seem the most major likely developments of a problematic nature, over a foreseeable time scale and taking account of what is most remediable.

Sometimes disability strongly distorts the previously stable power and dominance pattern in the family, first noted in classic work¹² but reiterated in evolving family therapy work¹³, so that, for instance, a forceful mother becomes dependent on a passive daughter. Relationships are always important and such phenomena can strongly influence outcome. They need to be understood and often complex ambivalence worked through¹⁴. Such factors are frequently important when carers seem reluctant to resume caring^{14,15} and need to be carefully teased out when juggling with the various elements of risk and risk minimization involved in supporting a vulnerable person at home¹⁵. The patient’s ‘crutch is not made of wood but of some other person’s tolerance or patience’¹⁶.

An agreed balance should be sought between the needs of carers and the patient’s right and desire for continued comparative independence despite significant disability – bearing in mind the team’s prime responsibility to the patient.

In effect, carers should be ‘recruited’ as rehabilitation therapists’ ‘aids’. But often they will need practical help and advice on rehabilitation techniques, and, always, the reassurance of the services’ continuing availability for support and sensitive expert response. This is less easy both to offer and in practice as services increasingly become, as in recent years, driven towards short-term involvement and a short-term perspective.

Similar considerations apply with any support staff necessary to help the patient at home – principally social services staff in the UK. Their early involvement and integration into the assessment and rehabilitation process can be logistically difficult but generally is most effective. Again, a longer term perspective and continuity are invaluable.

Good teamwork is of the essence. Clarity and consistency within the multidisciplinary specialist team are essential. Nurses and therapists, for instance, must communicate well, each complementing and enhancing the other’s approach.

Specialist and general practitioner must be in accord. The specialist team must carry the confidence of those who will work with the patient outside hospital. (Table 130.2 lists many of the team members and resources requiring coordination for rehabilitation – inevitably there is great overlap.)

Clear goals should be set, in accord with those of the patient and carers, and clearly understood by all^{15,17–20}. This is much easier said than done with the vulnerable frail older person; but vitally important is good communication.

Patients are taught what they can learn or relearn but often only modification of domestic equipment, provision of aids or modifications of the home will overcome their disability. More often still problems are only overcome through support services – home-delivered meals or a home help/community care assistant – coming into the home. Ingenuity and diplomacy may be needed with an old person reluctant to accept such necessary support. The great majority of support is provided by relatives/carers and supporting the supporters is the main task. This may require a day hospital or community venue for therapy, day care centre or respite admissions. Maintaining confidence that there will be reliable and appropriate care interventions and responses by the service is vital. Such confidence and such a reality become harder to maintain as there

Table 130.2 People and facilities to aid rehabilitation of the older person with psychiatric disorder

	<i>Specialist psychiatric team</i>	<i>Social services and local authority services</i>	<i>Primary care team</i>
People	Psychiatrists Hospital specialist nurses Community psychiatric nurses/Admiral nurses Physiotherapist Occupational therapist (OT) Clinical psychologist Social worker Ready access to geriatricians (Speech therapist – sometimes) (Dietician – sometimes) Carers groups	Social workers Domiciliary services manager Home help/community care assistants Meals on wheels Community OT Support to voluntary sector Sitter services Carers groups Preferably multiagency specialist home support team	General practitioners Practice nurse District nurse Health visitor Specialist community nurse Specialist community health support teams
Facilities	Assessment ward Nursing home Day hospital Outpatients Longer stay and respite care facilities	Luncheon club (often voluntary) Day centres (often voluntary) Long stay and short stay residential care and nursing homes Housing adaptation Sheltered and super-sheltered housing	Health centre

is more pressure on services to be short term in their outlook and activity.

At some stage with hospital patients, except in the most grossly deteriorated person, a home assessment is advisable with an occupational therapist or physiotherapist, or both, and perhaps with other team members.

Hospital-based staff can be too pessimistic and, allowed to function in her familiar environment, even a person with quite significant dementia can sometimes perform surprisingly well. Often serial home assessments are helpful with increasing challenge, leading to overnight stays. Also, failure initially to manage satisfactorily should not preclude the possibility of later improvement with further therapy or support.

A model of how a person-centred multi-agency specialist home support team for people with dementia and their carers works to achieve valued results has been quoted in the National Dementia Strategy²⁰ and evaluated in pilot form²¹. This highlights many of the issues arising when striving for a more bespoke, individual approach.

Above all, rehabilitation with older people requires flexibility allied to a realistic but constructively optimistic approach. Innovation and ingenuity are frequently necessary. The complex interaction between physical, social and psychological factors in older patients is further complicated by the likelihood that circumstances, especially perhaps physical health, may change dramatically; this demands a flexible response. The solution, carefully constructed and successful on one day, may need major change on the next as the situation radically alters. For this reason rehabilitation with older people is rarely completely finished, and 'maintenance' measures are often necessary. Careful planning of continuing care, follow-up and continuing availability as problems arise are essential features. The strength and determination of patients, relatives and support staff

are considerably bolstered by the knowledge that this approach is backing them up^{15,20,21}.

REHABILITATION AND LONG STAY CARE

Many patients, especially among those with dementia, despite support end up requiring long-term care but rehabilitation must remain a strong theme. Eventually, multiply disabled people, particularly with dementia, are likely to require 24-hour care. They may often exhibit both difficult, disturbed behaviour and the need for heavy physical care. Providing the best quality of life, given often quite limited resources, is the aim and a major strategy is preventing unnecessary dependency and promoting the maximum retention of function. With descriptions^{22–25} of the care of such patients in various settings, a frequent theme has been the availability of skilled and expert staff from the multidisciplinary team to help maintain good function. Evaluation of such long-term care programmes has proved complex and difficult^{22,23}.

Earlier concerns expressed in the UK that such disabled patients would be excluded from hospital long stay care, largely seemingly for funding reasons, in favour of publicly funded and means-tested placements in private residential or nursing home care^{26–28} have been superseded by this reality. In the USA (and many other countries) long-term care of older people has long been provided largely in the private or charitable sector. But in the USA the Omnibus Budget Reconciliation Act (OBRA Act)²⁹ requires nursing homes to ascertain and meet any needs for therapy and treatment. In the UK the fear is that the drive previously striven for in the best hospital care to provide a good quality of life can be replaced in private and independent care homes by a desire for a quiet life, leading to residents showing unwarranted passivity and dependency, possibly resulting from unnecessary

tranquillizing medication^{30–32}. Financial constraints could make this more acceptable than the patient's exercise of individuality, movement and self-expression.

Reports of high levels of depression in homes for older people^{33–35} emphasize the worry about effective rehabilitation and care for older people with chronic psychiatric disorder. Any institution providing shelter is at risk of providing a relatively impoverished environment^{16,22,23} and undue restriction of independence.

Bennett¹⁶ called unnecessary social inactivity and dependence the psychiatric equivalent of contractures. Hospitals (and social services) and care home settings have provided much good practice. Accounts of good long stay care for people with dementia emphasize the invaluable input of occupational therapy, physiotherapy and person-centred approaches^{2,36,37}. Sensibly ensuring activity in a structured day and enriching the environment with, for example, music therapy, art therapy, drama therapy or other stimulatory approaches²⁰ are important wherever the setting (p. 58). Emerging innovative work in Nottingham, logged as commissioned research³⁸, is usefully looking at the ethnography of the nursing teams in various health settings providing care for people with dementia and how this relates to staff well-being as they strive to deliver quality person-centred care. Preliminary results very much support the theme of the National Dementia Strategy²⁰.

Community Psychiatric Nurse (CPN) support (indeed, availability of all the specialist team to give support) to such homes is both feasible and helpful, and should be developed³⁹. But concern remains about how to monitor effectively and maintain standards in private and all long stay care, especially with people with dementia, epitomized by Objective 10 of the National Dementia Strategy²⁰. Ultimately good care here depends on the commitment of sufficient appropriately trained staff to help disabled old people experience to the full their remaining scope for independence and capacity for joy.

NEUROREHABILITATION AND COGNITIVE STIMULATION APPROACHES WITH PEOPLE WITH DEMENTIA

Considerable focus has been placed in recent years on psychological and individual training approaches that help to maximize or maintain function in older people, especially those with dementia, despite the challenge of pathological ageing⁴. Cognitive stimulation therapy has shown promise and much can be achieved by practical and individual approaches exploiting the older person's continuing good function and tendency to adapt most successfully to coping in his/her own individual environment. While work in this area has been promising and should be encouraged⁴⁰, the Cochrane Database shows a limited evidence base⁵.

DEVELOPING THEMES WITH REHABILITATION IN THE OLDER PERSON

A dominating theme is the need for a more person-centred, individual, bespoke approach, particularly to the older person with dementia, especially when working to support individuals with dementia and their carers at home. Each person with dementia/carers dyad has its own specific problems requiring a bespoke individually tailored solution²¹. Task-centred care, one size fits all, designed to suit the needs of the service provider, will not do.

The emphasis with support of this clientele at home needs to be different from the normal rehabilitation aim of restoration of function.

Here rehabilitation instead seeks to maintain maximum autonomy and participation by the individual despite deterioration. This means flexibly and individually working to promote continuing participatory activity in some form, rather than simply restoring function (no longer possible) or replacing function⁴¹. Supporting individuals in participating in making cups of tea is preferable to doing it for them when they can no longer relearn this skill. There is considerable challenge here to the standard rehabilitation approach, which focuses on recovering or relearning lost function. The standard rehabilitation approach fits ill with supporting chronic neurodegenerative disease.

Considerable attention in various health fields, including in psychiatry, especially in general adult psychiatry, has focused over the past decade on early and concentrated intervention into the home, often via special teams to give special support⁴². The hospital at home scheme in geriatric medicine has been an example in one area, and assertive outreach schemes, perhaps in tandem with crisis resolution teams, have been another. One emphasis here has been prevention of hospitalization but necessarily emphasis has also been needed on promoting recovery and good function. Linked to this has been promoting earlier discharge from hospital, either with a move to a less acute facility but with an intensive rehabilitative input and/or intensive rehabilitative input into the home following earlier discharge. In the UK intermediate care, with this short intensive input, has been the name applied to this approach. Such approaches and teams have been defined as very short term in their intervention (usually a maximum of six weeks)^{43–46}. While the supportive rehabilitative effort has been welcome, there has been a danger of lack of overall coordination and continuity of care for patients and families. Compartmentalized services can fail to link optimally for the patient's benefit across the divides between teams. In the UK such tendencies have arguably been exacerbated by short-termism in funding with performance target management requiring quick discharge. Chronic and degenerative health problems (especially mental health problems in older people) can be especially sensitive to perverse incentives here. They do not fit in well with such short-term approaches. With hospital discharge the fear has been expressed that the target of recovery may have been replaced with 'fit for discharge to a care home'. Again, such difficulties would be avoided more easily by having the dominant focus on individual bespoke outcomes and person-centred care, respecting autonomy^{21,41}.

With such major interaction in this population between physical health and mental health (and with each commonly interacting with other issues), there is a great need for collaboration between geriatric medicine and old age psychiatry. The area of liaison between these specialties is a prominent theme. More broadly, there is a need for spreading of the knowledge and expertise of old age psychiatry into all physical health care settings that may deal with older people with mental health problems⁴⁷. The area of how older people with medical crises and mental health problems fare in the general hospital is a major issue and concern in the UK. Particular dissatisfaction with this area has been expressed especially by the carers of people with dementia, meriting highlighting in the UK government's National Dementia Strategy²⁰ and by NICE/SCIE¹⁹. It is clear that improved collaboration and improved working by such services could impact beneficially in a considerable way on such rehabilitation here.

In terms of service organization, in the UK there seems to have been quite a restriction on and even a move away from the use of old age psychiatry day hospitals with older people. This seems potentially detrimental to rehabilitation approaches. Some of this has been accompanied by spreading mental health expertise more widely into day centres but the main emphasis appears, unfortunately, to have

been on cost cutting in specialist services. Good, expert, readily and locally accessible assessment and therapeutic ambulatory facilities on a day or sessional basis remain an essential component necessary for proper rehabilitation approaches with this patient population.

Another service area concerns people termed 'graduates' in the UK – these are people who have developed mental health problems earlier in life and with whom these have endured into old age, beyond 65 years. Many of these people need considerable psychiatric rehabilitation expertise and support. Arguments arise as to who should care for them. The answer is that there should be no age discrimination⁴⁸ and that people of any age should receive the service and expertise they need regardless of their age. This may mean them staying with services which predominately deal with younger people or may mean an older person with dementia receiving help from an old age service⁴⁹. It is essential that services plan and agree together the appropriate care for the individuals concerned, so that people do not fall between the 'gap'.

Antidementia drugs (cholinesterase inhibitors) merit mention and should be a part of a broader rehabilitative approach. There is great hope, and some accumulating evidence, that these will have a prophylactic and preventative effect with mild cognitive impairment, such that 'conversion' to Alzheimer's disease is delayed or prevented, with encouraging evidence also in mild/moderate Alzheimer's^{50,51}. Neurorehabilitation may usefully come into play with this approach.

The UK National Dementia Strategy²⁰ emphasizes 'living well with dementia', advocating that with proper information, support and attitudes people with dementia can experience a good quality of life. It lays great emphasis on changing attitudes more positively, educating widely with accurate information and thereby raising expectations so that a good quality of life becomes both expected and the norm. In a tacit way, perhaps, this plays into the rehabilitation approach of maintaining participation and autonomy despite the threat of cognitive decline.

In the UK a new strongly pursued theme in social care involves individuals managing and commissioning their own supportive social services. Known as self-directed care⁵², and well used in the USA, this process directly awards individual budgets to clients who have been appropriately assessed, to purchase services as they wish, within some limits. This is being piloted also now in some health care settings. Clearly this is relevant to rehabilitation work and the scheme has been seemingly well demonstrated with younger physically disabled people. Again, a rehabilitation approach focusing on individual answers, promoting participation and autonomy, seems relevant. However, older, frailer, multiply disabled people with mental health problems and possibly inadequate mental capacity may be more vulnerable to exploitation with such a system or unable or just disinclined properly to grapple with it. Such fears arise more prominently with a multi-provider, private provider and market dominated system, towards which the UK has moved significantly, especially with a perceived weakening of the regulating inspecting systems, as exemplified by concerns in the case of the Mid-Staffordshire NHS Foundation Trust⁵³. Good advice, availability of brokers and strong, effective regulation are greatly needed with such an approach.

The theme of supporting vulnerable older people at home, particularly people with dementia, raises consideration of the use of 'extra care housing' and the usefulness of assistive technology approaches^{54,55}. Both, especially perhaps the latter, must increasingly loom large in most societies around the world in rehabilitation and support approaches for the rising population of older people with mental health problems.

Living at home, with such helpful support, contrasts, particularly for people with dementia, with the experience of living in an institutional care home, which is less good. The UK Alzheimer's Society²⁵ sadly reported people there having 'little to do' with 'little interaction' and very limited time devoted to them individually by staff. Another study³⁷ in a similar vein found very uncomfortable depersonalized experiences for people living in such care homes.

ATTITUDES

Adverse feelings about older people have been noted by many^{37,56,57}. Commentators have addressed helpful and unhelpful attitudes in health professionals of all kinds, including especially doctors^{58–60}. Modern medical education is inculcating a better knowledge base for tomorrow's doctors and also better attitudes⁶¹. The educational potential of old age psychiatry services, not least exploiting the educational opportunity afforded by rehabilitation (and other concerns) with the most disabled, has been described and remains valid⁶². Not only medical students⁵⁷, but all varieties of medical and other professional staff concerned with older people with mental health problems, and also carers and lay audiences, benefit from this educational effort. Public education especially is vital in engendering constructive attitudes in society, on which ultimately will depend all efforts towards care in the community and the political will to provide decent services. These efforts and seeking better intergenerational empathy and understanding should never cease.

CONCLUSIONS

Rehabilitation of older people with psychiatric disorder means restoring/maintaining the best level of psychological, physical and social function despite the disabling effects of illness: preventing unnecessary handicap accompanying illness, unnecessary handicap secondary to maladaptive responses to illness and combating the deadening effects of low expectations with older people. Managing chronic disease and disability is the greatest challenge to modern medicine, within which rehabilitation of many older people with psychiatric disorder looms large – a fundamental and inseparable part of old age psychiatry using a judicious mixture of the 'therapeutic' (curative) and the 'prosthetic' (supportive) approaches.

In summary:

- focus on home
- ensure comprehensive multidisciplinary assessment
- encourage normal function
- treat the treatable
- analyse disabilities, chart progress
- clarify team goals with patient and carers early
- clarify team goals with support workers early
- promote realistic relearning
- adapt the adaptable
- coordinate support and follow-up
- encourage flexibility and ingenuity
- promote realistic optimism, participation and autonomy.

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Anaesthetics and Mental State

Andrew Moore Severn¹ and David Gwyn Seymour²

¹*Royal Lancaster Infirmary, Lancaster, UK*

²*Medicine for the Elderly, University of Aberdeen, Aberdeen, UK*

INTRODUCTION

Modern surgery and anaesthesia have transformed the lives of millions of older people. However, while the great majority of these will emerge without any long-term cognitive sequelae, absolute guarantees cannot be given. Anaesthesia is a complicated process in which many drugs are administered synchronously in combinations that allow for considerable individual preferences. It is not surprising that unravelling the mental state side effects is a complicated task. The task of assessing which drugs may contribute to a specific change in mental state is also complicated by the physiological response to surgery, and the 'stress', physical and mental, experienced by an elderly patient undergoing elective or emergency surgery.

It is over 50 years since Bedford¹ wrote about 18 elderly patients who had 'never been the same' after surgery and anaesthesia, and concluded that 'operations on elderly people should be confined to unequivocally necessary cases'. While there have been major advances in our understanding of postoperative cognitive dysfunction and the methodology used to investigate it, many questions remain to be answered. Although new drugs and monitoring techniques have supplanted those used in Bedford's day, much of the practice and process of modern general anaesthesia would be recognizable to him. Indeed, the birth of modern anaesthesia was heralded by the introduction of curare, a skeletal muscle relaxant, some 13 years before the Bedford paper.

General anaesthesia requires hypnosis and suppression of motor and autonomic reflexes: until 1942 this was achieved by using a single agent, such as diethyl ether, in high concentrations. Modern anaesthesia, by contrast, involves combinations of agents, in smaller doses, and the use of specific agents to suppress reflex activity, so called 'balanced anaesthesia'. In this way the complications associated with large doses of single agents, such as cardiovascular depression and prolonged coma, are avoided. There has also been a realization of the potential and social acceptability of local anaesthesia. 'Balanced anaesthesia' in today's anaesthetic practice may include a combination of an epidural infusion of local anaesthetic with opioids to provide segmental reflex suppression and a 'light' general anaesthetic to provide a suitably controlled environment for the theatre team and patient.

Local anaesthesia without the concurrent use of general anaesthesia, whether by peripheral nerve block, or by a more substantial spinal or epidural block (collectively referred to as 'regional anaes-

thesia') is not the panacea for prevention of mental state changes that some might suppose. While it is true that the great 'unknown' – the reversible coma – of general anaesthesia is avoided, the metabolic consequences of all but the simplest of operations outlast the duration of the block and exert a humoral effect on the brain. Furthermore, an operation performed under regional anaesthetic may be conducted under sedation, which in itself may have consequences for postoperative mental state changes.

Admission to hospital for major surgery can be considered a 'major life event', accompanied as such events are by anxiety and other changes in mental health status. The factors that contribute to delirium in older patients in hospital are well known² but acute surgical wards rarely provide the environment in which these factors can be managed. For example, devices such as urinary catheters and bed restraints, known to be factors that exacerbate delirium, are used as part of routine surgical practice on many wards, arguably as much for the convenience of hospital staff as for the individual benefit to patients.

In an attempt to bring some structure to the complexity of the subject, it will be considered under the following headings:

- The state of current knowledge of the clinical syndromes of delirium and postoperative cognitive dysfunction
- Mechanisms of anaesthesia and possible interactions with neural pathways involved in higher cortical functions.

In regard to the second heading, mention will also be made of the hypothesis that, in conditions of limited 'cerebral reserve', anaesthetic agents might act on the fragile brains of older patients to accelerate or unmask latent changes of dementia.

DELIRIUM

Classic descriptions of the mental changes that can follow general anaesthesia describe 'emergence delirium' (on immediate awakening from anaesthesia) and 'interval delirium' (occurring in the first few postoperative days). Modern anaesthesia, with its attention to matters such as intensive supervision and pain control by specialist staff in the immediate postoperative period, has almost entirely consigned emergence delirium to history in the case of adults, although publications continue to appear in the field of paediatric anaesthesia. It

Table 131.1 Risk factors for delirium in a group of patients aged 50 and over undergoing non-cardiac surgery

Age over 70
Alcohol abuse
Poor cognitive status
Poor functional status
Serum electrolyte/glucose disturbances
Thoracic surgery
Aneurysm surgery

Source: Marcantonio *et al.*⁵

is of note that sub-anaesthetic doses of barbiturates have historically had a role in the psychotherapeutic modality known as abreaction.

Emergence delirium aside, postoperative delirium remains a problem. The causes of postoperative delirium, as in delirium in other settings, include acute illness, drugs and drug withdrawal^{2–5}. Estimates of the incidence of postoperative delirium in the over-65s range between 7% and 50%, depending on the definitions used and the clinical circumstances^{2–5}. The incidence tends to rise with age, the urgency of surgery, the use of sedative and anticholinergic drugs and the degree of preoperative cognitive impairment. Factors (such as sepsis) that favour the development of delirium in a non-surgical situation may also be of relevance postoperatively. Inouye and co-workers have made a major contribution to our understanding of delirium in both medical and surgical situations, by introducing the concept of an interplay between one or more *predisposing* factors (such as age, dementia, co-morbidity and multisensory impairment) and one or more *precipitating* factors (such as acute sepsis, hypoxia, metabolic derangement, or sedating or anticholinergic drugs)⁶. Thus patients who are highly vulnerable because of significant predisposing factors such as dementia or physical frailty might need only a minor precipitating factor to develop delirium, whereas a more robust patient with few or no predisposing factors would require a more major precipitant. O’Keeffe and Chonchubhair⁴ concluded that, in at least 90% of cases of delirium following general surgery, it is postoperative medical or surgical complications that are to blame, which implies that the appearance of delirium should lead to a diligent search for underlying physical medical problems. The increased incidence of postoperative delirium with age is likely to be due to age-associated predisposing and precipitating factors rather than direct pharmacological effects arising from age-related differences in the actions of anaesthetic agents⁷.

Recent advances in the study of postoperative delirium have included attempts to standardize definitions⁴ and a large study in the USA by Marcantonio *et al.*⁵, which aimed to develop a clinical prediction rule based on the outcome of 1 341 patients aged 50 and over having major non-cardiac surgery. The latter authors found seven preoperative factors (see Table 131.1) that had an independent relationship with postoperative delirium. When the anaesthetic records of patients who had become delirious were compared with those of patients who had not, certain drugs, notably pethidine and long-acting benzodiazepines, appeared to confer an increased risk of delirium⁷.

POSTOPERATIVE COGNITIVE DYSFUNCTION

The widest interpretation of a ‘changed mental state’ following surgery and/or anaesthesia could embrace many conditions, ranging

Table 131.2 The European Test Battery used in the ISPOCD studies (see text and Table 131.3 for details)

Verbal learning test
Concept shifting test
Stroop colour word interference test
Letter boxes test
Broadbent Cognitive Failure Questionnaire
Zung Depression Score Questionnaire

(The Geriatric Depression Scale is used in ISPOCD2 studies)

from mild subjective alterations in concentration or mood at one extreme to major psychosis or coma at the other. For purposes of detailed study, it is helpful to consider a much narrower definition of postoperative cognitive dysfunction (POCD). Indeed, such has been the influence of the work of Moller, Cluitmans, Rasmussen and other colleagues in the International Study of Postoperative Cognitive Dysfunction (ISPOCD) Group⁸ that their definition has monopolized the use of the term POCD. A key feature of ISPOCD studies has been the use of the European psychometric test battery (EUPT battery; see Table 131.2), which has been designed as a sensitive and standardized research tool for the detection of postoperative neuropsychological deficits and which can be administered over a 45-minute period. The definition of POCD has been reached by comparing changes in the normalized (Z) scores of individual patients with age-matched controls who were not undergoing surgery, who were studied at the same time intervals^{8,9}. Such an approach has allowed sound epidemiological evidence to be gathered and hypothetical risk factors to be investigated and it has also given us useful information about the time course of mental state changes. However, studies to date have told us little about the precise mechanisms of cognitive decline or the determinants of severity in individual cases, and have largely been confined to those with normal cognitive function prior to surgery.

The first ISPOCD study (ISPOCD1) collected data between 1994 and 1996 on 1 218 patients aged 60+ who were undergoing major non-cardiac surgery in 13 hospitals in 8 European countries and the USA⁸. This was a major undertaking, which was intended to answer many of the questions about early and late postoperative cognitive dysfunction in older people that had been raised in the literature over the previous 30 years. As summarized in Table 131.3 and described below, this landmark study has spawned a series of important follow-up studies using the same methodology.

ISPOCD1⁸ was particularly concerned to test the hypothesis that hypoxaemia and/or hypotension were causative factors in POCD. Accordingly, oxygen saturation was measured by continuous pulse oximetry before surgery, throughout the day of surgery, and for the next three nights. Similarly, blood pressure was recorded by oscillometry during the operation and every 30 min for the rest of the operative day and night. Patients received general anaesthesia but no restriction was placed on the type of anaesthetic or surgical technique, which conformed to local practice in the study centres. In order to avoid the cerebral vasoconstrictor effects of hypocapnia, normocapnia (as assessed by extrapolation from analysis of the end-tidal CO₂ concentration of the exhaled gas mixture) was a requirement.

Analysis of the data from ISPOCD1 showed that 25.8% of patients had POCD seven days after surgery and that 9.9% of all patients still had evidence of POCD on the repeat neuropsychological tests carried out at three months (corresponding values for controls were 3.4% and

Table 131.3 Studies that have used methods developed by the ISPOCD group to define post-operative cognitive dysfunction following non-cardiac surgery. All studies used pre- and postoperative cognitive testing with a standard test battery (see text and Table 131.2). Standardized (Z) scores were constructed and POCD was defined as described in the text and reference⁹. Most studies also included measures of depression, self-assessed cognitive function and activities of daily living. All patients underwent major surgery, except for those in Canet *et al.*¹⁰. Postoperative cognitive testing was carried out at approximately 1 week and 3 months in all studies, but Abildstrom *et al.*¹¹ also followed a subset of the ISPOCD1 patients for 1 to 2 years. Exclusions (see ISPOCD1) include a Mini-Mental State test of 23 or less, certain medications, and a number of medical conditions

Reference	Age; no. of subjects; other details of study	Cognitive findings in subjects (S) and controls (C) (95% confidence intervals in brackets)		Other comments and conclusions
		At 1 week or hospital discharge	At 3 months, unless specified	
ISPOCD1 (Moller <i>et al.</i> ⁸)	Age 60+ <i>N</i> = 1 218 Controls: age-matched non-operated UK volunteers (<i>N</i> = 176)	S: 25.8% (23.1–28.5) C: 3.4% (1.3–7.8) <i>P</i> < 0.0001	S: 9.9% (8.1–12.0) C: 2.8% (0.9–6.5) <i>P</i> = 0.0037	The only major risk factor for POCD at 3 months was age. At 3 months, 39 out of 532 patients (7%) aged 60–69 and 52 out of 378 patients (14%) aged 70 and over had POCD; hypoxia, hypotension and depression were <i>not</i> correlated with POCD at 1 week or at 3 months
Abildstrom <i>et al.</i> ¹¹	Age 60–86 <i>N</i> = 376 (47 controls) 1–2 year follow-up of subset from ISPOCD1		NB: 1–2 year follow-up S: 10.4% (7.2–13.7) C: 10.6% (1.8–19.4) <i>P</i> = not significant	Differences in POCD between subjects and controls could not be demonstrated after 1–2 years (but note wide confidence intervals due to small numbers of controls)
Johnson <i>et al.</i> ¹²	Age 40–60 (i.e. middle-aged) <i>N</i> = 508 (183 controls)	S: 19.2% (15.7–23.1) C: 4.0% (1.6–8.0) <i>P</i> = 0.001	S: 6.2% (4.1–8.9) C: 4.1% (1.7–8.4) <i>P</i> = 0.33	While one in five middle-aged patients had evidence of POCD at week 1, by 3 months their rate of POCD was not significantly different from that of non-operated controls. Note that 29% of patients at 3 months reported <i>subjective</i> symptoms of impaired cognitive function but this was associated with markers of depression rather than with the objective criteria for POCD
Rasmussen <i>et al.</i> ¹³	Age 61 – 87 <i>N</i> = 428 randomized to GA or RA	GA: 19.7% (14.3–26.1) RA: 12.5% (8.0–18.3) <i>P</i> = 0.06	GA: 14.3% (9.5–20.4) RA: 13.9% (9.0–20.2) <i>P</i> = 0.93	Results for GA vs. RA were reported on an ‘intention to treat’ basis, but 10–15% of subjects did not receive the allocated method of anaesthesia. A <i>per protocol</i> analysis showed no difference at 3 months, but at 1 week <i>P</i> = 0.04
Canet <i>et al.</i> ¹⁰	Age 61–80 <i>N</i> = 372 <i>Minor</i> surgery cases only	S: 6.8% (4.3–10.1) (cf. 25.8% for major surgery and 3.4% for controls in ISPOCD1) <i>P</i> = N.S. between S and C	S: 6.6% (4.1–10.0) (cf. 9.9% for major surgery and 2.8% for controls in ISPOCD1) <i>P</i> = N.S. between S and C	On logistic regression, age over 70 and inpatient (vs. outpatient) treatment were predictive of POCD at 1 week but not at 3 months

Table 131.3 (continued)

Reference	Age; no. of subjects; other details of study	Cognitive findings in subjects (S) and controls (C) (95% confidence intervals in brackets)		Other comments and conclusions
		At 1 week or hospital discharge	At 3 months, unless specified	
Monk <i>et al.</i> ¹⁴	Three age groups: 'young', 18–39 <i>N</i> = 331 (64 controls) 'middle-aged', 40–59 <i>N</i> = 378 (62 controls) 'elderly', 60+ <i>N</i> = 355 (56 controls)	Age 18–39: S: 36.6% (31.3–41.8) C: 4.1% (0.9–11.5) Age 40–59: S: 30.4% (25.7–37.1) C: 2.8% (0.3–9.6) Age 60+: S: 41.4% (36.2–46.7) C: 5.1% (1.1–14.2) <i>Statistical tests</i> <i>P</i> = 0.01 for elderly S vs. middle-aged S <i>P</i> < 0.001 for S vs. C, in all three age groups	Age 18–39: S: 5.7% (3.0–8.5) C: 6.3% (1.7–15.2) Age 40–59: S: 5.6% (3.2–8.1) C: 4.8% (1.0–13.5) Age 60+: S: 12.7% (8.9–16.4) C: 1.8% (0.0–9.6) <i>Statistical</i> <i>tests P</i> = 0.001 for elderly S vs. other two groups <i>P</i> < 0.001 for S vs. C, in elderly group only	Independent risk factors for POCD at 3 months were age, lower educational level, a history of previous cerebral vascular accident with no residual impairment, and POCD at 1 week. Deaths within a year of surgery: patients who had POCD at both 1 week and 3 months were more likely to die in the first year after surgery (<i>P</i> = 0.02)

GA, general anaesthesia; RA, regional anaesthesia; N.S., not significant.

Source: Modified with permission from Seymour DG and Severn A¹⁵. Copyright (2009) The British Geriatrics Society.

2.8%). Contrary to expectations, no relationship was found between perioperative hypoxaemia and/or hypotension and the development of 'early' (one week after surgery) or 'late' (three months after surgery) POCD. Indeed, despite analyses of the effects of more than 25 other clinical parameters, only age showed a statistically significant correlation with late POCD. Age was also positively correlated with early POCD, as were duration of anaesthesia, a lesser level of education, a second operation, postoperative infections and respiratory complications. The overall conclusion of the ISPOCD1 investigators was that their study had demonstrated a measurable degree of postoperative cognitive change in a minority of older patients three months after surgery (in about 10% of patients vs. about 3% of non-operated controls) and that the risk increased with age. However, the expected relationship between hypoxaemia and/or hypotension and POCD did not emerge. It was also disappointing that, despite a large number of statistical analyses, the study failed to find any specific risk factors for late POCD that were amenable to therapeutic or preventive intervention. In addition, the hope that the study would give better insight into the pathophysiology of POCD was not fulfilled.

Several well-designed 'ISPOCD2' studies using the basic ISPOCD1 design (Table 131.3) have also failed to identify the major factors contributing to POCD. For example, Rasmussen and colleagues¹³ were unable to demonstrate any long-term cognitive benefit of regional anaesthesia over general anaesthesia for major surgery, thus apparently exonerating the drugs and processes of general anaesthesia in the development of the syndrome. As to whether there are any markers of brain damage that might correlate with the appearance of POCD, the answer is inconclusive: markers such as neuron specific enolase (NSE) and S-100 protein fail to correlate with severity of the syndrome. However, for cardiac surgery, different pathological mechanisms may apply as the brain is subjected to a different sort of insult from the process of cardiopulmonary bypass. Rasmussen *et al.*¹⁶ noted that for a cohort

of patients undergoing cardiac surgery the incidence of POCD at 1 week and 23 months was 38.7% and 13.8%, respectively, but found that some 10% of the original sample were so confused that they could not be tested at 1 week, and a further 15% dropped out of subsequent testing. Rises in plasma concentrations of NSE correlated with the syndrome of POCD. Significantly, the largest single rise in the series was noted in one of the patients who was too confused to be tested at 7 days.

A major practical disadvantage of the ISPOCD methodology is that it requires a baseline preoperative assessment, which limits its application to elective surgical procedures. However, the advantage of the approach over earlier studies that simply looked at postoperative cognitive status is that it is not open to the suggestion that some or all of the cognitive impairment observed postoperatively had been present but unobserved preoperatively. For reasons of space, Table 131.3 is limited to studies that have used the ISPOCD technique, but a list of influential 'pre-ISPOCD' studies was given in the previous edition of the present textbook¹⁷.

By design, the ISPOCD studies to date have excluded patients with preoperative Mini-Mental State Examination (MMSE) scores of 23 or less. This was a pragmatic decision because such patients were thought likely to have difficulty in completing the preoperative cognitive test battery. However, this means that a systematic study using ISPOCD techniques in patients who were cognitively impaired prior to surgery has not been carried out, even though theoretical considerations and the clinical experience of anaesthetists and others would suggest that it is this group of patients who are likely to have the highest incidence of short- and long-term POCD². Silverstein *et al.*¹⁸ reanalysed some of the earlier ISPOCD data by dividing patients into a lower (1.5 SD below controls on the ISPOCD battery) and a higher cognitive group but, as stated above, all patients had MMSEs of 24 or more. They found no evidence that those in the

lower cognitive group preoperatively had an increased incidence of POCD.

While it is good clinical practice for a simple cognitive test to be recorded in all older people prior to surgery, tests such as the MMSE are blunt instruments that may miss minor degrees of cognitive impairment. The question then has to be asked whether the detection of an unexplained POCD represents a new disease or an unmasking of a previously latent problem. We do not have accurate data about the incidence of long-term cognitive decline in patients who already have a degree of preoperative impairment. If the ISPOCD battery is too complicated a tool to assess such patients then perhaps a simplified battery needs to be employed. However, there would be additional problems of gaining informed consent for studies that set out to study the effects of surgery and anaesthesia in patients with a degree of preoperative dementia. At the other end of the spectrum, some individuals who *subjectively* report impaired concentration after surgery may not be classified as having POCD by the standard ISPOCD method, which might indicate that it is insufficiently sensitive in some situations.

It is not easy to summarize the evidence from Table 131.3 and other literature into a form that can give guidance to individual older people who fear subtle changes in postoperative cognitive function. In a recent Commentary¹⁵ we have attempted to stimulate discussion on this topic with a fictitious scenario of a cognitively well-preserved patient of 75 who is considering whether or not to undergo elective hip surgery for osteoarthritis. We drew three broad conclusions from the data contained in the studies in Table 131.3:

1. If we accept the ISPOCD criteria, POCD one week after major non-cardiac surgery carried out under general anaesthesia is surprisingly common in all age groups. While the incidence in the over-60s was estimated at 19.7–41.4% compared with 3–5% in controls^{8,13,14}, similar incidences were reported in the 40–60 age group^{12,14}, and even in those aged 18–39¹⁴.
2. Unlike the situation for POCD at one week, the incidence of POCD at three months appears to be positively associated with advanced age. Thus, in the under-60s, the incidence of POCD three months after surgery was around 5% in both patients and controls^{12,14}. However, in the over-60s, POCD incidence at three months was 9.9–14.3%^{8,13,14}, which was significantly higher than the 1.8–2.8% rates found in controls. Very elderly patients are under-represented in the ISPOCD studies, but in ISPOCD1 those aged 70–79 had twice the rate of POCD of those aged 60–69 (14% vs. 7%)⁸.
3. Our ability to draw firm conclusions about POCD beyond three months is limited by lack of long-term follow-up data. However, using a subset of ISPOCD1, Abildstrom *et al.*¹¹ reported that 10.4% of the over-60s fulfilled the criteria for POCD 1–2 years after surgery. While this was the same as the rate found in non-operated controls (10.6%), only 47 of the latter were available, so confidence intervals were wide. The link between POCD and death has also been mentioned by two studies. Monk *et al.*¹⁴ reported an association between POCD at three months and mortality at one year. Steinmetz *et al.*¹⁹ followed up a cohort of ISPOCD patients for a median of 8.5 years and linked the presence of POCD at three months with increased rates of mortality: the hazard ratio (adjusted for age, gender and cancer) was 1.63 ($p < 0.01$). Visual inspection of the survival curves¹⁹ suggests that the main difference between the mortality rates in the two groups occurred between two and four years after surgery and anaesthesia.

The above three conclusions come with the caveat that some patients who report *subjective* cognitive impairment three months after surgery are classified as normal under the standardized POCD definition used in the above studies. A possible explanation is that some of these patients are depressed rather than cognitively impaired¹², but there is also the possibility that subtle cognitive effects are being missed by the ISPOCD psychometric battery. For example, Hanning²⁰ cited a case of a patient who needed to take early retirement despite being classified as 'normal' on ISPOCD criteria. It should also be noted that the extent of individual disability and distress caused by different levels of POCD has so far attracted little research attention, although Price *et al.*²¹ have recently explored the effects of impaired memory and/or executive function on activities of daily living. One of the most interesting conclusions from the ISPOCD work relates to the difference between outpatient (day stay) and inpatient minor surgery and appears to support the practice of day stay surgery in the over-70s as a way of reducing POCD at one week¹⁰.

MECHANISMS OF ANAESTHESIA AND POSSIBLE INTERACTIONS WITH NEURAL PATHWAYS INVOLVED IN HIGHER CORTICAL FUNCTIONS

Xie *et al.*²² and Inouye² have explored the hypothesis that the same mechanisms might cause postoperative delirium and dementia and that anaesthetic agents might sometimes be involved in such mechanisms. The popular scientific press has reported this hypothesis under the alarming headline 'Alzheimer's alert over anaesthetics'²³, although Xie *et al.* have been quick to point out that sweeping clinical conclusions should not be drawn from 'test tube' studies²⁴. Indeed, in their refutation of the more extreme extrapolations, Xie and colleagues have stated, 'The available epidemiological evidence shows no association between Alzheimer's disease and previous surgery requiring anaesthesia. If elderly patients put off necessary surgery for fear that the anaesthetic will harm them, they may place themselves at higher risk of disease or death than any small cognitive effect caused by surgery and anaesthesia'.

The tenets of the hypothetical arguments of Inouye and Xie *et al.*^{2,22} are:

1. There may be common mechanisms underlying delirium (a common postoperative complication) and dementia, as they share several pathophysiological features such as decreased cerebral metabolism, cholinergic deficiency and inflammation. However, a causal relationship has yet to be proved.
2. The two characteristic histological features of Alzheimer's disease are plaques (containing amyloid) and neurofibrillary tangles (containing tau protein). Certain anaesthetic agents can trigger changes of oligomerization of beta-amyloid protein (Abeta) and apoptosis in animal models and cell culture²⁵. The halogenated ether isoflurane can induce apoptosis in cell culture, a process which can be inhibited by Congo Red, an agent which is known to inhibit Abeta production²². Halothane, a halogenated hydrocarbon has been shown to increase the oligomerization of Abeta amyloid peptide *in vitro*²⁶.
3. Cholinergic mechanisms are known to play a part in delirium and dementia. It is of considerable interest, though not surprising given the importance of the cholinergic system in maintaining consciousness, that the cholinergic system is a site of binding of

anaesthetic drugs. Thus, Fodale *et al.*²⁷ describe nicotinic receptor binding and inhibition by the three volatile inhalational agents in current use in the developed world (isoflurane, sevoflurane and desflurane), and muscarinic blockade by intravenous barbiturates. A discussion of the role of the cholinergic system in the pathophysiology of dementing diseases is outside the scope of this chapter. However, as the types of receptors that mediate anaesthesia appear very similar to the types of receptors that decline in patients with Alzheimer's disease, then it is conceivable that anaesthesia might worsen or hasten the dementing process or unmask latent dementia. In finishing this discussion it is worth noting that acetylcholinesterase inhibitors, administered to patients without dementia, do not reduce the incidence of delirium after elective hip replacement²⁸.

The review by Culley *et al.*²⁵ summarized the field up to 2007 and included more laboratory evidence that anaesthetics could alter the metabolism of amyloid protein. It also mentioned the theoretical possibility that tau proteins, contained in the neurofibrillary tangles of the brains of people with Alzheimer's disease, might also be affected. Two recent papers have indeed reported the effects of anaesthesia on tau proteins in animal experiments^{29,30} although the study of Planel *et al.*²⁹ in mice described the process as being associated with a severe hypothermia occurring under anaesthesia, rather than being specific to any particular anaesthetic (and was avoidable with proper attention to temperature control). The degree of hypothermia observed by Planel *et al.*²⁹ was far more than the hypothermia occurring in ordinary anaesthetic practice, with the notable exception of cardiopulmonary bypass. This is of interest as cardiac surgery tends to have higher rates of cognitive impairment than non-cardiac surgery. While this difference has usually been attributed entirely to the direct physical effects of the cardiopulmonary bypass apparatus, the cognitive effects of hypothermia should perhaps be considered as a possible confounder in future studies, with particular attention to the effect of the process on tau production.

As far as patients, relatives and health care personnel are concerned, the major unanswered question is whether the various phenomena discussed in the previous three paragraphs are of clinical relevance. Do certain anaesthetic agents have the potential of triggering the process that leads to the evolution of a degenerative brain disease?

When one considers the history of the development of anaesthetic drugs, the possibility of an uncommon but potentially serious side effect involving long-term cognitive function cannot be dismissed out of hand. The number of potential anaesthetic drugs is enormous – there are huge numbers of variants and isomers of organic compounds such as ethers and alkanes. Volatile inhalational anaesthetics evolved from 1846 by a matter of trial and error with the emphasis, naturally, being on their immediate anaesthetic properties and the lack of any short-term side effects. While many compounds were rejected early on for reasons of toxicity, more subtle toxic effects continued to bedevil clinical experience with these drugs for years after their introduction. Today's volatile inhalational anaesthetic agents, the halogenated ethers sevoflurane, desflurane and isoflurane, derive historically from the original discovery of the anaesthetic properties of diethyl ether. Another class, obsolete in the developed world, comprises the halogenated hydrocarbons. Halothane was the most prominent example of this class, and it was a major advance when introduced in 1950, because of its inert properties, but the association with an idiosyncratic reaction leading to

hepatotoxicity led to its obsolescence. An early halogenated ether, enflurane, became obsolete because of fluoride-induced nephrotoxicity.

Conventional classic models of the mechanism of action of general anaesthetics considered that all the inhalational agents worked in a similar way by a purely physical mechanism, the potency of agents correlating with the physical property known as the oil/water partition coefficient. Techniques such as magnetic resonance spectroscopy demonstrated that lipid-soluble molecules with anaesthetic properties interpose themselves into the cell membrane, increasing fluidity of the membrane and interfering with ion channel function. Given the clear correlation between potency and lipid solubility, the key strategy in pharmaceutical development has been finding a molecule whose effects, in terms of rapid changes of anaesthetic depth, could be most easily manipulated by the anaesthetist. For this purpose the physical property of blood/gas solubility coefficient has consistently been shown to be *the* property determining clinical usefulness. Modern anaesthesia is more predictable and safer because of this development, and older patients have benefited at least as much as the young in this respect. Patients regain consciousness and regain protective reflexes within minutes and can go home within hours. As a consequence they are spared prolonged hypoxia, hypotension and hostile ward environments – factors that we know predispose to delirium. Physical models also give the impression that changes induced by the addition of an agent, in this case an anaesthetic agent, are completely reversible. But the classic physical models of action fail to explain the significant pharmacodynamic differences between volatile agents. To explain these, mechanisms such as differential ion channel blockade are useful. For example, for a given depth of anaesthesia, isoflurane causes more vasodilatation than halothane, and this is an important clinical difference. It is against this background of action – specific ion channel or receptor blockade – that theories on the comparative neurotoxicity of general anaesthetics are being tested.

The link between the *in vitro* studies mentioned above, the theory of interference with the cholinergic system, and the possibility of a dementing process being triggered by a single exposure to anaesthesia in clinically relevant concentrations, is of course tenuous. The Food and Drug Administration (FDA) in the US has judged that it is inappropriate at the present time to make any recommendations about specific anaesthetic agents²⁵ but this remains a very emotive area, as any search of the internet using the keywords 'anaesthesia' (or anaesthesia) and 'dementia' will testify. Suffice for the moment to notice that there is fundamental clinical and laboratory work still to be done, and that this is an area where collaboration between anaesthetists and mental health specialists should be particularly rewarding.

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Nutritional State

David N. Anderson¹ and Mohammed T. Abou-Saleh²

¹*Mossley Hill Hospital, Liverpool, UK*

²*Division of Mental Health, St George's University of London, London, UK*

Dietary surveys of elderly people in several countries over the past three decades have shown that a substantial proportion of subjects had intake below recommended standards. Two US National Health and Nutrition surveys showed that 50% of the populations, especially the elderly, were deficient in one or more nutrients. In 1979, a Department of Health and Social Security survey in the UK suggested that 7% of those aged 65 years or more may be undernourished and twice this proportion of those aged 80 years or greater¹. In Sidney, Australia deficiency in the intake of nutrients by older people was similar to that found in the UK at that time².

There is little evidence that the situation has improved. The National Dietary and Nutrition Survey in the UK has reported since 1992 and, while most older people seem to receive adequate nutritional intake, the most recent survey has drawn attention to greater risk in particular groups of older people, including those who have lost their own teeth, those in institutions, the older age groups and those with low socioeconomic status³. A study of people aged 65 years or greater, using a validated malnutrition screening tool, identified more than 10% at medium or high risk of malnutrition^{4–7}. Single nutrient deficiency is much more common than malnutrition, and in people in this age group, 29% of those who were independent and 35% of those in institutions were found to be folate deficient and 14% and 40%, respectively, deficient in vitamin C³.

Of great concern is clear and consistent evidence that the highest rates of malnutrition reported in developed countries are those older people in hospital or care homes. In these populations malnutrition has been reported in 10–60% depending on age and medical conditions^{4–7}. These populations will have high proportions of people with physical and mental illness. Inevitably, malnutrition is a common cause and consequence of illness but the number of undernourished people leaving National Health Service hospitals in England rose by almost 85% in the 10 years up to 2006, reaching almost 140 000 in 2006–7⁸; and 70–80% of malnourished people enter and leave hospital without a diagnosis or treatment^{9,10}.

Those older people at most risk include the housebound, those with cognitive impairment, a history of depression or long-term conditions, and the oldest old. Poor dentition, swallowing difficulties and not having regular cooked meals are further factors placing people at risk of malnutrition (Table 132.1).

The prevalence of malnutrition is certainly higher in older people where countries report this data. Poor financial reserves, isolation, physical handicap, dental problems and mental disorder all

contribute, and the effects of disease, disability and ageing can combine to change a marginally sufficient diet into a grossly deficient one. Higher proportions of older people in these circumstances live in relative poverty and have greater prevalence of disease. The diet of lower socioeconomic groups provides cheap energy and is lower in essential nutrients like calcium, iron, magnesium, folate and other vitamins¹¹.

Malnutrition is a state in which a deficiency of energy, protein and/or other nutrients causes measurable adverse effects on tissue/body form, composition, function or clinical outcome⁶. It has significant implications for people at risk, causing increased vulnerability to infection by compromising the immune system, delayed wound healing, impairing function of heart and lungs, muscle weakness and depression and, in the extreme, death¹².

It increases rates of medical attendance, admission to hospital, length of hospital admissions and mortality. People with malnutrition have two to three times more complications following surgery¹³. Furthermore, the consequences of malnutrition include depression, apathy, decline of social interaction and confusion, which will conspire to produce a spiralling decline of nutritional status⁷. Malnutrition is a significant predisposing factor for the development of delirium in older people admitted to hospital medical wards¹⁴. Finally, malnutrition will affect the way the body handles prescribed medications.

Despite this information 30–40% of malnourished people do not receive care according to present scientific evidence and 20–25% receive care that is not needed or is potentially harmful¹⁵. Though single nutritional deficiencies are more common than malnutrition they commonly co-exist⁷.

But the most common nutritional problem in developed countries is obesity. This has direct relevance to mental health as it contributes significantly to vascular risk and the metabolic syndrome. It is now clear that vascular risk is not only important for the development of vascular brain disease, which may manifest as dementia, depression or psychosis in later life, but also as a risk factor for the development of Alzheimer's disease. Obesity can impair independent function and ambulation, add to the burden on arthritic joints or impaired cardiopulmonary function and exacerbate other long-term conditions, creating a situation where older people can then become depressed.

While ageing is usually accompanied by weight loss, some older people will become vulnerable to weight gain if their lives become more sedentary and their diet unbalanced. Of course, obesity may also be associated with single deficiencies and people who are obese can

Table 132.1 People at most risk of poor nutrition

Circumstances
• Increasing age
• Low socioeconomic status
• Care homes
• Hospitals
• Housebound
• Isolated
Clinical
• Dementia
• Depression
• Alcohol misuse
• Poor dentition
• Dysphagia
• Low body mass index
• Unintentional weight loss
• Poor absorptive capacity
• Increased nutrient loss
• Catabolic states

become malnourished. Drugs used for the treatment of mental illness often carry the risk of weight gain and the metabolic syndrome.

Those most at risk of malnutrition or who may need nutritional support are summarized in Table 132.1.

ASSESSMENT AND DIAGNOSIS

Part of the problem is difficulty diagnosing malnutrition and agreeing diagnostic criteria. The assessment of nutritional state is complex and any single measure seems inadequate. However, anthropometric measurements, including body mass index (BMI), are the foundation but this needs to be done by professionals with expertise who understand the clinical context. Biochemical markers are often unreliable, particularly with people who are ill, as these are affected by acute phase responses. People most at risk of being malnourished are those who are thin or with recent unintentional weight loss, including people who are obese^{6,7,16}. Other clinical circumstances will further identify people at risk of becoming malnourished, for example, people with dysphagia or excessive nutrient loss¹³.

Routine screening of people on admission to hospital or care homes is now recommended and identification of those likely to need nutritional support based on a combination of BMI, unintentional weight loss and clinical contexts placing people at risk¹³. Screening instruments like the Malnutrition Universal Screening Tool can be useful, easy to use and require little training⁶. Screening is considered cost effective for older people admitted to hospital¹³. While over 95% of malnutrition is in the community (including care homes), most malnutrition-related expenditure occurs in hospitals^{17,18}.

MENTAL HEALTH

Malnutrition and nutrient deficiencies are more likely to be a consequence rather than a cause of mental illness in older people. Classical single deficiency states as cause of mental illness are rare in developed countries though there is a strong suspicion that suboptimal nutrition often contributes to ill health in old age. The

immediate significance of single deficiency states is confined to a few specific circumstances, for example, thiamine deficiency and the Wernicke–Korsakoff syndrome; B12 and folate with cognitive impairment, dementia and depressive states¹⁹. In most instances, the import of nutritional status on mental function is less direct and more subtle.

Certainly, the consequences of malnutrition will complicate treatment of mental illness and impair prospects for recovery. In addition, effects on physical strength, organ function and the immune system increase the risk of falls, fractures, pressure sores, infection, hospital admission and mortality. These risks will need to be addressed in care plans and will substantially increase the hazards associated with prescribing psychotropic drugs to older people.

Under-nutrition may arise from quantitative and qualitative dietary inadequacy, and a number of problems facing older people and the mentally ill place them at particular risk. Social isolation, loneliness, poor socioeconomic position, physical and sensory disability and comorbid long-term conditions are common accompaniments of mental health problems in later life. Depression and dementia, in particular, are associated with reduced appetite, weight loss and poor attention to diet resulting from apathy, loss of interest and cognitive difficulties. Furthermore, effects of nutrient deficiency, including apathy, depression and cognitive impairment, will compound an already difficult situation and may lead to a spiral of decline.

PREVENTION

The overwhelming priority in the management of under-nutrition among elderly populations is prevention. A major impetus must ultimately come from changes in public policy that improve the older person's social, material and financial position in society, address inequalities and ensure the efficient provision of services to those in need.

The market-led approach to nutrition that operates in many food-rich countries has been found to increase the disparity between the nutrition and health of the rich and poor²⁰. The provision of domiciliary care services is inequitably distributed, often inefficiently organized and frequently determined by demand rather than need²¹. In the UK a younger person with equivalent need to an older person has much greater access to social care and mental health services^{22,23}.

In the modern era food suppliers are often large impersonal stores sited some distance from communities, making shopping difficult for physically and mentally disabled people. Low income with disability not only restricts ability to afford a protective diet but also limits access to retailers where healthy food can be purchased more cheaply. Local shops in developed countries are less prevalent and can be significantly more expensive than distantly sited supermarkets²⁴.

Often the presentation and supervision of meals is poor. This is particularly evident in hospitals and care homes. A leading charity for older people in the UK²⁵ has drawn attention to the problem in hospitals and this report along with other national guidelines recommends a number of changes to practice that could address this need^{13,26}. The National Diet and Nutrition Survey in the UK found the food supply in care homes to be sufficient but biochemical measures revealed poor vitamin and mineral status³. While the explanation of this is not clear it may be the result of poor intake and absorption due to poor presentation and timing of food, need for more assistance with eating or changes in absorption and the general medical condition.

Simple measures like providing meals in a form that is appealing and easily edible, at a time when appetite is greatest or when people

are most motivated, providing assistance and allowing enough time for meals to be eaten are often all that is required yet all too often not part of the regimes of hospitals or care homes. Some people, particularly people with dementia, will take food from family or friends and not care staff or from certain care staff, and these institutions need to provide greater flexibility of approach and ensure that areas catering for older people and people with dementia have sufficient number of staff. The ready availability of fresh produce, particularly fruit and vegetables, is lacking. Modern catering is not always sensitive to the needs and preferences of older people.

Diet is a poor source of vitamin D, which depends on exposure to ultraviolet light for its formation. More exposure to natural sunlight is the most important preventive measure but for those older people at risk of little exposure, calcium and vitamin D supplements are recommended²⁷.

Easy access to health and dental care is important. People with long-term conditions and poor dentition are at particular risk of dietary deficiency. Dental care is especially overlooked yet a study of hospitalized people aged 61–99 years found 60% to have disease of the oral soft tissue²⁸. For those living in the community, preventive dental and health care with early recognition and treatment of illness is needed.

The elderly population may benefit from greater education and advice about healthy and affordable eating, issues normally targeted at younger people. The judicious use of fruit juice, frozen foods and some convenience foods might ease the burden of food preparation in those at risk of neglecting their diet. Occupational therapy assessments can find practical solutions to problems arising from visual impairment, arthritic joints and disability or the need for someone to help with shopping and food preparation. The teaching of culinary skills may be particularly helpful to the older bereaved man who never cooked while his wife was alive.

Diet is connected with lifestyle and opportunity and so moderate alcohol consumption is associated with better health and less risk of developing depression but also with a more active and sociable lifestyle, better self-rated health status²⁹ and higher intake of various nutrients³⁰. Whether these variables are independent is not clear but the evidence would suggest that older people who can remain active, exercise and remain socially connected seem to take a better diet and protect themselves from some of the mental health problems occurring in later life.

In a prospective study of relatively healthy and active European men aged 70–89 years, low cholesterol but not dietary factors was associated with increased risk of developing depression³¹. The relationship of cholesterol levels to mental health in later life remains confusing as, while raised levels might suggest increased vascular risk, high levels may reduce risk of dementia, with declining levels reported before incident dementia³².

TREATMENT

Recommendations for the treatment of malnutrition and the maintenance of optimal nutrition are available¹³. But assessment and treatment require considerable expertise as there are dangers. If correction is too rapid there is the risk of precipitating re-feeding syndrome or Wernicke–Korsakoff syndrome. The former seems to arise from the body's adaptation to malnourishment when rapid change precipitates micronutrient deficiency and dangerous change in fluid and electrolyte balance. This may lead to cardiac failure, pulmonary oedema, cardiac dysrhythmia, fluid overload or depletion, low levels

of phosphate, potassium and magnesium, and raised glucose. People with alcohol problems, in particular, are at risk of rapid re-feeding, causing increased thiamine demand and the Wernicke–Korsakoff syndrome.

The preferred approach is always to improve dietary intake by natural means. Guidance on the risk benefits and approaches to artificial nutrition are available though studies have rarely involved older people with mental illness¹³.

Where single nutrient deficiencies are found it is usually better to replace them though there is little evidence to demonstrate that this has clinically detectable effects on mental health other than in exceptional circumstances. Thiamine replacement in Wernicke's encephalopathy is curative. Thiamine supplementation in people with serious alcohol misuse or undergoing detoxification and correction of B12 and folate deficiency in cognitive impairment or dementia may protect or enhance cognitive function. Because single deficiencies often co-exist with more general under-nutrition or the risk of developing malnutrition they should prompt a more detailed assessment of nutritional status. If it clearly arises as a consequence of mental disorder the imperative is to treat that and address the disability or need underlying dietary neglect.

There are a large number of heterogeneous randomized controlled trials of nutritional supplements of mixed quality and results that, in general, show benefits of producing weight gain with fewer complications and mortality and they are acceptable to patients¹³. Similarly, studies of vitamin and mineral supplements produce conflicting results and, although of uncertain benefit, are thought to be beneficial for older people where there is concern about their food intake¹³. These studies rarely consider the effects on mental state.

In extreme circumstances assisted enteral or parenteral methods, including surgical procedures like percutaneous endoscopic gastrostomy (PEG), are considered to sustain nutrition with clear evidence-based guidelines for their use¹³.

DEMENTIA

Particular concerns arise about decisions on feeding for people with dementia. While all general principles apply, dementia raises issues rather different from the rest of mental health due to the combination of people who lack capacity to make decisions and who are also suffering a terminal illness.

There are a number of reasons why people with dementia have difficulty sustaining nutrition. Dietary intake may be reduced due to a natural decline of appetite and hunger, difficulty with the feeding process or food preparation due to cognitive deficits, and problems swallowing.

Furthermore, weight loss is a recognized consequence of dementia, regardless of diet, which may develop before the diagnosis is made. A 32-year prospective study showed increasing difference in BMI between people with and without dementia during the 6-year period before the diagnosis was made³³. Though the reasons are not entirely clear, a number of possibilities are proposed, not least that this is part of the neurodegenerative process³⁴.

If people with dementia suddenly lose appetite or weight the possibility of other causes must be considered. New physical illness, pain, oral and dental problems, newly prescribed medication, constipation or impaction, and depression may present this way and can be difficult to recognize in more severe dementia when the person's ability to communicate symptoms is compromised. This situation requires a more detailed examination of physical and mental function followed by appropriate investigation.

Many of the essential approaches to facilitating dietary intake and maintaining nutrition have been covered and the prevailing view, when these begin to fail, is to continue with a conservative, palliative care approach rather than take recourse to more invasive and artificial procedures. In advanced disease there is no good evidence that tube feeding prevents aspiration pneumonia (paradoxically the most common adverse association), malnutrition, pressure ulcers or infection, or improves survival, function or comfort³⁵. Similar lack of benefit and adverse consequences has been found with PEG³⁶.

However, this is a difficult situation because while the evidence for tube feeding or PEG fails to provide convincing evidence of benefit in people with dementia, and does demonstrate significant risks, these studies have been conducted on frail people with advanced disease and there is an absence of evidence for people with earlier disease at risk of nutritional deficiency³⁷.

All commentators emphasize the need for clarity about the purpose of artificial nutrition in this situation, recognizing that there are occasions when such procedures may be warranted; for example, when the problem is reversible and not a direct result of the dementia³⁸.

Ultimately, decisions will need to be made on an individual basis, acknowledging the evidence base and considering what is in the best interest of a particular individual should they be unable to express their own wishes or have not made that clear through an advance statement.

CONCLUSION

A great deal more needs to be known about the relationship between diet, nutrition and mental health in older people – not only understanding how nutritional deficiency might exert effects on mental function but also identifying people who may be predisposed to develop mental disorder where modification of diet and lifestyle could afford protection³⁹. There is no doubt that lifestyle characteristics affect health; improving diet would be expected to improve general health and, thereby, reduce the risk of certain mental health problems in later life. For example, intake of fruit and vegetables is an independent risk factor for stroke⁴⁰, a physical health problem with significant psychiatric morbidity.

At present nutritional deficiencies and malnutrition are far more likely to be a consequence than a direct cause of mental illness though in less developed parts of the world they may have greater relevance to the causation of mental disturbance. What is very clear is that older people, people in isolation with long-term conditions and those who are socioeconomically disadvantaged are at greater risk of malnutrition and these are groups also at greater risk of mental illness.

Despite many countries having national policies on nutrition and there being many guidelines and recommendations from professional bodies, the problem of malnutrition continues to be significant. Public policy will also have to address the serious inequalities that exist for older people in many parts of the world. Training for doctors, nurses and medical students on nutrition will need to improve^{8,41–43} and rates of malnutrition are highest in hospitals and care homes, where guidance does not seem to be changing practice. Stronger enforcement of this guidance, including routine screening, is probably necessary⁸.

The evidence connecting nutrition and morbidity that impairs function, and increases risk and mortality makes this an essential area of knowledge for all professionals working with older people. There is a good case for a specialist practitioner able to provide nutritional

assessment and advice to be available to mental health teams working with older people, and these assessments should now be routine for all people admitted to hospital and care homes. The consequences of malnutrition will have significant impact on the treatment of mental illness, risk and recovery.

Further exploration of the relationship between dietary constituents and the course of mental illness may yet yield significant information relevant to the management of mental illness in later life. The chicken and egg question is difficult to unravel, and large prospective studies that control for a substantial number of variables will be needed to address this intriguing association. What is certainly the case at present is that the fundamental need for a nutritious diet to maintain optimal health is still missing in the lives of many older people and its importance overlooked or ignored by health and social care services.

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Caregiver Support

Kathleen C. Buckwalter, Mary Ellen Stolder, Charlene S. Aaron and Catherine Messinger

University of Iowa College of Nursing, Iowa City, IA, USA

INTRODUCTION

Alzheimer's disease and related dementias (ADRD) are neurodegenerative, progressive, chronic illnesses with an unpredictable clinical course. Compounding this tragedy is that caregivers' mental and physical well-being suffers, and their activities and social relationships are disrupted, leading them to discontinue home care. This chapter highlights the vital caregiver role, and the costs to and support for home caregivers and those in the process of relocating a patient to an institutional setting. We review the positive and negative effects of caregiving, the psychosocial and physiological outcomes, and variables that mediate the stressors inherent in caregiving.

THE CAREGIVER ROLE

Of the estimated 5.3 million Americans with ADRD, over 80% are cared for by family members and friends, typically spouses¹⁻³. Most families want to forestall or avert institutionalization of those with ADRD, so the aging US population presents a significant societal challenge.

Who are Family Caregivers?

Caregiving typically falls to women, who provide 72% of care: 29% are adult daughters and 43% are wives⁴. Nonetheless, both men and women caregivers of persons with dementia (PwDs) devote a similar amount of time to caregiving service and, more importantly, perceive similar levels of stress. Most stress arises from dealing with behavioural problems. This stress is a common precipitant of institutionalization^{5,6}.

Public Policy and Cost Implications of Caregiving

Policy makers recognize that families are the mainstay of caregiving and that such care comes at considerable cost (i.e. home modifications, assistive devices, special food, high utility costs and lost wages⁷⁻⁹). Conservative estimates indicate that family caregivers of PwDs saved the US health care system \$350 billion in 2006¹⁰. With the population ageing, this estimate will increase. Although family caregiving greatly relieves costs to society, it concentrates financial

burdens onto caregiving families. Moreover, monetary estimates in no way reflect the human costs of this devastating disease. Indeed, caregiving correlates with other adverse consequences, such as poor health¹¹⁻¹³.

CAREGIVER STRESS AND BURDEN AND ITS IMPACT ON CAREGIVER WELL-BEING

The concept of caregiver burden is used as an all-encompassing term referring to the financial, social, physical and emotional effects of caregiving. Numerous studies have examined the burden and stress of caring for a PwD, the effects on mental and physical health, and the use of a variety of interventions to relieve caregiving burden.

Family caregivers of persons with ADRD experience stressors that affect their health and well-being, and precipitate institutionalization of the care recipient. Hence, 'stress' has emerged as an important concept, with the words 'stress', 'burden', and 'distress' often used interchangeably. Spouses may be at greatest risk, as they are often elderly themselves¹⁴. In a common pattern, the distress and depression caregivers experience precipitates physiological changes and poor health habits, leading to illness¹⁵.

Models of Caregiver Stress

Several theoretical frameworks have guided studies of PwDs, their family caregivers and how interventions affect both¹⁶. Stress models, in particular, have guided much of this research, showing that the care recipient's level of impairment is not a linear predictor of caregiver stress^{17,18}; instead, caregiver stress is moderated by many factors, including the caregiver's physical health, social support, financial assets, coping abilities and personality. For example, Vitaliano *et al.*^{19,20} stratified resources and vulnerability variables of both the caregiver and care recipient, to pinpoint relationships among stressors, resources and burden. Vitaliano considered both psychological and biological markers of distress, and expressed them in a mathematical formula in which the level of caregiver distress (burden) decreases with reduced undesirable variables or increased desirable variables:

$$\text{Distress} = \frac{\text{Exposure to stressors} + \text{Vulnerability}}{\text{Psychological resources} + \text{Social resources}}$$

Other studies, examining racial differences in caregivers of PwDs, found stress levels to be affected by overarching factors that reflect personal context (e.g. being able to financially provide for their family and getting leisure time away)²¹.

Stressors Associated with Family Caregiving

The profound cognitive and behavioural changes of ADRD include progressive loss of memory, judgment, the ability to interpret abstraction, and language and motor skills, as well as personality changes. ADRD culminate in an inability to perform instrumental activities of daily living (IADLs), such as cooking and managing money and, as the disease progresses, more basic activities like bathing and toileting. Researchers disagree on whether the level of a care recipient's functional or cognitive impairment correlates with caregiver burden^{22,23}. Notably, however, a recent study found caregivers' quality of life did correlate with the severity of the care recipient's behavioural disorders and duration of the disease process²⁴.

ADRD has an unpredictable course and pace of decline; the only certainty is that the disease is progressive. As dementia progresses, caregivers must be increasingly vigilant, since a PwD may unexpectedly leave home or injure themselves. In the final stages, patients are often completely dependent on their caregivers, making caring for a PwD eventually an all-consuming job.

Behavioural Impairments in Care Recipients

Most commonly, the reported behavioural changes of ADRD include lethargy, withdrawal, sleep disturbance, restlessness, wandering, aggression, destroying property and verbally disruptive or sexually inappropriate behaviour^{25–27}. The stress of providing 24-hour care mounts when the PwD becomes agitated, stressed or disoriented. Behavioural abnormalities appear in up to 67% of care recipients upon diagnosis²⁸, in 65% of institutionalized persons²⁶, and in 70–90% of persons with advanced dementia^{29,30}. They worsen with disease progression and may be related to fatigue, change, overstimulation, excessive demands or physical stressors³¹. Moreover, the care recipient's behavioural problems are the characteristic that overwhelmingly predicts caregiver distress^{22,32}, making this a strong predictor of institutionalization³³.

Other Factors that Influence Caregiver Stress

Caregiving for persons with ADRD entails years of constant demands. Over the disease trajectory, the intensity and/or frequency of a caregiver's level of distress may vary widely. To understand this variability, investigators try to identify factors associated with differing outcomes. Stress may be influenced by whether the caregiver and recipient reside together, the abruptness of the disease onset, the family relationship, and the caregiver's coping strategies^{34,35}; also caregiver burden was reportedly more intense for spouses than for adult children³². Positive outcomes, however, are associated with a strong social network and satisfactory support³⁶.

In sum, the relationship between the caregiver's psychological distress and physical impairment depends on many variables, for instance the care recipient's behaviours and caregiver vulnerability (e.g. age, gender, neuroticism, pre-existing hypertension, and social support). Nonetheless, the factors contributing to caregiver distress have only recently been delineated well enough to effectively direct interventions or preventative strategies^{37–40}.

Dementia Versus Non-dementia Caregiving

The risk for health problems increases with the physical demands of caregiving, prolonged distress and the biological vulnerability of older caregivers. Research suggests that caring for a PwD is more demanding than caring for physically impaired older adults⁴¹. In a review of studies of caregiving in different types of illnesses, Biegel, Sales, and Schulz⁴² observed different patterns of distress. Distress peaked after the initial diagnosis, but, as time passed, the level of distress fell. This pattern, however, was not observed in family caregivers of persons with a gradual onset, where no relief of distress was observed⁴³.

POSITIVE AND NEGATIVE OUTCOMES OF FAMILY CAREGIVING FOR PERSONS WITH DEMENTIA

It is notable that mounting evidence suggests that some caregivers find satisfaction in the caregiving role and report life satisfaction, emotional uplifts, enhanced self-esteem and self-efficacy, optimism, and growth and meaning^{44–49}. Interviews of 50 caregivers of PwDs found 58% experienced 'self-fulfilling' experiences during caregiving, with the same percentage expressing 'losses and difficulties'⁵⁰. Positive aspects of caregiving were related to the caregiver's competence. Brown and colleagues⁵¹ found that caregivers who provided instrumental support to friends, relatives or neighbours, or who provided emotional support to their spouses, had lower five-year mortality rates.

IMPACT OF CAREGIVING ON HEALTH OF CAREGIVERS

Despite some inconsistent findings concerning how caring for PwDs affects mental and physical health, most but not all studies find increased psychiatric and physical morbidity^{52–55}. This suggests that inconsistencies are attributed to differences in caregivers' coping strategies.

Mental Health Outcomes

Caring for an older person with ADRD puts one at risk for extreme psychological distress. A number of studies link stress to factors such as the strain of providing direct care, grief from witnessing the decline of their loved ones, social isolation and role changes. These effects occur with home care, following institutionalization, and during bereavement^{37,56}.

Depression

Depressive symptoms are among the mental health changes most frequently reported by family caregivers of PwDs. A complex interaction of cultural factors^{57,58}, caregiver and receiver characteristics come into play, predicting depression^{59–61}. Moreover, depression among caregivers is associated with the intensity of their reactions to the patients' memory and behaviour problems⁶² and to other outcomes such as increased physical and subjective burden^{63,64}, and the use of psychotropic medications^{22,65}.

Predictors of caregiver depression include a younger age of caregiver and care receiver, Caucasian race, Hispanic ethnicity compared to black ethnicity, higher education, activities of daily living

dependence, and the recipient's behavioural abnormalities (particularly aggressive or angry behaviour). Other predictors include low income, spousal status, hours spent caregiving and functional dependence of the caregiver^{61,66}. Depression is greater among females than males⁶ and appears to increase over time among residential caregivers and decrease over time following institutionalization and bereavement⁶⁷. Compared to non-caregiving men, male spouse caregivers have higher levels of depression, respiratory symptoms, and poorer health habits, although the groups did not differ on other measures of physical and mental health⁶⁸.

Anxiety

Several investigators incorporated self-reported measures of anxiety when examining depression among caregivers. Some found that caregivers who presented with symptoms of depression also often reported symptoms of anxiety^{18,69}. Overall, strong evidence suggests caregivers are at risk for psychiatric symptomatology. Yet, caution must be exercised when interpreting the generalizability of these findings, since many samples may be biased towards more distressed caregivers. For example, most caregivers are recruited from chapters of the Alzheimer's Association, support groups, or through referrals by health professionals; either individuals who have little difficulty with the caregiving role or are so distressed or constrained that they cannot participate in supportive programmes or visit health care professionals, may be under-represented. Additionally, transient psychiatric symptoms may be more common than diagnosable depression. Moreover, caregiver burden does not always predict depressive symptoms, suggesting that the relationship between caregiver burden and caregiver depression is complex⁶⁶.

Physical Health Outcomes

Most studies examining the physical effects of caregiving used one or more indicators of caregiver health: (i) self-reported health status; (ii) self-reported incidence of illness-related symptoms; (iii) self-reported utilization of health care services; (iv) self-reported medication use; and (v) disease susceptibility. Predictors of poor physical health outcomes for caregivers include being older, a spouse and female^{22,70}. Interestingly, however, in some cases caregiving was also reported to improve physical health. Family caregivers with coronary heart disease (CHD), who experienced emotional uplifts, also showed less severe metabolic signs that predict CHD^{20,71}.

The psychoneurological and immunological effects of caregiving are receiving increased attention. One study indicated that long-term residential caregiving for PwDs decreased measures of cellular immunity and increased the duration of infection; most affected were caregivers who reported less social support and more stress⁷². Stress-induced changes in physiological function increase the probability of illness⁷³. Caregiver wear and tear, from repeated arousal and inefficient control of the physiological responses of stress, can also lead to pathophysiology^{74,75}. Stressors can cause impaired health habits, physiological responses, physical illness and even death^{11,20,76,77}.

Similarly, psychological stress can increase caregiver vulnerability to disease by compromising immune system integrity^{20,78}. A well-controlled study examined caregiver depression and distress as immunological modifiers and linked the poorer immune response to lower levels of helper T-lymphocytes and natural killer (NK) cells⁷⁸. Here, caregivers also reported nearly three-fold more stress-related symptoms and higher rates of psychotropic drug use, especially if

they lived with the PwD. While some studies reported that caregivers use more psychotropic medications^{22,72}, most reports suggest use of somatic medication does not significantly increase^{20,79}.

In summary, the findings for the effects of caregiving on physical health are more equivocal than those for mental health; however, the evidence is still generally weak. This may be due to different definitions of health, health outcome measures, caregiving and control samples (varying levels of vulnerability and resources), care recipient samples (functional versus behavioural impairments), and that some self-report measures of physical health may primarily reflect life satisfaction. Moreover, caregivers who provide assistance with activities of daily living (ADLs) exhibit poor nutrition and poor decision-making regarding their own health care appointments⁸⁰.

Evaluating links between caregiver distress and health will ultimately require testing complex, multivariate models. Despite methodological challenges inherent in evaluating caregiving outcomes, data suggest chronic stressors do contribute to affective disorders and may alter caregivers' sympathetic, neuroendocrine and immunological function.

FAMILY CAREGIVING: RELOCATING THE CARE RECIPIENT

Placing a relative in a nursing home is stressful for both caregiver and patient. Yet PwDs are usually placed in nursing homes only when all other avenues and resources are exhausted^{81,82}. Generally, the decision is postponed long past the time when more objective persons see it as appropriate⁸³. One reason for this delay is that some caregivers, especially spouses, believe their role obliges them to sole caregiving responsibility and to reject institutionalization⁸⁴. Although children are comparatively more likely to rely on formal services and place the PwD in institutional care, they nevertheless often delay placement decisions because of reluctance to reverse roles and take charge of a parent's life⁸⁵.

Overall, the literature indicates a care recipient's extent of cognitive impairment, loss of self-care abilities, and disruptive behaviours are predictive of institutionalization. Cohen *et al.*⁸¹ described seven variables that affect a caregiver's decision to institutionalize a dependent elder with dementia: use of services, enjoyment of caregiving, caregiver burden and health, caregiver rating and reaction to care receiver behaviour and memory problems, and presence of troublesome behaviours. Six variables predicted actual institutionalization: caregiver health and burden, use of services, care receiver cognitive function and troublesome behaviours, and caregiver reaction to behaviours. Montgomery and Kosloski⁸⁵ compared predictors of placement for adult child caregivers and spouse caregivers. Higher income, eligibility for Medicaid, lower morale and age of the elder were associated with placement for both groups, but other predictors were different. Notably, the level of affection predicted placement for children, but not spouses, while sense of obligation was predictive for spouses, but not children, who were always more likely to institutionalize the PwD. The probability of placement declined with time for a while, levelled off, and then rose as caregiving exceeded 30 months, with the probability increasing more sharply for adult child caregivers than for spouses.

Increasingly, services are supporting family caregiving in the home, but the extent to which they are meeting needs is questionable^{86,87}. Neither should it be assumed that family members know how to provide all of the needed care or have access to the resources to assist them with providing care in the home⁸⁷. One

study found that 40% of family caregivers who had placed their loved one in a nursing home reported that at least one additional community service would have delayed institutionalization⁸⁸.

Relocation raises the prospect of sharp role transition. For most spouses, relocation changes a long-standing pattern of living together and providing for the other. For children, it can restore a pattern in which the child is not living with and/or is not directly responsible for the care of the parent. PwDs placed in nursing homes may be highly resistant and fearful of the change. Given their diminished capacity for reasoning, it can be challenging to convince them they require institutionalization. This presents a stressful dilemma, and one that may be more difficult for child caregivers, because of the need to reverse roles. Constant requests to be taken home are especially stressful to families. Spouses may find it more difficult if their relationship has been loving. Family Involvement in Care (FIC) interviews⁸⁹ revealed the regret felt when placing the relative in a nursing home, but also often reflected ambivalence because a burden was lifted.

When caregivers cannot manage the care recipient's difficult behaviours, such behaviours often escalate^{31,90}; this is often the primary reason for institutionalizing a family member with dementia^{91,92}. Considering the psychological and financial expense associated with institutionalizing a PwD, interventions that help caregivers prevent or manage behaviours are significant. Appropriately, national recommendations emphasize research that focuses on reducing the burdens of care for family members of PwDs¹. Indeed, the American Association of Geriatric Psychiatry, the Alzheimer's Association and the American Geriatrics Society agree, 'Interventions that reduce the risk of caregiver depression and improve tolerance and the capacity to care for patients in the home, including educational materials, counseling support groups, day care and respite care' are among the most urgent areas for research⁹³.

Dang *et al.*⁹⁴ recommend that clinicians use the American Medical Association's 'Caregiver Self-Assessment Questionnaire', which can be placed in waiting rooms, handed to caregivers of patients with dementia, or mailed to them prior to the scheduled appointment. The questionnaire could alert providers to problems (e.g. signs of potential abuse or caregiver 'burn out'), prompting them to suggest education or counselling interventions. Although providing educational materials alone does little to relieve caregiver burden, a meta-analysis of 34 studies concluded that it significantly benefits caregiver psychological distress, caregiver knowledge and patient mood⁹⁴. Another study showed that counselling caregivers delayed nursing home placement for an average of six months, and was particularly effective for adult-daughter caregivers⁶⁹.

CONCLUSION

Caring for a PwD is a responsibility usually shouldered by family members, and can be chronically demanding and often overwhelming¹. Informal caregiving of elders with chronic illnesses and disabilities has become commonplace, in part from demographic shifts. Although medical advances are increasing life expectancy, escalating health care costs shortens hospital stays and limits reimbursement for at-home professional care. Adverse outcomes depend upon the unique characteristics of both the caregiver and the care receiver. Accordingly, research suggests that combined interventions, tailored for both caregivers and care receivers, can significantly improve caregiver well-being and health and, in some instances, problematic care receiver behaviours⁹⁵.

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Elder Abuse – Epidemiology, Recognition and Management

Alexander M. Thomson¹ and Martin J. Vernon²

¹*Department of Elderly Care, Salford Royal Hospitals NHS Foundation Trust, UK*

²*Department of Elderly Medicine, University Hospitals of South Manchester NHS Foundation Trust, UK*

INTRODUCTION

During the 1980s elder abuse emerged as a health and social issue of international importance¹. It is defined as 'a single or repeated act or lack of appropriate action occurring within any relationship where there is an expectation of trust which causes harm or distress to an older person'². While most authorities include self-neglect within the broad definition, acts which threaten an elder's well-being as a consequence of their competently made decisions are specifically excluded.

Abuse may occur in one of two settings. Domestic abuse is perpetrated within the home of the victim or a caregiver by either a relative or other care provider. Institutional abuse occurs within a designated care facility (residential or nursing home or hospital) perpetrated by one or more individuals having an obligation to care for and protect the victim.

Five major categories of abuse have been identified^{3,4}:

1. Physical: any activity involving force to generate bodily injury or pain, including striking or burning. This includes the use of physical or pharmacological restraint (e.g. by means of over-sedation or withholding medication to assist movement such as analgesics or medications for Parkinson's disease).
2. Sexual: any form of non-consensual sexual contact, including unwanted touching, rape, sodomy and coerced nudity.
3. Psychological: the infliction of emotional distress through verbal or non-verbal acts, including insults, threats, humiliation, infantilization and harassment.
4. Financial: the improper use of an elder's property or assets, including theft, deception, coercion and misuse of authority to act, such as power of attorney.
5. Neglect: the refusal or failure to fulfil basic care obligations including the provision of food, water, clothing, medication, comfort and protection.

PREVALENCE AND INCIDENCE

Variability in case definition obscures direct comparison, although the prevalence of elder abuse is broadly similar throughout Europe and

North America. To date there are few data from developing countries. With the exception of the United States, a paucity of robust national incidence data reflects widespread absence of formal mechanisms for case reporting and validation.

Differing study populations and sampling techniques have also contributed to a range of prevalence and incidence estimates⁵. The work by Thomas⁶ described a range of estimates across studies of between 2% and 10%. This suggests elder abuse is sufficiently prevalent to be regularly encountered by all health care workers looking after older adults. Lachs and Pillemer⁵ estimate that for every 20–40 older adults seen, there is one victim of abuse.

VICTIM CHARACTERISTICS

Likelihood of abuse increases with age⁷. Older women are more likely than men to be victims⁸ but this observation may be confounded by greater likelihood of longer life expectancy³. Poverty elevates the risk of abuse⁷.

Shared living is considered a major risk factor, due to increased opportunities for contact. Living alone is associated with lower risk, except for financial abuse^{9,10}. Social isolation from other family members and friends (apart from the perpetrator(s)) is an additional risk factor¹¹.

Dementia is associated with higher rates of abuse than in cognitively intact older adults^{11,12}. Cooper *et al.*¹³ described an abuse prevalence of 52% from carers among a population with dementia. They discussed the 'spectrum of behaviour' in patterns of abuse, with 34% reporting seemingly important levels of abuse and lower rates of more serious abuse or physical harm. Behaviour disturbance, agitation or aggression is likely to fuel caregiver abuse. Carers are themselves also at risk of physical abuse from those with challenging behaviours. In one series, a third of carers reported physical abuse by the patient, which in turn was associated with abuse of the patient by the carer¹⁴.

Interestingly, neither the level of dependency of an older adult on a caregiver nor the severity of caregiver stress have been identified as risk factors in a variety of research studies⁵. Similarly there is no proven relationship between degree of physical impairment and abuse.

Abuse in institutional care settings has been associated with a number of factors: inadequate staffing levels, frequent use of non-permanent staff, poor staff training, development and supervision, and inadequate incident reporting systems.

Vulnerability to abuse has been associated with certain personality traits¹⁵. Victims of psychological abuse have less ability to control problem situations and tend to react aggressively when feeling anger or frustration. In contrast, physical abuse victims pursue passive or avoidant behaviour, while financial abuse victims possess negative beliefs of self-efficacy and turn aggression or frustration on themselves.

ABUSER CHARACTERISTICS

Greater understanding of abusive situations has focused attention on those perpetrating abuse. Nearly half of all abusers are related to the victim, but only a small minority are the primary carer³. Carers who do abuse suffer social isolation, feel unsupported and may be financially dependent on the person they are abusing.

The strongest associations with perpetrators of abuse are with mental health disorders and drug and alcohol misuse. In particular depression and anxiety among carers are associated with abusive behaviour^{16,17}.

Abusers identified as misusing substances are likely to be male children of the victim, less likely to provide care and more likely to cause physical or psychological abuse than financial abuse¹⁸. Alcohol misuse and dependency have been demonstrated to have a strong association with the abuser across a number of studies^{19,20}.

NATURAL HISTORY OF ABUSE

The inconsistencies in definitions, poor recognition and under-reporting of cases create difficulties in examining outcomes. Corroborated abuse is associated with greater risk of death for elderly victims (odds ratio 3.1; 95% confidence interval 1.4–6.7) after adjusting for co-morbid and demographic factors²¹. However abuse rarely leads to homicide: in one American study only 2% of elderly homicides could be attributed to abuse²².

Association has also been established between abuse and adverse outcomes including depressive illness and entry to 24-hour care²³. Victims are also more likely to use behavioural health services²⁴.

RECOGNITION

Diagnosis of elder abuse requires a high index of suspicion. Professionals should be alert to the presence of one or more risk factors for abuse (Table 134.1) and sensitive to principal abuse signals. Although advocated by some authorities, no good evidence exists to support the routine use of screening tools to detect abuse⁵. Some assessment instruments have had limited value, but are poorly validated and lack outcome improvements to support their regular employment. There is no replacement for the general vigilance of health care workers supported by high-quality training in recognition, assessment and management.

In cases of suspected abuse, a coordinated multi-agency approach must identify all care needs and deficiencies. Corroborated history must be obtained from all participants including victim, alleged

Table 134.1 Risk factors for abuse

Victim	Age >75 Living alone (financial abuse) Living with spouse or child (physical, sexual or psychological abuse) Low income Cognitive impairment Poor premorbid relationship with carer Abusive, passive or avoidant behaviour
Abuser	Male (physical abuse) Female (psychological abuse) Social isolation Financial dependency Impaired physical or mental health Substance abuse History of receiving or perpetrating abuse

abuser and designated carers with careful verification of information obtained from cognitively impaired individuals.

Symptoms and signs of abuse must be elicited during a comprehensive clinical assessment to which the victim consents (Table 134.2). Accurate documentation including note keeping, radiology and photography will facilitate planning and may be vital for future prosecutions.

MANAGEMENT

Central to effective management is the establishment of a single co-ordinating agency providing education, advice and access to resources. Intervention models should be low cost, multidisciplinary, collaborative and capable of evaluating outcomes²⁵. Denial, resistance to intervention, ignorance of intervention protocols, confidentiality and fear of reprisal have all been cited as professional barriers to the management of elder abuse²⁶.

Identification of incipient abuse should generate a brisk response to avoid escalation. Integral to management of cases is the aim to preserve autonomous choice for the victim and avoid paternalistic action which seeks to provide a speedy resolution, perhaps through institutionalization. Assessment of mental capacity is essential to determine the extent to which they can contribute to the assessment and management process. Accurate identification of unmet care needs should generate planned and effective care strategies which engender safety without intrusion. Given that abuse may be multidirectional, attention may need to be focused on both victim and abuser.

Overtly criminal activity such as theft or assault should be dealt with by prevailing criminal law. Most countries have eschewed a legislative approach to elder abuse, relying instead upon health and social service agencies to develop locally applicable policies and procedures. In the United States mandatory reporting laws have achieved only limited success and professionals remain unfamiliar with reporting procedures²⁷. Of greater potential benefit for the future is the emergence of national organizations aiming to prevent the abuse of older people by disseminating research, informing public policy and providing specialist advice and training to both professionals and the general public²⁸.

Table 134.2 Symptoms and signs of abuse (National Center on Elder Abuse, 2000)

Physical abuse	Carer refusal to permit examination Reports of being hit, kicked or mistreated Unexplained behavioural disturbance Presence of unexplained bruises, lacerations, ligature marks, fractures Untreated injuries in various stages of healing Inappropriate use of prescribed medication
Sexual abuse	Reports of sexual assault or rape Bruising of breasts or genital area Torn, stained or bloody underclothing Unexplained genital infection or bleeding
Psychological abuse	Reports of verbal or emotional mistreatment Withdrawal, non-communication or non responsiveness Unexplained or unusual agitation or behavioural disturbance
Financial abuse	Reports of financial exploitation Unauthorized or unexplained changes in banking practice Abrupt, unauthorised or unexplained changes to financial documentation Unexplained disappearance of assets Unmet care needs in the presence of adequate financial resources Sudden appearance of individuals asserting their rights to an elder's assets
Neglect	Reports of mistreatment Failure to provide food and hydration Failure to meet clearly identified care needs Hazardous or unsanitary living conditions

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Care of the Dying

Adrian Treloar, Monica Crugel and Waleed Fawzi

Oxleas NHS Foundation Trust, Memorial Hospital, London, UK

MENTAL ILLNESS AND DYING

It is well recognized that serious mental illnesses of all kinds are associated with higher morbidity and mortality^{1,2}.

In dementia, the average life expectancy after diagnosis is only 4.7 years³. A variety of reasons contribute to mortality from almost all medical conditions occurring during a dementia illness. Dementia itself makes patients prone to acquire pneumonia (due to swallowing difficulties), urine infections (due to poor fluid intake, incontinence) and fractures (due to mobility problems). Dementia will also lead to late diagnosis with consequent higher mortality from many conditions. It limits the treatment options for conditions such as cancer, where the dementia may make intensive and painful treatments too burdensome to consider. Poor compliance with treatment also causes mortality. When dementia occurs in people with Parkinson's disease or Huntington's disease, these increase mortality as well⁴. However, in practice, most death certificates for people who die with dementia make no mention of any contribution made to the death by the dementia⁵.

Delirium, which has a high incidence in the elderly and especially in those with multiple physical pathologies, is also associated with a high mortality⁶. While the mortality of delirium is most often thought to be due to its medical causes, death is also undoubtedly more likely due to the poor compliance and reduced motivation to rehabilitate that will be seen in delirium. People with a hyperactive delirium may pull out their drips and resist treatment just when they really need it.

In delirium, the therapeutic aim would be, of course, to make people better and avoid the excess mortality. Much too can be done in schizophrenia to reduce mortality through optimizing treatment, risk management, advice on smoking, diet, exercise and treatment for the antipsychotic-associated diabetes, hyperlipidaemias etc. However, in conditions such as dementia and Parkinson's disease it becomes clear at a certain time that life is indeed drawing towards an end. At such time, care rightly becomes more palliative (with the aim of maximizing comfort and quality of life), ahead of curative treatment.

Palliative care is the active holistic care of patients with advanced progressive illness. Management of pain and other symptoms and provision of psychological, social and spiritual support is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families. Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with other treatments. Palliative care should help people to live as well as

possible until they die. It accepts natural death but seeks neither to prolong nor shorten life.

Clinicians, patients' families and nursing home staff need to recognize and treat advanced dementia as a terminal illness requiring palliative care^{7,8}.

INTERNATIONAL PERSPECTIVE

Internationally, practice is not uniform but there is a widespread interest and increasing understanding of the need to develop a good evidence base and improved palliative care for people with advanced dementia^{7,9,10}. Although in the USA, people with advanced dementia do not need to have another serious illness to qualify for hospice care⁷, access of people with advanced dementia to palliative care services is limited both in Europe and in the USA¹¹. In the UK, despite the willingness to see non-cancer patients, people with dementia in acute hospitals are only a third as likely to be referred to palliative care as other patients¹², and few are admitted to inpatient hospices¹³. A recent US study has highlighted the low referral rate to palliative care services (22%) and high occurrence of burdensome interventions in people with advanced dementia (40.7% in their last three months of life)⁸.

In Germany there is concern about the lack of clear clinical and ethical guidance for decision making in advanced dementia, including the appropriateness of using tube feeding¹⁴. In France there is increasing interest in developing adequate specific services which follow a palliative care model and a few studies are underway⁹. In some countries (e.g. USA, Germany) it is much commoner to use artificial nutrition and hydration in those dying with dementia¹⁵. The insertion of PEG tubes (as well as the use of mittens and restraints which are sometimes needed to enable this practice) may be seen as preserving life or, by some, as a burdensome medical intervention which may not be appropriate. UK practice is quite firmly against such methods¹⁶. But conversely, there is substantial concern in the UK about the underuse of hydration in those who are dying and there are clear reports of a harrowing death occurring without the use of any fluids¹⁷. We suspect that there is a need for balance here. European continental practice does include more use of parenteral fluids when these are well tolerated by the patient⁹.

In other jurisdictions, where euthanasia is legal (e.g. Holland, Belgium, Switzerland, Oregon), euthanasia can also be applied without consent to people with dementia who lack capacity to decide

for themselves. But many worry that the availability of euthanasia may make good palliative care less important, and training of lower quality¹⁸. Deep sedation has been seen as an alternative to euthanasia in Holland¹⁹. Concern has also been expressed in the UK about the use of some care pathways for those who are dying²⁰. Perhaps the biggest worry is that if a diagnosis of dying is made in someone who is not actually imminently dying, the care consequent upon that diagnosis (such as administration of inappropriate sedatives and withdrawal of fluids) may sometimes assure a death that was not imminent. But in the end whichever the jurisdiction there is a very clear need for good and appropriate care for those who are dying. It is entirely unacceptable that those who are dying might not have access to good palliative care in whichever jurisdiction they live. After all, palliative care exists to help people live as well as they can until they die and that must, surely, be available to all.

WHAT ARE THE KEY AIMS OF GOOD PALLIATIVE CARE OF DEMENTIA?

1. Perhaps the greatest aim of good care of the dying is to enable people to live as well as possible until they die. Frail and demented elderly often contribute in many ways to their family and others during their last illness and many people with dementia live well.
2. When patients with dementia or other terminal illnesses are distressed, then that distress ought to be alleviated.
3. Discussion about dying, with a willingness to inform both patients and carers, is important. Discussions enable advance illness planning which can be of great help later on in enabling those with dementia to live as well as possible and also to die well. Last-minute trips to hospital via A&E are to be avoided, and this will most likely be through good discussion and planning.
4. Care of the dying should seek to ensure that treatments given are effective, appropriate and not burdensome, primarily focused on enabling the patient to live well until they die and to reduce suffering.

PRINCIPLES OF PALLIATIVE CARE AS THEY APPLY TO DEMENTIA

Upon its founding, the hospice movement saw symptom control and the alleviation of distress as priorities. Hospices moored this alongside high-quality care and good environments providing oases of quality that were originally mainly afforded to those dying with cancer.

Dame Cicely Saunders, who founded the hospice movement, identified the reality of 'total pain':

- Pain is not just physical, but mental and existential too. All forms of pain/distress must be addressed and treated. It should be said here that the notion that pain (distress) can be both mental and physical is hardly alien to dementia care. Such an understanding has always been a central part of old-age psychiatric care.
- She saw that the patient is a whole person, an interplay of physical, psychological, social and spiritual dimensions. These all have an effect in a single individual and interplay together. So doctors must recognize and respond to psychosocial and spiritual distress, and not just deal with physical disease.
- She saw that the family was the unit of care and that care had to become centred around the person by recognizing the broader family and community.

- She established that symptoms could be analysed scientifically in the same way as any other illness so as to enable best care²¹.

The models of palliative care bring with them some useful ethical views. It has long been accepted that sometimes the importance of distress reduction may mean that side effects of treatment might shorten life (double effect). A comfortable death can often be achieved by the appropriate use of medicines, and this may be one reason (see below) why antipsychotics may be justified. The oft-quoted ethics of 'first do no harm' may work a little less well. If the only aim is to avoid harmful treatments, it may not be possible to adequately alleviate distress. The Hippocratic position of 'I will never intend harm' would apply better as all treatment may bring a risk of harm but the intention must always be to improve the patient's condition. So, in the end, the purpose of care is central. If in the care of the dying the primary purpose of care may well be to reduce suffering, while accepting some risk of harm, that is fine. But if the primary purpose is to shorten life, then of course that is not.

The other key concept here is burden of care. When we are mentally well we will accept burdensome treatments so as to become well again, but as frailty increases and death nears, it becomes increasingly wrong to apply burdensome treatments. This helps to define appropriate and inappropriate care.

WHEN IS A MOVE TOWARDS PALLIATIVE CARE INDICATED IN DEMENTIA AND SIMILAR ILLNESSES?

Palliative care may be provided from the onset of an illness if symptoms are distressing. But generally, early on in illness, attempts at a cure and active treatment have more prominence. In progressive, fatal conditions there will, however, be a switch towards a more palliative approach. Factors that indicate that a switch is appropriate are set out in Box 135.1²².

Box 135.1

Indicators for a transition towards more palliative care

Severe distress (mental or physical) which is not easily amenable to treatment

Or

Severe physical frailty which is not easily amenable to treatment

Or

Another condition (e.g. co-morbid cancer) which merits palliative care in its own right

Occurring in someone with a diagnosis of moderate or severe dementia or other progressive and fatal mental illness.

Therefore, in a frail and weak person with dementia, who can barely walk and is unlikely to survive acute medical care, a gentler and more palliative approach is needed. Similarly, in someone who is suffering due to ongoing mental distress or physical pain a palliative approach is needed. Finally, if someone has cancer and the demands of chemotherapy would be too great (due to the dementia), the focus of treatment must be palliative.

The *Gold Standard Framework* also sets out two ways of identifying when end-of-life care is appropriate²³. Firstly it asks whether

or not the clinician would be surprised if the patient died in the next year. This is a simple question but it is clear that accurate prognosis is very hard in dementia. So, the question will often not be answered positively even in advanced dementia. Many who die would not have been identified by clinicians using the Surprise Question²⁴. Moreover, those living happily with dementia may not need specific end-of-life care.

The Gold Standard Framework also suggests that the following indicate the need for end-of-life care:

- unable to walk without assistance; and
- urinary and faecal incontinence; and
- no consistently meaningful verbal communication; and
- unable to dress without assistance;
- Barthel score < 3;
- reduced ability to perform activities of daily living (ADL).

Plus any one of the following: 10% weight loss in previous six months without other causes; pyelonephritis or UTI; serum albumin <25 g/l; severe pressure scores, e.g. stage III/IV; recurrent fevers, reduced oral intake/weight loss; aspiration pneumonia.

However, these indicators are very physical in nature and there is a lack of consistency in the indicators of severity. Inability to communicate meaningfully sits awkwardly alongside reduced ADL skills as an indicator of severity. More importantly, these indicators do not recognize the importance of distress reduction in those with a difficult dementia complicated by behavioural challenge and psychological distress.

WHAT ARE THE FEATURES OF DISTRESS IN PEOPLE WITH ADVANCED DEMENTIA AND OTHER CONDITIONS WHERE IT IS HARD FOR THEM TO EXPRESS THEMSELVES?

Distress might be demonstrated by some or all of the following:

- anger/frustration
- aggression/agitation
- fear/anxiety
- tearfulness/misery
- pain when still
- discomfort on moving
- restlessness
- insomnia
- calling out/vocalization
- wandering and persistent challenging behaviours when these appear to be driven by distress or fear
- autonomic arousal, sweating, tachycardia, hypertension.

WHAT ARE THE CAUSES OF DISTRESS?

Distress may be caused by mental illness, other mental and psychological difficulties and physical difficulties/pain. Distress is in essence pain that is either mental or physical and no sort of distress is less worthy of palliation than any other. So the following causes of distress must be explored:

- depression
- psychosis
- pain

- poor understanding
- fear and anxiety
- insomnia
- hunger and diet
- boredom, isolation and lack of spiritual care
- poor environment including poor staff practices, etc.

In a chapter of this length we can but mention the causes and make a few comments. Physical pain is frequently missed and undertreated in dementia. Its treatment provides a real modality to reduce distress in patients dying with dementia and other mental illnesses. The prevalence of pain in US nursing homes has been estimated between 26% and 83%²⁵. Pain is not reported by the elderly who are cognitively intact as it is often attributed to 'natural ageing' and those with dementia are often unable to express their pain²⁶. However, studies have demonstrated that patients with a diagnosis of dementia are less likely to receive analgesia compared to those without this diagnosis²⁷.

Those who appear depressed may well respond to an antidepressant and those who show evidence of psychosis may respond to antipsychotics. Of course, given the harm that we know they do²⁸, a discussion about risk of harm must always be had whatever the indication or the use of antipsychotics. But if, in the end, antipsychotics represent the best way to reduce severe distress in someone with dementia, then their use may be justified²⁹.

ADVANCE CARE PLANNING

Receiving a diagnosis such as dementia will rightly lead to a desire to think about and make plans for the future. But the fear that dementia brings may be huge and it is important to give an opportunity to discuss and allay fears where possible. In truth, dementia is a distressing condition, but patients need reassurance that distress is usually managed with the right care, support and medications. Discussion of living well with dementia may be very reassuring. Understanding the palliative model of care may help considerably. A discussion on prognosis and advance care planning can start at diagnosis, and be developed further during the transition from restorative care towards more palliative care.

Of course, early on it is right to treat the memory impairment and to work out ways to delay or reduce disease progression. But, as the illness progresses, treatment is more focused on symptom control and reduction of distress. Various methods allow the planning of care as dementia advances:

Advance Patient Statements

These are broad statements of preference about future care and can be very useful. Patients may ask for specific care at specific times, or ask for assurance that fluids will be given³⁰. Most often a simple statement such as "If I have an untreatable or terminal illness I ask for sensible treatments that have a reasonable chance of benefit and that avoid excessive burden" may be helpful. Such statements can enable the patient to guide others towards more appropriate care once capacity has been lost.

Preferred Priorities of Care

The preferred priorities of care protocols³¹ enable people with any diagnosis to set out what their priorities are and where they would like to be cared for during their last illness. Of course most choose home,

but other preferences too may be helpful. Some will wish a certain style of care, others to see the right people, some to have the right spiritual care etc. Of course such statements should preferably be advisory and not binding as it is hard to predict precisely what needs there will be. In dementia care it is not infrequent to find patients have an expressed desire not to go into nursing care, but that at the time, it turns out that this may be the best care and that they are demonstrably happier (see problems with advance refusals below).

Illness Contingency Planning

As illness progresses it is sensible to consider the scenarios that may lead to change of care. In the UK there is anxiety that death at home is uncommon and also that transfer to acute hospitals from nursing care at a time when patients are, in fact simply dying, occurs too often³². It is perfectly sensible to hope to avoid the chaos of acute hospital care at a time when death is inevitable, but with dementia there are special difficulties in achieving this and support for dementia at home until death (though highly effective and well regarded by carers³³) is rarely available and there are very few specialist services that aim to support such care. This is in complete (and unjustifiable) contrast to the situation for cancer care and other illnesses.

Inevitably though, infections and pneumonias may, unless already thought through, trigger a referral to an emergency department. Several questions can be usefully asked and discussed with carers and advocates and may take into account the declining physical functions and increased risk of other illnesses, infections, falls and fractures associated with dementia, see Box 135.2. It is probably true that the most effective part of this is the discussion itself. A discussion with carers will often have a good effect and enable confidence around ongoing care and dying.

Box 135.2

Advance illness planning questions

Is cardiopulmonary resuscitation, ventilation or intensive care medicine appropriate?

Would treatments with severe side effects be appropriate?

Would complex surgical procedures (such as a major abdominal operation) be appropriate?

Would hospital admission be appropriate for injuries such as fractures?

Would hospital admission be appropriate for illness such as chest infections?

If dehydration occurs and is causing the patient to suffer then would hospital admission be appropriate to treat?

When dying is imminent and the patient is distressed *we would expect* that medication will be given to alleviate the distress that may occur during death.

For some problems the solution will still be hospital. The best treatment of a broken hip is to mend it. The best treatment of a urine infection is antibiotics. But with a pneumonia, oral antibiotics with care at home by usual carers may well be associated with a better outcome than a transfer to hospital. So any plan must always remain flexible to a degree so that contingency can be dealt with.

Advance Decisions to Refuse Treatment

Advance decisions to refuse treatment (ADRTs) may be more challenging in dementia care. In England, Wales³⁴ and Scotland they are binding but are, fortunately, subject to stringent tests of validity and applicability. As with advance statements, they may well be helpful and give good advice but must be specific and valid. They do enable those who lose capacity to continue to guide their care, but they also carry some risks, and a binding decision might cause unanticipated effects³⁵.

Case Example

A person with dementia has stated that he only wants symptomatic treatment once his dementia is moderate or severe. Restorative treatment is refused, in the hope that this will enable comfort and that he will not suffer unduly. He then develops a urine infection.

- Does the ADRT prohibit treatment of the infection or can the antibiotic be construed as symptomatic treatment? If it cannot, must the enhanced suffering of living without antibiotics be accepted even though the intention was to reduce distress?
- What if he develops a fractured hip? Is surgery the best analgesic and is it prohibited by the ADRT?
- What if, at the stage of dementia he has, he is happy, enjoying living with his family and all seems well?

The Mental Capacity Act gives some helpful clues here. The ADRT would be invalid if:

- the person withdrew the decision while they still had capacity to do so
- after making the ADRT the person made a lasting power of attorney (LPA) giving an attorney authority to make treatment decisions that are the same as those covered by the ADRT
- the person has done something, which is not in accordance with the ADRT remaining their fixed decision (i.e. they have changed their mind).

The ADRT would be inapplicable if:

- the proposed treatment is not the treatment specified in the ADRT
- the circumstances are different from any specified in the ADRT
- there are reasonable grounds for believing that circumstances have now arisen, which were not anticipated by the person when making the ADRT and which would have affected the ADRT had he anticipated them at the time.

In the case set out, there is a lack of specificity about treatment of a UTI or broken hip making the ADRT not applicable. There would also be reasonable grounds to think that the current circumstance was not anticipated. And, of course, questions about the level of understanding at the time of making the ADRT must be raised. Finally, note that ADRT's are not valid if they apply to life sustaining treatment and are not in witnessed and writing.

Given the complexity, possible benefits and also the possible harms of ADRTs, it is clearly appropriate that dementia specialists ought to advise those thinking of making an ADRT of the risks of making them as well as some of the possible benefits³⁵.

Lasting Power of Attorney (LPA)

The Mental Capacity Act in England and Wales and Adults with Incapacity Act in Scotland also allow people to appoint decision makers (such as a relative, friend or solicitor) to make decisions for them at a time when they lose capacity. Generally an LPA will trump an advance statement. Authority passes from the ADRT to the LPA if an LPA is appointed. The LPA, of course, must include a respect for the previous wishes and views of the patient in their decision-making process.

PARTNERSHIP WITH PALLIATIVE CARE

Specialist palliative care services do not have the capacity to provide the palliative care needs for those with dementia. Moreover, old-age psychiatry settings, including continuing care units can be seen as providing palliative care by virtue of the work they do in reducing the distress of severe and complex dementia. It is true that old-age psychiatry often underestimates physical pain in dementia, but, on the other hand, specialist palliative care services may struggle with patients who wander and present challenging behaviour. In each district therefore both old-age psychiatry and specialist palliative care can form useful partnerships and undertake mutual learning from each other. This is described in much fuller detail elsewhere²².

CONCLUSION

The care of the dying is an integral part of good care of the elderly. Mental health services will do well to acknowledge this and develop their understanding of what they already do in terms of palliative care and to then learn more about what they do not do well.

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Prevention of Mental Disorders in Late Life

Pim Cuijpers¹, Filip Smit², Barry D. Lebowitz³ and Aartjan T. F. Beekman⁴

¹*Department of Clinical Psychology and EMGO Institute for Health and Care Research, VU University and VU University Medical Centre, Amsterdam, The Netherlands*

²*Trimbos Institute (Netherlands Institute of Mental Health and Addiction), and EMGO Institute for Health and Health Care Research, VU University Medical Centre, Utrecht, The Netherlands*

³*University of California, San Diego School of Medicine, La Jolla, CA, USA*

⁴*Department of Psychiatry VU Medical Centre and GGZ inGeest and EMGO Institute for Health and Care Research, VU University and VU University Medical Centre, Amsterdam, The Netherlands*

INTRODUCTION

Prevention in the mental health field has been seen, traditionally, as an area that has been implicitly restricted to issues in childhood and adolescence. If anything, prevention in geriatrics was seen as an oxymoron. Theory and research in prevention were, for a long time, restricted to issues of child development and intervention early in the life course. In an influential report, the Institute of Medicine (IoM) of the US National Academy of Sciences assessed the state of knowledge in prevention research in the 1990s, but could find hardly any studies aimed at prevention of mental disorders in older adults¹. A more recent follow-up report on prevention of mental disorders by that same institute is aimed completely at children, youth and young adults, while prevention in older adults is not mentioned at all².

At the same time, however, prevention of mental disorders in older adults has been the focus of a new line of research. This research has resulted in a growing body of knowledge on how to identify those with the highest risk of developing a mental disorder, several preventive interventions, and some randomized controlled trials showing that prevention may be possible and effective in older adults. Furthermore, considerable progress has been achieved in the field of prevention of mental disorders for younger adults in recent years. The growing number of randomized controlled trials has shown that prevention of depressive and anxiety disorders in adults in general is probably effective, and there is no reason to assume that interventions which are effective in younger adults would not be effective in older adults.

Why be concerned with prevention in late life? As is well covered in other sections of this text, there is the demographic imperative brought about by the overall ageing of the world population and in particular by the ageing of the older population. As pointed out in the classic paper by Kramer (1980)³, the same dynamics: public health measures, technological development and lifestyle changes, that created this growth in the overall population were also relevant to growth of the population of those with chronic illnesses and disabilities. They

conclude that, in the absence of cures or effective preventive strategies, we will see an explosion in the number of older persons with serious and persistent disabling illnesses, particularly mental disorders. The availability of more efficacious treatments and the accessibility of appropriate services in the community combined to produce huge gains in the life expectancy of those with mental disorders, who in earlier times would have died long before reaching old age. This demographic imperative leads to the conclusion that prevention must be an important part of the agenda of geriatric psychiatry.

For example, major depression currently affects about 3.6–4.8% of persons of 60 years or older, and many more report clinically relevant depressive symptoms^{4,5}. At this moment, major depression in all age groups is the fourth disorder worldwide in terms of disease burden, and it is expected to be the disorder with the highest disease burden in high-income countries by the year 2030⁶. Furthermore, the prevalence of depressive disorders in older adults is projected to double from its present level by 2050⁷. Depression is not only a highly prevalent disorder, but it is also associated with a huge loss of quality of life in patients and their relatives^{8,9}, with increased mortality rates¹⁰, with high levels of service use and with enormous economic costs. The economic costs of depression in the United States were estimated to be \$83 billion in 2000¹¹.

Another reason why prevention is important is that current treatments can reduce the disease burden of depression only to a limited extent. A recent study in Australia estimated that about 16% of the disease burden of major depression is averted in the current health system¹². Because many patients do not receive an evidence-based treatment, this percentage could rise to 23% if all patients received such an evidence-based treatment. Furthermore, about 40% of all people with a depressive disorder do not receive any treatment. If it would be possible to deliver treatment to all patients with a depressive disorder, 34% of the disease burden of depression could be averted. So, although current treatments are usually considered to be effective in treating depressive disorders, it is estimated that these treatments can reduce the disease burden of

depression by a maximum of 34%¹². Prevention of the incidence of new cases of major depression has been suggested as an alternative for treatment which may reduce a part of the 66% of the disease burden which is not averted by current treatments^{13,14}.

In the current chapter we will give an overview of the field of prevention of mental disorders in older adults. First, we will give a definition of prevention in the mental health field. Then we will focus on recently developed methods of identifying the optimal high-risk groups for preventive interventions. Finally, we will describe the interventions that have been developed and the results of research examining the effects of these interventions.

WHAT IS PREVENTION?

The traditional public health view derives from infectious disease and is divided into primary, secondary and tertiary prevention. Primary prevention is directed towards maintaining health by isolating the causes of disease and eliminating or counteracting them. Secondary prevention is directed towards enhancing recovery by case identification and prompt intervention early in the course of illness. Tertiary prevention is directed towards those already ill and emphasizes treatment and rehabilitation.

There is a growing consensus that the traditional public health view is not optimal in mental health. The components of this approach including, for example, concepts such as pathogens, risk factors, disease vectors and definitions of caseness do not translate easily into psychopathology or chronic disease. In the definition of depression which is currently used by most researchers and practitioners in the mental health field, prevention comprises all interventions which are conducted before subjects meet the formal criteria of a mental disorder (according to the DSM-IV¹). Curative interventions are given to persons who suffer from acute disorders, and maintenance treatments are given to patients with chronic disorders. In this spectrum of interventions, three types of prevention can be distinguished:

Universal prevention is aimed at the general population or parts of the general population, regardless of whether they have a higher than average risk of developing a disorder. The best-known examples of universal prevention include school programmes aimed at all students, whether they have an increased likelihood of developing a mental disorder or not; and mass media campaigns, aimed at the general population.

Selective prevention is aimed at high-risk groups, who have not yet developed a mental disorder. High-risk groups include people who have recently experienced a stressful life event or who experience a chronic stressor, such as divorce, losing a family member through death, caring for an ill family member, and unemployment.

Indicated prevention is aimed at individuals who have some symptoms of a mental disorder but do not meet diagnostic criteria.

In this chapter, we will give an overview of selective and indicated preventive interventions for older adults. Because universal interventions have not been developed systematically or examined in well-designed trials, we will not discuss these possibilities here. Then we will look at the research examining whether preventive interventions are actually capable of preventing the incidence of new cases of mental disorders, and we will describe new methods of identifying optimal target groups for prevention of mental disorders in older adults.

SELECTIVE PREVENTION

In the past decades, several indicated preventive interventions for older adults have been developed, including interventions aimed at widows and widowers, caregivers of frail older adults, older adults with a chronic general medical illness, and inhabitants of homes for the elderly and nursing homes. Several of these interventions are not specifically aimed at older adults, because there are also younger adults who lose their spouse or get a chronic general medical disorder, but the chance of belonging to such a high-risk group is much greater among older adults. Therefore, it seems reasonable to consider such interventions as prevention for older adults.

One important group of selective preventive interventions is aimed at widows and widowers. They are an important high-risk group for mental disorders¹⁵, and several preventive interventions have been developed, including social support groups and widow-to-widow programmes. In social support groups, widows and widowers come together in small groups to exchange experiences and emotions, with a clear preventive focus. However, research examining the effects of these groups has not resulted in strong evidence for their effectiveness¹⁶. Another preventive intervention developed for widows and widowers are the so-called 'Widow-to-widow' programmes^{17,18}. In these programmes, widows who have recently lost their spouse are visited by another widow who lost their spouse some time earlier. Early research showed promising effects of these programmes, but a larger recent trial did not find any beneficial health effects of such a programme¹⁹.

Another group of selective preventive interventions is aimed at caregivers of frail older adults. Because of the stressful situation they live in and the burden of care, this is an important high-risk group for the development of mental disorders²⁰. Several types of interventions have been developed for caregivers, many of which have a clear preventive goal in terms of preventing mental disorders or severe stress-related problems. Interventions for these caregivers include support groups and psycho-educational interventions²¹, respite care²², home visits²³, and multi-component interventions in which different interventions are combined and adapted to the need of the caregiver²⁴. Research examining these interventions has typically resulted in small to moderate effect sizes on mental health outcomes in caregivers, with limited clinical impact^{25,26}, although multi-component interventions seem to be more effective²⁷.

Several multifaceted interventions have been developed for the prevention of late-life depression in residential care^{28,29}, where the prevalence of depressive disorders is very high³⁰. Such interventions focus on the training of nurses and doctors, on consultation and on supportive interventions for the residents. A few trials have found encouraging effects of these interventions^{28,29}. Another study found significant effects for screening and early intervention in residential homes for the elderly³¹, although this should be considered as indicated prevention or even treatment.

Older adults with chronic general medical illnesses are another important target group for selective prevention. In this area, several well-designed studies have been conducted, and these studies have actually examined whether preventive interventions are capable of preventing the onset of new cases of mental disorders. Rovner and colleagues (2007)³² screened older patients with neovascular macular degeneration, and found that problem-solving treatment resulted in a significantly lower incidence rate of new cases of depressive disorders at two and six months follow-up. Robinson and colleagues

(2008)³³ found that both problem-solving treatment and antidepressive medication resulted in a significantly lower incidence rate of major depressive disorders in stroke patients.

This overview of selective preventive interventions is not comprehensive, but it gives a good idea of the possibilities that are available for developing preventive interventions for older adults at risk of getting a mental disorder.

INDICATED PREVENTION

In the past decades, several indicated preventive interventions, aimed at older adults with sub-threshold symptoms but no mental disorder, have been developed. Until now, these interventions have focused mainly on depression. The first type of indicated prevention we want to present is the psycho-educational 'Coping with Depression' course (CWD). This intervention was originally developed as a group treatment for depression. However, because of its psycho-educational nature, it can also be applied relatively easy as a preventive intervention. As we will see later on, the CWD (for all age groups) has been used in 6 of the 19 randomized controlled trials which have examined the effects of prevention on the incidence of major depression in those who did not have a depressive disorder at baseline.

The CWD is a cognitive behavioural intervention which is usually conducted in group format with 8 to 12 participants. Because of the psycho-educational format, there is no therapist or patient, but only teachers and students. Therefore, older adults with depressive symptoms do not have to go into treatment, but only go to a course where they learn how to improve their mood. Apart from behavioural activation, the students also learn cognitive restructuring skills, and social skills. The CWD is not only used in older adults, but also in many other target groups, including adolescents, minority groups, primary care patients, and general medical patients. There is much research examining the effects of the CWD as treatment of existing depressive disorders and as prevention of new cases^{34,35}. These studies show that the CWD is an effective treatment for depression, but is also effective in preventing new cases of depressive disorders. A recent randomized controlled trial in the Netherlands, where the CWD is offered as a preventive intervention to older adults in about 80% of the regions, showed that the CWD effectively reduces the level of depressive symptoms in participants in these courses³⁶. However, this study also showed that about 40% of the participants in these courses in routine care did have an established major depressive disorder, and so it cannot be seen as a purely preventive intervention. However, because of the low threshold for participation, and the reluctance of many older adults to seek treatment for existing depressive disorders³⁷, this does not seem to be a problem from a public health point of view.

Another preventive intervention for depression in older adults is life review and reminiscence. In life review interventions, older adults discuss their life and the evaluation of each important period in their life with a trained professional. Several randomized controlled studies and meta-analyses have shown that these interventions are effective in reducing existing depressive symptoms³⁸, as well as increasing life-satisfaction and emotional well-being³⁹. Although the effects have not yet been examined in target groups in which sub-threshold depression was established with a diagnostic interview, life review seems to be an excellent intervention for indicated prevention, because of its low threshold for participation, because the stigmatizing word 'depression' is not needed, and because no understanding of negative thoughts or other complex psychological issues is necessary for participating successfully in this intervention.

More recently, the internet has been found to offer promising new opportunities for the prevention of mental disorders in all age groups, including older adults. A considerable number of studies have found that internet-based cognitive behaviour therapy (CBT) is effective in the treatment of depression and anxiety disorders⁴⁰. In one study, internet-based CBT has been found to be effective in the treatment of sub-threshold depression in older adults⁴¹, which can be seen as indicated prevention. This study showed that internet-based CBT had large effects on depressive symptomatology in older adults, and was as effective as a preventive group intervention.

Another recent development is the use of stepped-care models for the prevention of depressive disorders in older adults with sub-threshold depression or anxiety^{42,43}. In a large, randomized, controlled trial, older adults with sub-threshold depression or anxiety were recruited from primary care and assigned to a preventive stepped-care programme or usual care. Stepped-care participants sequentially received watchful waiting, CBT-based bibliotherapy, CBT-based Problem Solving Treatment, and finally referral to primary care for medication, if required. It was found that cumulative incidence of DSM-IV major depressive disorder or anxiety disorder after 12 months was reduced from 24% (20/84) in the usual care group to 12% (10/86) in the stepped-care group, which indicates a relative risk of 0.49 (95% confidence interval: 0.24–0.98). These results are better than those found in the meta-analysis of preventive interventions for depression⁴⁴, and may indicate that stepped care is an excellent method for the prevention of mental disorders in older adults.

IS IT POSSIBLE TO PREVENT THE INCIDENCE OF MAJOR DEPRESSION?

In the past decades, hundreds of controlled studies have examined the effects of mental health programmes aimed at preventing mental health problems in children, adolescents, adults and older adults^{14,20}. This considerable body of research has shown that some prevention programmes in mental health are capable of strengthening protective factors, such as social skills, problem-solving skills, stress-management skills, pro-social behaviour and social support; that these programmes can reduce the consequences of risk factors, psychiatric symptoms and substance use; and that they may have positive economic effects. Despite this large body of research, however, relatively few studies have examined whether these prevention programmes are actually capable of reducing the incidence of new cases of mental disorders defined according to diagnostic criteria, although this research question can easily be regarded as one of the most important ones, both from a public health perspective and from a scientific point of view.

In the past 15 years, a growing number of studies has examined whether it is possible to prevent the incidence of mental disorders in persons who do not have an established disorder at the start of the preventive intervention. Most of these studies are aimed at the prevention of depression⁴⁴, and some are aimed at the prevention of anxiety disorders^{45–48}. A recent meta-analysis of studies examining the effects of preventive interventions on the incidence of depressive disorders found that the incidence rate ratio of developing a depressive disorder was 0.78 (95% confidence interval: 0.65–0.93) for participants in the prevention conditions compared to control subjects, which indicates that participants in the preventive interventions have 22% less chance of developing a depressive disorder in the next year⁴⁴.

Only a few of the studies in this area have been conducted with older adults^{32,33,43}, but those that have been conducted find results which are comparable to the studies that have been conducted with younger adults. More research is clearly needed to establish the possibility of preventing the incidence of mental disorders in older adults, but research in younger adults suggests that this is a promising field of investigation.

IDENTIFYING TARGET GROUPS FOR PREVENTIVE INTERVENTIONS

As we have seen earlier in this chapter, several interventions have been developed for older adults who are at risk for developing a mental disorder, such as caregivers of frail elderly, those who have lost their spouse, people who have chronic general medical disorders, and people with sub-threshold depression. Although many of such risk indicators for mental disorders are known, their specificity is low. This means that most people in these high-risk groups will never develop a mental disorder^{14,49}. Although much epidemiological research is available showing that such indicators are associated with an increased risk of developing a mental disorder, this research is not very useful in identifying the optimal high-risk groups for preventive interventions. The traditional indicators of the strength of a predictor for the incidence of such disorders, such as a relative risk or odds ratio, are not sufficient for identifying the best target populations for preventive interventions. Suppose, for example, that the risk of developing a major depressive disorder in the general population is 2.5% in one year^{50,51}. If a high-risk group has a relative risk of developing a depressive disorder of 4.00, this will be highly significant (if the research population is large enough). But, this means that still only about 10% of the high-risk group will actually develop a depressive disorder, and 90% will not. A high-risk group will probably be difficult to motivate for participation in a preventive programme if only 10% eventually will develop the disorder, apart from the question of whether it is ethically acceptable to intervene in such a population. Furthermore, such an intervention is probably not very efficient and cost effective, because by far the majority will never develop a disorder and the intervention has no preventive effect in this majority.

Recently, more advanced methods have been developed to identify the optimal target groups for preventive interventions in at-risk older adults. After the identification of significant risk indicators, this method starts with calculating three other statistics that can help us in identifying the optimal target populations. First, the exposure rate (ER), which gives the percentage of the population exposed to the risk indicator. The second statistic is the population attributable fraction (AF), which indicates by how many percentage points the current incidence rate of depression in the population would be reduced if the adverse effect of the risk indicator is completely blocked^{13,52}. This equals the maximum possible impact of a completely successful preventive intervention. Third, the number-needed-to-be-treated (NNT) can be interpreted as the number of people that should be targeted by a preventive intervention to avoid the onset of the disorder in one person (assuming that the preventive intervention is completely successful in containing the adverse effect of the risk factor).

When target populations for preventive interventions are selected, the ER and the NNT should be as small as possible, while the AF of the target population should be as high as possible. This allows us to identify small target populations with the largest possible proportion of new incident cases, while the number of subjects that

have to be treated with the preventive intervention is as small as possible. There are several ways of finding the most optimal combinations of risk indicators (small ER and NNT, large AF), including a straightforward exploration of all possible combinations of significant risk indicators¹³, but also more sophisticated methods such as CART analyses (classification and regression tree analysis), and bootstrap aggregation (bagging).

In one study, it was found that older adults with (subclinical) depressive symptoms, functional limitations, a small social network, and female gender comprised only 8% of the total older population (ER), while 24.2% of the new incident cases could be attributed to this group (AF)⁵³. The number of subjects from this population that would have to receive a preventive intervention in order to prevent one incident case (NNT) was 4 (assuming that the intervention was 100% successful). In another prospective study among older adults, CART analyses were used to identify the optimal groups for indicated prevention (high-risk groups) and universal prevention (sub-threshold depression present)⁵⁴. In the selective prevention model, spousal death showed the highest risk, becoming even higher if the subjects also had a chronic illness. In the indicated prevention model, sub-syndromal symptoms of depression were associated with a risk of almost 40% of developing depression and an NNT of 5.8, accounting for 24.6% of new cases. Adding more risk factors raised the absolute risk to 49.3%, with a lower NNT, but also lower AF values. Overall, the attributable fraction values in the indicated model were found to be higher, identifying more people at risk. A third prospective study was aimed at the identification of the optimal target groups for prevention of anxiety disorders among older adults⁵⁵. In this study it was found that several factors were significantly associated with increased risk of developing anxiety, including sub-threshold anxiety, depression, two or more chronic illnesses, poor sense of mastery, poor self-rated health and low educational level.

Although this methodology of identifying the optimal target groups for preventive interventions in epidemiological research has been developed well, it has not yet been used in actual intervention studies. Designing such studies is certainly one of the most important challenges for interventions researchers in the years to come.

CONCLUSIONS

In this chapter, we have tried to illustrate why prevention of depression in older adults is important. Reasons for its importance include its very high prevalence, incidence, disease burden and the huge economic costs of depression. It is also important because current treatments can reduce the disease burden by about one-third, while two-thirds cannot be avoided, even when only evidence-based treatments are given and all depressed patients receive such an intervention.

We also showed that traditional epidemiological research cannot identify the best target populations for prevention. Relatively simple statistics, such as the exposure rate, the population attributable fraction, and the numbers-needed-to-be-treated can be used to select those high-risk groups which are as small as possible, but explain as many of the new incident cases as possible.

Research in the past decade has also shown that preventive interventions in all age groups are probably effective and can reduce the incidence by about one-quarter, and the few studies that have been conducted with older adults find comparable results. Psycho-educational cognitive behaviour therapy is the most used preventive intervention for depression and is already implemented in some countries. In the next few years, the internet will probably give new

opportunities for the broad implementation of preventive interventions, because access is easy, scalable, economically affordable and effective. Another important development is stepped-care interventions with more intensive treatments when no reduction of depressive symptoms has been realized. It is expected that this type of intervention will be able to reduce the incidence of depression in older adults further.

There is a significant epidemiological transition towards older age and greater morbidity. This process is equally manifest in the workforce for health. After all, the average age of the health care professionals is increasing rapidly. To illustrate, over 50% of the nurses in the European Union are older than 45 years, and their mean age is still on the increase. Increasing demands for health care and restricted supply is one of the key problems in the near future. Therefore a health care system needs to be able to produce significant health gains in an acceptable, effective, scalable and economically affordable way. Empowering people to become the managers of their own good health via preventive self-help interventions offered over the internet is probably one of the most important steps that we need to take now for a better future.

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The Principles of UK Mental Health Law: A View from the Clinic

Julian C. Hughes

Northumbria Healthcare NHS Foundation Trust and Institute for Ageing and Health, Newcastle University, UK

INTRODUCTION

On 12 November 1962, in *The New York Times*, Earl Warren, the Chief Justice of the United States, wrote:

In civilized life law floats in a sea of ethics. Without law, the least scrupulous might prevail, but without ethics, law itself could not exist... without ethical understanding, the law, as a ship of state, would be stranded on dry land.

Mental health is the branch of clinical practice where clinicians can deprive people of their liberty and enforce treatments on them against their wishes. Our clinical decisions are, at one and the same time, ethical; but our ethical decisions must also be, at one and the same time, legal. Our concepts – ‘mental disorder’, ‘incapacity’ – carry clinical, ethical and legal weight and show the links between law, ethics and practice.

In this chapter, I shall sketch the mental health legislation that governs England and Wales. For the sake of brevity and prudence, I shall mention other UK jurisdictions only in passing. (Fuller accounts of the laws governing England and Wales can be found in standard texts^{1,2}.) I shall attempt to raise some broader issues of principle. In this I want to take my lead from Earl Warren, because I want to point to the ways in which there is a necessary interaction between ethics, which in this context I take to imply practice, and law.

In the spirit of questioning, I shall first set the historical scene and gesture at areas of debate. I shall then briefly sketch the main provisions of the two laws now governing practice in England and Wales: the *Mental Capacity Act 2005* (MCA) and the *Mental Health Act* (MHA) 2007.

SLOW BIRTHS AND CONTROVERSIES

Law is not static, but evolving. The MHA 1983, which was amended by the MHA 2007, had its roots in the 1959 Act, which incorporated the recommendations of the Percy Commission of 1957. That Commission had concluded:

...that the law should be altered so that whenever possible suitable care may be provided for mentally disordered patients with no more restriction of liberty or legal formality than is

applied to people who need care because of other types of illness, disability or social difficulty³.

The Percy Commission recommended that compulsory detention should only be employed where necessary. They made it clear that they wished to see ‘the need for care’ and ‘the justification for compulsion’ as two quite separate questions³. The assumption, they suggested, that compulsory powers must be used unless the patient can express a positive desire for treatment should be abandoned and replaced by ‘the offer of care without deprivation of liberty, to all who need it and are not unwilling to receive it’³. This seems very humane and it got rid of the previous situation in which incapacitated compliant patients had to be detained, because they could not agree to treatment. However, although the subsequent 1959 Act was,

heralded as a great piece of liberalising legislation, ... its reputation became tarnished by concern about failures of services and abuses of professional power. The Act was seen as being deficient in safeguarding the rights of detained patients⁴.

So the pendulum swung in favour of greater safeguards for patients. Now we are concerned that the pendulum has gone too far: beyond safeguarding patients to protecting the public from the risks of the potentially dangerous mentally ill⁴. The insistence on reform of the 1983 Act on the part of the government came about when Michael Stone, who had an antisocial personality disorder and had been under psychiatric care, killed a mother and daughter. This led to the home secretary, Jack Straw, offering the following condemnation of psychiatrists:

Quite extraordinarily for a medical profession, they have said they will only take on those patients they regard as treatable. If that philosophy applied anywhere else in medicine there would be no progress whatsoever. It’s time, frankly, that the psychiatric profession seriously examined their own practices and tried to modernize them in a way that they have so far failed to do⁵.

The strength of feelings was shown by the response of Robert Kendell, then the President of the Royal College of Psychiatrists, in a radio interview:

There may be a place for some form of preventative detention for men like this. That is an issue for parliament. The home secretary cannot expect psychiatrists to do his dirty work for him when it is at present excluded by law⁶.

On the grounds that the 1983 Act was intended for a time when community treatment was in its infancy, when detention in hospital was the main issue, the government set about modernizing mental health law in England and Wales⁴. The subsequent history is well documented: following an expert scoping report, a green paper, a white paper, two draft bills and eight years, in the face of 'vehement, sustained, and almost unanimous opposition from those with an interest in mental health care'⁷, the government announced that it would simply amend the 1983 legislation rather than try to bring in a new Act. Nonetheless, as many feared⁷, it is arguable that the government's agenda of public safety won the day.

There are certainly contradictory views of the MHA 2007. Writing just before it was passed, Lepping highlighted 'a clear shift away from liberal individualism towards utilitarian thinking'⁸. His complaint was that the government was focusing largely on risk. He felt that innovations such as community treatment orders and the broadening of the definition of mental disorder favoured 'public safety considerations over individual rights'⁸. Responding to this paper, just after the Bill became law, Maden retorted that, 'The best that professionals can do under the 1983 law is sometimes not enough to prevent foreseeable disaster'⁹. He was somewhat dismissive of medical ethics ('...much of medical ethics consists of coming to terms with scientific discoveries') and upbeat about the possibility of predicting violence. In his view, the new Act was a continuation of a process that started with the murder of Jonathan Zito by a psychotic patient in 1992. Since then, he argued, there had been,

a general increase in aversion to risk which is not confined to mental health or, indeed, to any one country. There is no ethical basis for arguing that mental health should remain exempt from this trend, which has swept through most democracies⁹.

Maden then referred to changes to criminal justice legislation in England and Wales that 'resulted in judges imposing about 150 indeterminate sentences each month on the grounds of public protection'⁹. This reference was to the *Criminal Justice Act 2003*, which allows dangerous offenders to be given indeterminate sentences, even if their offences do not otherwise justify such detention. Maden presents this almost as a justification for the changes to mental health legislation, as if to say that psychiatrists should stop moaning about rights and get on with accepting their duty to protect the public. Other psychiatrists, however, have not been so happy with the *Criminal Justice Act 2003*, and specifically not with its ethical implications. For,

... under the 2003 Act, psychiatrists are required to give evidence about risk to the sentencing court in relation to a person's mental disorder, irrespective of the treatability of that disorder. This poses similar ethical dilemmas concerning the use of psychiatry solely for public protection, as well as for punishment of offenders, rather than for treatment⁷.

Furthermore, the emphasis on public protection flies in the face of recommendations made by the government's own scoping committee – the Richardson Committee:

We are convinced that whatever the precise scope of a mental health act it must primarily be seen as a health measure and must be consistent with the professional ethics of the health services. This is not to deny the importance of public protection but to place it within the appropriate context within which it can best be promoted. The importance of respecting and enhancing patient autonomy is now gaining increased recognition within the health services generally... and we are satisfied that it must acquire similar recognition within mental health services specifically¹⁰.

If the MHA 2007 took almost 10 years to be born, the MCA took even longer. It emerged in response to high-profile cases in the late 1980s of people with learning disabilities and enforced sterilization¹¹. Whereas reform of the MHA has been surrounded by controversy, the MCA developed from an exceptionally well-argued Law Commission Report¹², which led to a very cogent document from the government¹³ and a good deal of agreement as subsequent documents emerged prior to its delivery. One largely groundless concern has been that the MCA might bring in euthanasia by the back door. The Act, however, contains a number of defences against this possibility. More alarming to the clinician, perhaps, is the amendment to the MCA – the Deprivation of Liberty Safeguards (DOLS) – brought in by the MHA 2007, to which we shall return.

Nevertheless, there was debate concerning whether, in fact, there should be two Acts (for capacity and for mental health) or just one. It has recently been announced that Northern Ireland will have a single Act, which many elsewhere in the UK will regard with envy. Meanwhile, in Scotland, capacity legislation was amongst the first Acts to be passed by the Scottish Parliament in the form of the *Adults with Incapacity (Scotland) Act 2000*. There is separate mental health legislation, but in the *Mental Health (Care and Treatment) (Scotland) Act 2003*, decision-making ability is a criterion for both emergency detention (36(4)(b)) and for short-term detention (44(4)(b)), where 'because of the mental disorder, the patient's ability to make decisions about the provision of medical treatment is significantly impaired'.

The argument about whether incapacity should be the criterion for compulsory detention and treatment harks back (in a sense) to the aspiration of the Percy Commission³ that mental illness should be treated no differently from other illnesses. The suggestion is that the rationale for imposing treatment on someone should only be that the person lacks the capacity to make a decision him- or herself. Because this could be applied equally to people with mental illness and to those with other illnesses, it has been argued that this is a way to decrease discrimination and stigma.

The message is as follows, though ill, those with a mental disorder are somehow different. That is why they require separate legislation. They may be treated against their will irrespective of whether they have the capacity to consent to treatment. This suggests a pervasive and disturbing notion that 'mental' patients somehow are incapable of possessing a full degree of autonomy; mental disorder automatically diminishes the sufferer; he or she is not a complete 'person'¹⁴.

Pursuing this point is beyond my present remit and, in the context of England and Wales, is purely academic. I shall turn to consider some of the details of the Acts, with the caveat that what follows is merely a sketch (see^{1,2}).

MENTAL HEALTH ACT 2007

The MHA and the MCA both have accompanying Codes of Practice. Whilst the Codes merely provide guidance, it is clear that they cannot be ignored or deviated from without good reason. Box 137.1 contains the five guiding principles of the MHA Code of Practice.

Box 137.1

Summary of Guiding Principles in the MHA Code of Practice

Purpose Principle: Decisions under the Act must be taken with a view to minimizing the harm done by mental disorder, maximizing the safety and well-being of patients and protecting the public from harm.

Least Restriction Principle: People taking action without a patient's consent must attempt to keep to a minimum the restrictions they impose on the patient's liberty, having regard to the purpose for which the restrictions are imposed.

Respect Principle: Diverse needs, values and circumstances, including race, religion, culture, gender, age and sexual orientation must be respected.

Participation Principle: Patients must be involved as far as is possible in planning care. The involvement of carers and others with an interest in patients' welfare should be encouraged unless there are particular reasons to the contrary.

Effectiveness, Efficiency and Equity Principle: Resources are to be used in the most effective, efficient and equitable way.

Some of the changes to the MHA are less likely to affect the older patient. For instance, the MHA 2007 now defines mental disorder simply as 'any disorder or disability of the mind' (Section 1(2)). As in the past, dependence on alcohol or drugs is excluded from the definition of a disorder or disability of the mind, but promiscuity, other immoral conduct and sexual deviancy have been removed from the exclusions. The presumed reasoning behind this change and others is that they allow the detention of a broader range of people who can be subjected to a broader array of treatments. It is coupled with a change that broadens the professional groups that undertake particular roles, so that, instead of 'responsible medical officers', the MHA 2007 talks about 'responsible clinicians', who no longer need to be medical doctors. In addition, the treatability test has been replaced by an 'appropriate treatment test' (Section 4), where this means that the medical treatment is appropriate to the person's case and broadly conceived to alleviate or prevent a worsening of the person's disorder, or one or more of its symptoms or manifestations.

Of more relevance to older patients is the new right to apply to a county court to change the nearest relative (Section 23). This can be seen as a way for patients to maintain their autonomy. Similarly, the amendments in the MHA 2007 include the provision that patients have a right to an advocacy service when under compulsion (Section 30). Patients who are detained should be offered an Independent Mental Health Advocate (IMHA). Again, this could be potentially very helpful to older patients, although how this will work in practice is as yet unsure.

Perhaps the most significant change that could potentially affect older patients is the new provision of Supervised Community Treatment (SCT) (Sections 32–36). SCT provides a framework for the management of patient care in the community, following detention

under e.g. Section 3, and gives the responsible clinician the power to recall the patient to hospital for treatment if necessary. SCT is an alternative to Guardianship, concerning which the law has also been changed. It is now possible to convey the person to the place where he or she is required to reside, which is one of the powers given to the Guardian. The other two powers are: to require the patient to attend for treatment and to allow relevant professionals to have access to the place where the patient lives. In deciding between guardianship and SCT, the Code of Practice suggests that under SCT the focus is on ensuring that the patient continues to receive necessary medical treatment for mental disorder without having to be detained again and it allows compulsory recall, especially where speed is likely to be important (Chapter 28 MHA Code of Practice). On the other hand, the focus of Guardianship is on the patient's general welfare rather than being specifically on medical treatment. Guardianship should be considered where there is little risk of the patient needing to be admitted compulsorily and quickly to hospital. But Guardianship is required where there is a need for enforceable powers to require the patient to reside at a particular place. However, this does not allow the person to be deprived of their liberty and, if this is likely to be the case, then this must be authorized separately under the MCA. The Code also says that it will not always be best to use guardianship as the way to decide where patients who lack capacity must live, since it would be possible to, more simply, use Section 5 of the MCA, which allows that the person's liberty can be restricted. However, some legal experts suggest that Guardianship provides a greater degree of protection to all concerned.

MENTAL CAPACITY ACT 2005

The MCA is much more routinely applicable to older patients, being relevant whenever a person cannot make decisions for him- or herself. It has a dual function: it enables people to retain some control or influence over the decisions that are made on their behalf and it protects those who must provide care to people who cannot decide for themselves. Box 137.2 shows the principles that summarize the intent of the MCA.

Box 137.2

Principles of the MCA (Section 1)

- A person is assumed to have capacity.
- All practicable steps must be taken to help the person to make a decision.
- People are entitled to make unwise decisions.
- Any actions taken on behalf of a person who lacks capacity must be in the person's best interests.
- Before any action is taken it should be the least restrictive of the person's rights and freedom of action.

Section 2 of the MCA defines incapacity as follows:

... a person lacks capacity in relation to a matter if at the material time he is unable to make a decision for himself in relation to the matter because of an impairment of, or a disturbance in the functioning of, the mind or brain.

This leads to a two-stage test of incapacity: first, does the person have an impairment of, or a disturbance in the functioning of, their mind or brain? Secondly, does the impairment or disturbance mean the person is unable to make a specific decision when they need to? This is judged by asking whether the person is able to retain (at least for a short while), understand and weigh up the relevant information and communicate his or her decision.

If the person lacks capacity, the central plank of the MCA is that decisions must be made in the person's best interests (Section 4). The MCA Code of Practice explains that 'best interests' cannot be defined because it will be so particular in different circumstances for different people. But it sets out (in Chapter 4) a checklist to help judgements to be made. At the heart of the checklist is the idea that the person's past and present wishes and feelings, values and beliefs, should inform the decisions that are made on his or her behalf. In addition, the views of anyone else engaged in caring for the person or anyone who might have an interest in the person's welfare must be consulted if at all possible. Whilst the details of the MCA should be consulted, this brings into view two other important aspects of the Act. First, it confirms the legal standing of valid and applicable advance refusals of treatment (but they must be both valid and applicable). Secondly, it establishes the concept of a Lasting Power of Attorney (LPA), to make decisions about matters of welfare, which include decisions about healthcare and changes to the place of residence. A LPA, like the previous Enduring Power of Attorney, can also be made to cover property and finance. But a welfare LPA means that a doctor might be faced by a relative with the power to give or withhold consent to the patient's treatment. However, as with all decisions for people who lack capacity, the decisions made by the donee of the LPA must be in the person's best interests and they can be challenged in the Court of Protection if they are not.

Unlike the MHA, the MCA does not allow everyone to have an advocate, but where serious medical treatment decisions or changes to the place of residence are being contemplated, *if the person is not supported* other than by professionals, an Independent Mental Capacity Advocate (IMCA) must be appointed. This is yet another way in which the MCA seeks to protect and enhance the rights of people who lack capacity. This brings to mind Sabat writing:

The means by which we evaluate, and arrive at our conclusions about, the afflicted person's competency may well ultimately be a test of our own competency as thoughtful, judicious, humane human beings¹⁵.

Sections 5 and 6 of the MCA allow that a person may be restrained as long as this is proportionate. However, by an amendment to the MCA brought in by the MHA 2007, it is made clear that, even if restrictions of liberty can be sanctioned under certain circumstances, a deprivation of liberty requires greater safeguards and must be avoided if at all possible. If, where the person lacks capacity and in his or her best interests, a deprivation of liberty is required, then appropriate authorization must be sought. These are the Deprivation of Liberty Safeguards (DOLS). The technicalities of DOLS are beyond the scope of this chapter (see¹⁶). The distinction between a restriction of liberty and a deprivation of liberty seems crucial in this connection, but it, too, like 'best interests', cannot be pinned down. This makes life difficult and uncertain at the coalface, but is of con-

siderable conceptual interest. The issue is nonetheless clear: as a matter of human rights, vulnerable people must be protected by the law.

CONCLUSION

This brief foray into the law brings us back to Earl Warren: 'Without law, the least scrupulous might prevail, but without ethics, law itself could not exist'. We can see how the laws establish principles as guides to practice, but in the end it is practitioners who must put the law into effect. It is our patterns of practice – be they ethical or unethical – that shape our lives and thereby, collectively, the moral standing of our societies.

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Training Requirements for Old Age Psychiatrists in the UK

Susan Mary Benbow¹ and Aparna Prasanna²

¹*Centre for Ageing and Mental Health, Staffordshire University, Stafford, UK*

²*Wolverhampton Primary Care Trust, Penn Hospital, Wolverhampton, UK*

In the UK over the past 30 plus years increasing numbers of psychiatrists have specialized in working with older adults. Various terms are used to describe this area of work: psychogeriatrics, geriatric psychiatry, old age psychiatry and older people's mental health are probably the most common. In 1978 the Royal College of Psychiatrists formed a Section (which later became a Faculty) of Old Age Psychiatry and in 1989 the Department of Health recognized old age psychiatry as a specialty: this was regarded as a milestone in the specialty's development at the time. The Royal Colleges of Physicians and Psychiatrists produced a Joint Report in 1989, which devoted a chapter to education and training in the psychiatry of old age¹. Prior to this there was no designated training programme for psychiatrists aiming to work with older people.

BACKGROUND: GROWTH OF THE SPECIALTY

In the early 1980s two surveys of old age psychiatry services reported considerable growth in the developing specialty^{2,3}, and over 200 consultants were identified by late 1983. The authors predicted continuing growth in the specialty and a need to expand training placements. At that time the Joint Committee on Higher Psychiatric Training at the Royal College of Psychiatrists required higher trainees to spend 12 to 18 months in posts where the majority of the work was in old age psychiatry, and 28 senior registrar placements were identified.

In 1990 there were 360 consultants working mainly in old age psychiatry and by 1993 the total had increased to 405⁴. Figures collected by the Faculty of Old Age Psychiatry showed a continuing gradual increase in consultant numbers, but with a high vacancy rate.

The first Joint Report¹ had recommended that each medical school should have a senior academic in old age psychiatry and that all medical undergraduates should receive training in the subject. Faire and Katona⁵ surveyed undergraduate teaching in the UK and reported a considerable expansion in academic old age psychiatry posts. However, they also found a great variation in the amount of clinical experience on offer and the authors felt there was a strong case for all medical students having clinical experience in the specialty as recommended by the Joint Report. Gregson and Dening⁶ surveyed teaching hospital psychiatrists and found that many teachers set no

learning objectives in old age psychiatry. Most respondents wanted their teaching to impart enthusiasm for the subject, a sense of hope in working with mentally ill older adults, and an awareness of issues specific to ageing and ageism.

The second Joint Report⁷, published in 1998, recommended that the characteristics of mental disorders in older people and the principles of good quality care should be included in the core curricula of all schools of medicine and nursing, and by the time the second edition of this book was published, there were chairs or readerships at a number of medical schools in the UK, although some gaps remained. The twenty-first century brought with it the National Service Framework for Older People⁸, which estimated that by 2009, extrapolating from the numbers of existing trainees, there would be 670 old age psychiatrists. It argued the case for increased staff numbers to improve the mental health of older people, and also noted that its recommendations had implications for education and training in undergraduate and postgraduate medicine.

Despite growth in the specialty of old age psychiatry, the long-term prospects continue to cause concern. The Dean of the Royal College of Psychiatrists wrote in his May 2009 newsletter⁹ that recruitment into psychiatry as a medical specialty is 'in crisis' with only 6% of candidates for paper 2 of the Membership examination in summer 2008 having gained their primary medical qualification in the United Kingdom. One response to this has been initiatives to try to attract more UK medical students into the specialty, e.g. an official Royal College of Psychiatrists group has been set up on a popular social networking website.

Alongside these developments, postgraduate education has undergone considerable reorganization over recent years. *Modernising Medical Careers*¹⁰ was published in 2004. It aimed to streamline training based on competency-based curricula, and also brought in the foundation programme for newly graduated doctors. In 2005 the Postgraduate Medical Education and Training Board (PMETB)¹¹ took over responsibility for standards and quality assurance of postgraduate education, training and assessment in medicine and dentistry. The foundation programme has introduced foundation posts in psychiatry to many areas, and with it an opportunity to attract new medical graduates into the psychiatric specialties.

SPECIALIST TRAINING IN OLD AGE PSYCHIATRY

The total minimum duration of specialist training in old age psychiatry is currently six years, of which three years is in core or generic training (core trainee CT1–3) and three years in advanced training (specialty registrar ST4–6). A new curriculum for specialty training in psychiatry and its specialties was approved by PMETB in April 2009 and was introduced in August 2009¹². Figure 138.1 illustrates the structure of training.

Core Training

A newly qualified doctor intending to specialize in psychiatry will first spend two years on a foundation programme. Following this, competitive recruitment into psychiatry in England is by a standardized national recruitment programme through the Royal College of Psychiatrists. The trainee will undertake core training, which lasts three years and concentrates on providing a range of experience in the specialties and subspecialties of psychiatry. This part of training is common to the various psychiatric specialties. Core training aims to develop history taking, formulation and case presentation skills, therapeutic skills and clinical judgement, relationship with patients/carers and colleagues, and appropriate use of mental health legislation. Experience in old age psychiatry is regarded as an important part of core training because of the increasing elderly population and the high rates of mental illness in older people.

During this time the trainee is preparing to take his/her examination for membership of the Royal College of Psychiatrists. The minimum requirement to sit the Parts 1, 2 and 3 written papers for the Membership examination is 12 months' experience in psychiatry. This may include four or six months of experience of old age psychiatry. The Clinical Assessment of Skills and Competencies (CASC) exam can only be taken after 30 months of experience in psychiatry and is a requirement for entry into advanced training in the different specialties.

In addition, throughout their core and advanced training, trainees undergo a series of workplace-based assessments (WPBA). A number of assessment tools such as assessment of clinical expertise (the trainee's ability to assess a case), case-based discussion (discussion of a clinical case in which the trainee has made a significant contribution) and direct observation of procedural skills (assessment of a practical procedure) can be used¹⁴. Evidence of achieved competencies is collected using a combination of electronic and paper portfolios.

By the end of three years of approved supervised placements in core training, the trainee is ready to move onto advanced training and will hold the Membership of the Royal College of Psychiatrists (MRCPsych). They will have had sufficient exposure to the psychiatric specialties to decide on their career intentions.

Advanced Training

Higher training offers an educational programme that aims to prepare a trainee for independent practice in psychiatry. Following competitive entry into a specialty training programme, a National Training Number (NTN) is awarded by a Postgraduate deanery. The PMETB sets the standards for training and approves the curriculum, which is developed by the Royal College of Psychiatrists¹⁵. Trainees receive educational and clinical supervision by approved trainers. On successful completion of an advanced training programme, the Certificate of Completion of Training (CCT) is awarded by the PMETB on recommendation by the Royal College¹⁶. This gives entry to the General Medical Council's Specialist Register¹⁷. Since 1997, entry into the Specialist Register has been mandatory for specialists who wish to take up a consultant post in the National Health Service.

Currently, trainees can gain a single CCT in six psychiatric specialties: General Adult, Old Age, Forensic, Child and Adolescent, Learning Disabilities, and Psychotherapy. General Adult psychiatry trainees can gain further endorsements in Liaison, Substance Misuse and Rehabilitation psychiatry. Old Age psychiatry trainees spend three years in advanced training of which one year may be spent in General Adult psychiatry or one of its subspecialties. Academic Clinical Fellows and Clinical Lecturers can (with prior approval) count the time spent in such posts towards a CCT.

During their training, specialty registrars are expected to develop their professional attributes, core knowledge and skills, carry out audit, get involved in teaching and management, and develop research and/or special interests. Eight 'core' sessions are devoted to experience in old age psychiatry (or other specialty). This involves working with a multidisciplinary team to provide a service to a defined population. Two sessions are available to develop research and audit experience or other special interests. Trainees could opt to gain formal higher qualifications relevant to old age psychiatry during this time. Many trainees choose to gain further experience in psychological therapies¹⁸. They are also expected to gain experience of geriatric medicine at some stage of their training, and this is usually achieved either as a short-term attachment or using special interest sessions.

CONTINUING PROFESSIONAL DEVELOPMENT AS A CONSULTANT

Loane and Barker¹⁹ surveyed newly appointed old age psychiatrists to investigate their views of their higher training experience. Overall their respondents felt that clinical experience was satisfactory, but management experience was lacking in a number of areas, and training was identified as insufficient in relation to experience in dealing with complaints, dealing with difficult professional relationships, recruitment and disciplinary proceedings. Higher trainees are

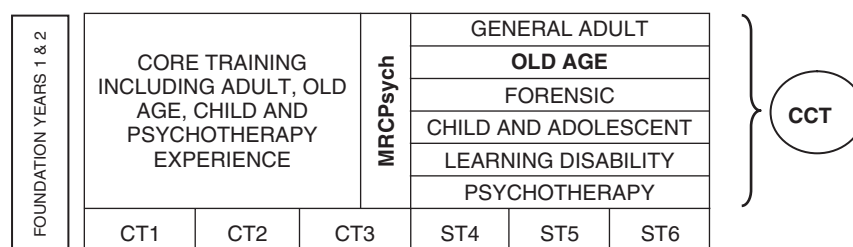


Figure 138.1 Training pathway in psychiatry (adapted from six-year psychiatry plan, Royal College of Psychiatrists¹³)

expected to get training in management but it is difficult to pitch it at the right level, and constant changes in the health service are challenges to confidence and competencies.

Today lifelong learning is regarded as essential for all health care professionals²⁰. Learning does not stop at the transition from trainee to consultant; indeed, some might say that this is the point at which learning really starts. In 2001 the Royal College of Psychiatrists introduced personal development plans (PDPs) as a way of planning continuing professional development prospectively and linked to clear objectives; together with this, participation in peer groups is required in order to review and assist in developing PDPs²¹. This means that consultant old age psychiatrists plan their CPD, although it needs to be flexible and to evolve with the specialty, the individual and the job, since increasingly consultants' interests, disciplines and posts evolve as their career progresses. This may be one way for people to re-energize and deal with the stresses of their multiple roles²². CPD is a positive opportunity for consultants to continue learning and developing throughout their working lives.

LIFELONG LEARNING

Learning starts in medical school and continues throughout the working life of the old age psychiatrist. As is true of the whole of medicine, the context within which the specialty operates is constantly evolving, and the specialty itself continues to develop and change²³. There are always threats and opportunities on the horizon. Old age psychiatry and its practitioners cannot stand still. The enthusiasm which teaching hospital psychiatrists aim to impart to their medical undergraduates can be maintained throughout specialist training and boosted during the course of a consultant career by continuing professional development and the challenge of working in a constantly changing health and social services context.

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Training Requirements in North America

Paul D. Kirwin¹ and Kirsten M. Wilkins²

¹Associate Professor of Psychiatry, Geriatric Psychiatry Fellowship Director, Yale University School of Medicine, VA CT Healthcare System

²Assistant Professor of Psychiatry, University of Oklahoma College of Medicine-Tulsa, Tulsa, OK

The imperative for training specialists in geriatric psychiatry has never been greater. As the United States' 76 million baby boomers near retirement age, the number of Americans over age 65 will double to 70 million, one-fifth of the U.S. population. Americans older than 85 represent the fastest growing segment of this population and are projected to grow from five million today to an estimated 21 million by 2050. By the year 2010, there will be approximately 40 million people in the United States over the age of 65¹. Almost 20 percent of those people will experience mental health problems².

Facing this exploding demographic imperative is a shrinking workforce of those with specialty training in the diagnosis and treatment of neuropsychiatric disorders in late life. In 2001, there were about 2,600 geriatric psychiatrists in the U.S. By 2007 there were only 1,596 geriatric psychiatrists—rather than the 5,000 needed to provide adequate care for the current population of older adults. The steep decline in the numbers of geriatric psychiatrists is accounted for by attrition and a failure of many who remain in active practice to recertify. Recruitment into the field is also waning, with less than half of geriatric psychiatry fellowship positions filled in 2006–2007. We are currently graduating approximately 80 new geriatric psychiatrists a year. By the year 2030 accounting for attrition, we are projected to have approximately 1,659 geriatric psychiatrists, or one geriatric psychiatrist per 20,195 older Americans. The field of geriatric medicine faces parallel workforce shortages with a 25% drop in geriatricians in the last five years. Over the next 20 years this disproportion is expected to worsen: from 1 geriatrician per 2,456 elderly currently to 1 per 4,254 older Americans by 2030. By 2030, it is projected that less than one third of the required geriatricians will be available for older Americans. Clearly there is a pressing need to train more experts in geriatric psychiatry and medicine, and to expand clinical training in geriatrics in both general psychiatry and medicine residency programs to adequately prepare a workforce ready to care for the expanding U.S. elder population³.

The problem extends to other specialists in mental health and aging. In social work, only about 1,115 (3.6%) of Master's level social work students specialize in aging and only about 5% of practitioners at any level identify aging as their primary area of practice, even though the National Institute on Aging projected that by 2020, 60,000–70,000 gerontological social workers will be needed. Among psychologists, only about 3% view geriatrics as their primary area

of practice and only 28% of all graduate psychologists have some graduate training in geriatrics⁴.

Training in general psychiatry and then in the sub-specialty of geriatric psychiatry is extensive. The Accreditation Council for Graduate Medical Education (ACGME) in conjunction with the American Board of Psychiatry and Neurology stipulate that one must complete four years of post medical school graduate training in general psychiatry before being eligible to enter advanced training in geriatric psychiatry. One month of general psychiatry residency is dedicated to training in geriatric psychiatry. The quality of this geriatric psychiatry experience, in particular, the quality and attributes of the educators providing the training are associated with the development of interest in the field⁵. Following completion of the general psychiatry residency, the geriatric psychiatry fellowship is typically one year in length. Many programs offer additional training years for research, but these are optional and not required to sit for the advanced board exam in geriatric psychiatry.

The ACGME provides program requirements that specify the scope and content of training in general psychiatry and all psychiatry subspecialties. Programs undergo periodic "site visits" by the ACGME to ensure that the quality of the training program meets the expectations outlined in the program requirements. The twenty-plus page ACGME Geriatric Psychiatry Program Requirements necessitate that training experiences are rooted in six core competencies. The program must demonstrate that fellows have educational opportunities to gain knowledge, skills, behaviors and attitudes in these six domains: Patient Care, Medical Knowledge, Practice-Based Learning and Improvement, Interpersonal and Communication Skills, Professionalism, and Systems-Based Practice. These six core competencies have been adapted to fit the scope of training needs of a geriatric psychiatry fellow⁶.

Ideally, training in geriatric psychiatry offers a rich combination of experiences designed to provide psychiatrists with expertise in the diagnosis and treatment of psychiatric and neuropsychiatric disorders in late life, to develop skills as educators, and to stimulate interest in research. A training program should provide opportunities to learn about the socio-cultural, legal, ethical and financial issues associated with the care of older adults. Supervised clinical training should occur in a broad array of settings, including outpatient and inpatient environments, nursing home and long term care

settings, cross disciplinary consultation opportunities, home-based services, community-based offices and clinics, and both inpatient and outpatient-based research programs.

A critical element in a successful geriatric psychiatry training program is mentorship. Unlike large residency training programs, fellows often work side-by-side with their program directors and senior attending psychiatrists. This day to day interaction is fundamental to a fellow's professional and personal development as a colleague. Imparting enthusiasm, attending to a fellow's interests, encouraging their abilities, and assisting with their limitations are essential for a fellow's growth. Successful mentorship relationships often last far beyond training and become an essential resource during the development of a career. They also serve as powerful models for developing one's own mentorship sensibilities. Mentorship is a deeply satisfying process and is vital to the overall success of the training program.

In 2008, the Institute of Medicine (IOM) released a study of the readiness of the nation's healthcare workforce to meet the needs of its aging population. *Re-tooling for an Aging America: Building the Health Care Workforce* called for immediate investments in preparing our health care system to care for older Americans and their families⁷. Yet the prescient and insightful report precluded in-depth consideration of the workforce needed for treating mental illness. The American Association for Geriatric Psychiatry (AAGP) formally requested that the study be followed by a complementary study focused on the specific challenges in the geriatric mental health field. The AAGP asserts that "virtually all healthcare providers need to be fully prepared to manage the common medical and mental health problems of old age. In addition, the number of geriatric health specialists, including mental health providers, needs to be increased both to provide care for those older adults with the most complex issues and to train the rest of the workforce in the common medical and mental health problems of old age. The small numbers of specialists in geriatric mental health, combined with increases in life expectancy and the growing population of the nation's elderly, foretell a crisis in health care that will impact older adults and their families nationwide. Unless changes are made now, older Americans will face long waits, decreased choice, and suboptimal care"⁸. Then, in December of 2009, after extensive efforts by the AAGP and other organizations, Congress passed legislation designating \$900,000 for the Institute of Medicine (IOM) to conduct a study on the mental health workforce necessary for our nation's growing geriatric and ethnic populations, which promises to provide guidance on how to address geriatric mental health workforce inadequacies.

Multifaceted incentives to enter training in geriatric psychiatry are necessary. Initiatives in the public policy arena include legislation to provide loan forgiveness for health care professionals who enter geriatric specialties. The AAGP has promoted legislation to create a new program for loan repayment for specialists across disciplines that enter geriatric specialties. The AAGP also supports legislation to allow fellows in geriatric medicine and geriatric psychiatry to include fellowship training as part of their obligated service under the National Health Corps Loan Repayment Program, a program designed to encourage health professionals to provide clinical care to underserved populations. The AAGP has also requested that the ACGME review the current structure of fellowship training to allow for more flexibility and promote recruitment of psychiatrists into the field of geriatric psychiatry. Specifically, the AAGP has asked the ACGME to consider allowing residents to use their fourth year elective time in general residency training to specialize in geriatric psychiatry and then be eligible to sit for the general and subspecialty certification at the end of four years of training. The organization also

supports a training model to integrate research training in geriatric mental health over a two year period, the fourth and fifth year of training, to stimulate and encourage academic research careers.

Recently, there have been promising developments which should promote easier access to skilled mental health care for the elderly. The U.S. Congress passed legislation (over President Bush's veto) on July 15th, 2008 that eliminated long standing discriminatory copayment rates for Medicare outpatient psychiatric services. Cost sharing for outpatient mental health services will phase down from 50 percent to 20 percent by 2014. On the private insurance side, in 2008 Congress also passed legislation to ensure mental health parity which stipulates that for employers with greater than 50 employees, any limits on mental health treatments (including substance abuse) must be no greater than the limits placed on medical and surgical benefits.

The demographics of aging and mental illness clearly indicate a growing need for specialists trained in comprehensive psychiatric care of older adults. Despite the availability of geriatric psychiatry training and the growing population of older adults, current statistics suggest an alarming paucity of psychiatrists who are specialty trained in geriatrics. As such, it is essential to increase the geriatric psychiatry workforce. This includes increasing recruitment of general psychiatric trainees into the geriatric psychiatry sub-specialty, in order to both provide care for the growing population of older adults and to train general psychiatric and medical practitioners, who will likely be providing the bulk of the psychiatric care of older adults. Several strategies to increase the geriatric psychiatry workforce are currently being explored, including structural changes in sub-specialty training programs, financial incentives such as loan repayment programs, and earlier and broader experiences with geriatric psychiatrist educators during general psychiatry residency training. Equally important in ensuring that the elderly will receive optimal care are initiatives directed at improving their access to specialty mental health services.

In spite of an evolving economic landscape, a decision to enter the field of geriatric psychiatry has always been a decision of the heart, and not the pocket-book. It attracts those who love to hear stories from those who have lived the longest and acquired wisdom borne of life long experiences. For most elderly, the onset of mental illness is a new and horrifying experience. Their distress is profound, as is their gratitude for skilled intervention. One gets to make a difference in geriatric psychiatry, and this ability to intervene with patients and families in both curative and supportive ways brings the geriatric psychiatrist deep satisfaction. Working with the elderly attracts those with a sense of mission, a calling to take care of our most vulnerable citizens – those who face the double prejudice of old age and mental illness.

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Education in Old Age Psychiatry: Recent and Future Developments

Hugo de Waal

East of England Postgraduate School of Psychiatry, Fulbourn, Cambridge, UK

INTRODUCTION

Over the past few decades geriatric psychiatry has developed as a psychiatric subspecialty to varying degrees in different countries¹: while in some it is recognized as such at governmental level (e.g. the UKⁱ), elsewhere it developed a defined medical identity more within the medical profession (e.g. the USA, Australia, Canada), or it functions as a less well circumscribed area of special interest of medical practitioners, whose designation often lies in other specialties, such as general psychiatry, neurology or geriatric medicine (e.g. the Netherlands).

In 1998 the World Health Organization (WHO) in collaboration with the International Psychogeriatric Association (IPA) published three consensus statements on geriatric psychiatry, the third of which focused on education. Its aim was 'to propose wide guidelines favouring an education of good quality, taking into account the complexity of the subject to teach and of the public concerned'² – not a straightforward ambition, given the fact that worldwide geriatric psychiatric services and education range from non-existent to highly sophisticated and mature, well-embedded in health provision and educational accreditation systems.

The following presents the impact of various circumstances and factors upon the development of education in geriatric psychiatry and highlights some trends that may prove important for the future of training and education in this subspecialty.

THE LINKS BETWEEN EDUCATION, CAREER CHOICE, SERVICE PROVISION AND SUBSPECIALTY RECOGNITION

Career Choice

Training and education in geriatric psychiatry are influenced to a considerable extent by factors related to career choices made by medical graduates in general. In the United States, Bragg and Warshaw reported that problems persist in recruitment and retention of 'high-quality USMGs' (United States Medical Graduates) in both geriatric

medicine and geriatric psychiatry. They identified early exposure to geriatrics as an important factor in selecting it as a career³, as did Lieff *et al.*, who investigated more fully which particular experiences showed a positive effect: they mention specific teacher attributes, training experiences, personal experiences with seniors, and the medical, neuropsychiatric and multifactorial nature of the field⁴. Similarly, in the United Kingdom, McParland *et al.* showed how undergraduate experience is essential in choosing the specialty and the more so if that experience is positive and of a high quality⁵.

There are other, related factors at play with regard to career choice: Goldacre *et al.* report that in the United Kingdom non-white consultants who qualified abroad were at 18.4% significantly over-represented in geriatric psychiatry⁶. This pattern of skewed ethnic representation can be recognized in general in British psychiatric training: in his recent newsletter the Dean of the Royal College reported that at the last sitting of the final membership examination (the so-called Clinical Assessment of Skills and Competencies) only one out of eight candidates was a UK graduate⁷. It is therefore clear that the UK remains a net importer of doctors, and this pertains to geriatric psychiatry even more than to some of the other psychiatric subspecialties. He believes that two important explanatory factors can be found in 'the current dismal experience of many medical school clinical attachments' and 'the poor penetration of psychiatry into the Foundation years' (the British version of post-qualification, pre-registration training). One could therefore conclude that even in the UK there are major difficulties in recruitment and retention in psychiatry (and therefore in geriatric psychiatry), regardless of the fact that internationally the UK could be regarded as advanced in its development of geriatric psychiatric services and related training and education.

Service Provision

Surveying the international picture of education in old age psychiatry, it soon becomes clear that it appears mature and sophisticated in those countries where psychogeriatric services exist, which themselves are mature and established. On the contrary, education tends to be poorly structured, educationally isolated and occurring in an ad hoc fashion in those countries where psychogeriatric services are either non-existent, or are an 'afterthought' featuring in other medical specialties.

ⁱOld Age Psychiatry is recognised in the UK by the Postgraduate Medical Education and Training Board as a subspecialty, carrying its own Certificate of Completion of Training.

In 2001 the World Psychiatric Association (WPA) section on old age psychiatry surveyed the level of development of medical education in geriatric psychiatry in 93 countries. A total of 48 countries responded, which in itself at 52% was a worryingly low response rate – even for a postal questionnaire – given that the survey was particularly aimed at those clinicians who were known to have a special interest in and affinity to the subspecialty. Of the responders, 40 countries reported the existence of old age psychiatric services and 44 formal teaching at undergraduate level, but only 13 full recognition of the discipline as a subspecialty. The member societies furthermore considered support for the development of postgraduate training as their most pressing need⁸.

In those countries where there is a drive to develop both services and education, there is often the problem of how to tackle the ‘chicken and egg’ phenomenon: it is, perhaps predictably, quite difficult to get education going when clinically there is no defined basis for that to occur in, although it must be pointed out that in the case of geriatric psychiatry some lessons have been learned from geriatric medicine. The same survey found that chairs in geriatric medicine – as a reasonable indication of structured advanced educational activity – only exist in countries where geriatric medicine is recognized as a subspecialty. This appeared not to be the case for geriatric psychiatry; several countries reported chairs in geriatric psychiatry to be in existence, even when the discipline was not yet formally recognized.

Subspecialty Recognition

The process of developing services when there are only a few appropriately skilled and motivated medical specialists pushing the psychogeriatric agenda is understandably a laborious exercise. But even when there are such interested parties present, the response from the wider professional body may be felt to be less than supportive. For example, in Canada Herrmann⁹ pointed out that there exists a very active geriatric psychiatric subspecialty. The Canadian Academy of Geriatric Psychiatry counted in 2004 more than 190 members and organizes annual academic meetings, residency training programmes, numerous undergraduate and postgraduate training programmes and fellowship awards. It developed the Canadian Coalition for Seniors' Mental Health (CCSMH), which – among many activities and initiatives – co-hosted and organized the 9th Congress of the International Psychogeriatric Association. Yet the Canadian Royal College of Physicians and Surgeons did not demand any particular clinical and training time requirement in geriatric psychiatry until 2008, when it incorporated a mandatory six months' placement in geriatric psychiatry into its junior residency training programme¹⁰ and to this day it does not recognize geriatric psychiatry as a subspecialty, while it does list geriatric medicine as such¹¹. Herrmann points out that such subspecialty recognition is vitally important to ‘strengthen the awareness and profile of geriatric psychiatry, increasing the likelihood of recruitment into the practice’. If such recognition is not forthcoming in a country such as Canada, then how difficult will it be in countries that do not feature highly regulated professional bodies and training accreditation processes?

With or without such support from regulatory bodies, there is no doubt that high-level insistence on guidelines and standards has a positive effect on further developments. The earlier mentioned WHO consensus statement has led to a number of initiatives with immediate impact. In Europe it led to a consensus curriculum on Skill-Based Objectives in Old Age Psychiatry in 2002 (the so-called

Lausanne statement). Apart from formulating a comprehensive list of areas of competence and learning objectives, Gustafson *et al.* express the hope that implementation of the curriculum ‘should help ensure that . . . each European country has a number of specialists who can provide leadership in clinical service development, training and research’¹². In the USA Lief *et al.* formulated core competencies for geriatric psychiatric training and certification; their list appears equally inspired by the WHO consensus statement¹³.

Implicitly they may be considered to base such expectations on the experience in the UK, where geriatric psychiatry managed to become a fully-fledged, mature and sophisticated subspecialty on the back of the energetic advocacy from initially only a few ‘pioneers’, such as Sam Robinson, Felix Post, Klaus Bergmann, Tom Arie, David Jolley, Brice Pitt, Elaine Murphy, Gordon Langley and John Wattis, to name the most prominent ones. Their inspirational efforts span across close to three decades, and to gain some understanding of how such pioneers and champions went about creating a new subspecialty, the Guthrie Trust Witness Seminar, entitled *The Development of Old Age Psychiatry from the 1960s until 1989*, provides a unique account and an important insight into how enthusiasm on one hand and tenacity on the other proved to be essential cornerstones of the process of establishing and developing old age psychiatry in the UK¹⁴.

FUTURE DEVELOPMENTS

Research

Apart from the obvious and regularly reported demographic projections, which in themselves are likely to lead to increased attention and professional interest in geriatric psychiatric services on one hand, and subspecialty medical education on the other, there are other – very interesting – factors that may lead to a more fertile appreciation of the subspecialty within the medical profession at large. While historically geriatric psychiatry was quite limited in its therapeutic arsenal with respect to its most prominent disease category, i.e. dementia, the relatively recent availability of cholinesterase inhibitors, particularly in the developed countries, has served to improve its perceived status within the younger generations in medicine. This is likely to be further enhanced by the accelerated production of other therapeutic medications coming out of a research establishment which until fairly recently would have found it difficult to spend much time and energy on an illness category it considered to be largely beyond therapy or profit. The International Conference on Alzheimer's Disease (ICAD) in July 2009 in Vienna featured no fewer than eight distinct therapeutic target areas. Progress appears to be being made, for instance, in pyroglutamate-related pathways, tau aggregation inhibition, protection against tau hyperphosphorylation via activity-dependent neuroprotective protein (ADNP), normalization of metal–protein interactions via so-called metal protein attenuating compounds (MPAC), β -secretase inhibition, prevention of neuronal re-entry into the cell cycle, and so on (see www.alz.org/icad/overview.asp). Although many of these projects are some considerable time away from leading to clinically relevant therapeutic agents, there is little doubt that over time a more varied therapeutic arsenal will lead to more interest from all sorts of corners, including budding specialists.

Service Development

The link between such therapeutic power on one hand, and the ongoing development of a speciality and related focus on training and

education on the other, was recognized by Foucault, who described and analysed such links as cornerstones of a more or less mature specialist discourse, even if he then goes on to critique such discourse¹⁵. One unpredictable issue at this stage is the possibility that a super-specialty may develop within geriatric psychiatry, solely devoted to dementia: the inexorable and fast accelerating progress of therapeutic research into this area, combined with projections of an ageing population, would potentially lead to segregation between such a service and services for older patients with so-called functional illnesses. Such a path would follow Foucault's analyses of the medical discourse: whenever medicine is able to pinpoint causative pathophysiological processes it has a tendency to devote specialist attention to them, and this is further reinforced when therapeutic interventions become feasible and prove to be efficacious. Should this occur, then a new threat may be surfacing to the integrity and cohesion of geriatric psychiatry: one should be guarded if such a development leads to a decrease of specialist attention to the functional illnesses of old age, and it could be considered a negative and unintended consequence if the functional side of geriatric psychiatry winds up being reabsorbed into more generic psychiatric services.

Postgraduate Schools

From 2007 in the UK postgraduate training in all medical specialties is being commissioned and quality assured by newly established Postgraduate Schools, on behalf of the longer established Postgraduate Deaneries. Such Schools function through operational boards, which are almost exclusively manned by medical trainers and educationalists, with additional representation of senior management, Royal College officers, trainees, and patients and carers. These Schools are proving quite powerful in developing, driving and improving postgraduate training, and this is particularly important for those subspecialties that otherwise might wind up in a 'Cinderella position'. The British concept of the Postgraduate Schools may well prove an excellent mechanism through which other countries might try to foster such subspecialty developments. If so, it would be a rare example of a situation in which a high intensity of political interference with educational structures (as is the case in the United Kingdom) actually turns out to be beneficial to the profession and its training and education.

CONTENT OF TRAINING, ASSESSMENT AND APPRAISAL PROCESSES

With the establishment of Postgraduate Schools in the UK, the Royal College's role became more specifically focused on curricular development and the setting of standards for training and education. This gave the College the opportunity to formulate detailed, competency-based curricula, which directly link to assessment and appraisal processes, and these in turn form the core evidence on which specialist accreditation is based. The curricula undergo regular revision, and the latest version with respect to geriatric psychiatry can be accessed at www.rcpsych.ac.uk/PDF/Old_Age_Feb09.pdf.

Additionally the College took the lead role in developing workplace-based assessments particular to psychiatric training, which shifted the training experience from an apprentice model to a 'managed learning' model. These assessments replaced in part the traditional knowledge-testing function of the Royal College membership examination; workplace-based assessments specifically test clinical and professional competencies through direct observation and feedback, the latter being particularly important in providing a

learning tool to the trainee, with increased levels of self-reflection on performance.

Already in 2003 Gustafson *et al.* called for training programmes to:

- be rooted in evidence-based practice
- be clinically relevant
- have explicit evaluation criteria
- include feedback from trainees
- be reviewed regularly.

He also highlighted that 'training program participants should have both formative (constructive feedback) and summative assessments'¹¹. The former is thus now a crucial component of specialist training in the UK (as it has been for some time in the USA and Canada), while the latter is particularly important if one is to expect such training programmes and assessment processes to be linked to accreditation of specialists. Gustafson calls for the setting up of geriatric psychiatric accreditation through national systems in all European countries. All of this flows directly from the Lausanne statement¹¹, in turn the result of the WHO/IPA consensus statement².

It is worth noting that in the UK, with the implementation of the new streamlined postgraduate curriculum and assessment processes in 2007, totally new workplace-based assessments have been developed. These were to some degree based on the tools already in use in the USA and Canada, but they underwent extensive adaptation and re-validation for the purposes of psychiatric training. More recently a further assessment tool has been developed, particularly aiming to test for higher, non-clinical skills (the so-called Direct Observation of non-Clinical Skills, or DONCS); it tests and assesses the trainee's skills in competencies not directly related to the clinician-patient interaction, but more to do with higher, so-called 'meta-level', skills. The categories are taken from CanMEDS, the Canadian framework, which organizes core competencies around seven key physician roles:

- medical expert
- communicator
- collaborator
- manager
- health advocate
- scholar
- professional.

It aims to provide formative and summative learning opportunities to the trainee in their post-membership training, and is expected to aid in their preparation for their subsequent role as consultant old age psychiatrists. In the British National Health Service there is a strong appreciation that the consultant role must exceed the provision of clinical, patient-centred care, and should incorporate a variety of roles, such as team leader, service developer, inter-agency negotiator, strategic planner etc. Given that particularly in geriatric psychiatry there is a relatively strong emphasis on collaboration with other agencies and an ensuing interest in strategic service and educational development, the DONCS could be particularly powerful in fostering such skills in specialists being educated and trained in geriatric psychiatry, were it to be adopted elsewhere. More information about this assessment tool can be found at <https://training.rcpsych.ac.uk/doncs-assessor-guidance>.

CONCLUSION

With the large variety of political, cultural and economic factors on one hand and the huge diversity of service configuration and related

existence of medical education on the other, combined furthermore with the varying levels of governmental interest or disinterest in either, the way forward will at least have to be a two-pronged one: top-down with the involvement and guidance of institutions such as the World Health Organization and the International Psychogeriatric Association and bottom-up through 'champions and pioneers'.

The role of champions and pioneers should start with undergraduate training. One noteworthy initiative, recently started by the UK Royal College and led by its Psychiatric Trainees' Committee, is designed to engage with medical students: in medical schools up and down the country undergraduate Psychiatry Societies are starting up, linked into a network in which a new College grade of Student Associate of the Royal College features prominently. The UK Royal College website now has a dedicated section for medical students who are interested in psychiatry and who want to find out more about the specialty, the training and education, career options etc. (www.rcpsych.ac.uk/specialtytraining/students.aspx). It provides an opportunity for interested medical students to enrol as a Student Associate of the Royal College. Further information on the Old Age section of this website can be found at www.rcpsych.ac.uk/specialtytraining/students/subspecialties/oldagepsychiatry.aspx.

In short, one can discern a number of factors that should lead to a higher profile for geriatric psychiatry and its training and education:

1. continued efforts by international and national professional organizations
2. increased efforts to provide the relevant exposure to medical students
3. enthusiasm and active 'proselytizing' by clinicians and educators
4. the projected increase in the size of the older age groups
5. an expected increase in therapeutic options.

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Subject Index

Abbreviations

AD - Alzheimer's disease
 APP - amyloid precursor protein
 DLB - dementia with Lewy bodies
 DTI - diffusion tensor imaging
 FAST - Functional Assessment Staging
 FTD - frontotemporal dementia
 GDS - Global Deterioration Scale
 LBD - Lewy body dementias
 MCI - mild cognitive impairment
 MMSE - Mini Mental State Examination
 MTL - medial temporal lobe
 NAA - *N*-acetylaspartate
 OCD - obsessive-compulsive disorder
 PDD - Parkinson's disease dementia
 SSRIs - selective serotonin reuptake inhibitors (SSRIs)

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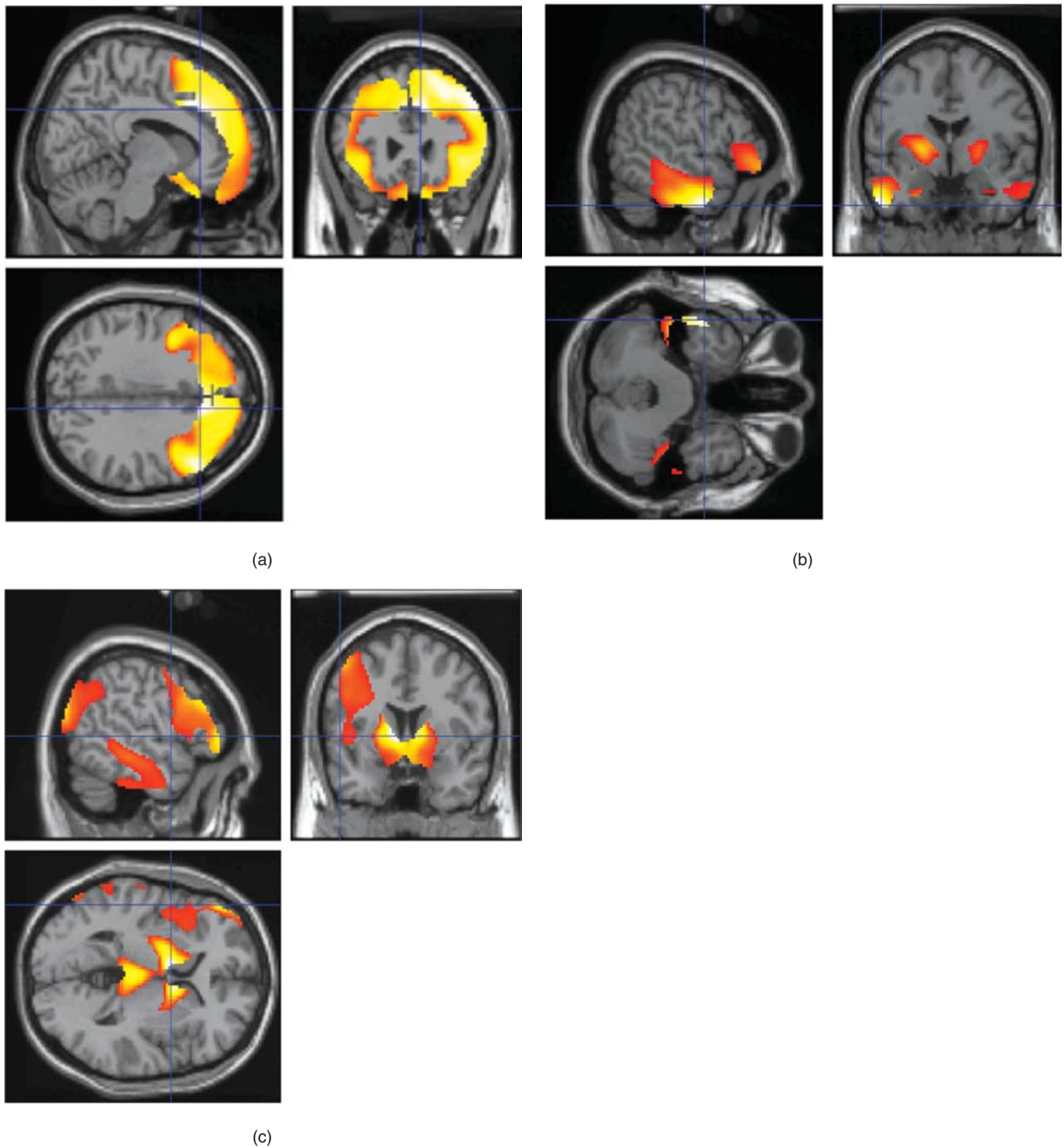


Figure 5.1 Reductions of regional cerebral glucose metabolism in ^{18}F -fluoro-2-deoxy-glucose positron emission tomography (FDG PET) studies of patients with (a) frontotemporal dementia, (b) semantic dementia and (c) progressive non-fluent aphasia compared with healthy control subjects (sagittal, axial, and coronal slices; areas with reduced metabolism are displayed in colour).

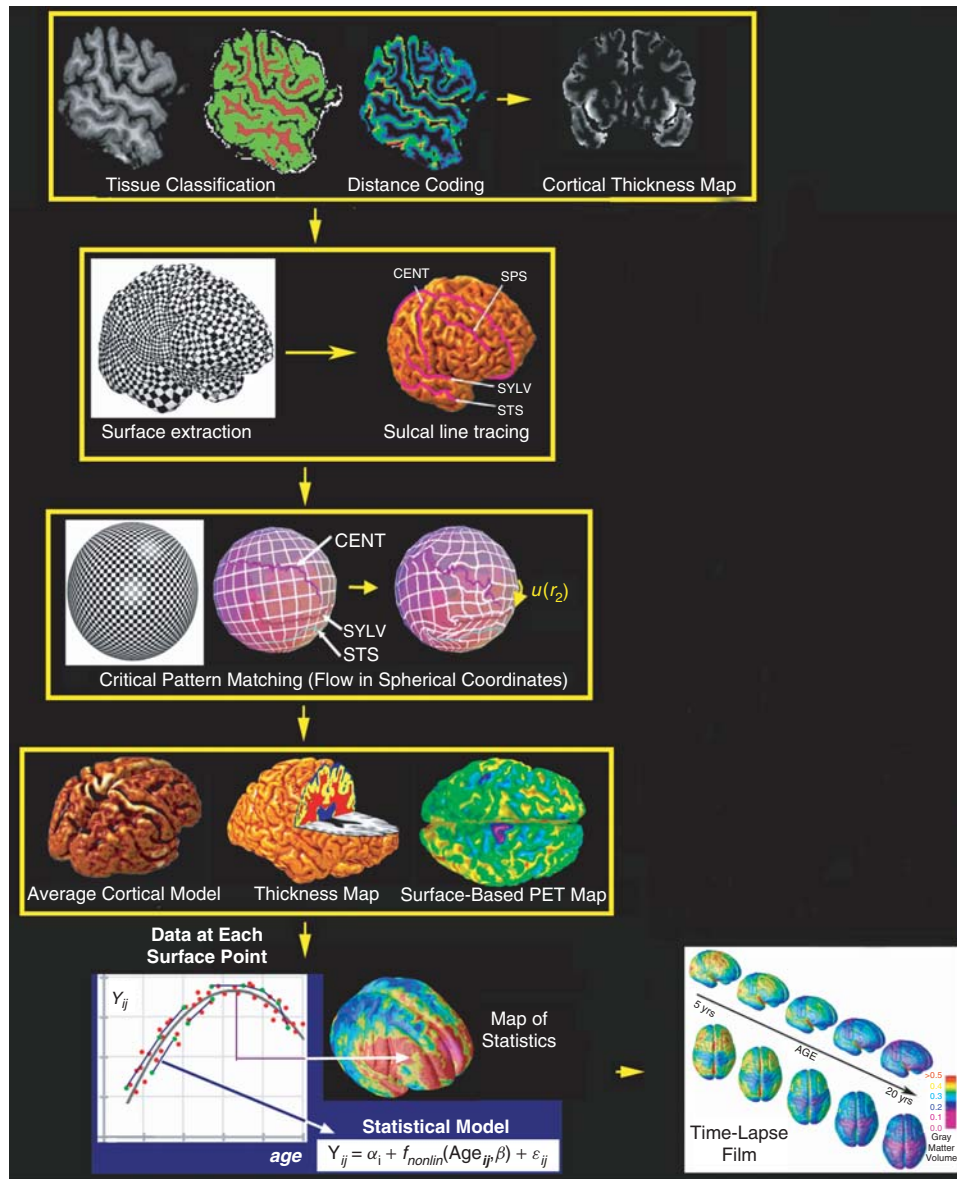


Figure 46.1 Flowchart showing an image analysis pipeline (adapted from¹⁰) that can map changes of various neuroanatomical measures in the cortex, such as grey matter atrophy. Cortical thickness profiles, for example, can be averaged across subjects or compared across time. Tissue classification techniques can be used to identify grey and white matter and to produce cortical thickness maps (row 1). The CPM approach can be applied by tracing sulcal landmarks on extracted brain surface models (row 2) that serve as anchors to guide a flow field matching gyral regions across subjects (row 3). Then maps of cortical thickness, or other cortical signals (such as co-registered PET images, shown here), can be fluidly aligned to an average cortical model (row 4). Statistical models are fitted to data from all the subjects at each cortical point. This can assess whether imaging signals are associated with age (bottom row), or other parameters of interest. Effects of ageing on cortical measures – or changes relative to baseline – may be animated as a time-lapse film to reveal the disease trajectory.

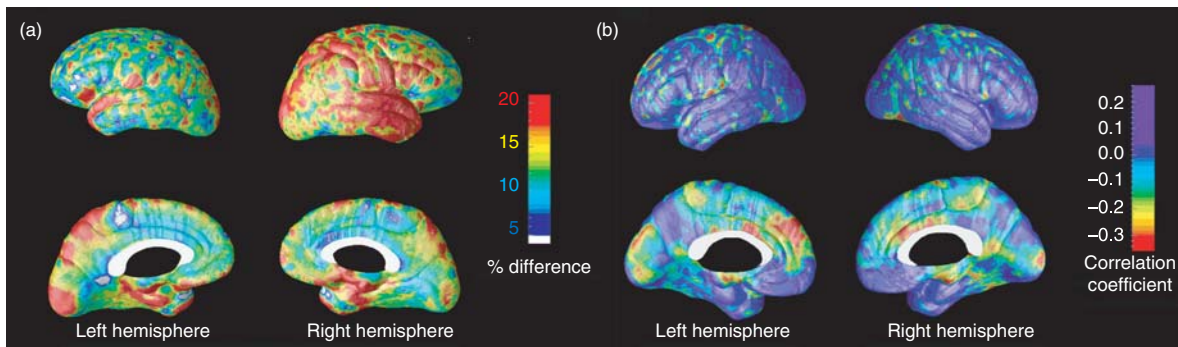


Figure 46.2 (A) Cortical thinning of up to 20% occurs between MCI and AD, in widely distributed cortical areas (greatest tissue loss is coded in red). (B). Grey matter atrophy in the anterior cingulate and supplementary motor cortices is correlated with the presence or absence of apathy in AD. Regions where structural variation correlates with clinical or behavioural differences can be identified using correlation maps such as these (strong associations are shown here in red colours). Data adapted from^{21,22}.

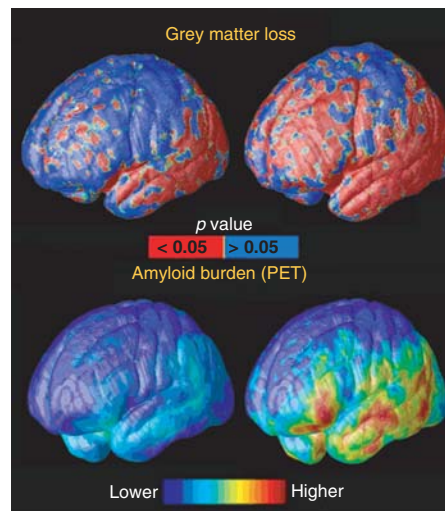


Figure 46.3 Progression of AD based on MRI and [¹⁸F]FDDNP PET. On MRI (top row), the areas with grey matter deficits in mild AD (left panel) include primarily the temporal lobe, but in moderate AD (right panel) these deficits have spread to involve the frontal cortex (adapted from a longitudinal study by Thompson *et al.*²⁵). Finally, cerebral amyloid estimated *in vivo* from the PET ligand FDDNP is low in controls, but higher in those with impaired cognition (bottom row; adapted from Braskie *et al.*⁸). The anatomical agreement is striking between these *in vivo* maps and the well-established postmortem maps for the staging of AD. In all maps, the sensorimotor cortex shows least disease-related degeneration.

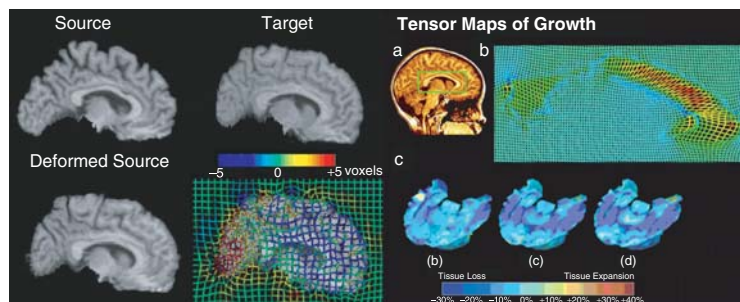


Figure 46.4 Tensor-based morphometry. In TBM, a fluid transformation (*deformed grid*) is applied to a baseline scan (*source*) to reconfigure it (*deformed source*) into the shape of a follow-up scan (*target*). The local expansions (*red colours*) or atrophies (*blue colours*) can be plotted in brain regions such as the corpus callosum (shown in the green box in [a]). Voxel expansions (*red colours*) or contractions (*blue colours*) can be plotted onto a sequence of scans collected from the same subject (shown here in axial view illustrating progressive temporal lobe atrophy in a subject with frontotemporal lobe atrophy) during a degenerative brain disease, emphasizing regions with progressive atrophy. These maps may be averaged across subjects or compared across populations to assess factors that influence degenerative rates in each region of the brain.

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ADNI 100
Alzheimer's Disease Neuroimaging Initiative

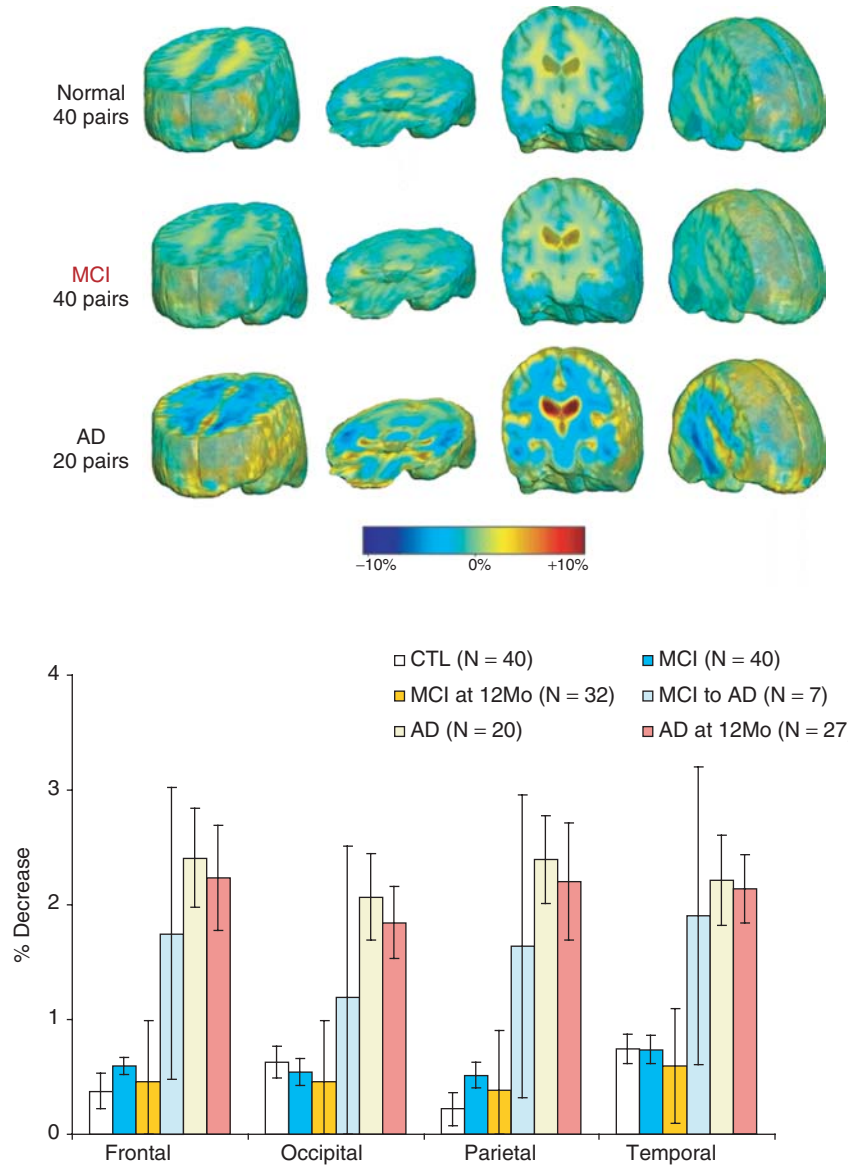


Figure 46.5 (Top panel) average longitudinal tissue atrophy/expansion rate for 40 normal, 40 MCI and 20 AD subjects, using serial MRI scans from the ADNI dataset scanned at 12 months apart. Ventricular expansion (third column) and temporal lobe atrophy (fourth column) are most prominent in the AD group. (Bottom panel) Percentage brain tissue loss from baseline to follow-up within each lobe can be computed by averaging the maps in the left panel for each region of interest (with CSF excluded). The diagnoses for the AD, MCI and CTL groups were determined at baseline. Here, MCI at 12Mo denotes subjects diagnosed as MCI at baseline who did not convert to AD at 12-month follow-up, whereas MCI to AD signifies those who had converted to AD at 12-month follow-up. One MCI subject's diagnosis converted back to control at follow-up, and thus was excluded from the MCI subgroups. The first bar in each group (coloured *white*) shows mild but significant progressive atrophy in controls. The second bar (*turquoise*) denotes MCI subjects at baseline, and is followed by bars denoting converters and non-converters. Mean rates are typically higher in the converters, comparable to subjects diagnosed as AD at both time-points, or AD at the last time-point (*last two bars*). This figure is adapted from the results in³³.

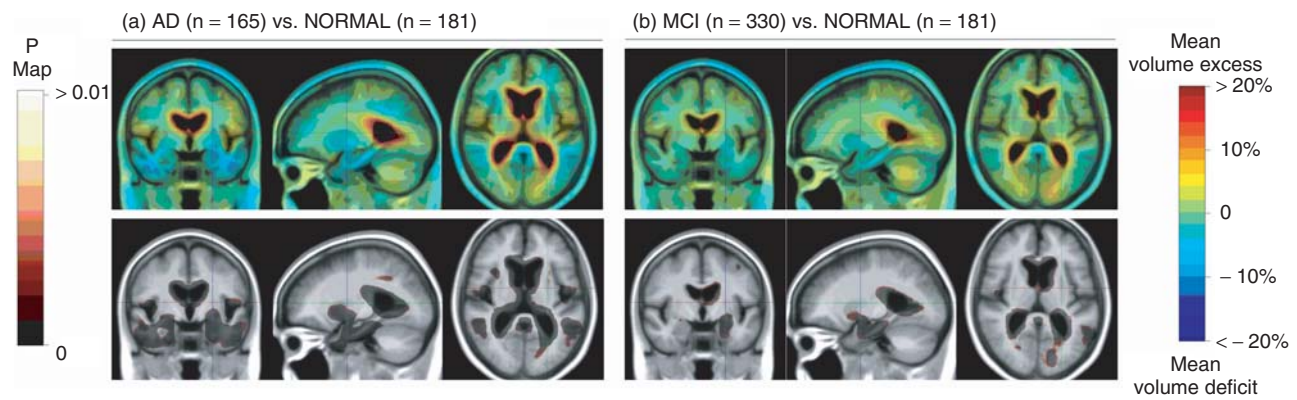


Figure 46.6 3D maps of brain atrophy comparing group differences between MCI ($n = 330$) versus normal ($n = 181$), and AD subjects ($n = 165$) versus normal. The top rows of panels (a) and (b) show the mean level of atrophy as a percentage reduction in volume. The bottom rows show the significance of these reductions, revealing highly significant atrophy in AD but a more anatomically restricted atrophic pattern in MCI. In MCI (b), atrophy is most prominent in the left hippocampus; ventricular expansion is also substantial. When AD is compared with MCI (not shown here), additional temporal lobe degeneration is evident. The overall level of ventricular expansion is about 10–15% for MCI and greater than 20% for the AD group. This figure is adapted from the results in³⁵.

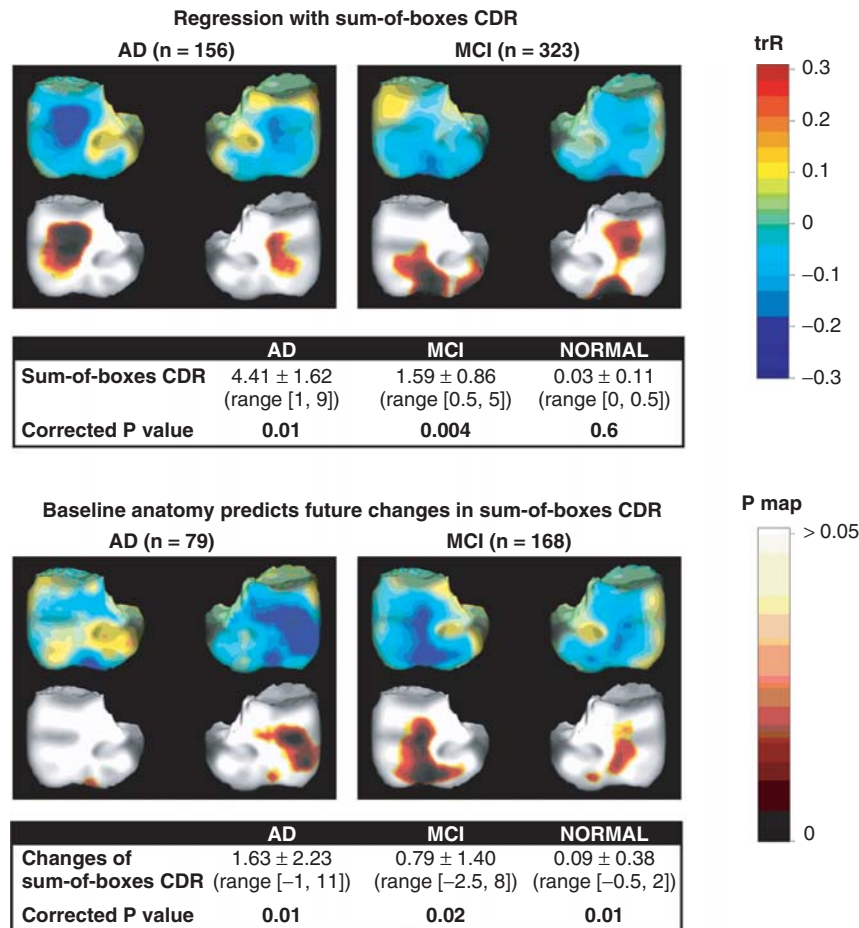


Figure 46.7 Temporal lobe atrophy correlates with sum-of-boxes clinical dementia rating and future clinical decline. Top row negative correlations are detected between temporal lobe atrophy and higher CDR scores at the time of the initial scan (i.e. a higher CDR score correlates with a faster rate of atrophy). The corrected P values in the table (inset) provide an overall estimate of significance, corrected for multiple comparisons. Bottom row atrophy of the temporal lobe also predicts future cognitive decline, as reflected by an increase in CDR scores, which indicates deteriorating cognitive function over the following year. trR denotes partial correlation coefficient. This figure is adapted from the results in³⁵.

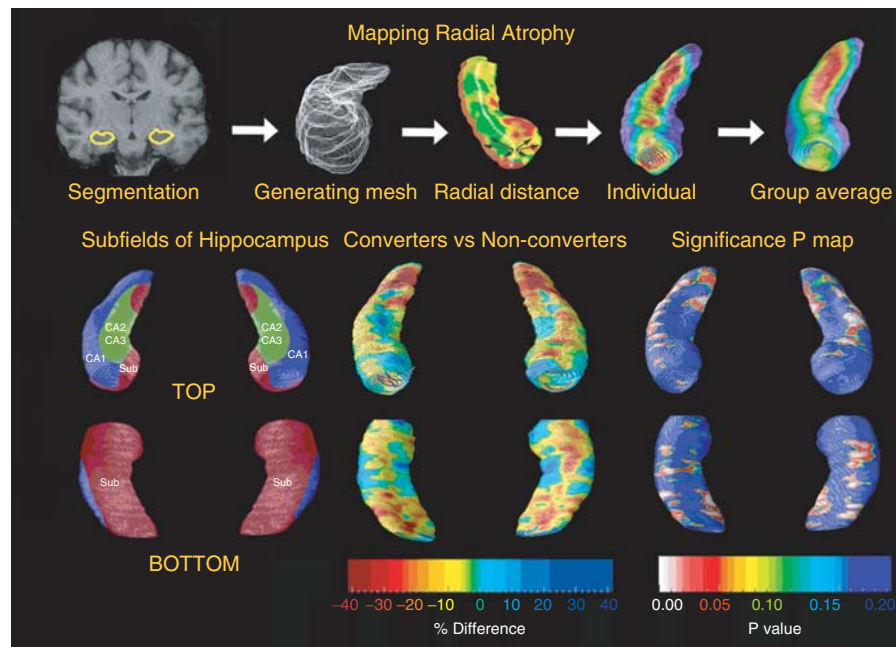


Figure 46.8 Mapping hippocampal atrophy. The radial atrophy mapping method (*top row*) relies on manually or automatically segmenting the hippocampus, computing a 3D parametric mesh model of the structure, estimating the distance between the central core of the structure to each surface point (i.e. the radial distance), and recording radial distance estimates at each surface point to create individual and group average colour-coded maps of the radial distance. These are then statistically compared between groups or conditions. One longitudinal 3D MRI study⁵⁰ compared baseline hippocampal atrophy in MCI subjects who converted to AD versus MCI subjects who remained stable or improved cognitively during three years of clinical follow-up. Greater atrophy at baseline was seen in the CA1 and subicular areas in subjects who subsequently convert to clinically probable AD (*bottom right panels*). The bottom panels show a schematic representation of the hippocampal subfields (*left*), the proportional difference in atrophy levels between converters and non-converters (in percentage points; *middle panels*), and the significance of these differences taking into account normal structural variation (*bottom right panel*).

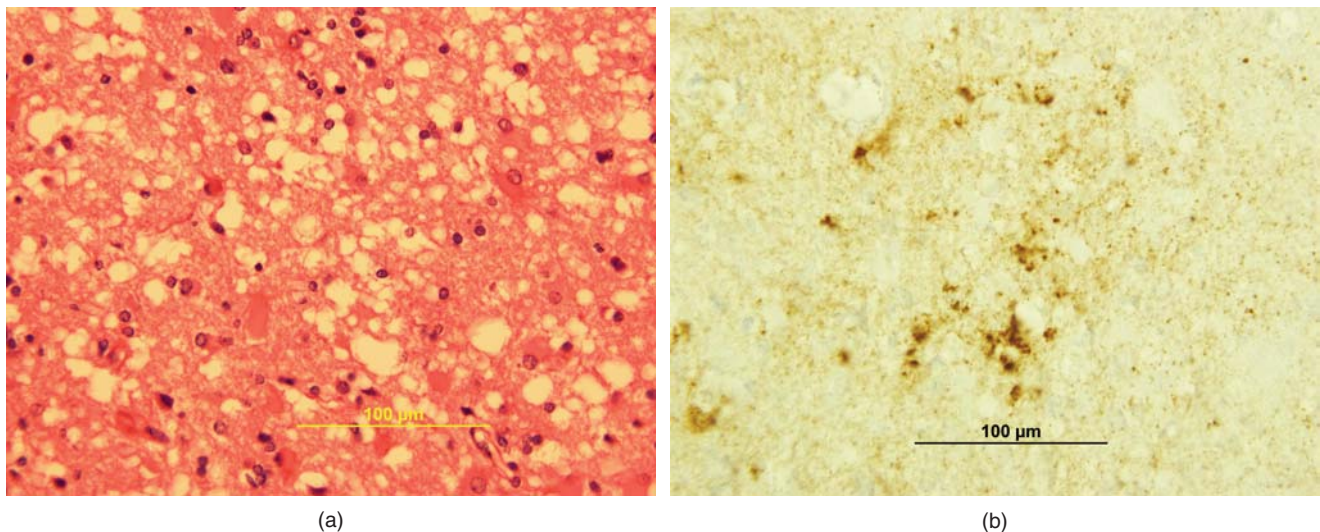


Figure 59.2 (a) Haematoxylin and eosin (H&E) stain of the temporal cortex and (b) monoclonal 3F4 antibody immunostaining of the hippocampus in a patient with Creutzfeldt–Jakob disease. The neuropathology is characterized by a spongiform appearance, astrogliosis and neuronal cell death. Immunostaining (b) reveals abnormal prion protein deposits (dark brown).

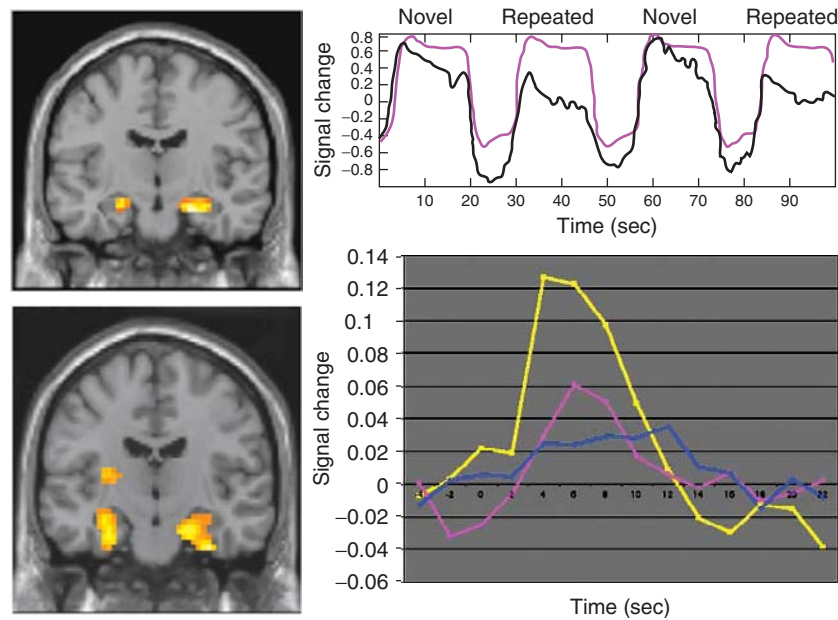


Figure 70.1 Functional MRI data during a face-name encoding paradigm. The top left figure demonstrates a statistical parametric map (SPM) of the hippocampus showing greater MR signal response to novel (N) face-name pairs compared to repeated (R) face-name pairs in a block-design fMRI paradigm. The top right shows a representative time course of the MR signal in the block-design paradigm, with marked increase in signal during novel blocks compared to blocks of visual fixation (+) or repeated blocks. The bottom left demonstrates significant hippocampal activation for an event-related face-name paradigm comparing successful vs. failed encoding. The bottom right graph shows the MR signal change in the right hippocampus for those face-name pairs correctly remembered with high confidence (yellow line), low confidence (pink line) or forgotten (blue line).

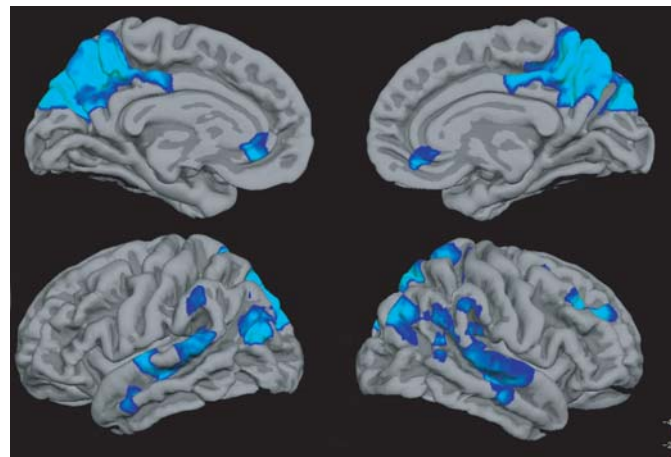


Figure 70.2 The default network, a set of regions that demonstrate higher fMRI activity during rest compared to challenging cognitive tasks. In this group fMRI data map, regions in blue demonstrate greater MR signal during rest (visual fixation) compared to novel face-name encoding.

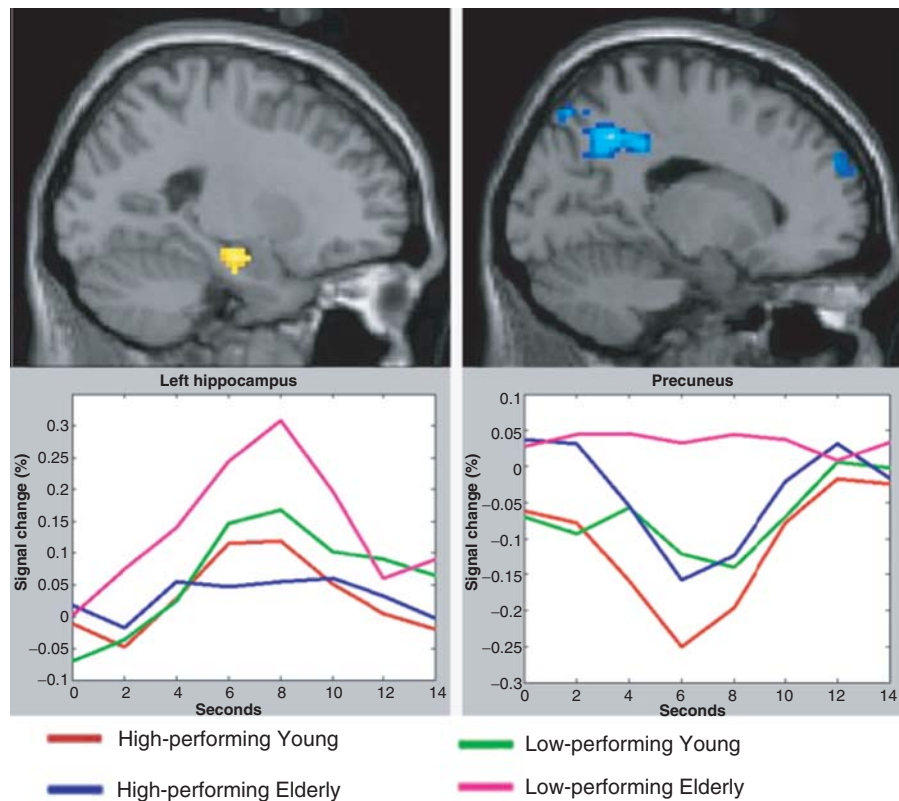


Figure 70.3 Group fMRI data maps (top) with MR signal time courses (bottom) for Young and Elderly controls show hippocampal activation (left) and precuneus deactivation (right) during the successful encoding of face-name pairs. Low-performing Elderly failed to deactivate the precuneus and demonstrated increased hippocampal and pre-frontal activation for successful but not failed encoding trials, perhaps as a compensatory response to failure of default network activity.

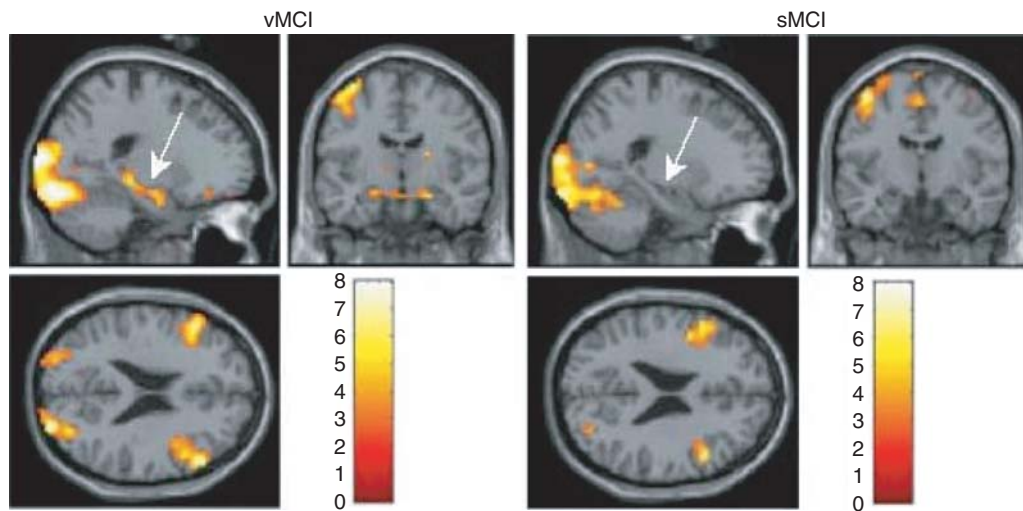


Figure 70.4 Group fMRI data from 15 very mildly impaired MCI (vMCI) and 12 significantly impaired MCI (sMCI) subjects on a face-name encoding task. The vMCI subjects showed evidence of hippocampal ‘hyperactivation’ compared to controls. The sMCI subjects showed significantly decreased hippocampal activation at levels similar to those seen in mild AD patients.