Treatment of dementia: where is it going?

Global levels of dementia are escalating but alongside this new innovations and service models are developing to improve outcome and the patient journey. This article describes some of the current and horizon issues in dementia care.

Dementia contributes 11% of all years lived with disability, higher than stroke (9.5%), musculoskeletal disorders (8.9%), heart disease (5%) and cancer (2.4%). Caring for a family member with dementia increases the caregiver's own risk of depression, chronic illness and even death. In the UK, there are currently around 700 000 people with dementia but this is estimated to rise to 1 million by 2020 and 1.7 million by 2050, an increase of almost 150% (Alzheimer's Society, 2007). In the USA about 3.4 million people aged 71 years and older have dementia. The number of older persons is expected to double from about 35 million in 2000 to more than 70 million in 2030, at which time nearly 1 in 5 Americans will be over the age of 65 years (Centers for Disease Control and Prevention, 2003). It has been estimated by the American Alzheimer's Association (2009) that every 72 seconds someone in the USA develops Alzheimer's dementia. By 2040, an estimated 80 million persons worldwide will have dementia (Ferri et al, 2005), and by 2050, an estimated 107 million persons worldwide will have Alzheimer's dementia (Brookmeyer et al, 2007).

The total costs of caring for people with dementia in the UK have been estimated at between £17 and £18 billion a year (Alzheimer's Society, 2007), more than heart disease (£4 billion), stroke (£3 billion) and cancer (£2 billion), and $100 billion in the USA annually (Brayne et al, 2007). The worldwide costs of dementia exceed $315 billion annually (Wimo et al, 2007). In the USA it is predicted that $20 trillion a year will be spent on the direct and indirect care of patients with Alzheimer's disease by the middle of this century (Alzheimer's Association, 2009). Without innovation in service delivery and new interventions, global health and social care provision will face increasing strain under the rising demand.

Dr Chris Fox *is Consultant Psychogeriatrician, Kent and Medway NHS and Social Care Partnership Trust, CHSS, University of Kent, Canterbury, Kent CT2 7NF, and Institute of Rehabilitation University of Hull, Hull,* **Dr Malaz Boustani** *is Associate Professor of Medicine, Indiana University Center for Aging Research, USA and* **Dr Esme Moniz-Cook** *is Professor of Clinical Psychology and Ageing and Consultant Clinical Psychologist, Institute of Rehabilitation, University of Hull*

Correspondence to: Dr C Fox

What is dementia?

Dementia is defined as a progressive and largely irreversible clinical syndrome that is characterized by a widespread impairment of mental function. People with dementia retain positive personality traits and personal attributes. As their condition progresses they may experience some or all of the following: memory loss, language impairment, disorientation, changes in personality, difficulties with activities of daily living, self-neglect, psychiatric symptoms (e.g. apathy, depression or psychosis) and out-of-character behaviour (National Institute for Health and Clinical Excellence and Social Care Institute for Excellence, 2006).

It is a syndrome with subtypes, the commonest of which are Alzheimer's dementia (42.0% of cases), vascular dementia (23.7% of cases), dementia of combined Alzheimer's and vascular pathology in 21.6% of cases and frontotemporal dementia in 4.0% of patients. The remaining 8.8% of patients have other dementia disorders including combinations other than that of Alzheimer's and vascular pathology. Cerebrovascular pathology appears to correspond with the dementia disorder, either entirely or partly, in almost half of patients diagnosed with dementia. The median survival time of dementia from recognition has been estimated to be 4.1 years for men and 4.6 years for women. However, age is a factor in this as those aged 65–69 years have a median lifespan of 10.7 years and those aged over 90 years have a median lifespan of 3.8 years (Jagger et al, 2009).

How to diagnose?

Dementia is a condition with stages and increasing research is being focused on recognition at early stages. There is some evidence showing this delays or decreases institutionalization, can improve patient and carer quality of life (Department of Health, 2009). However, there is also evidence of potential harm with early recognition (Justiss et al, 2009).

The route to presentation and diagnosis is recognized as being delayed because of stigma, normalizing and lack of awareness by relatives. It is reported that up to

70% of next of kin are unaware of their relative's difficulties at diagnosis.

Services can be poorly developed through lack of training to recognize dementia, as well as a perception that there is no benefit to recognition. Studies report difficulties in recognition of dementia, particularly in patients in the early stages, in those with comorbid depression, living at home and with preserved activities of daily living (Lopponen et al, 2003). This issue is complex involving patient factors, e.g. 70% of patients report distress when assessed cognitively (Lai et al, 2008), and primary care factors, e.g. time, training and access to specialist assessments. Primary care response to dementia is reported to be poor and, as a consequence, less than 20% of cases are documented in representative studies (Lavery et al, 2007). There are numerous tools available in primary care which are well validated and brief, e.g. 6-item cognitive impairment test (Brooke and Bullock, 1999), which can allow recognition and further planned assessment.

Specialist assessment of dementia includes a patient and informant interview. An appropriate cognitive function test should be included, such as the mini-mental state examination or the Addenbrooke's Cognitive Examination Revised (Mioshi et al, 2006). Further, more in-depth neuropsychological assessment may be indicated. A physical examination is necessary to delineate any neurological signs – this can help establish if it is dementia or if there is neurological co-morbidity. Cardiovascular assessment is important as it can give a clue to the aetiology but also allows safer targeting of psychotropic medication. It is important to realize that various specialists can feed into the assessment, including nursing, social work, occupational therapy and psychology. Aspects needing particular attention in the assessment include:

1. Safety. This can include home safety, road safety as both a pedestrian and driver, and protection from exploitation.
2. Legal. Financial affairs, potential criminal aspects such as neglectful care and capacity issues with regards to care, treatment and enduring health-care decisions
3. Physical investigations. Blood and urine tests to rule out physical causes or co-morbidity which needs considering in management. An electrocardiogram assists with initiation of psychotropic medication, e.g._cholinesterase inhibitors should be used with caution in patients with complete heart block, as well as comorbidity management. Imaging assists with ruling out other cerebral lesions, subtyping, promoting earlier diagnosis and may in the future assist with monitoring treatment response. Magnetic resonance imaging is preferred by the National Institute for Health and Clinical Excellence but computed tomography can be used. In Alzheimer's disease magnetic resonance imaging features of focal hippocampal and entorhinal cortex atrophy can be an early marker but atrophy of these structures is recognized in other dementias which limits its use. Presynaptic dopamine transporter marker scan (DaTSCAN) (123I ioflupane) which is single photon emission computed tomography can be used to help establish the diagnosis in those with suspected dementia with Lewy bodies if the diagnosis is in doubt. This can assist with safer medication provision, e.g. avoidance of antipsychotics.
4. Caregiver and family aspects. What are the difficulties? Do they have strategies? What other services are needed, e.g. respite care, Admiral nurse support?

Before dementia is diagnosed, the presentation must be distinguished from depression, delirium and mild cognitive impairment. Once dementia is diagnosed subtyping is needed to target drug treatments for which criteria are well established.

The place of the memory clinic

In the UK diagnosis of dementia is usually in psychogeriatric services, whereas in the USA it is more commonly undertaken by neurologists and geriatricians. Memory clinics are found worldwide (Jolley and Moniz-Cook, 2009). They arose in the USA at university centres in the 1970s, described as 'dementia or memory disorder clinics', and were research initiatives in specialist memory assessment procedures for the early diagnosis and development of drugs to treat Alzheimer's disease. They became popular in the UK in the 1980s, retaining their research focus, but further developing as local NHS early assessment services for patients. By the mid-1990s there were over 20 specialist multidisciplinary memory clinics in the UK, found in hospital outpatient old age psychiatry, geriatric medicine or neurology departments and sometimes at GP surgeries and health centres (Moniz-Cook, 2008).

In 2001, following the licensing of the antidementia drugs in the UK, their research focus on the pharmacological treatment for dementia informed National Institute for Health and Clinical Excellence recommendations that the cholinesterase inhibitors should be made available in such clinics, following specialist assessment including tests of cognitive, global and behavioural functioning (Department of Health, 2001). This resulted in an expansion of memory clinics and associated diversity in models of practice, ranging from single or dual professional screening for administering the anti-dementia drugs, to multi-professional projects on self-referral, mental health promotion, psychosocial intervention and 'one stop shop' multi-agency services for the early diagnosis and intervention of dementia (Moniz-Cook, 2008).

The 25-year UK debate on whether NHS resources should be directed at specialist memory clinics or towards localized community old age psychiatry services was recently addressed by the National Dementia Strategy (Department of Health, 2009). This recommends the development of centralized memory clinics in NHS areas, alongside localized community old age psychiatric

services, since these were seen to enhance access to early assessment by counteracting the stigma associated with dementia that prevented access as a result of labelling as a 'mental health' or 'old age psychiatry' provision. The specialized multidisciplinary investigations for suspected dementia or mild cognitive impairment (where it is thought that a third may go on to develop a dementia in the following 3 years) usually involve review for reversible causation or metabolic and endocrinological abnormalities, structural and sometimes functional imaging to exclude intracranial lesions or to inform sub-type diagnosis, neuropsychological assessment to inform diagnosis and sub-type diagnosis, and review of reported concerns in everyday living skills and behaviour.

Specialist multi-agency memory clinic services in the UK are now set to do more than acting as early assessment or policy-driven vehicles for administering the antidementia drugs. By acting as a reference point for older people with memory concerns, their families, professionals and the public, they can counteract stigma (Moniz-Cook and Manthorpe, 2009) and 'reassure those who are worried' (Jolley and Moniz-Cook, 2009). Their scope is in the provision of: interventions to promote health and wellbeing for those with memory problems who do not have a diagnosis of early dementia, family-based rehabilitation and psychosocial interventions, useful support to people, families and health-care staff following a diagnosis of dementia, support and guidance on best practice in dementia, and improved quality of care in early dementia (Moniz-Cook, 2008; Moniz-Cook and Manthorpe, 2009).

The memory clinic service can provide clinically effective, cost-effective services for the management of early dementia (Banerjee and Wittenberg, 2009).

How to manage?

Once patients are diagnosed there is a need for information and care-giver education. The stage of the illness affects the management. In the early stages there are a number of evidence-based early psychosocial interventions emerging which may be delivered in memory clinic settings, including new ways of talking with people and their families about the diagnosis and developing family-centred plans for promoting health and wellbeing, interventions to support cognition such as cognitive stimulation, rehabilitation or the use of assistive technology, and psychological treatments such as reminiscence-based therapy, cognitive therapy for people and family carers, and family counselling programmes (Moniz-Cook and Manthorpe, 2009).

Consideration of the issues around planning for the future is important with regards to care, driving and financial aspects. Information on dementia symptoms and disease progression should be available. Advice on lifestyle and diet can be helpful for both the patient and the caregiver. As dementia progresses access to respite and support information is needed. At any stage behavioural difficulties can arise and they are a key precipitant to intervention. These occur in up to 90% of patients at some stage in their illness (Lyketsos et al, 2000). The use of medication for behavioural difficulties is hindered by a lack of evidence of efficacy or limited efficacy (Campbell et al, 2008), adverse effects and increased mortality (Ballard et al, 2009). It is also apparent that use of medication is greatest in residential and institutional settings (Alanen et al, 2008). This may be because some families are more able than others to understand and cope with behaviour changes associated with dementia, which consequently delays the break down of care at home. In the care setting this may be associated with training and care delivery factors.

Increasingly it is recognized that mistreatment of patients with dementia occurs, with up to a third of family carers reporting significant abusive behaviour towards people with dementia (Cooper et al, 2009). This can start with cycles of behaviour between patient and carer which can escalate and lead to overuse of medication and injury as well precipitation of adult protection proceedings. Consideration of this in the assessment can prevent escalation by using a continuum model and offering, for example, respite or targeted interventions so that the abuse threshold is not crossed in the relevant care setting (Cooper et al, 2009).

Medication

The medication strategies used in dementia are: cognitive enhancers (of which there are two groups: the cholinesterase inhibitors and the N-methyl-D-aspartic acid (NMDA) antagonists), those which treat the behavioural and psychological symptoms of dementia, and anticholinergic drug sparing.

Cognitive enhancers

Cholinesterase inhibitors

There are three cholinesterase inhibitors licensed in the UK and in the USA there is also Tacrine. The primary licensed indication for these drugs is mild to moderately severe Alzheimer's dementia. Rivastigmine (Novartis) is available as a twice-daily capsule or as a novel patch once-daily that may reduce the gastrointestinal side effects noted with the oral preparations of cholinesterase inhibitors. Rivastigmine capsules have an additional license for Parkinson's disease dementia. Donepezil (Eisai/Pfizer) is a once-daily preparation which is also available as a dispersible tablet. Galantamine (Shires/Johnson and Johnson) is available as a once-daily slow release and twice-daily preparation. The evidence for efficacy of these drugs is established with about 10% more patients taking active medication responding than those taking placebo.

NMDA antagonist

Memantine (Merz, Lundbeck, Forest) is available as a twice-daily or once-daily medication. It is licensed for

moderately severe disease. In the UK its use was not recommended by National Institute for Health and Clinical Excellence. There is some evidence of benefit in agitation.

Behavioural and psychological symptoms of dementia strategies

Non-drug approaches should always be considered first. Functional analysis-based interventions are an approach that show promise where carers learn strategies to communicate with the person to prevent or alleviate behavioural and psychological symptoms such as agitation and aggression (Moniz-Cook et al, 2008).

There is limited evidence of efficacy for medication in treating behavioural and psychological symptoms of dementia (Schneider et al, 2006; Campbell et al, 2008). Medication side effects are an issue since they are associated with significant morbidity and mortality (Ballard et al, 2009).

Agitation and aggression are a target for medication. Specific medication approaches include: cholinesterase inhibitors (moderate evidence of efficacy), antidepressants (citalopram: some evidence; trazadone: insufficent evidence to recommend), antiepileptics (carbamazepine: some evidence of benefit in agitation and aggression; valproate: low dose no evidence, high dose poorly tolerated; memantine: some evidence, it is well tolerated and prospective study results are awaited later this year or next year). Mood symptoms can benefit from an antidepressant, but more evidence is required. Antipsychotics are used although not licensed and have notable morbidity and mortality risks.

The advice for use of medication to treat behavioural and psychological symptoms of dementia should include:

1. Documentation of reason for medication
2. Review of efficacy
3. Low doses and low dose increase
4. Documentation of discussion of the risk and benefits with the patient or next of kin if using antipsychotics
5. Limitation, through specialist review systems, of the length of time they are used for.

Aromatherapy oils using lavender or lemon balm can also, in some cases, improve behavioural and psychological symptoms of dementia (Nguyen and Paton, 2008).

Anticholinergic drug sparing

Medications with muscarinic receptor antagonism activities (anticholinergics) are commonly prescribed to older adults to directly or indirectly treat acute and chronic medical diseases such as incontinence, gastrointestinal diseases, allergies, depression and other psychiatric illnesses (Boustani et al, 2008; Campbell et al, 2009). At the same time older adults are prone to suffering from multiple chronic conditions and therefore they may be prescribed several anticholinergics (Schubert et al, 2006).

The reduction in the function of the central cholinergic neurotransmission system in the basal forebrain of patients with Alzheimer's dementia has been well recognized and enhancing this cholinergic system has been the target of current pharmacotherapy for Alzheimer's dementia. Although acute induction of muscarinic blockade with anticholinergics such as scopolamine has been associated with the development of transit cognitive dysfunction such as delirium, the effect of chronic suppression of these receptors on the development of neurodegenerative dementing illness is not well studied (Boustani et al, 2008; Campbell et al, 2009). However, animal studies found that chronic muscarinic receptor antagonism may increase the production of the beta-amyloid peptides (Aβ), the primary pathological feature of Alzheimer's disease (Caccamo et al, 2006). Caccamo and colleagues (2006) studied the effect of M1 antagonism on the development of Aβ peptides in transgenic mice that express several features similar to the human Alzheimer's dementia brain and found that blockade at the M1 receptor increased the presence of Aβ peptides in all areas of the brain measured, including the cortex, hippocampus and amygdala.

Despite the development of criteria aimed at identifying drugs with anticholinergic activity as inappropriate for use by older adults (Boustani et al, 2008; Campbell et al, 2009), the use of such agents ranges from 14% to 50%, depending on the definition of anticholinergic, the prevalence method and the setting (Boustani et al, 2008).

Over the past two decades numerous epidemiological studies identified, in addition to unmodifiable factors of age and genetics, a spectrum of modifiable risk factors for dementia such as lack of physical, cognitive and social activities, and the presence of high vascular burden such as diabetes, hypertension and hyperlipidaemia (Boustani and Ham, 2007). However, very few studies evaluated long-term exposure to medication as a possible modifiable risk factor for dementia (Campbell et al, 2009) despite the fact that a large proportion of older adults are suffering from multiple chronic medical conditions that require management with numerous medications with potential negative cognitive affect, such as those with anticholinergic activity. A systematic review of the literature has confirmed that anticholinergics have an acute negative effect on cognition (delirium) but found only a few longitudinal studies that identified long-term anticholinergic use as a risk factor for chronic cognitive deficit (Campbell et al, 2009). Given the current understanding of the roles that the central cholinergic system plays in cognitive functions of human brain and the widespread use of anticholinergic agents, there is a pressing need to avoid or at least inform the prescriber and the patient of the potential negative impact of anticholinergics on the ageing brain.

Psychosocial interventions

Psychosocial interventions can benefit the domains of dementia. The key to implementation is the assessment (Moniz-Cook, 2008). Such interventions may be undertaken on the patient, his/her carer or next of kin, and staff. Treatment targets can include mood, behaviour and wellbeing. Robust assessment can allow the treatment of an unmet need, e.g. lack of stimulation or depression, which can otherwise lead to deteriorating behaviour and precipitate inappropriate medication usage or need for transfer to a more specialized environment.

Another core issue is skills mix of the staff or carer. In nursing homes training and supervision of staff is needed, the latter as evidence suggests a tailing off of skills unless some form of top-up training is provided. In the domestic setting providing the carer with information on strategies can assist. These will vary depending on the nature of the behaviour and stage of the disease.

The journey for the patient diagnosed with dementia should begin with some psychosocial intervention. Perhaps the commonest is during the process of diagnostic feedback to patients and families. The grieving process following recognition of the illness commonly requires a counselling process. Consideration of the pressures of carers to care at home should be included in any assessment.

Support for patients and families facing the future of the illness can benefit them and training caregivers can reduce the stress they face and reduce placements. There is good evidence that six or more sessions of individual behavioural management given to a caregiver is effective at reducing depression in the caregiver both immediately and 32 months after treatment (Selwood et al, 2007).

Examples of specific treatments include cognitive stimulation and animal therapy. Cognitive stimulation therapy is a manualized treatment that aims to actively stimulate and engage people with dementia, while providing an optimal learning environment and the social benefits of a group. The effects of cognitive stimulation therapy appear to be comparable to those reported with the currently available antidementia drugs (Spector et al, 2008). Animal therapy, e.g. 'pat dog', is reported to facilitate relaxation, reduce apathy, agitation and aggression, and lower blood pressure in some patients (Filan and Llewellyn-Jones, 2006).

Recent evidence suggests effects of psychosocial interventions are generally modest with an unknown duration of action. The limited efficacy suggests that treatments will work best in specific, time-limited situations, tailored to individuals' requirements (O'Connor at al, 2009). Interventions with moderate effect size include recreation and music.

Delivering the intervention needs to be specific and may involve memory clinic multidisciplinary teams, community mental health teams, primary care teams, Admiral nurses and the voluntary sector.

Collaborative care models have established evidence of efficacy in behavioural symptoms (Ballard and Fox, 2006) and further developments are being undertaken in this area.

Horizon research

Research projects are in development and underway across the biopsychosocial spectrum of care delivery in dementia. Examples include:

1. Imaging developments with amyloid and tau markers with more sophisticated magnetic resonance imaging scanners and interpretation algorithms
2. New medication strategies which are currently in trial. Dimebon (Pfizer/Medivation) is an antihistamine which is currently in phase III large-scale international studies. Rember is a tau-targeted intervention which inhibits tau aggregation and facilitates tau oligomer dissolution. This is planned for a phase III study. Human monoclonal passive and active vaccine phase III licensing studies are underway and the outcomes of these studies should be available within 5 years
3. In psychosocial care there are studies looking at technology to assist carers and there are randomized control trials in non-pharmacological modalities, such as reminescence therapy and challenging behaviour.

Services have to develop and new innovations are urgently needed to cope with the increasing levels of the illness. During the next 5 years we should see changes in service models and treatment options (Kirkwood et al, 2008) for patients. **BJHM**

KEY POINTS

- There are increasing numbers of patients with dementia.
- Diagnosis needs to be considered systematically.
- Psychosocial interventions can benefit.
- Usage and management of medication requires careful consideration.
- There are new horizon innovations which offer potential significant benefit.

Conflict of interest: Dr Fox and Dr Boustani have received pharmaceutical industry funding for research, educational purposes and advisory purposes.

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