PSSRU

Mental Health in Old Age Bulletin
Issue 2

Editorial Board: Alistair Burns, David Challis, Judith Dennis and Jane Hughes

Contributors: Alistair Burns, Jane Byrne, Judith Dennis and David Findlay

Layout by: Sue Martin

Discussion Paper M117
September 2003

PERSONAL SOCIAL SERVICES RESEARCH UNIT

The University of Manchester

Dover Street Building
University of Manchester
Oxford Road
Manchester M13 9PL
Tel: 0161 275 5250

The University of Kent at Canterbury

Cornwallis Building
University of Kent at Canterbury
Canterbury
Kent CT2 7NF
Tel: 01227 823963/823862

London School of Economics

London School of Economics
Houghton Street
London
WC2A 2AE
Tel: 020 7955 6238

Email: PSSRU@manchester.ac.uk **Website:http://www.pssru.ac.uk**

MENTAL HEALTH IN OLD AGE BULLETIN
ISSUE 2

Editorial

Current Key Issues

Conference Report

Book Review

EDITORIAL – Inflammation and Alzheimer's disease

There is still considerable interest in this area. The recent vaccine story and the report of the post-mortem of a person who died in that trial has underscored the potential importance of inflammatory responses in Alzheimer's disease and the thought of a relatively cheap and preventative strategy always arouses interest. A recent editorial in the British Medical Journal (16th August 2003 – Anti-inflammatory drugs in Alzheimer's disease by Christopher Martyn) summarised some current thinking.

There are two strands of evidence. First, the Rotterdam study which examined nearly 7000 people concluded that there was a significant risk reduction for the development of Alzheimer's disease in those who took non steroidal anti-inflammatory drugs for more than two years, although other studies have not confirmed any protective effect. A systematic review published in the British Medical Journal (Etminan *et al.* Effective non-steroidal anti-inflammatory drugs and risk of Alzheimer's disease, systematic review and meta-analysis of observational studies. *British Medical Journal* (2003), 327, p.128) did show a reduction in risk when the treatments were taken in the long term.

Another line of evidence is the effect of these drugs in people with Alzheimer's disease. A study some years ago showed the positive effects of indomethicin on Alzheimer's disease were shown some 10 years ago (Rogers *et al.* (1993) Clinical trial of indomethicin in Alzheimer's disease. *Neurology* 43, pp.1609-1611). However, a more recent trial (Aisen (2003) *JAMA* 289, pp.2819-2826) has shown that neither naproxen or rofecoxib had any effect on people with mild to moderate Alzheimer's disease.

Martyn summarised the potential mechanisms of the actions of anti-inflammatory drugs, either in their ability to inhibit isoforms of the enzyme cyclo-oxygenase which converts arachadonic acid to prostaglandins or in its ability to directly reduce the production of the 42 amino-acid residue of the beta-amyloid peptide by changing proteolytic processing in the precursor protein. It may be that all anti-inflammatory drugs are not the same and the group which include ibuprofen, indomethicin and sulindac might have a more specific role in reducing production of the 42 amino acid residue and may therefore be more effective.

The disparity of the observations of epidemiological studies and those of clinical trials might be explained by either (a) the use of different anti-inflammatory drugs and/or (b) that their role in the prevention of Alzheimer's disease is different to providing symptomatic improvement once the disease has begun.

Professor Martyn adds a cautionary note from the studies involving the supposed protective effect of oestrogen on Alzheimer's disease saying that although reasonable sounding explanations for a mechanism of action were proposed, recent studies have shown that those taking a combination of oestrogen and progestogen have higher rates of dementia and cognitive decline. (Shumaker *et al.* (2003) *JAMA,* 289, pp.2663-2672).

The role of inflammation in the genesis of Alzheimer's disease has yet to be firmly established and there is some evidence to suggest a relationship role but nothing which is sufficiently firm to radically change practice. Having said that, certainty is not a thing that occurs in medicine in general or old age psychiatry in particular and even if a treatment is of proven benefit, there will always be people trying to detract from it and producing evidence to the contrary. However, there is no smoke without fire.

Alistair Burns
Professor of Old Age Psychiatry
University of Manchester
email: a.burns@manchester.ac.uk

CURRENT KEY ISSUES

Mild Cognitive Impairment

Luis, C. *et al.* (2003) Mild cognitive impairment: directions for future research. *Neurology,* 61, pp.438-444.

Mild cognitive impairment (MCI) is a clinical syndrome which represents a stage between normal ageing and dementia and has been defined by Peterson *et al*., 1999(b) as:
1) memory complaint preferably corroborated by an informant,
2) objective memory impairment for age and education,
3) largely intact general cognitive function,
4) essentially preserved activities of daily living and
5) not demented.
A recent review (Peterson, 2001(b)) reviewed a number of areas of the MCI syndrome including its heterogeneity but there is an understanding that there is a growing need to effect standardisation in the different methods which are used to study the syndrome. The paper summarises various aspects of MCI including its epidemiology, the cognitive deficits and MCI, functional assessment and MCI, assessment of progression and risk of dementia, subtypes of MCI and directions for further research. The justification for detailed studies of MCI is described, i.e. that a diagnosis at an early stage may result in earlier intervention and genetic counselling, improved management of any underlying illness and better long-term planning of care. In the developed world, early detection of Alzheimer's disease and vascular dementia is a significant impetus for promoting recognition of MCI whereas in other parts of the world, identification of infectious diseases such as HIV and nutritional disorders (e.g. vitamin deficiency) may be important. The point is made that interventions which achieve even a modest reduction in the rate in which people with MCI develop dementia, can result in significant saving for society.

Recommendation for further studies on MCI include,
1) development of guidelines on which particular neuropsychological assessments have the best sensitivity and specificity within the appropriate range of scores which occur in MCI – neuropsychological tests used tend to have been developed and validated in patients with dementia,

2) assessment of complex instrumental activities of daily living is important and the need is emphasised to develop objective tests as assessments up to now are all based on collateral sources which are potentially biased or unavailable,
3) MCI is a clinical syndrome and there is an acceptance that there is significant heterogeneity in its outcome. It is not simply the case that people either develop a dementia or do not. It is recognised in studies that spontaneous remission may occur and biological markers, such as hippocampal atrophy of apolipoprotein E status may be important in revealing markers which predict those who deteriorate and those who do not,
4) looking at it from the other direction, a more sophisticated understanding of the pre-clinical stages of the dementia syndromes is important,
5) epidemiological studies of MCI across hospital-based and community populations in a number of different settings are needed and it is important to use standardised and comparable assessment methods and validated diagnostic criteria to allow comparisons to be made. Finally, a workshop to develop a consensus around a clinical research issue regarding MCI should be encouraged using the model of the NINCDS-ADRDA criteria for Alzheimer's disease, which have been so successful.

Petersen, R.C., Doody, R., Kurz, A. *et al.* (2001) Current concepts in mild cognitive impairment. *Arch. Neurol.* , 58, pp.1985-1992.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tanglas, E., Kokmen, E. (1999) Mild cognitive impairment: clinical characterization and outcome. *Arch. Neurol.,* 56, pp.303-308.

Petersen, R.C., Steven, J.S., Ganguli, M.D. *et al.* (2001) Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology,* 56, pp.1133-1142.

Alistair Burns
Professor of Old Age Psychiatry
University of Manchester
email: a.burns@manchester.ac.uk

Donepezil and Vascular Dementia

Wilkinson, D. *et al.* (2003) Donepezil and vascular dementia: a randomised placebo-controlled study. *Neurology,* 61, pp.429-486.

This study served to evaluate the efficacy and tolerability of donepezil in patients with vascular dementia. 616 patients with a mean age of 75 with probable or possible vascular dementia, according to the NINDS/AIREN criteria were randomised to receive either 5 mg a day of donepezil (208 patients), 10 mg of donepezil (215 patients, 5 mg a day for the first 28 days) or placebo (193 patients for 24 weeks). 76% of those enrolled had probable vascular dementia, 75.3% of the 10 mg donepezil group, 80.8% of the 5 mg group and 83.4% of the placebo group, completed the study. Both groups treated with donepezil showed improvements in cognitive functioning on the ADAS-cog study compared with placebo with a mean end point treatment difference, as measured by the change from baseline score,

approximately 2 points. This was statistically significant for both the 5 mg and 10 mg doses. Greater improvements on the clinician's interview based impression of change (the version using care giver input) was observed in both drug treatment groups compared with placebo, 25% of the placebo group showed improvement compared with 39% on the 5 mg group and 32% of the 10 mg group. 8.8% of patients on placebo, 10.1% on 5 mg of donepezil and 16.3% on 10 mg withdrew due to adverse events. The conclusion of the study was that the donepezil treated patients demonstrated significant improvements in cognition and global function compared with placebo and the drug was well tolerated in this population.

Alistair Burns
Professor of Old Age Psychiatry
University of Manchester
email: a.burns@manchester.ac.uk

Prediction of Alzheimer Disease Pathology

Silbert *et al.* (2003) Changes in pre-morbid brain volume predict Alzheimer's disease pathology. *Neurology,* 61, pp.487-492.

The objective of this study was to assess whether ante-mortem changes in MRI brain volume would predict subsequent Alzheimer pathology. 39 people (15 without dementia and 24 with dementia) were followed until death, with regional post-mortem measures of senile plaques and neurofibrillary tangles being examined and compared to pre-morbid cross section of longitudinal volumetric measurement obtained from MRIs during life. The total brain volume change over time was related to the accumulation of cortical neurofibrillary tangles and the rate of ventricular CSF volume increase, was related to both cortical neurofibrillary tangles and senile plaques. The last measure of hippocampal volume before death was related to hippocampal neurofibrillary tangles but the rate of hippocampal volume atrophy was not related to neurofibrillary tangles in the hippocampus. The significant relationship held when non-demented subjects were excluded from the analysis. In people with cognitive impairment cortical neurofibrillary tangles and senile plaques were best predicted by the rate of ventricular volume increase and, excluding subjects in whom there was a long gap between their MRI scan and death, did not significantly alter the results. The main conclusion of the study was that MRI volumes measured over time, represent valid bio-markers of pathological progression of Alzheimer's disease, the rate of ventricular volume enlargement can be used to monitor disease progression or response to treatment in future clinical trials, which are targeted directly at neurofibrillary tangles and senile plaque pathology.

Alistair Burns
Professor of Old Age Psychiatry
University of Manchester
email: a.burns@manchester.ac.uk

Functional MRI

Machulda *et al.* (2003) Comparison of memory fMRI response among normal, MCI and Alzheimer's patients. *Neurology,* 61, pp.500-506.

The purpose of this study was to determine whether a memory encoding task on fMRI distinguishes between cognitive normal elderly people and those with mild cognitive impairment and those with Alzheimer's disease. 29 subjects (11 normal, 9 with MCI and 9 with Alzheimer's disease) were studied using an fMRI memory encoding task. Activation in the medial temporal lobe for the memory task and in the anatomic rolandic area for the sensory task were studied. Inter-group comparisons were performed using receiver operating characteristic analysis, medial temporal lobe activation was greater in normal subjects than people with MCI or Alzheimer's disease. There was no difference between Alzheimer's disease and MCI in the normal fMRI memory performance. There was no difference among the three groups on the sensory task. The conclusion was that MCI and Alzheimer's disease patients had less medial temporal lobe activation on the memory tasks than the normal subjects but similar activation as normal subjects on the sensory tasks. The findings are suggestive that decreased medial temporal activation may be a specific marker of limbic dysfunction as a result of neurodegenerative changes in Alzheimer's disease but also suggests that fMRI is sufficiently sensitive to the changes in the prodromal, MCI phase of the disorder.

Alistair Burns
Professor of Old Age Psychiatry
University of Manchester
email: a.burns@manchester.ac.uk

Post-stroke dementia

Linn *et al.* (2003) Post-stroke dementia. *Neurology,* 61, pp.343-348.

This study chose to investigate prospectively the frequency and clinical associations of post-stroke dementia in inpatients in Southern Taiwan. In patients where pre-stroke dementia was excluded, 283 patients were assessed three months following stroke. 9.2% met the criteria for post-stroke dementia age over 65 years, previous occupation as a labourer, prior stroke, left carotid vascular territory, moderate to severe stroke severity, cognitive impairment and poor financial status on admission, were associated with the presence of dementia. Using a logistic progression model, 93.4% of subjects were correctly classified. The study showed a lower frequency of post-stroke dementia compared to other studies from Western countries and this has been suggested to be due to the relatively younger age of the elderly population and the use of stricter diagnostic criteria (these were made according to the neurologic adaptation of the 10th International Edition of the *International Classification of Diseases Criteria for Dementia)*.

Alistair Burns
Professor of Old Age Psychiatry
University of Manchester
email: a.burns@manchester.ac.uk

CONFERENCE REPORT

11th International Congress of the International Psychogeriatric Association Chicago. 17th-22nd August 2003

The 11th Congress of the International Psychogeriatric Association (IPA) was held in Chicago from 17th – 22nd August 2003. This was a special meeting for the IPA as it represents its 21st birthday, the inaugural meeting being held in Cairo in 1982. Also, the base for IPA is in Chicago so there was a real sense of "coming home". The IPA has a congress every 2nd year, the last one being in Nice in 2001 and the next in Stockholm in 2005. The theme of the meeting was "Enhancing the Human Connection in the Age of New Technologies: implications and opportunities for ageing". Professor Sandy Finkel from Chicago outlined the rationale for the meeting – "Scientific innovations continue to lead the way to a better life for older people with new avenues of drug development, molecular biology and the genome project providing us with new clinical insights leading to a healthier and longer life". The question raised by the Congress was to consider how to take the further step of understanding the human implications of these new technologies and how they affect older people and health care systems, values, spirituality and the implications of extending the life span. A further question was raised about how we manage as individuals, families and societies five or even six generational families.

The Congress attracted around 1700 people from 62 countries.

The public lecture (something which opens the Congress) was given by Professor Tom Kirkwood from Newcastle. Professor Kirkwood summarized information on five related questions to longevity

1. What is happening to the age of the population.
2. Why and how we age.
3. What explains individual differences in ageing.
4. The relationship between normal ageing and disease and
5. Where things should go to next.

A few key points included that life expectancy has doubled in the last 200 years and has increased by 10 years in the last 50. Jeanne Calment is the oldest documented living person – she was born on 21st February 1875 and died on 4th August 1997. Two quotes, attributed to Jean Calmant are, first, when asked what one of the benefits of being the oldest person in the world , replied "the lack of peer pressure" and second also said that she was proud only to have one wrinkle on her body – and she was sitting on it! It was interesting to hear that twin studies have shown that genes account for about 25% of length of life, leaving 75% up to us. The importance of nutrition was emphasised citing the experience in Japan of a good diet being reflected in longevity and the good evidence that exercising both the mind and the body had a beneficial effect on individual life span. The interesting point was made that issues in the environment may often discourage an active lifestyle but that individual attitudes were also a key feature in terms of the environment. The importance of relating diseases to normal ageing was emphasised in particular in relation to osteoarthritis, osteoporosis and dementia.

There were about 100 symposia throughout the meeting and daily plenary sessions. Norman Sartorius gave the keynote lecture at the Gala Dinner on the Future of Treatment in Psychogeriatrics, which underscored the positive values of valuing older people and emphasising the positive role they have in society.

It is impossible to summarize adequately all the symposia which took place and inevitably any choice only serves to demonstrate the inherent interests and bias of this author.

Ethical issues were discussed in the symposium led by Lissy Jarvik from the USA. A discussion of research monitoring boards in the USA was provided with a debate of Real time Monitoring – essentially a continued interest by Ethics Committees in research which is ongoing rather than their usual periodic episodes of interest. It is useful for "risky" research and that involving patients who may not be able to give fully informed consent. There seems to be a head of steam for the development of real-time monitoring in the USA and this may be partly reflected in the UK by the Research Governance Agenda. Six responders gave a perspective on a number of different areas including the UK, Australia, Japan, Korea and also a representative from the pharmaceutical industry. A family carer from the USA gave an interesting account of her own experience in getting her mother enrolled in a drug trial, mentioning that some may have thought her and her family's attempt to gain some help for her mother was regarded as coercive.

Konrad Maurer from Germany presented a symposium on the life and work of Alois Alzheimer. His book with Ulrike Maurer is currently available from Columbia University Press, New York (*Alzheimer, the life of a physician and the career of a disease*, 2003. ISBN 0-231-11896-1).

Professor Maurer brought to life Alzheimer in addition to the usual facts and information known about his life. His wider contributions in terms of his practice of psychiatry, including forensic aspects (he was one of the first people to describe in detail cases of shoe fetishists – I guess he was quite lucky to have his name attached to one of the most important diseases in man rather than a shoe fetishist!) and also his sense of humour.

A number of awards were given out at the meeting – Robert Katzman from the USA was the recipient of the 2003 Luigi Amaducci Award, Ewald Busse from the USA and David Jolley from the UK received the Service to the Field of Psychogeriatrics Awards, Gene Cohen and Barry Lebowitz received the Service to the Field from the Congress to Host Country Awards and Ed Chui, Past President of the IPA received the Service Award to IPA. The Research Awards were as follows: 1st place Joella Storey, Australia – The Role of Universal Dementia Assessment Scale, 2nd place, Claudia Lai, Hong Kong – A Randomised Controlled Trial of a Specific Reminiscence Approach to Promote the Well-Being of Nursing Home Residents with Dementia and 3rd place to Yonas Geda, USA on the Genesis of Neuropsychiatric Symptoms in Mild Cognitive Impairment.

The meeting finished with two talks, one from Gene Cohen, USA regarding the positive images of ageing among young people and the second from Daisaku Maeda, Japan on aspects of intergenerational conflict.

Further information is available at the IPA website www.ipa-online.net

Alistair Burns
Professor of Old Age Psychiatry
University of Manchester
email: a.burns@manchester.ac.uk

BOOK REVIEW

Agitation in Patients with Dementia: A Practical Guide to Diagnosis and Management

Hay, D.P., Klein, D.T., Hay, L.K., Grossberg, G.T. & Kennedy, J.S. (eds) (2003) *Agitation in patients with dementia: a practical guide to diagnosis and management*. American Psychiatric Publishing, 250pp.

This compact, multi-author American volume (dedicated in memoriam to Linda Hay of the editorial team) has much to offer the broad range of professionals engaged in responding to behavioural disturbances in Alzheimer's disease. The generic term 'agitation' has a long tradition in this context, and in the vascular or Lewy body dementias which received much less mention, but a number of authors did feel an understandable need to address some inherent conceptual problems associated with its use. Tabulation of personal and environmental correlates for various types of agitated behaviour was one particularly helpful approach.

In real life the management of inappropriate behaviour in dementia falls largely to nurses and that fact did receive appropriate recognition here. Likewise, the precarious balance between non-pharmacological and drug-based approaches appeared carefully considered and ethical/legal dilemmas were not neglected. The use of 'ABC' to describe disturbances in Affect, Behaviour and Cognition in general plus Appearance, Behaviour and Comfort level in anxiety as well as the more usual Antecedents, Behaviour and Consequences of a behavioural approach seems regrettable given the need for clear messages and a coherent educational agenda for both professional and non-professional carers.

A certain amount of repetition is probably inevitable in a book such as this and did not seem excessive. I suspect, for instance, there can never be too many warnings about mistaking (drug-induced) akathisia for something that might actually benefit from antipsychotic medication. The topic of differential diagnosis was perhaps slightly laboured, and certain statements about attentional deficits in delirium, dementia and depression appeared ripe for disputation, but the sentiments expressed were appropriate and the management advice was suitably pragmatic.

Even given an avowedly practical approach, less usual topics as diverse as psychotherapy and bright light therapy received a gratifying level of exposure, with suitable health warnings, in this genuinely eclectic coverage. Overall the text and references provide a good deal to help update practice in a particularly difficult but common and important area of old age psychiatry. This is very much a guide rather than a manual; a lot will be familiar and that which is not should trigger careful reflection both about current procedures on the one hand and about associated

infrastructural plus personnel requirements of these on the other. Here is a work to foster constructive debate within multidisciplinary teams across a variety of care settings and I commend it accordingly.

David Findlay
Consultant Psychiatrist
Royal Dundee Liff Hospital
email: david.findlay@tpct.scot.nhs.uk

WEBSITE REVIEW

Thanks to funding from Novartis, I have recently been appointed as Library and Information Officer at the North West Dementia Centre hosted by PSSRU, within the Medical Faculty of the University of Manchester.

My initial training in librarianship took place over twenty years ago and, after being out of the profession working as a freelance for a number of years, I have recently returned to working in the information field (having first undergone substantial updating of skills). This gives me a non-clinical perspective and the means of comparing then and now. The first striking thing to notice is the plethora of information sources – no one (surely) lacks information. Secondly, not all sources of information are of equal value and in no field is this more apparent than in medicine and health. Anyone who wishes to do so may set up a website and promulgate ideas ranging from the highly orthodox to the entirely suspect. So the main problems for many are how to reduce the amount of information to manageable quantities and how to ensure that the information you have is accurate. Over the coming months we shall alert readers to information sources which can be trusted.

Without question the newest bright star in the health information firmament is the National Electronic Library for Health (NeLH) www.nelh.nhs.uk. Launched in 2001 after an investment of millions of pounds, NeLH ('Nellie' to its friends) is intended to become the first port of call for NHS staff – its goal is to provide every kind of information needed by NHS staff from the latest research findings, through Guidelines, Care Pathways to information about drugs and management information.

It gives access to the major bibliographic databases, although some require the user to have an Athens password. These include Medline, the Cochrane Library and other evidence-based resources. For example, it offers the evidence-based journal Bandolier in electronic format as well as access to the publications of the National Institute for Clinical Excellence (NICE). Perhaps therefore its main benefit is that it can offer access to a number of frequently used resources from one site. An indication of the scope of resources on offer is given by the reproduction of the page displayed when 'dementia' was typed into the Pilot Search Engine box on the Home Page. You will notice that it offers the facility to search the *BMJ, NEJM* and *JAMA* for additional relevant material; these hits do not include relevant material available through bibliographic databases such as Medline and Psychinfo.

Of particular interest may be the fact that NeLH offers pages aimed at special interest groups under the link to 'Specialist Libraries'. One of these is for those working in the mental health area – there is a link to this (and to all the other features mentioned) from the Home Page. Exploring the content of NeLH is certainly something to pass away the idle hour or two. We shall explore some of these links in future editions of the *Bulletin*.

Judith Dennis
Library and Information Officer
North West Dementia Centre / PSSRU
email: judith.dennis@manchester.ac.uk

YOUR PROBLEM ANSWERED

I run a Nursing Home in which a number of residents suffering from dementia are frequently agitated. Staff have become aware in recent months of the adverse effects of medications used in dementia care and are urging me to review medication in those who are agitated for no apparent physical or psychiatric reason (apart from their dementia of course). They have bought a bright light box and are insisting on trying it out.

Could you please advise about best practice in this field and if we might expect a positive response?

It is clear from your letter that you have done a careful psycho-social as well as physical assessment of agitation in your patients which I agree is always the first step in their management. The use of bright light therapy has been reviewed in a leading article, published in the *British Medical Journal* in 2002. This certainly suggests that bright light therapy at a dose of 10,000 lux given in the mornings, may improve either agitation or sleep disturbance in people with dementia. However, some very recent findings presented at the International Psychogeriatric Association Congress in Chicago (17 - 22 August) from my own group suggest that whilst bright light therapy may improve both agitation and circadian rhythms in winter time, it is not beneficial in summer time.

There are as yet no clear guidelines to best practice, as we do not yet have sufficient studies with a randomised design to draw from. The few RCTs and controlled trials that are available are relatively concordant in the use of morning treatment at a dose of 10,000 lux. The Manchester work suggested it may be useful to wait until about 10.00 in the morning, rather than dawn therapy which has been used by others. The treatment will not work in people within impaired visual acuity or cataracts and of course presents a challenge in agitated patients who find it difficult to keep still or to remain in one room for periods of time. As with most treatments, compliance will

significantly affect the results. There is insufficient data to provide guidelines on potential adverse effects.

I would suggest that although the research results are encouraging, in clinic practice it has not yet been established whether the treatment is practical or not.

Dr E Jane Byrne
Senior Lecturer in Old Age Psychiatry / Honorary Consultant Old Age Psychiatry
Wythenshawe Hospital
email: ejbgob@aol.com

References

Burns *et al.* (2002) Sensory stimulation in dementia. *BMJ,* letter 325, pp.1312-1313.

Byrne, E.J. *et al.* (2003) A randomised controlled trial of bright light therapy for dementia. *International Psychogeriatrics,* 15 (supplement 2), pp.97-98.