Alzheimer's Disease International

World Alzheimer Report 2011
The benefits of early diagnosis and intervention

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Cathy Greenblat's photos in the Report are taken from her forthcoming book 'Love, Loss, and Laughter: Seeing Alzheimer's Differently' which will be released in March 2012.

Cover photo: Facunda and Esther arrived early for the drum circle at Baycrest, in Toronto, Canada, knowing from prior experience that they would love the activity. It was clear that in addition to enjoying the music itself, they were happy to have this shared experience of participation.

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This is the full version of the World Alzheimer Report 2011.
An Executive Summary can be accessed free at www.alz.co.uk/worldreport2011

The full Report documents the review process and the sources in detail, and includes a careful critique of the quality, the relevance and the strength of the available evidence. The Executive Summary highlights the main findings, and briefly describes the evidence that supports them.

Contents

Summary

Alzheimer's disease and other dementias can be devastating not only for people who have dementia, but also their families and carers. Alzheimer's Disease International (ADI) works for an improved quality of life for people with dementia and their carers around the world, believing that policy and practice should be based on the best available evidence.

Our earlier reports

ADI's evidence-based advocacy is beginning to bear fruit

Our first two World Alzheimer Reports have helped to reset health and social care policy worldwide, increasing awareness of the burden of Alzheimer's disease and dementia to society. In the World Alzheimer Report 2009, ADI estimated that 36 million people worldwide are living with dementia, with numbers doubling every 20 years to 66 million by 2030, and 115 million by 2050. Much of this increase was found to be in low and middle income countries; 58% of those with dementia currently live in low and middle income countries, rising to 71% by 2050. The worldwide costs of dementia (US$604 billion in 2010) amount to more than 1% of global GDP, according to the World Alzheimer Report 2010. If dementia care were a country, it would be the world's 18th largest economy.

Together, these reports clearly demonstrate that Alzheimer's disease is among the most significant social, health and economic crises of the 21st century. Yet, if governments act urgently to develop research and care strategies, the impact of this disease can be managed.

ADI's evidence-based advocacy, supported by our national member societies, is beginning to bear fruit. There is welcome evidence of increased attention and priority being given to dementia. Australia, England, France, Norway and South Korea have recently launched comprehensive national Alzheimer strategies, and in January 2011 the National Alzheimer's Project Act was signed into law in the United States. The World Health Organization (WHO) made dementia one of the seven mental and neurological disorder priorities in its Mental Health Gap Action Plan (mhGAP), seeking to reduce the treatment gap in resource poor countries.

The treatment gap

Most people currently living with dementia have not received a formal diagnosis

Research shows that most people currently living with dementia have not received a formal diagnosis. In high income countries, only 20-50% of dementia cases are recognised and documented in primary care. This 'treatment gap' is certainly much greater in low and middle income countries, with one study in India suggesting 90% remain unidentified. If these statistics are extrapolated to other countries worldwide, it suggests that approximately 28 million of the 36 million people with dementia have not received a diagnosis, and therefore do not have access to treatment, care and organised support that getting a formal diagnosis can provide.

This is clearly a major concern, given that the world's population is growing older, new cases of dementia and Alzheimer's disease are increasing relentlessly, and – as this Report shows – earlier diagnosis and early intervention are important mechanisms by which the treatment gap can be closed.

Research review

For this year's World Alzheimer Report 2011, we have commissioned an independent research group to collate and review, for the first time, all of the available evidence relating to early diagnosis and early intervention. Key questions include:

- Is it possible to promote earlier diagnosis of dementia, and how might this be achieved?
- What are the overall benefits or disadvantages of earlier diagnosis and intervention for people with dementia and their carers?
- What treatments or interventions are effective in the early stages of dementia?
- Is there evidence that some interventions are more effective when applied early in the disease course?
- Can earlier diagnosis and intervention reduce health and social care costs?

These are all questions of great consequence for policymakers and planners, and we anticipate that the insights provided here will give additional stimulus to existing national programs while encouraging other countries to give much more attention to closing the treatment gap.

Pathway through the dementia crisis

The World Alzheimer Report 2011 signposts a pathway through the dementia crisis.

We have identified that lack of detection is a significant barrier to improving lives of people with Alzheimer's disease and other dementias, their families and carers. Medical treatments and other beneficial interventions are only available for those that have sought and received a diagnosis. For example, the systematic reviews carried out for this Report provide evidence that currently available drug treatments, psychological and psychosocial interventions can be effective in ameliorating symptoms for people with dementia and for reducing strain among their carers during the early stages of the disease. Interventions for carers may be more effective in allowing them to continue to provide care at home (avoiding or delaying institutionalisation of the person with dementia) when applied earlier in the disease course.

Scientists are developing and testing new drugs that may slow or stop the relentless progression of the disease. Scaling up the coverage of existing evidence-based treatments, particularly for those in the early stages of the disease, will make health systems better prepared to provide new, more effective treatments and diagnostic technologies, as they become available.

> Lack of detection is a significant barrier

Significant savings

In high income countries, according to the World Alzheimer Report 2010, the average annual societal costs are US$32,865 per person with dementia. Set against this, the one off costs of a high quality dementia diagnosis are around US$5,000 per person. Even taking this and the additional costs of early intervention into account, we find that these costs are more than likely offset by projected future savings from delayed institutionalisation, with net savings of around US$10,000 per person with dementia across the disease course. Improved health and quality of life of carers and people with dementia would make this an even more cost-effective investment. Though the evidence comes from a limited number of studies, there are indications that a significant amount could be saved at a time where governments are rightly concerned about increasing health and social care costs.

> Costs of early detection are more than likely offset by projected future savings

Lifting dementia out of the shadows

Earlier diagnosis has the potential to change the way societies view and approach Alzheimer's disease and other dementias. Unfortunately, the main barriers to access to care – the stigma of dementia that prevents open discussion, the false belief that memory problems are a normal part of ageing, and the false belief that nothing can be done for people with dementia and their families – are too prevalent even in well-resourced, well-informed, high income countries. Nonetheless, the evidence and detailed recommendations presented in this Report, if heeded, have the potential to lift dementia out of the shadows and prepare the way for greatly enhanced treatment and care. At the very least, everyone with dementia is entitled to a 'timely' diagnosis at the moment when they and their families first express concerns and have a need for advice, treatment or support.

> The false belief that nothing can be done for people with dementia is too prevalent

Those closely involved in the Alzheimer's and dementia movement have long promoted earlier detection as a way to empower people with dementia to participate as fully as possible in planning their own lives following diagnosis, and in making important decisions about future treatment and care. In that spirit, people from various parts of the world have sent statements to ADI about their diagnosis, which are showcased in this Report. They give an impression of how painful this process can be, but they also show that the diagnosis can mark a new start to the rest of their lives. We must heed the voices of those most affected.

Key findings

- Dementia diagnosis provides access to a pathway of evidence-based treatment, care, and support across the disease course.

- Perhaps as many as 28 million of the world's 36 million people with dementia have yet to receive a diagnosis, and therefore do not have access to treatment, information, and care.

- The impact of a dementia diagnosis depends greatly upon how it is made and imparted. Evidence suggests that when people with dementia and their families are well prepared and supported, initial feelings of shock, anger and grief are balanced by a sense of reassurance and empowerment.

- Earlier diagnosis allows people with dementia to plan ahead while they still have the capacity to make important decisions about their future care. In addition, they and their families can receive timely practical information, advice and support. Only through receiving a diagnosis can they get access to available drug and non-drug therapies that may improve their cognition and enhance their quality of life. And, they can, if they choose, participate in research for the benefit of future generations.

- Most people with early stage dementia would wish to be told of their diagnosis.

- Improving the likelihood of earlier diagnosis can be enhanced through: a) medical practice-based educational programs in primary care, b) the introduction of accessible diagnostic and early stage dementia care services (for example, memory clinics), and c) promoting effective interaction between different components of the health system.

- Early therapeutic interventions can be effective in improving cognitive function, treating depression, improving caregiver mood, and delaying institutionalisation. It is simply not true that there is 'no point in early diagnosis' or that 'nothing can be done'. Some of these interventions may be more effective when started earlier in the disease course.

- Available evidence suggests that governments should 'spend to save' – in other words, invest now to save in the future. Economic models suggest that the costs associated with an earlier dementia diagnosis are more than offset by the cost savings from the benefits of anti-dementia drugs and caregiver interventions. These benefits include delayed institutionalisation and enhanced quality of life of people with dementia and their carers.

Norm McNamara, who has dementia, UK

I have never had any trouble telling anyone in my family I love them, but telling them that I had Alzheimer's was a totally different thing, but once done it was one of the best decisions I have ever made. Within a week of ... being diagnosed, I had sat all my family down and explained all about my diagnosis and the implications of what might happen in the future. Their reaction? After the tears, hugging and many questions about this awful disease, it was a case of "Right! That's that then. So, what are we going to do about it?"

I expected nothing else from my family and the knowledge that they had accepted and cleared another hurdle thrown in front of them made me feel so relieved and also so hopeful for the future. I knew with their support and understanding I would continue to live a life as full as I have always been used to and for as long as possible.

Since then my wonderful wife and I have discussed end of life plans, my wishes and all my "House" (business) has now been put in order, if you know what I mean. Why? I hear you ask. Because I can now live my life along with my family and friends to the best of my ability without any additional worry, and also, in the future, when I do some things that probably make no sense to anybody else, at least I know my family will understand my actions.

Recommendations

- Every country should have a national dementia strategy. National dementia strategies should promote early diagnosis and intervention through awareness raising, training of the health and social care workforce, and health system strengthening.

- All primary care services should have basic competency in early detection of dementia, making and imparting a provisional dementia diagnosis, and initial management of dementia.

- Where feasible, networks of specialist diagnostic centres should be established to confirm early stage dementia diagnoses and formulate care management plans.

- In resource-poor settings with limited or no access to specialist dementia services, earlier dementia diagnosis can still be achieved, for example through scaling up the WHO mhGAP evidence-based intervention guide across primary care services.

- The availability of effective drug and non-drug interventions for people with dementia and their carers should be publicised to health and social care professionals through initial training and ongoing professional development, and to the public through population health promotion, and health and social care facilities.

- Purchasers and providers of dementia care services should ensure that evidence-based interventions are made available to people in the early stage of dementia, and audit this process.

- More research should be commissioned and funded, including investigation of:

  - The efficacy of drug and non-drug interventions specifically designed to meet the needs of people in the early stages of dementia.

  - The real-world costs and benefits of scaling up earlier diagnosis and early-stage dementia care services, specific to the settings in which the economic evidence is to be applied.

  - The effect of earlier diagnosis on outcomes (overall health, cognitive functioning, quality of life, etc.) for people with dementia and their carers.

  - The progress towards closing the 'treatment gap'.

CHAPTER 1

Background

This is the third World Alzheimer Report that ADI has commissioned. The first two, the World Alzheimer Reports 2009 and 2010, focused on the global prevalence and economic impact of the disease, respectively. These reports have helped to reset health and social care policy worldwide, increasing awareness of the burden of Alzheimer's disease and dementia to society. They have made governments more aware of the impact of dementia on their health systems; they have clarified the contribution made by dementia to escalating health care costs and the need to better manage these costs.

People with dementia actively participated in the 2011 Alzheimer's Disease International meeting in Canada. We see them here in an animated private session on ways to decrease the stigma of dementia. They participated in a number of capacities, sometimes as speakers or chairs of panels. Back row: Jan Philips, Lynn Jackson, Debbie Browne (accompanying her husband Graham) and Richard Taylor. Front row: Lynda Hogg, Christine Bryden, Graham Browne, Agnes Houston and Helga Rohra.

Skills and technology are advancing and we are at a stage where diagnosis can be made increasingly early in the disease process. ADI and its member organisations seek to raise awareness, encourage early help-seeking by those affected, and lobby for improved coverage of better, more effective and more responsive services to meet the needs of the world's estimated 36 million people with dementia, and their families and carers. ADI is also fully committed to the principle that policy and practice should be based on the best available evidence. Accordingly, ADI commissioned a study for the 2011 World Alzheimer Report, to answer the following key questions on early diagnosis and early intervention:

• What are the benefits and disadvantages of early diagnosis and intervention for people with dementia and their caregivers?

• How does early diagnosis and intervention affect health and social care costs?

• What are the best evidence-based practices in early intervention around the world?

Early diagnosis and early intervention as policy priorities

Early diagnosis and early intervention have consistently emerged as key policy priorities in recently formulated national dementia strategies for high income countries.

The English Secretary of State for Health, launching the country's first National Dementia Strategy, said:

> "Current best estimates are that only one-third of people with dementia ever receive a diagnosis of their illness. We can't hope to address their needs fully, or those of their carers, without a diagnosis being made, appropriate information being given and effective intervention at an early stage. Some have argued in the past that it is best not to let people know. We have long accepted that this should not occur with cancer sufferers. The same should be true for those with dementia. This was one of the most consistent messages emerging from the consultation process from people with dementia."
>
> Living Well with Dementia: A National Dementia Strategy. Foreword by Alan Johnson MP, Secretary of State for Health[1]

The first two objectives in the National Dementia Strategy for England are 'Improving public and professional awareness and understanding of dementia' and 'Good-quality early diagnosis and intervention for all'. The rationale was described as follows:

> "We have heard clearly that knowledge is power with respect to diagnosis, giving those affected and their families an understanding of what is happening and the ability to make choices themselves. Making the diagnosis early on in the illness means that there is the chance to prevent future problems and crises and to benefit more from positive interventions."[1]

Improvements in early diagnosis of Alzheimer's disease also features prominently as one of the six main purposes of the US National Alzheimer's Project Act (NAPA) signed into law by President Obama in January 2011. The fourth objective of the French Plan Alzheimer is 'improving access to diagnosis and care pathways'.

The right to a diagnosis

From the early 1990s, attention began to be drawn to the need for people with dementia to have their rights properly respected as autonomous individuals. The Fairhill guidelines on ethics of the care of people with Alzheimer's disease, derived from a dialogue between family caregivers, people with dementia and an interdisciplinary group of professionals in the US, asserted that "because individuals have a right to control their own lives, and because true control depends on knowing about oneself, individuals have a right to full disclosure regarding a dementia diagnosis"[2]. The first item in an Alzheimer's Disease Bill of Rights (1995) reads,

> "Every person diagnosed with Alzheimer's disease or a related disorder deserves to be informed of one's diagnosis".[3]

Patient advocacy groups have also been forthright on this point, for example, the US Alzheimer's Association states simply that

> "Except in unusual circumstances, physicians and the care team should disclose the diagnosis to the individual with Alzheimer's disease because of the individual's moral and legal right to know".[4]

The absolute right to a diagnosis is complicated, at least potentially, by ethical and practical issues relating to patient and carer preferences. What if the patient prefers not to be told? Should the clinician share the information with the carer but not the patient, if the carer expresses a wish for the patient not to be told? There is evidence, at least in the recent past, that both non-specialist and specialist clinicians would often withhold dementia diagnoses, acting from a paternalistic impulse to protect the patient or carer from a perceived risk of harm or distress[5].

Over the last 15 years there have been many studies of patient and carer preferences, and the evidence generated has been largely reassuring. An early, and much cited study from a memory clinic in Ireland showed that 83% of carers did not wish the patient to be told of the diagnosis, the main reasons given being concern that the diagnosis would depress or agitate the patient[6]. However, 71% of those same family carers expressed a wish to be told of the diagnosis should they develop the illness, the main reasons being that it was their right to know (51%) so that they could then make provisions for the future (37%).

Since that study was conducted in the mid-1990s, there is evidence to suggest that carer attitudes are changing, probably as a result of growing public awareness. In a UK study conducted between 1999 and 2001, 54 of 100 carers of those with recent diagnoses of dementia wished the patient to be told of the diagnosis[7]. Interestingly, in that study carers of those with mild dementia were much more likely to want the diagnosis

to be communicated, suggesting that earlier diagnosis might ease carer concerns about sharing information with patients. A study of 50 people with mild dementia, recruited through a memory clinic in Nottingham, UK in 2000, showed that 74% of the carers were willing for the patients to be informed of the diagnosis of dementia[8]. Again, an even higher proportion of carers (98%) would have liked to be informed if they developed the disease.

There are much fewer data available on the views and preferences of people with dementia regarding receipt of diagnosis. However, in the Nottingham study 92% of those with mild dementia would have liked, in principle, to be informed of a diagnosis of dementia[8]. Almost without exception, they were also overwhelmingly of the view that their family members should be informed.

The impact of a diagnosis

Dementia is a profoundly life changing condition. It is perhaps not surprising that formal disclosure of the diagnosis is sometimes experienced as a severe shock, particularly when patients and carers had no prior suspicions[9]. People with dementia often recall their emotional response to the news rather than the specific information provided by the clinician[10]. Initial reactions reported from qualitative research include feelings of disbelief, anger, loss and grief [9-11]. In a US study of carers attending a support group, while 72% said that in principle a person with dementia should be told the diagnosis, slightly more than half of those whose relatives had been informed felt that they had 'reacted poorly' to the disclosure[12].

Not all research confirms such negative short-term reactions. For example, the only quantitative study to assess prospectively the impact of disclosure on patient and carer depression and anxiety symptom scores indicated no change in depression scores and a reduction in anxiety symptoms three days after diagnostic evaluation[13]. There is also marked individual variation; some patients and carers report, for example, that the diagnosis had helped by confirming their suspicions and validating their experience of cognitive difficulties[9-11]. With growing awareness, such suspicions may be quite widespread; in a rare study, 28% of patients with early stage dementia, but 82% of carers, suspected that the patient might have dementia at the time of presentation to a UK memory clinic service[8].

Immediate reactions to the diagnosis often give way to a period of reflection and adaptation, in which the receipt of a diagnosis is viewed more positively. US carers expressed feelings of regret that they had not received a diagnosis earlier than they did, which would have enabled them to have been more patient, understanding, and less apt to blame their family member for his or her actions[11]. A detailed qualitative analysis of the responses of Dutch patients and carers to diagnosis two and ten weeks after diagnosis revealed that formal disclosure seemed to pave the way for future planning and allowed them to express feelings of loss and grief[9].

The disclosure of a diagnosis also provided an incentive for family members to adapt to the role of a carer[9], for example by taking more initiative in decision making and assuming some responsibility for the cared for person[9-11].

The response of patient and carer to the disclosure of a diagnosis of dementia will depend, critically, upon the manner in which the diagnosis is imparted. Many problems have been identified, both from the perspectives of patients and carers (being unprepared for the bad news, diagnosis imparted insensitively, inadequate information, no follow-up) and clinicians (limited knowledge and experience, too little time). Current evidence-based recommendations include eight key elements of good practice – preparation; involving family members; exploring the patient's perspective; disclosing the diagnosis; responding to patient reactions; focusing on quality of life; future planning; and effective communication[14]. This process has been termed 'making the diagnosis well'[15].

Underdiagnosis – the 'treatment gap'

It is clear that in most if not all health systems dementia is underdiagnosed, and when diagnosis occurs this is typically at a relatively late stage in the disease process. Studies conducted over the last 10 years in high income countries show that only one-fifth to one-half of cases of dementia are routinely recognised and documented in primary care case note records; with a median proportion from six studies of 39%[16-20]. To our knowledge there has only been one such study conducted in a low or middle income country, with 90% of those recruited for a caregiver support trial not having previously received any diagnosis, treatment or care[21]. The World Health Organization recently identified dementia as one of seven priority mental and neurological disorders to be addressed in its Mental Health Gap Action Plan (mhGAP) targeting conditions that were burdensome, chronic and undertreated, particularly in resource poor countries.

A consultation exercise recently carried out for the National Dementia Strategy in England highlighted a combination of three factors contributing to low rates of detection of dementia; the stigma of dementia preventing open discussion, the false belief that memory problems were a normal part of ageing, and the false belief that nothing could be done; that resulted in inactivity in seeking and offering help[1].

As yet, no country has been effectively monitoring trends in the size of the treatment gap, although this will be a feature of several of the recently developed national Alzheimer plans and strategies. Nevertheless, it is likely that the treatment gap is shrinking at least in some high income countries, with growing public awareness, earlier help-seeking, better prepared and incentivised primary care services, and rapidly expanding national networks of memory clinics. The evidence to support this is presented in Chapter 2.

What do we mean by early diagnosis?

Dementia is conventionally diagnosed when progressive cognitive decline has occurred, and this has had noticeable impacts upon a person's ability to carry out important everyday activities. It is a clinical diagnosis, supported by careful neuropsychological testing, a history from the patient (subjective impairment in memory and other cognitive functions) and from a key informant (objective signs suggestive of cognitive decline, and evidence of impact on social and/or occupational functioning). Neuroimaging is used, where available, to exclude other organic causes of cognitive impairment, and to provide information supporting definition of subtype. Other tests may be done to rule out other causes of cognitive changes such as thyroid disease, vitamin deficiencies or infection.
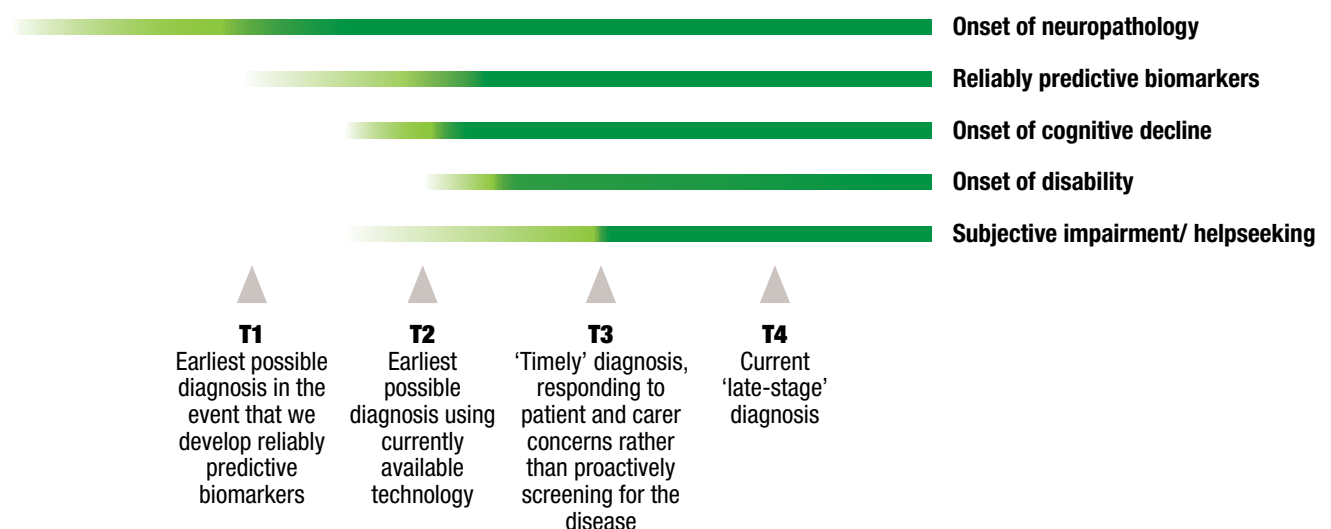
The pathological changes in the brain that will eventually lead to the symptoms of dementia are likely to have commenced well in advance of the time at which the person's symptoms would first have been noticed. For example, the brain changes underlying Alzheimer's disease probably develop over a period of at least 20-30 years prior to the onset of symptoms, with earliest signs around the base of the brain in the fifth decade of life, plaques and tangles later spreading up to the cortical regions[22]. The time course and pattern of development of cerebrovascular pathology is likely to be much more variable. As the brain pathology develops, then so, gradually, do the symptoms and signs that may, with progression, ultimately validate the diagnosis of dementia. Hence, the person affected may begin to notice deterioration in memory, language, or other cognitive abilities. These same problems may be remarked upon by others who know them well. Formal neuropsychological testing may be able to detect cognitive impairment relative to expected norms, or to that person's previous performance on the same test. In the absence of clear evidence of social or occupational impairment, evidence of these changes have been used to define several prodromal syndromes, particularly

1 subjective memory impairment (SMI)

2 cognitive impairment no dementia (CIND)[23]

3 mild cognitive impairment (MCI)[24]

Different definitions of these syndromes have been proposed and applied. The syndromes are overlapping. Thus, SMI may or may not be accompanied by objective cognitive impairment, and vice versa. Most definitions of MCI require SMI and cognitive impairment not meeting dementia diagnostic criteria (in particular with no impairment in core activities of daily living). Each of these syndromes has been shown in prospective studies to increase risk of what is often described as 'conversion' to dementia[25-28]. Conversion rates are probably highest for the amnestic form of MCI in which the prominent impairment is one of memory – these range from 10-15% per year in clinic-based studies with lower rates (5-10%) seen in longitudinal population-based studies[25]. However, these are all highly heterogeneous groups. Conversion is by no means inevitable, and indeed, even for MCI, up to a quarter in some studies who meet criteria show subsequent recovery of normal cognitive function[25].

When speaking of promoting early diagnosis with respect to Alzheimer's disease and other forms of dementia it is important therefore to clarify what we mean. We have seen that, currently, the diagnosis is often not made at all, or made very late in the process by which time cognitive impairment, disability and behavioural symptoms may be all quite marked (T4 in figure 1). One aim may therefore be to advance the time at which the diagnosis is made to the earliest stage possible using current routinely available diagnostic technologies and health system structures (T2). A European primary care consortium have qualified this aim by proposing that we should aim for 'timely' rather than 'early' diagnosis, responding to concerns raised by older people and family members (T3), rather than screening older populations proactively for early signs and symptoms[29].

Figure 1: **Timeline of disease progression**

Onset of neuropathology

Reliably predictive biomarkers

Onset of cognitive decline

Onset of disability

Subjective impairment/ helpseeking

T1
Earliest possible diagnosis in the event that we develop reliably predictive biomarkers

T2
Earliest possible diagnosis using currently available technology

T3
'Timely' diagnosis, responding to patient and carer concerns rather than proactively screening for the disease

T4
Current 'late-stage' diagnosis

In principle, it may be possible to advance the diagnosis much earlier than this (T1) by improving the predictive validity of the prodromal risk indicators based upon cognitive decline and subjective impairment. One widely advocated approach is the incorporation of disease biomarkers that may indirectly represent the extent of underlying neuropathology[30]. Candidates include those derived from structural neuroimaging (medial temporal lobe or hippocampal volume[31]), functional neuroimaging (Aβ ligands, such as 11C-labelled Pittsburgh compound B (PiB) to visualise amyloid plaques in vivo[32]) and cerebrospinal fluid (reduced concentrations of Aβ and higher concentrations of total tau and hyperphosphorylated tau[33]). Although some research supports the notion that some of these biomarkers may help in predicting conversion among those with MCI[30], these are as yet experimental procedures, and while some would make claims to the contrary, there is as yet no clear evidence that the time of diagnosis (as opposed to suspicion) of dementia can be reliably advanced from T2 towards T1.

What is the purpose of earlier diagnosis?

All of the recently developed national dementia strategies make it plain that the primary purpose of early diagnosis is timely access to information, advice, and support and access to a pathway of effective intervention and care from the time of diagnosis to end of life care.

> "Contrary to social misconception, there is a very great deal that can be done to help people with dementia. Services need to be re-engineered so that dementia is diagnosed early and well and so that people with dementia and their family carers can receive the treatment, care and support following diagnosis that will enable them to live as well as possible with dementia… diagnosis and contact often occur late in the illness and/

or in crisis when opportunities for harm prevention and maximisation of quality of life have passed."
Living Well with Dementia: A National Dementia Strategy. UK Department of Health[1]

The clinical indication for an earlier diagnosis would be that, at least hypothetically, a critical period for some effective interventions may lie between the earliest point at which the diagnosis can be made (currently T2 or T3 in figure 1) and the time at which diagnosis is currently made (T4). From this perspective, if the critical period for intervention falls after T4, or before T2, then there would be no point in advancing the diagnosis. Currently available pharmacotherapies are symptomatic treatments only; acetylcholinesterase inhibitors are licensed for mild to moderate AD, and memantine for moderate to severe dementia. They do not appear to benefit people with MCI[34]. However, compounds with the potential to slow disease course may be developed in the future. Such compounds are likely to have maximum efficacy when applied before extensive and irremediable damage has occurred, and hence before the disease is clinically manifest. Identification of any such agents would be highly likely to promote and justify efforts to advance the time of diagnosis to T2 or even T1.

Of course, there are many effective non-pharmacological interventions for people with dementia and their carers. These include psychological, psychosocial and psychoeducational interventions, with the potential to improve cognitive function, delay institutionalisation, reduce carer strain and psychological morbidity and improve quality of life. Information regarding the critical period, if any, for the effectiveness of these interventions is not readily available. Some interventions, for example those that target behavioural symptoms such as aggression and agitation, or psychotic symptoms such as as delusions and hallucinations are likely mainly to be indicated in the later stages of the disease.

Table 1: **Needs assessment, carried out by the Illinois chapter of the Alzheimer's Association (USA)**

	People with Dementia	**Carers**
1	Educational information on disability benefits/employment issues	Public policy programs
2	Financial and legal counselling	Educational information on research and clinical trials
3	Educational information on research and clinical trials	Educational information on disease
4	Emotional support programs	Emotional support programs
5	Brain fitness	Peer-to-peer programs
6	Public policy activities	Brain fitness
7	Useful tips for everyday living	Financial and legal counselling
8	Physical fitness programs	Educational information on disability benefits/employment issues
9	Peer-to-peer programs	Useful tips for everyday living
10	Educational information on disease	Safety programs

Relatively little attention has been paid to the specific needs of people with dementia and their family members in the early stages of the disease. In a needs assessment, carried out by the Illinois chapter of the Alzheimer's Association (USA), of people with early stage dementia, there was an expressed need for practical information, financial and legal counselling, emotional support (particularly provided by peers, that is other people with dementia, and carers), and an interest in research, including clinical trials for the disease (see table 1 opposite)[35].

Conclusion

Earlier diagnosis and early intervention for people with dementia are widely advocated, and initiatives to achieve these goals are at the centre of recent national policies and plans. There is some lack of clarity as to what we mean by 'early' diagnosis, in particular whether this refers to the earliest point at which a diagnosis could be made using existing technologies (which might require population screening), or only when patients and carers, as well as professionals, recognised a problem. More advanced technologies, including the use of biomarkers with underlying progressive brain pathology, may in the future make it possible to identify asymptomatic individuals likely to go on to develop features of dementia. What is clear is that, currently, the diagnosis tends to be made very late in the day, if at all, and, as a consequence, most affected individuals have not had the chance to receive help. The main rationale for earlier diagnosis is timely access to information, advice, and support and a pathway of effective intervention and care from the time of diagnosis to end of life care. As yet, the evidence base to support earlier diagnosis and intervention has not been comprehensively reviewed, or effectively summarised. This is the primary purpose of this World Alzheimer Report 2011.

In the following five chapters, we consider five key questions with respect to the feasibility and desirability of actively promoting and investing in early diagnosis of dementia:

1 How might it be possible to promote earlier diagnosis (bringing the time of diagnosis forward from T4 towards T3 and T2)? (Chapter 2)

2 Does early diagnosis benefit people with dementia and their carers? (Chapter 3)

3 Which interventions are effective for people in the early stages of dementia? (Chapter 4)

4 Are there some interventions that work better in the earlier, compared with the later, stages of dementia? (Chapter 5)

5 Spending to save – does early diagnosis and intervention reduce the societal cost of dementia? (Chapter 6)

We took some of these questions and expressed them more formally to assist the design of search strategies to identify relevant research. The format and results of these searches are described in the subsequent chapters of this report.

Question 1 (Chapter 2)
Can practice-based educational and/or organisational interventions, compared with usual care, promote earlier diagnosis of dementia?

Question 2 (Chapter 3)
Is earlier, compared with later diagnosis of dementia associated with benefits or disbenefits for people with dementia and their carers?

Question 3a (Chapter 4)
For which pharmacological, psychological or psychosocial interventions, when compared with placebo/usual care is there evidence of clinical benefit/disbenefit for people with dementia and their carers, specifically when applied in the early stages of dementia?

Question 3b (Chapter 4)
Are enhancements to protocols for the delivery of packages of care for those in the early stages of dementia (e.g. case management), compared with usual care, associated with benefits/disbenefits for people with dementia and their carers?

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CHAPTER 2

How might it be possible to promote earlier diagnosis?

The effectiveness of health systems in identifying people with dementia depends upon the potential consumers, as well as the providers of health and social care. Encouraging help-seeking by raising awareness of dementia is an essential component of any comprehensive strategy to close the treatment gap. However, increased demand needs to be met by adequately prepared and resourced services, trained and able to make accurate diagnoses in a timely and efficient manner, and to ensure that the diagnosis leads seamlessly to the provision of evidence-based care. While acknowledging the importance of promoting demand for services, the focus for this chapter is upon service responses.

Six women at this Silverado Senior Living residential Alzheimer's community in Texas, USA, were taken by staff members to a flea market to select and purchase a hat. The next day a special table was set for them in the dining room. Each woman arrived, sporting her new hat or was helped to put it on. They all had a good time.

Introduction

The effectiveness of health systems in identifying people with dementia, making diagnoses, and initiating appropriate management will depend upon factors relating to the potential consumers, as well as the providers of health and social care. Put another way, it will be influenced by the demand for as well as the supply of services. In general, help-seeking is a pre-requisite for symptoms and signs to be recognised, and diagnoses to be made. Effective help-seeking will require recognition and acknowledgement that there is a problem, by the person affected and/or others, coupled with knowledge of an accessible service where appropriate help may be obtained. Help-seeking (and recognition and acknowledgement of a problem) can be bypassed, at least to some extent, through whole population or population subgroup screening programs. The cost-effectiveness, or otherwise, of such programs is an important consideration, and this will depend critically upon the benefits of earlier diagnosis, and the avoidance of harm. Raising awareness of dementia among the general population is an essential component of any comprehensive strategy to close the treatment gap. The government, the media and health professionals all have important roles to play, supported by the advocacy and public engagement work of Alzheimer's associations worldwide. Having acknowledged the central importance of raised awareness and help-seeking, the focus of this chapter will be upon the supply of services, and their providers, rather than the demand. Increased demand needs to be met by adequately prepared and resourced services, trained and able to make accurate diagnoses in a timely and efficient manner, and to ensure that the diagnosis leads seamlessly to the provision of evidence-based care.

Service provision for dementia diagnosis and early stage care

High income countries

Early dementia diagnosis is currently actively promoted in several high income countries that benefit from well developed primary care services, supported by national networks of specialist centres with access to all modern diagnostic technologies[1]. However, in the past, secondary care services have not encouraged early referral of uncomplicated cases. So, as we have seen, diagnoses tend to be made late, if ever. Non-specialists, particularly in the primary care sector, have an important part to play. In many health systems, primary care centres are the natural 'first port of call' for those seeking help for a new health problem, and general practitioners play an important gate-keeper role, deciding which patients should and should not be referred on for specialist assessment and treatment. In a case-note study from the UK, 96% of patients on a primary care register with confirmed or suspected dementia had their diagnosis first made in primary care, and two-thirds of those identified in primary care were then referred immediately for specialist attention[2].

Effective coordination between primary and secondary specialist care services is important both to ensure accurate early diagnosis, and access to appropriate early and continuing care. People with dementia vary greatly in their needs for intervention and support. However, in many high income country health systems it is possible to discern two branches of specialist service, which have been characterised as an 'early intervention' stream (mainly outpatient memory clinics, focussing on early differential diagnosis and early intervention to minimise future harm, risk and cost for the patient) and a 'serious mental illness' stream (co-ordinating community care in the more advanced stages of the disease treating severe and complex disorders with high levels of risk and co-morbidity)[3].

Low and middle income countries

Health systems in many low and middle income countries are hampered by the same set of obstacles to early diagnosis identified in high income countries; lack of awareness, stigma, poor provider skills; but to a much greater degree. Hence dementia remains to a large extent a hidden problem. Although the symptoms and syndrome are widely recognized and named, it is often considered to be a normal part of ageing, not a medical condition[4-6]. Family members rarely seek help, and primary care doctors rarely come across cases[5,7]. The treatment gap in south India was recently estimated to be as high as 90%[8]. Due to resource limitations, particularly of specialists to confirm early stage dementia, earlier diagnosis would initially involve identification of established, moderate to severe cases by non-specialists. The World Health Organization has prepared evidence based guidelines for management of dementia by non-specialists in low and middle income countries with a view to scaling up treatment and reducing the treatment gap[9,10]. Effective case identification by non-specialists is an essential component for these resource poor countries, where there are far too few specialists to provide a comprehensive national service[10]. Identification and management of unequivocal cases should be a core competency; in this way, they could make considerable inroads into the enormous treatment gap.

Is diagnosis feasible in primary care?

Studies from high income countries show that only one-fifth to one-half of all cases of dementia in the population are routinely recognised and documented in primary care case note records; with a median proportion from six studies of 39%[11,15]. However, evidence suggests that primary care physicians and nurses can, if specifically prompted to do so, make a dementia diagnosis with reasonable accuracy, using their knowledge of the patient, available case note information, and their own routine assessments in the limited time available during a typical consultation[16,17]. Such diagnoses are easier for those with moderate or severe rather than mild or early stage dementia. In 10/66 Dementia Research Group 'casefinder' studies conducted in India and Brazil, community healthcare workers could, with a few

hours training, identify dementia in the community with a positive predictive value of 66%, based solely upon their prior knowledge of older people from their routine outreach work[18,19]. The discrepancy between what non-specialists might and do, in practice, achieve is explained partly by limited help seeking. It may also be that non-specialists either are not attentive to the possibility of dementia or are not motivated to confirm and record the diagnosis when the possibility occurs to them.

Screening to facilitate identification of dementia in primary care

Population screening for dementia has not generally been considered to be cost-effective in high income countries[20]. The United States Preventive Services Task Force (USPSTF) concluded in 2004[21] that they could not determine whether the benefits of screening for dementia would outweigh the harms, citing:

1   Insufficient evidence to determine whether the benefits of treatment observed in drug trials are generalizable to patients whose disease would be detected by screening in primary care settings.

2   Lack of information regarding the accuracy of diagnosis, the feasibility of screening and treatment in routine clinical practice, and the potential harms of screening (e.g., labelling effects).

However, the USPSTF, in common with other agencies, does recommend that clinicians should assess cognitive function whenever cognitive impairment or deterioration is suspected, based on direct observation, patient report, or concerns raised by others who know them well[21]. This approach, sometimes referred to as 'indicated screening', can be used to promote detection among primary care attendees. Research in developed countries has highlighted the short period of time available for each primary care consultation, and the need accordingly for very brief assessments, ideally taking five minutes or less to complete[22]. Screening involves cognitive testing of the older person or informant interview for a history of cognitive and functional decline. Sometimes both approaches are combined in a single test. The Mini-Mental State Examination[23] is widely used in high income

countries, and adapted versions have been developed for use in many low and middle income countries[24,26]. However, it takes 10 minutes to administer and is prone to educational and cultural bias[27,28]. A brief version of the MMSE, the 'six item screener', performed as well as the full MMSE in clinical and population samples in the USA[29]. Three tools that are brief enough, and at least as valid as the longer MMSE (General Practitioner Assessment of Cognition (GPCOG[30]), the Memory Impairment Screen (MIS[31]) and Mini Cog[32]) have been validated in high income countries[22]. None is suitable for use in low and middle income countries where many older people have little or no education. The Community Screening Instrument for Dementia (CSI-D) is extensively validated in diverse low and middle income country settings with age and education specific norms[33-35]. It combines culture and education-fair cognitive testing of the participant (32 items) and an informant interview enquiring after the participant's daily functioning and general health (26 items) into a single predictive test. The 10/66 Dementia Research Group analysed CSI-D cognitive and informant scale data from 15,022 participants in representative population-based surveys in Latin America, India and China, to identify a subset of just seven cognitive items and six informant items with excellent hierarchical scaling properties[36]. Validity for the identification of dementia was as good as for the full assessment, and cutpoints did not vary between regions. Thus, the brief CSI-D (administered in 5 minutes) shares the favourable culture- and education-fair screening properties of the full assessment, and may be a useful tool for primary care screening.

Is screening enough?

Screening assessments can help to identify those with a strong probability of dementia, but do not provide adequate information to make a formal diagnosis. This will require a more detailed history and examination, and further investigations, and, particularly in difficult cases, would require confirmation by a specialist. The formal diagnosis is just one part of the process of engaging the patient and family with a system of ongoing care and support. Research has revealed a wider problem of limited knowledge and skills, and negative perceptions,

Dr Myrna Blake, who has dementia, Singapore

Since the diagnosis of my condition (Alzheimer's disease), I have learnt to accept and manage it. I have come to deal with it when things happen. Over the years, I have lost some of my independence and have moved on to engage two domestic helpers to assist in my daily living.

among some non-specialist health professionals. A survey in the UK found that one-third of general practitioners lacked confidence in their ability to make a diagnosis[37]. The main limitations they identified were talking with patients about the diagnosis, responding to behaviour changes and coordinating support services, about which they often had little specific knowledge. This study also identified a cluster of negative beliefs about the value and importance of dementia care held by a significant minority of practitioners, and a tendency to view this as the sole responsibility of specialist services, which correlated with less knowledge about dementia. If one screens one then needs to have the capacity to make the diagnosis in those who screen positive, to break that diagnosis well and then provide the immediate care and support needed[38]. Professional education for primary care staff that is limited to the use of screening instruments and the differential diagnosis of dementia may be misdirected. There may, instead, be a need for more multi-faceted educational interventions that

1 change attitudes, by raising awareness of the importance of dementia, the extent of the unmet need, and the potential for intervention to make a difference once the diagnosis has been made

2 provide knowledge and skills regarding dementia diagnosis, provision of information and support, and basic management strategies

Multi-faceted practice-based educational interventions to promote earlier dementia diagnosis

We used the following scoping question:

Can practice-based educational and/or organisational interventions, compared with usual care, promote earlier diagnosis of dementia?

We identified a relevant systematic review[39]. Inclusion criteria were that the intervention aimed to influence professional practice, by means of educational interventions targeting primary care providers, and focused on detection and management of dementia. Randomised controlled trials (RCTs), and controlled but not randomised study designs, were considered. For the purposes of the review, professional interventions included any or all of 10 types of intervention: distribution of educational materials, educational meetings, workshops (with active participation), seminars (with passive participation), local consensus processes, educational outreach visits, use of local opinion leaders, patient mediated interventions, audit and feedback, reminders (including computer decision support systems), marketing and mass media.

The systematic review yielded six articles describing five studies. Three of the studies were randomised controlled trials[40-42], one a controlled non-randomised trial (incorrectly described as an RCT in the review)[43], and one a controlled before and after study[44].

Of these studies, the most relevant to our scoping question were two cluster-randomised controlled trials, one conducted in UK general practices (primary health care centres)[41], the other conducted among general practitioners across France[42]. In the UK trial, thirty-six general practices were randomly allocated to a CD-ROM tutorial (8 practices); decision support software (8); practice based workshops (10); and control (no intervention – 10 practices). Detection of dementia was ascertained through a case-finding exercise carried out before and nine months after the educational intervention. Practices conducted electronic searches of their clinical record system for the terms dementia, confusion, memory loss, and cognitive impairment. Medical and nursing staff updated this electronic search manually. The yield of newly identified cases was significantly greater in the post-intervention period for the practices that received practice-based workshops and those that used decision support software, compared to control practices. However, there was no difference between any of the four arms in 'diagnostic concordance', defined as a score out of 10 for adherence to 10 indicators of good diagnostic practice including: request for blood tests, referral to specialist services, taking a history of patient's symptoms, completing cognitive testing, considering depression before diagnosis, scan conducted before diagnosis, diagnosis disclosed to carer or patient or both. The average post-intervention diagnostic concordance score varied between 3.1 and 3.6.

In the French trial[42], 684 GPs were randomised either to receive a two hour group educational meeting conducted by specialists focussing on the use of a battery of four brief neuropsychological tests (n=353), or to continue 'usual practice' (n=331). All of the GPs were then asked to recruit the next five patients aged 75 or over presenting with a spontaneous memory complaint, or who were reported to have this problem by an informant. The GPs rated the patients as having 'suspected dementia', 'no dementia', or as having 'uncertain' diagnostic status. Those with suspected dementia were to be referred to a specialist for diagnostic confirmation. In the intervention group compared with the control group there was a higher proportion of suspected dementia (36.4% vs. 26.8%, p < 0.0001) and a lower proportion of no dementia (45.6% vs. 50.9%, p=0.004) and uncertain diagnosis (18.0% vs. 22.3%, p=0.004). In both groups, 40% of patients identified as having suspected dementia declined a specialist referral. The proportion of those assessed among whom a diagnosis was confirmed (the positive predictive value of the GP suspicion of dementia) was similar in the intervention and control clusters; 60.9% vs. 64.4%, p=0.41. Neither was there any increase in the net yield of confirmed dementia cases associated with the intervention, since although more suspected cases were confirmed in the intervention clusters, more 'uncertain' cases were subsequently assessed and confirmed in the control clusters.

In the controlled study conducted in Denmark, 757 physicians from 553 general practices were mailed a clinical practice guideline on identification and diagnostic evaluation of dementia, comprising a 27-page booklet and a quick reference guide[44]. The main recommendations were to conduct an initial diagnostic evaluation of dementia including the Mini Mental Status Examination (MMSE), to screen for thyroid stimulating hormone (TSH) and either vitamin B_{12} or methylmalonate, and to involve caregivers. The need for a specialist referral would then be considered. The practices were then allocated by district to a control arm (216 physicians), outreach visits from a specially trained GP facilitator (135 GPs), reminders (203 GPs) and continuing medical education sessions (173 GPs). All intervention GPs were invited to seminars introducing the guidelines, and covering aspects of the investigation and treatment of dementia. Only 32% of GPs attended the seminars, and 7% chose to take up the CME sessions, but 55% accepted outreach visits. There were no before and after differences observed in dementia diagnostic evaluations or reported use of cognitive testing in either the intervention or control district general practices.

The ACCESS trial[40,45], conducted among health maintenance organisation providers in the US, was a cluster randomised controlled trial of a complex intervention comprising provider education and the introduction of a care management program. Provider education included a module on the recognition and treatment of dementia and depression. This important trial focuses principally on the effects of the intervention on the management of dementia and patient and carer outcomes, and is described in more detail in Chapter 4. Providers in the intervention practices were no more likely than those in the control practices to consider that 'older patients should have dementia screening'[45]. Provider practice or knowledge with respect to dementia diagnostic procedures was not tested.

The second controlled study indicated larger increases in knowledge regarding dementia assessment and management among German GPs when three hours of training in diagnosis was supplemented with two hours training in treatment[43]. In a subsequent cluster randomised controlled trial from the same research group (not included in the review), there was no difference in knowledge outcomes between GPs trained using blended learning approaches (lectures combined with e-learning) and lectures and structured discussions alone, although there were modest improvements in both groups[46]. This study did not assess changes in practice or in detection rates for dementia.

What have we learnt from these studies?

1 There is some potential for educational interventions to change practice, specifically with respect to increased attention towards and identification of probable dementia cases, although the evidence base is limited to just two trials.[41,42]

2 There is a problem with low participation rates in many trials. In France, 684 of 3,000 invited GPs agreed to participate (23%)[42], and in the UK trial only 35/124 (28%) invited practices agreed to participate and completed the trial, despite financial reimbursement[41]. This may indicate a lack of interest in research, or in education to improve knowledge and skills in dementia care, or both. There may be problems with the generalisability of the trial results, since if only interested and well-motivated practices participated, improvements in detection may be less marked if the intervention was scaled-up nationwide, or possibly more marked if knowledge and skills were already good in the participating practices.

3 There is also evidently a problem with adherence to recommended educational activities, particularly evident in the pragmatic study conducted in Denmark, where only outreach facilitation visits were accepted by more than half of the GPs, and seminars and CME events had very poor uptake[44]. Unfortunately adherence to the educational interventions is not reported in either of the two most relevant cluster randomised controlled trials[41,42]. Adherence to e-learning tools provided via the internet seems to be particularly poor, with only 5% of Danish GPs participating in an e-learning training program distributed by their professional organisation[47].

4 There is clearly a need to identify barriers to participation in educational programs, and to seek to overcome these by re-tailoring interventions, and/or providing suitable incentives to participate.

5 Increased detection is of limited value unless the diagnoses are appropriately and sensitively shared with those directly affected, accompanied by support, timely intervention and access to a continuing care pathway. Interventions to date have not proven successful in improving concordance with basic indicators of dementia care quality, although the outcomes studied to date have focussed mainly only on the more mechanical aspects of dementia diagnostic practice.

As an indication of continuing interest in this area, we identified two protocols for ongoing large cluster RCTs of educational interventions in primary care centres in the UK[48] and Netherlands[49]. Both trials seek to build on the success of an earlier UK intervention trial[41] in increasing the detection of dementia, but noting also the failure in that trial to improve concordance with good management guidelines. Besides diagnosis and referral, both trials focus on education and training to build skills and confidence to manage dementia across the course of the illness, and will use practice based workshops coupled with computerised decision support software integrated into the computerised medical record system. While earlier interventions have focussed mainly upon physicians, these trials will use collaborative

interdisciplinary primary care teams, including, particularly, primary care nurses. An innovative aspect of the UK trial is a plan to develop individualised training programs (based upon practice based workshops and decision support software) with each practice completing its own review of training needs, with attention to individual needs of different staff members with different baseline levels of knowledge and experience[48].

Memory clinic services

There is some indirect evidence that, in high income countries, the growth of memory clinics may have been one factor contributing to a trend towards earlier dementia diagnosis. For example, in the Netherlands, where this process has been monitored between 1998 and 2009, the number of clinics has increased from 12 to 63, the number of new clients seen annually has risen from 1,700 to 14,175, and the estimated proportion of all incident cases of dementia in the Dutch population that receive a formal diagnosis through a memory clinic has risen from 5% to 27%[50]. Over time the case mix of clients seen in the Dutch memory clinics has changed; the proportion with dementia has declined from 85% to 59% suggesting a higher proportion with mild cognitive impairment and subjective memory complaints, hence, in general, earlier help-seeking. In the UK, national surveys revealed an increase in the number of memory clinics from 20 in 1993 to at least 58 in 2000, the rise in numbers attributed mainly to the advent of acetylcholinesterase inhibitor treatments, and hence the need for early accurate diagnosis[51]. A comparative study from the UK has suggested that patients diagnosed in memory clinics are younger and have MMSE scores that are on average six points higher (19.8 vs 14.0) than those diagnosed by old age community mental health teams, suggesting presentation on average two years earlier in the disease course[52]. In Croydon, UK, the introduction of a new community-based memory service saw an estimated 63% increase in diagnoses by specialist services, with 77% of referrals to the new memory service comprising those in the early stages of dementia, or with subjective impairment only[3]. Crucially, and unusually, assessment and care is provided in the patients' own homes. The model was specifically designed to maximise efficiency and acceptability, and only 5% of those referred refused an assessment. Ease of access and acceptability may be important factors as suggested by the comments of a local general practitioner in the evaluation of the Croydon Memory Service:

> "… but these much more subtle early memory losses where the patient has got insight, the memory service feels a far more logical step, where we can say 'look we are going to do a very thorough assessment and see if there is actually a significant memory problem' rather than saying 'I think you need to see an elderly care psychiatrist'".
>
> Quote from GP, qualitative interview

In the National Dementia Strategy for England the development of a comprehensive national network of memory clinic services is a core component of the plan to realise early diagnosis and early intervention for all[1]. Likewise the France Plan Alzheimer envisages a major effort to ensure that each health district (territoire de santé) has its own memory unit (consultation mémoire). requiring investment of 7 million euros over 5 years to create 38 new memory clinics and an additional 1 million euros to create three more memory resource and research centres to provide diagnosis in the most complex cases and earliest forms.

Conclusion

The underdetection (and hence undertreatment) of dementia is a complex phenomenon, and there are no simple solutions to this problem. Early diagnosis and intervention in dementia relies on systems as a whole rather than being the province of any single element.

The important role of primary care in this process has been neglected until comparatively recently, in research, policy and practice. The optimal extent and nature of that role is still debated, and is likely to vary considerably between health systems according to their resource level. Most would accept that initial identification of likely cases should be an important function of primary care. Many would suggest that formal diagnosis should be the preserve of specialist services; this is explicitly stated in the France Plan Alzheimer, and is implicit in the UK government policy that determining eligibility for and initiation of anti-dementia drug prescriptions should be carried out only by specialists in the field. There are two potential problems with this approach. First, this may be taken to imply that the role of primary care should begin and end with tentative diagnosis and referral. Second, in resource poor settings, particularly many low and middle income countries, there will be insufficient specialists to diagnose and treat all those affected. Indeed, even in well-resourced high income countries it may be challenging to maintain this policy while closing the diagnosis and treatment gap.

We have seen that being alert to symptoms and signs, and using validated screening tools may help to boost detection in primary care. It seems also that primary care professionals may need to be convinced of the importance and relevance of dementia diagnosis, in order for sustained changes in clinical practice to occur. Therefore, detection might be further boosted if primary care professionals were better skilled and more involved in effective, rewarding aspects of the care of people with dementia. Shared care, within a chronic disease care framework[53], offers many potential advantages to the person with dementia and their family, to the primary and specialist care services, and to purchasers seeking to limit the costs while maintaining the quality of care. The World Health Organization's mhGAP intervention guide provides evidence-based examples of simple intervention and management strategies that have the potential to be delivered by suitably trained and supervised non-specialist staff, across the disease course[54]. While this guide was intended for use in

resource poor settings with few specialists, much of its content may be relevant to higher income country settings as well.

Research in this area is in its infancy. Primary care studies are mainly confined to the most affluent European countries. The new generation of more sophisticated practice-based interventions are welcome, but intensive individualised training programs and technological innovations (e.g. decision support software) may not be applicable in low and middle income countries where the treatment gap is currently most pronounced. There is a need for the World Health Organization's mhGAP guidelines to be implemented and evaluated in these settings. Experience from high income countries has demonstrated that access to guidelines is insufficient, and that training, facilitation and continuous quality assurance are essential. Sustaining the potential benefits of educational interventions is a major challenge that has yet to be addressed or assessed in research conducted to date.

While the focus of the chapter has been upon the supply of responsive and competent diagnostic services, it is highly likely that increased demand for earlier dementia diagnosis will play a major part in closing the treatment gap. It is also likely that there is a relationship between demand for and supply of diagnoses. There is some evidence from studies of the recent growth of memory clinics in northern Europe that an increased demand for care (specifically anti-dementia drugs) has been one of the factors stimulating a growth in the numbers of clinics, and that establishing and promoting accessible memory clinic services boosts demand for the diagnostic service that they provide.

Those who plan and commission services for people with dementia will need to pay careful attention to the respective roles of primary care, memory clinics and specialist community care services, and the interactions between them. These may vary across the disease course, from diagnosis, to early stage care and support, to advanced disease and end of life care.

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CHAPTER 3

Does early diagnosis benefit people with dementia and their carers?

A clear demonstration of benefits associated with an early diagnosis would help to counter negative attitudes among the general population, families affected by Alzheimer's and dementia, medical professionals and service providers, in particular the false beliefs that 'dementia is a normal part of ageing' and that 'nothing can be done'.

Altagracia Nuris, 93, Arcelis, 76, Mercedes, 97, Elsa, 82, and Luz Candida, 80, live in the same house in the Dominican Republic and help each other with all aspects of life. One key responsibility is caring for Elsa as her Alzheimer's advances.

The question *'Does early diagnosis benefit people with dementia and their carers?'* is crucial, since a clear demonstration of net benefits associated with an early diagnosis would help to counter negative attitudes among help-seekers and service providers; in particular the false beliefs that 'dementia is a normal part of ageing' and that 'nothing can be done'. It is of course likely that any benefits of early diagnosis would be mediated through the earlier application of effective interventions. The effectiveness of specific interventions when applied in mild or early stage dementia is the focus of the scoping questions described in the next chapter. One advantage of the current scoping question is that 'early diagnosis' can act as a proxy for the full range of potentially beneficial interventions, none of which is likely to be applied without diagnosis and service contact.

Rationale for the systematic review

It seemed unlikely that there would have been any randomised controlled trials addressing this question, given the broad consensus that early diagnosis is desirable, and the impossibility, for ethical reasons, of making a diagnosis and then withholding this information and not acting upon it.

We therefore decided to look for evidence from naturalistic observational studies. People seek help, and diagnoses are made, at different stages in the disease process. Studies that record such information could be used to help to discern the effect of earlier versus later diagnosis on important clinical and social outcomes for the person with dementia and their carers. The main limitation of such studies is that of confounding factors. Those who seek help late and those that are identified late are likely to differ from those diagnosed early in many other important ways that could influence outcome; it will therefore always be difficult to infer that any differences in outcome were caused, specifically, by the timing of the diagnosis.

Strategy for systematic review

Therefore, for studies of clinical populations, we sought any longitudinal studies that included information on disease stage at time of diagnosis (defined broadly as duration of symptoms before diagnosis, or any appropriate indicator of dementia severity, e.g. MMSE score or other indicator of cognitive impairment, or Clinical Dementia Rating (CDR) or any other indicator of disease staging) and the subsequent course and outcome of dementia (see Box 1 for list of outcomes considered relevant). We used the same approach in our search for informative population-based studies, bearing in mind that such studies would also identify people with dementia who have not yet sought help or received a diagnosis, as well as those who have received a diagnosis at varying stages in the disease process; this information could also therefore be correlated with future outcomes.

We used three search strategies to identify relevant studies. First we sought to identify any longitudinal studies of course and outcome conducted in memory clinic settings (search 1). Memory clinics usually have a standardised approach to recording clinical information at diagnosis, which usually includes information regarding dementia severity or stage. Often, outcome data is also collected systematically for clinical and research purposes. Second, we conducted a search based upon keywords for 'disease stage' limited to studies of dementia (search 2). Finally, we conducted a series of searches focussing upon key relevant outcomes – institutionalisation (search 3), disease progression

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Box 1 – Relevant outcomes for scoping question 'Does early diagnosis benefit people with dementia and their carers'

Outcomes (person with dementia)
Slower cognitive decline
Better maintained functional status
Decrease in mortality
Delayed admission to institutional care
Better quality of life
Better psychological wellbeing
Improvement in challenging behaviour (e.g. aggression, agitation, wandering)
Improved opportunities for social participation (social, employment, education, leisure etc.)
Enhanced dignity and rights
Outcomes (carer)
Better quality of life
Better psychological wellbeing
Reduced strain
Outcomes (other)
Reduced healthcare and/or societal costs

(search 4) and mortality (search 5) – again all limited to studies of dementia. Details of the search terms used can be found in Annex 1 on page 31.

In the search for relevant evidence, we sought to identify

1   primarily, quantitative findings from observational epidemiological or clinical research (as described above)

2   expert consensus statements and guidelines

3   non-evidence based narratives asserting the benefits of early diagnosis and their attendant justifications. Many such narratives were found in the background or introductory sections of papers that were scrutinised for possible relevance, while not being informative with respect to 1 or 2 above.

In all 8039 papers (abstracts and titles) were identified and assessed. Only three papers provided relevant quantitative evidence, one relating years since first symptoms at diagnosis to subsequent mortality[1], and two relating dementia stage at diagnosis to subsequent cognitive decline/disease progression[2,3]. We also identified five consensus statements or practice guidelines that referred specifically to early diagnosis, and numerous narratives attesting to its benefits.

Summary of the results of the systematic reviews

Search 1 (memory clinics): 711 publications were identified and titles and abstracts were reviewed. Thirty-two papers were selected for further scrutiny. One publication was identified with data on an association between timing of diagnosis and mortality[1].

Search 2 (disease stage): 519 publications were identified and titles and abstracts were reviewed. Thirty-three papers were selected for detailed scrutiny. Several publications were related to biomarkers and early stage dementia diagnosis, while others sought consensus on the best design for clinical trials in early stage dementia. None assessed the influence of disease stage at time of diagnosis on subsequent outcomes.

Search 3 (institutionalisation): 1198 publications were identified and titles and abstracts were reviewed. Fifteen papers were further scrutinized. While many of these publications focussed on predictors of institutionalisation, none considered the effect of time of diagnosis on this outcome.

Search 4 (disease progression): 4515 publications were identified and titles and abstracts were reviewed. Seventy-three papers were initially selected and examined in more detail. While many of the publications focused on predictors of progression, only two considered to some extent the impact of disease stage at diagnosis[2,3].

Search 5 (mortality): 1096 publications were identified and titles and abstracts were reviewed by CF. Eighty-seven papers which contain data specifically relating to dementia were initially selected and looked at in more detail.

Effects of earlier diagnosis on mortality

We identified one study in which investigators had reported on the impact of a diagnosis earlier in the disease course, and subsequent survival. This study, conducted in a memory clinic in France, comprised 970 people with dementia, who had been assessed on at least two occasions with at least one year of follow-up[1]. The main aim of the study was to assess the effect of dementia subtype (Alzheimer's disease vs. vascular dementia vs. Alzheimer's disease with cerebrovascular disease) on cognitive decline and survival. Information on death was routinely collected from relatives or physicians. Survival analysis was conducted using a 'delayed entry' Cox proportional hazards model in which survival time was counted since the onset of dementia, rather than since study entry. An incidental finding from the survival analysis was that of a strong association between the time interval between first symptoms and first visit to the memory clinical and survival. Regardless of diagnosis, the shorter the time between first symptoms and first visit, the longer the patients survived (HR 0.7, 95% CI 0.6-0.7, for each year earlier in the disease course that the first visit occurred). It is unclear exactly what other variables were controlled for in this analysis, although in general the authors report having controlled for age, sex, educational level, diabetes, hypertension, presence of an informant, and baseline cognitive function.

This is a large and apparently well-conducted observational study. The main limitation regarding the relevant findings for our review is the reliability of information on the time of onset of symptoms. This information was obtained by retrospective recall of patients and relatives at the first visit to the clinic, and its reliability is likely to vary according to dementia severity at presentation, among other potential sources of bias. It was also not clear whether the first visit to the memory clinic (which was a regional tertiary referral centre) was the occasion when dementia diagnosis was first made, and substantive contact with services initiated. There are also concerns, acknowledged by the authors, regarding the representativeness of this clinical cohort, given that they were all recruited through a specialist centre. Finally, this does seem to have been an incidental finding in a study that focused on the effect of dementia subtype on disease progression and mortality. In the absence of an a priori hypothesis, we must be cautious in any inferences that we make. More research needs to be conducted to confirm, or refute, this potentially interesting finding that survival may be enhanced by diagnosis and service engagement earlier in the disease course.

Effects of earlier diagnosis on cognitive decline

We identified two studies in which investigators had reported on the impact of disease stage at diagnosis on subsequent cognitive decline.

The first was an analysis of data from the University of Western Ontario Dementia Study, a prospective longitudinal study of 172 dementia patients in a university memory disorders clinic, with clinical and six monthly psychometric follow up through to the death of the patient[2]. Cognitive function was assessed six monthly using the extended scale for dementia (ESD). Previous research had shown that progression of moderate Alzheimer's disease is linear over the middle phase of decline when measured with this neuropsychological battery. The initial ESD score (at time of enrolment in the memory disorders clinic) was not associated with the subsequent rate of decline. However, this analysis could only be carried out on 66 patients with sufficient ESD data to compute rates of decline.

The second was a longitudinal study of 154 people with mild to moderate probable Alzheimer's disease consecutively admitted to a specialized clinic for the diagnosis and treatment of dementia in Rome, Italy[3]. Survival analysis was used to assess factors associated with disease progression with time to a 5-point decrease in the MMSE score as the outcome (the date of the visit when the 5 point reduction was recorded marked the time of occurrence of progression). The mean follow-up time was 23 months (SD 15.6), and on average patients had 3.3 (SD 1.6) follow-up visits. Sixty-one patients (39.9%) experienced a five-point decline in MMSE score over the follow-up period. Severity of cognitive impairment at enrolment in the clinic, as measured by the MMSE, was not associated with subsequent progression. There was a reduced hazard of progression for those with a one to two year disease duration at enrolment compared to those within one year of disease onset (adjusted HR 0.5, 95% CI 0.2-0.9). However, any effect of disease duration was non-linear since those with more than two years disease duration had a similar hazard of progression to those with less than 1 year (adjusted HR 1.0, 95% CI 0.6-1.9).

Expert consensus statements and clinical guidelines

We identified five sets of consensus guidelines addressing specifically the issue of early diagnosis:

1 The United Kingdom National Institute for Health and Clinical Excellence (NICE) and Social Care Institute for Excellence (SCIE) issued a joint guideline 'Dementia. Supporting people with dementia and their carers in health and social care'[4]. Regarding early identification of dementia, they made the specific recommendations that:

"1. Primary healthcare staff should consider referring people who show signs of mild cognitive impairment (MCI) for assessment by memory assessment services to aid early identification of dementia, because more than 50% of people with MCI later develop dementia.

2. Those undertaking health checks as part of health facilitation for people with learning disabilities should be aware of the increased risk of dementia in this group. Those undertaking health checks for other high-risk

groups, for example those who have had a stroke and those with neurological conditions such as Parkinson's disease, should also be aware of the possibility of dementia.

3. Memory assessment services that identify people with MCI (including those without memory impairment, which may be absent in the earlier stages of non-Alzheimer's dementias) should offer follow-up to monitor cognitive decline and other signs of possible dementia in order to plan care at an early stage."

2 The Quality Standards Subcommittee of the American Academy of Neurology issued a 'Practice parameter' on the early detection of dementia: Mild cognitive impairment linked to an evidence-based review[5]. This included the practice recommendation that:

"Patients with mild cognitive impairment should be recognized and monitored for cognitive and functional decline due to their increased risk for subsequent dementia. (Guideline)".

3 The European Dementia Consensus Network (EDCON) comprised European experts in the field of dementia supported by the pharmaceutical company Janssen-Cilag. EDCON aimed to promote the use of recommendations developed on the basis of the consensus statement so as to improve care for patients and their caregivers. In a 2007 publication[6] on 'access to diagnostic evaluation and treatment for dementia in Europe' the group expressed a conviction "that early access to diagnosis and treatment is beneficial for patients with dementia, for their families, and for society" concluding that:

"A multidisciplinary approach based on clear-cut division of responsibilities between the primary and secondary healthcare sectors and clearly defined standard of care may be the best model for early accurate diagnosis and subsequently early pharmacological and psychosocial interventions. Memory clinics should be made available to a larger proportion of the rapidly growing population of patients with cognitive problems in Europe. For all health care professionals, there should be specialised training in dementia and up-to-date clinical guidelines to provide the framework for standard of care."

EDCON further recommended the adoption of the following consensus statement:

"1. Policy makers, health authorities and health professionals as well as the general public should be made aware of the magnitude of problems related to dementia and of the benefits of its early recognition and treatment.

2. Access to diagnosis and treatment for patients with dementia should be facilitated by appropriate legal, educational, administrative and economic measures.

3. Specific training programmes about various aspects of dementia management should be developed and introduced into the undergraduate and postgraduate education of health-care staff.

4. Health-care professionals, in collaboration with non-professional caregivers and relevant authorities should develop guidelines concerning the recognition and management of dementia, monitor their implementation, and ensure that they are updated when necessary."

4   Members of the INTERDEM group (a pan-European network of researchers on early detection and psycho-social interventions in dementia – www.interdem.org) conducted an analysis of 'The primary care diagnosis of dementia in Europe' using multidisciplinary, multinational expert groups, in an attempt to establish the potential for a consensus guideline[7]. This group differed from the earlier EDCON group consensus by recommending 'timely' as opposed to 'early' diagnosis.

"Timely diagnosis is defined as the time when the patient or caregiver and the primary care physician recognize that a dementia syndrome may be developing. The preference for timely diagnosis implies that methodologies should concentrate not on population screening, but on a speedy response to the first reported signs of changed behaviour and functioning in the patient."

In this decision, the group was apparently motivated largely by the concerns of primary care professionals regarding the potential adverse effects of labelling and stigmatising patients with early dementia[7].

5   The Dementia Study Group of the Italian Neurological Society has published guidelines for the diagnosis of dementia, including a section on early diagnosis[8]. This states:

"Although there is evidence that the initial phases of dementia often go unrecognised in clinical practice, an early diagnosis would allow:
- timely intervention against the causes of reversible dementias;
- the start of therapies that can slow disease progression;
- the start of therapies that can potentiate the cognitive performance of patients by exploiting the non-complete impairment of their neuronal circuits;
- the implementation of measures that reduce the effects of the comorbidity associated with dementia;
- the timely implementation by patients and their families of the measures necessary to solve the problems related to the progression of the disease"

Expert opinion and other narratives supporting early diagnosis of dementia

Several of the papers that we reviewed in the course of our systematic review contained statements regarding the benefits of early diagnosis. Many were unreferenced, and where references were provided these were generally to other papers making similar, non-evidence-based assertions. These statements should therefore be considered, at best, to represent expert opinion. The importance of early dementia diagnosis has also

been highlighted and supported by many stakeholders including, importantly, Alzheimer's associations representing and advocating for the interests of people with dementia and their carers.

We have subjected all of this material to narrative analysis, and have attempted to categorise the perceived benefits of earlier diagnosis under nine broad themes:

1   Optimising current medical management
2   Relief gained from better understanding of symptoms
3   Maximising decision-making autonomy
4   Access to services
5   Risk reduction
6   Planning for the future
7   Improving clinical outcomes
8   Avoiding or reducing future costs
9   Diagnosis as a human right

1   Optimising current medical management

(Early detection) triggers a search for potentially treatable or reversible disorders (Alzheimer's Association (US))

Symptoms similar to dementia can be caused by several different diseases and conditions, some of which are treatable and reversible, including infections, depression, medication side-effects or nutritional deficiencies. (Alzheimer's Australia)

(Early detection) alerts physicians that treatment plans for other health conditions must factor in comprehension and compliance challenges faced by a person with dementia (Alzheimer's Association (US))

(Early detection) alerts physicians of the need to avoid medications with anticholinergic effects, which further suppress activity in one of the chief neurotransmission systems affected by Alzheimer's disease (Alzheimer's Association (US))

A diagnosis can also help in the management of other symptoms that may accompany the early stages of dementia, such as depression or irritability. Factors that might exacerbate cognitive problems can be checked for and treated. For example, vascular risk factors, poor nutrition, lack of stimulation and activity and some medications can contribute to cognitive impairment. (Alzheimer's Australia)

2   Relief gained from better understanding of symptoms

(Early detection) may positively impact the individual by ensuring greater understanding and awareness of what is happening to him or her …(and) provides the patient and family with a framework for understanding and adapting to cognitive and behavioral changes; may reduce the tendency to blame or be impatient with the diagnosed individual (Alzheimer's Association (US))

You may have been wondering what is happening to you and have been worried and anxious about the changes

you have noticed. Although being diagnosed with dementia can be an upsetting experience, it can also be a relief because knowing the causes of your problems can resolve the anxiety felt by both you and your family. (Alzheimer's Disease International)

A medical review of any symptoms and identification of the cause of symptoms can bring relief … timely diagnosis enables persons with dementia and their families to receive help in understanding and adjusting to the diagnosis of dementia. (Alzheimer's Australia)

If dementia is not diagnosed early, carers can become demoralised due to lack of recognition and support and having to cope with apparently unexplained behavioural changes (National Service Framework for Older People. Department of Health (UK), 2001)

3 Maximising decision-making autonomy

Early diagnosis facilitates full involvement of the patient and caregivers in planning medical, educational, and psychosocial interventions suited to their needs and expectations.

While individuals will vary in the choices they make, most people concerned about their memories and their families take the view that early intervention is necessary if they are going to be able to properly plan their finances, lives and care for the future. (Alzheimer's Australia)

(Early detection) identifies the condition at a time when the patient can still participate in medical, legal and financial decisions and make proxy plans. (Alzheimer's Association (US))

Early recognition and diagnosis of AD provide patients and families with an opportunity to plan for future while the patient still has the capacity to participate in the process[9].

Perhaps most importantly, early diagnosis provides time for patients and families to prepare for future care and maximizes patient's opportunities to contribute to the care planning process[10].

4 Access to services

(Early detection) opens the door for the patient and family to take advantage of appropriate programs and services. (Alzheimer's Association (US))

On a practical level there is a lot that can be done. Check on any state or social support that you or your family may be entitled to. It may be useful to start making enquiries about what support services are available in your area. You may wish to participate in an early stage support group and form new peer relationships to share feelings, information and coping strategies. (Alzheimer's Disease International)

5 Risk reduction

Undetected dementia places older adults at risk for delirium, motor vehicle accidents, medication errors, and

financial difficulties to name a few. (Alzheimer Society of Canada)

(Early detection) provides time to address safety issues before accidents or emergencies occur. (Alzheimer's Association (US))

Some medications, such as anticholinergics, can exacerbate dementia symptoms. Memory problems may interfere with a person remembering to take important medications such as those for diabetes, heart disease or high blood pressure. A Webster pack can help to simplify administration of medication. (Alzheimer's Australia)

6 Planning for the future

The early recognition and detection of dementia enables people with dementia, their families and clinicians to plan more effectively for the future (National Institute for Health and Clinical Excellence – Commissioning Guide; Memory assessment service for the early identification and care of people with dementia)

(Early detection) alerts the patient and family to begin thinking about safety and security issues, including living arrangements, driving, cooking and managing medication. (Alzheimer's Association (US))

(Early detection) can encourage exploration of options for job accommodations, early retirement or disability for individuals with younger-onset Alzheimer's before reduced performance jeopardizes employment and financial security. (Alzheimer's Association (US))

You may wish to review your financial situation. This might include arranging for bills to be paid. If you are still at work, you could think about reducing your hours or switching to another job. (Alzheimer's Disease International)

7 Improving clinical outcomes

"There is a broad consensus that early identification of dementia symptoms and appropriate interventions tailored to the individual are mainly beneficial, leading to improved outcomes for people with dementia and their family carers. There are good practice examples of early intervention and evidence to support their wider application"[11]

"An early detection and therapy of the illness helps to decelerate the patients' cognitive decline, prolongs a self-determined, independent life and, thus, would reduce the immense care-giving expenses."[12]

"Earlier diagnosis is desirable for several reasons. It allows the patient, family, and clinician to plan more effectively for the future, reduces the likelihood of catastrophic events such as motor vehicle accidents, and permits more effective administration of medications to delay symptom progression.[13]

"Early treatment aims to maintain the highest level off functioning when cognitive symptoms and impairment of activities of daily living are mild (Seltzer et al., 2004) and may prove to be more effective in improving long-term treatment outcome if initiated at a stage when neuronal

circuits have not been extensively damaged (Sorbi et al., 2000)."[6]

Timely diagnosis allows for prompt access to medications and medical attention. There is evidence that the currently available medications for Alzheimer's disease may be more beneficial if given early in the disease process. In some people, these medications can help to maintain daily function and quality of life as well as stabilise cognitive decline. However, they do not help everyone and they are not a cure. (Alzheimer's Australia)

8 Avoiding or reducing future costs

Experts and the Department of Health agree that early diagnosis and intervention in dementia is cost-effective, yet there is a significant diagnosis gap, and only between a third and a half of people with dementia ever receive a formal diagnosis. (National Institute for Health and Clinical Excellence – Commissioning Guide; Memory assessment service for the early identification and care of people with dementia)

Early detection of dementia can improve the quality of life for the patient and the caregiver and ultimately reduce total care expenditures by delaying the time to nursing home admission and other costly outcomes[13].

"The literature points strongly to the value of early diagnosis and intervention in delaying or preventing transitions into care homes"[14]

"…early diagnosis would also permit early symptomatic treatment and potential prolongation of the disease at a milder stage. Because the costs of AD care increase with advancing severity of the disease this ability to delay progression may have substantial economic implications[13].

"The prevailing evidence indicates that early diagnosis and treatment may foster the maintenance of a milder and less costly disease state. Because the currently available treatments do not prolong life, their application earlier in the disease process can be cost effective."[13]

"Early diagnosis and treatment, if implemented on a larger scale, can potentially reduce the total costs by maintaining the patients' functional level, reducing comorbidities and related hospital admissions, and alleviating caregivers burden."[6]

9 Diagnosis as a human right

Alzheimer Scotland believes that people with dementia are entitled to an accurate and timely diagnosis, and they have a right to be told their diagnosis (as well as a right to refuse the information if they so wish).

Conclusion

Despite an extensive search of the scientific literature, we found almost no research conducted into the effect of the timing of dementia diagnosis upon subsequent disease course and outcomes for the person with dementia and their carers. The evidence that we did find is supportive of a possible beneficial effect of earlier

help seeking and/or earlier diagnosis and/or earlier intervention upon survival, but this requires confirmation in other studies. The two studies of the effect of disease stage at diagnosis upon subsequent cognitive decline showed no association, but were too small in size to reach any clear conclusion. This is clearly a case of 'absence of evidence' rather than 'evidence of absence' of an association. The lack of research evidence relevant to the scoping question for this chapter is surprising. It is likely that the data necessary to attempt to answer the question have been routinely collected, probably in a systematic manner, in memory clinics around the world. There are certainly methodological complications in using observational data because of the problem of confounding. Nevertheless, it is important to establish at least whether there may be benefits associated with earlier diagnosis and intervention. Given the implausibility of conducting randomised controlled trials, carefully controlled analyses of observational data may provide the best obtainable evidence, and would certainly help to inform expert opinion. For these reasons, it may be helpful to sketch out possible options for future research studies.

For research conducted in clinical facilities, information on disease stage and duration of symptoms is generally routinely collected at the time of diagnosis. In using this as the exposure of interest, it would be important to control for as many as possible of the known predictors of future disease course (the outcome of the analysis), and for factors that are strongly associated with a propensity for earlier versus later diagnosis. It would also be important to set a later baseline (sometime after first contact and diagnosis) for the beginning of the longitudinal study with a fresh assessment of dementia severity, as otherwise disease stage at the time of diagnosis would be completely confounded with disease stage at the baseline of the study, which would itself be associated with dementia outcome. Thus, one option might be to recruit all clients of a dementia diagnostic and treatment service who are currently just into the moderate stage of dementia, with a MMSE score of, say, 14-18. One could then extract information from clinical records regarding their CDR severity, MMSE score and duration of symptoms at the time of diagnosis/first contact. One could then hypothesise that those with an earlier diagnosis, at a less severe stage of dementia, and hence who had received earlier intervention, would show slower subsequent cognitive decline, delayed institutionalisation and slower clinical progression to CDR severe dementia state.

The use of epidemiological (population-based) studies is both advantaged and disadvantaged by the fact that many of those identified through the survey as having dementia will not have sought help, or received a diagnosis. In principle this provides the opportunity to control for dementia severity at the baseline of the survey, and estimate the effect of having a diagnosis and/ or service contact at that time on subsequent disease course. Here, the problem is that help may have been

sought, and a diagnosis provided, precisely because of indicators of concern that may predict or be part of a more adverse disease course. This problem is well recognised in pharmacoepidemiological studies where the indications for, or contraindications against, being prescribed a particular drug may confound estimation of the effects of that drug on other outcomes. In such studies, it is common practice to generate and control for a 'propensity score', from knowledge of factors associated with the propensity to be prescribed the drug[15]; a similar approach could be used from knowledge of factors that predict the propensity to receive a dementia diagnosis, conditional upon having the condition. A more substantial obstacle to use of epidemiological data is that surprisingly few dementia prevalence surveys have systematically gathered data on whether or not a formal diagnosis has been made, and what, if any, services the person with dementia may be receiving as a consequence. Furthermore, the orientation of longitudinal population-based studies has tended to be predominately towards the incidence of dementia, focusing therefore upon those free of dementia at baseline, and ignoring those with dementia who are no longer 'at risk'. Population-based studies of the course and outcome of dementia, other than mortality, are therefore few and far between.

Despite the lack of quantitative data, it is clear that informed and expert opinion is generally of the view that early dementia diagnosis is beneficial to patients, carers and society, and should therefore be promoted. Our qualitative review of expert opinion and stakeholder views indicates that nine broad rationales are consistently advanced in support of earlier diagnosis: optimising current medical management; relief gained from better understanding of symptoms; maximising decision-making autonomy; access to services; risk reduction; planning for the future; improving clinical outcomes; avoiding or reducing future costs and diagnosis as a human right. These largely chime with the reasons recently proposed by Prof Henry Brodaty in an article entitled "Six reasons why early diagnosis of dementia does not occur and ten reasons why it should" (possibility of a reversible cause, a relief!, legal planning, financial planning, medical planning, life planning, work, driving, relations with the family, medication)[16]. Prof Brodaty concludes his article with the comment that

> "Ten reasons are provided why earlier diagnosis is better. The reasons given are based on clinical experience as, unfortunately, as yet there are no control studies to prove that earlier diagnosis does have these advantages."[16]

Unfortunately there has been little further progress since 2005. Of the nine rationales we identified, only the last (diagnosis as a human right) is not amenable to empirical testing in research studies. One might argue that the benefit of having access to services is self-evident, as diagnosis is indeed the only route to specialist dementia care; even then it might be important to assess whether those that receive a more timely diagnosis tend to be better served with fewer unmet needs than those that

are diagnosed late in the disease course. The list of rationales could perhaps best be viewed as informing hypotheses for future research. For example, that early diagnosis is associated with

1 better general medical care

2 better understanding of symptoms, less resulting anxiety and better quality of life

3 more advanced directives (by the person with dementia, indicating their wishes in future scenarios, made at a time when they retained decision-making capacity)

4 fewer unmet needs for dementia-specific care

5 fewer accidents

6 better clinical outcomes

7 lower annual or cumulative health care and societal costs

We recommend that research funders, particularly those linked to government, give urgent attention to the commissioning of longitudinal research specifically to address the deficits identified in this review. We further recommend that in population-based descriptive studies that focus on dementia prevalence, an attempt should be made to assess who has and has not received a diagnosis of dementia, together with information regarding access to specialist dementia care services and evidence-based interventions (see Chapter 4). This information is useful in itself, to understand better the progress that is being made towards shrinking the treatment gap, and to plan future service needs. It would also create the possibility to study the effect of early diagnosis on outcome in any prospective waves subsequently conducted.

ANNEX 1: SEARCHES

SEARCH 1 – Memory Clinics

PUBMED (NCBI) on 16.03.2011; Single key word: "memory clinics"

PUBMED (OVID) on 17.03.2011; "memory clinics" or "memory services"

SEARCH 2 – Dementia and its subtypes, disease stage, early diagnosis

PUBMED (OVID) on 17.03.2011

1   Dementia or vascular dementia or multi-infarct dementia or frontotemporal dementia or Alzheimer's disease

2   Disease stage or early diagnosis

3   (1) and (2)

SEARCH 3, 4, 5 – predictors of institutionalization, mortality and disease progression

SEARCH 3

PUBMED (OVID) on 28.03.2011

1   institutionalization.mp. or exp Institutionalization/

2   nursing home placement.mp.

3   nursing home admission.mp.

4   1 or 2 or 3

5   dementia.mp. or Dementia, Vascular/ or Dementia, Multi-Infarct/ or exp Dementia/ or Frontotemporal Dementia/

6   (4) and (5)

SEARCH 4

PUBMED (OVID) on 28.03.2011

1   disease progression.mp. or exp Disease Progression/

2   dementia.mp. or exp Dementia, Vascular/ or Dementia, Multi-infarct/ or exp Dementia/ or exp Frontotemporal Dementia/

3   (1) and (2)

SEARCH 5

PUBMED (mesh) on 06.05.2011

(("Mortality"[Mesh]) OR "Survival"[Mesh] AND"Dementia"[Mesh])

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CHAPTER 4

Which interventions are effective for people in the early stages of dementia?

Many trials have been conducted into the efficacy of interventions for persons with dementia. However, until comparatively recently much less evidence has been available on the benefits of these interventions in the earliest stages of the disease. The aim of this chapter is to review the available literature on randomised controlled trials of interventions targeting people with early stage or mild dementia.

Ovidio and Antonia have been married for 51 years. The portraits of them at ages 29 and 27, now displayed in their home in the Dominican Republic, are family treasures. They also treasure each other.

Figure 2: **Classification of interventions**
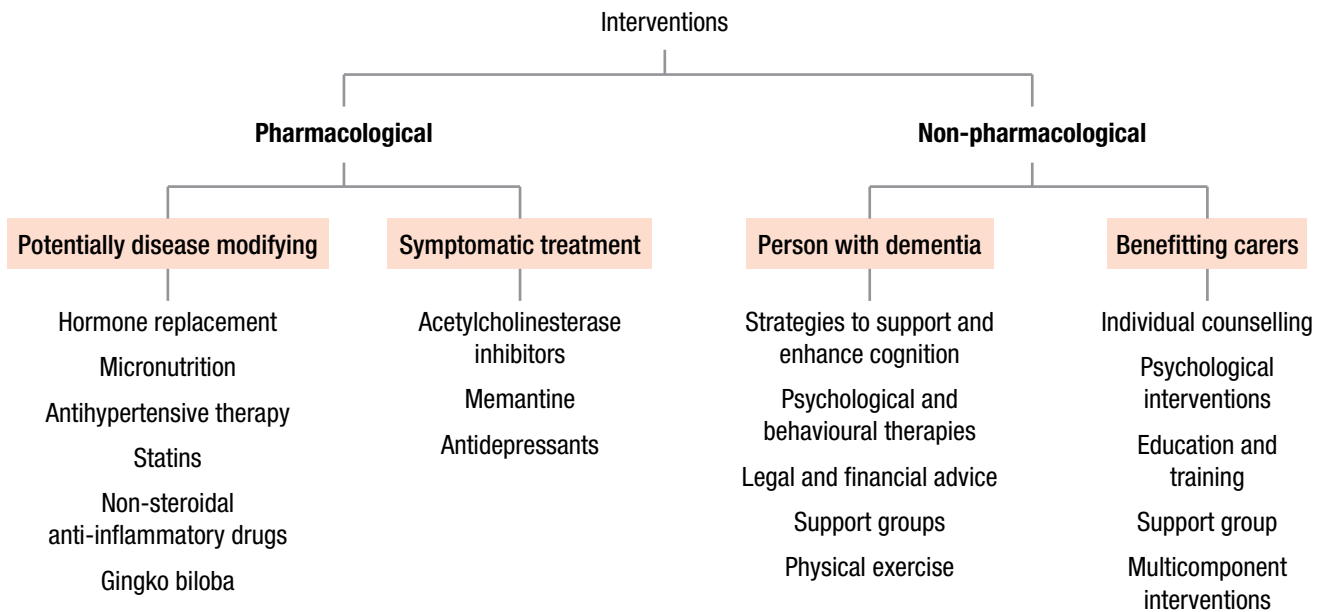
Introduction

For the purpose of this review, we used the following scoping question:

For which pharmacological, psychological or psychosocial interventions, when compared with placebo/usual care is there evidence of clinical benefit/ harm for people with dementia and their carers, specifically when applied in the early stages of dementia?

Early stage dementia or mild dementia was defined by any of the following criteria:

1 Mini-Mental State Examination (MMSE)[1] scores of >18

2 Clinical Dementia Rating (CDR) Scale[2] scores of 0.5 to 1.0

3 Global Deterioration Scale (GDS) scores of 2.0 or less

4 Alzheimer's Disease Assessment Scale (cognitive subscale) (ADAS-Cog) scores of 4 to 28

There are two main domains of intervention that may be relevant to early stage dementia:

1 Pharmacological interventions, including

a (acetylcholinesterase inhibitors and memantine) and depression. Drug treatments for psychotic and behavioural symptoms were not considered in this review, since their use is rarely indicated in early stage dementia.

b other treatments, targeting underlying disease mechanisms that may in principle modify disease course – for example, drugs that treat underlying cardiovascular risk factors, hormone replacement therapy (HRT) for post-menopausal women and non-steroidal anti-inflammatory drugs (NSAIDs).

2 Non-pharmacological interventions, including

a strategies to support and enhance cognitive abilities in the person with dementia, such as reality orientation, cognitive stimulation, reminiscence therapy. These target the person with dementia but may also involve the carer.

b psychological and psychosocial interventions for the person with dementia, that may have particular relevance in the early stages of the disease (psychological therapies, counselling, support groups, legal and financial advice).

c psychosocial interventions that target the carer, but often also involve the person with dementia (carer support, counselling, education, training and respite).

We have provided a classification of interventions to be considered in figure 2.

Outcomes considered most relevant were

– *for the person with dementia*: cognitive function, functional status, quality of life, psychological wellbeing, and social participation (social, employment, education, leisure).

– *for carers*: quality of life, psychological wellbeing, and strain.

General search strategies

We first identified relevant systematic reviews conducted through the Cochrane Collaboration using the Cochrane Reviews website (Dementia and cognitive improvement review group) and Cochrane Library. We also consulted UK National Institute for Health and Clinical Excellence (NICE) guidelines for dementia management[3], together with specific evidence-based guidance for individual therapies. We also accessed the US Alzheimer's Association's systematic reviews

on non-pharmacological interventions specifically for early stage Alzheimer's disease, conducted in 2007[4]. We supplemented these systematic reviews with a new search in PubMed looking for more recent randomised controlled trials focusing on early stage dementia. We used the following terms "Randomized Controlled Trial"[Publication Type] AND "Dementia"[Mesh] AND ("early stage"[All Fields] OR "mild"[All Fields]) and restricted the time from June 2005 to June 2011. Finally, we contacted specialists in the area enquiring about more recent data on interventions for early stage dementia and cross checked their responses to the evidence gathered so far.

We were principally interested in trials that recruited only people with mild or early stage dementia. However, mindful that in many cases trials might include people with mild / early stage disease as well as those with more advanced dementia (moderate or severe) we also included such trials in our narrative review. For these trials we sought to ascertain the proportion of participants that had mild / early stage dementia, and the mean MMSE score as a further indicator of the distribution of severity. We also clarified if the trial results had been analysed by severity either a) a stratified analysis with results presented separately for those with mild dementia or b) a test for interaction, testing formally whether the effect of the intervention varied by dementia severity.

Pharmacological interventions – symptomatic treatments

Acetylcholinesterase inhibitors

Background
Mainstream pharmacological treatments for the cognitive deficits of dementia comprise the acetylcholinesterase inhibitors (AChEI), and memantine. There has also been interest in their potential to treat behavioural and psychological symptoms of dementia (BPSD)[5]. The three AChEIs in current use are donepezil (Aricept®), galantamine (Reminyl®), and rivastigmine (Exelon®). Donepezil is a specific and reversible inhibitor of AChE, galantamine is a selective, competitive and reversible inhibitor of AChE and rivastigmine is an AChE and butyrylcholinesterase inhibitor[6]. Memantine (Ebixa®) is an N-methyl-D-aspartate (NMDA) receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction[6].

Methodology
We accessed Cochrane reviews, NICE guidelines and technology appraisals (NICE-SCIE guideline on supporting people with dementia and their carers in health and social care [NICE clinical guideline 42], amended to incorporate the updated NICE technology appraisal guidance for donepezil, galantamine, rivastigmine and memantine for Alzheimer's disease[7]) and a Medical Research Council (MRC) Biostatistics Unit review of industry submissions to the NICE AD appraisal

committee conducted with the aim of investigating some additional questions raised by NICE[8]. The industry submissions comprised data from 8,111 patients included in 23 trials of donepezil, galantamine, rivastigmine, and memantine. Crucially, they included subgroup efficacy analyses by dementia severity for ADAS-Cog and MMSE outcomes. There is likely to be overlap between the trials included in the Cochrane reviews, NICE technology appraisals and the MRC Biostatistics unit review of industry submissions to NICE. NICE guidelines and the MRC meta-analyses used individual patient data mostly provided by pharmaceutical companies, whereas the Cochrane reviews relied to a greater extent, but not exclusively, on trials with published data.

Results – Cochrane reviews
We found four Cochrane reviews on individual anti-dementia drugs (galantamine, rivastigmine, donepezil, memantine)[9-12] and one review covering the three main AChEIs (galantamine, rivastigmine, donepezil)[13]. All five Cochrane reviews reported a positive effect for the use of AChEIs for patients with mild to moderate Alzheimer's disease when compared to placebo groups, and for memantine for moderate to severe AD. However, results were not stratified by dementia severity.

The Cochrane review on donepezil[9] comprised content assessed as up-to-date on 4 April 2006. It included 24 trials with 5,796 participants, of which results could be meta-analysed from 15. Twenty trials included patients in the mild to moderate stages of the disease. Donepezil improved cognition significantly irrespective of dosage, in trials of those with mild to moderate, or severe dementia after 12, 24 and 52 weeks. At 24 weeks there was a significant effect on the ADAS-Cog at 5mg/day donepezil (weighted mean difference [WMD] -2.02, 95% CI -2.77 to -1.26) and 10 mg/day donepezil (WMD -2.81, 95% CI -3.55 to -2.06). The reviewers concluded that the drug is beneficial to patients at all levels of dementia severity. However, results were not stratified by dementia severity, and hence no evidence was provided on efficacy exclusively for mild AD.

The Cochrane review on rivastigmine[10] comprised content assessed as up-to-date on 8 September 2008. Thirteen trials were included but only nine were used in the analyses totalling 4,775 participants. Of the original 13 trials, ten included patients with mild to moderate dementia. High-dose rivastigmine (6 to 12 mg daily) had a significant effect on the ADAS-Cog compared with placebo (WMD -1.99, 95% CI -2.49 to -1.50). The authors concluded that the drug appear to be beneficial for people with mild to moderate AD. Results were not stratified by dementia severity.

The Cochrane review on galantamine[11] comprised content assessed as up-to-date on 15 November 2005. Ten trials were included with 6,805 participants, of which eight included participants with mild or moderate dementia. Randomisation to galantamine was associated with a significantly greater reduction in ADAS-Cog score, i.e. improvement in cognition, at all doses from 8mg to

32mg/day. For the four trials assessing 24mg/day versus placebo the WMD for ADAS-Cog was -3.13, 95% CI -2.55 to -3.70. The authors concluded that galantamine at doses of 16 mg/day and above improves cognitive function and either improves or maintains global function for at least 6 months, these findings applying to those with mildly to moderately severe cognitive impairment. However, results were not stratified by dementia severity.

The Cochrane review on memantine[12] comprised content assessed as up-to-date on 21 February 2006. Three trials were identified that studied the effect of memantine on patients with mild to moderate Alzheimer's disease. There was a significant difference in favour of memantine on the ADAS-Cog (MD 0.99, 95% CI 0.21 to 1.78) supported by a small positive effect on the clinical impression of change measured by the CIBIC-Plus (MD 0.13 points, 95% CI 0.01 to 0.25). These results, while in favour of memantine, were considered to be of negligible clinical significance. Results from two trials in patients with mild to moderate vascular dementia suggested a beneficial effect of 20mg/day of memantine on cognitive function at 28 weeks (MD 1.9 ADAS-Cog points). However, these results were not supported by an effect on the clinical impression of change. The authors concluded that there is evidence to support the use of memantine for the treatment of moderate to severe AD only.

Results – MRC Biostatistics Unit review
The review and investigation of industry submissions to NICE AD appraisal committee, conducted by the MRC Biostatistics Unit, appraised re-analyses of the six donepezil trials included 928 people with dementia randomised to donepezil and 895 randomised to placebo. Subgroup analyses by dementia severity were provided using intention to treat and observed cases analysis. Five out of six trials included patients with mild or mild-to-moderate dementia severity, with one trial including only moderate patients. Of those five trials, three assessed ADAS-Cog and MMSE, one assessed only ADAS-Cog and one only MMSE. Forty-seven percent of those randomised to donepezil and 44% of those randomised to placebo had MMSE scores in the mild dementia range, 60% of those randomised to donepezil and 64% to placebo had ADAS-Cog scores in the mild dementia range. There was a statistically significant effect of donepezil on ADAS-Cog after 24 weeks for the subgroup (n=548) with MMSE scores in the mild dementia range (MD 2.03, 95% CI 1.02 to 3.04) and for the subgroup (n=768) with ADAS-Cog scores in the mild dementia range (MD 3.24, 95% CI 0.30 to 6.17). Overall there was considered to be little difference in the effect sizes by dementia severity subgroups.

Re-analyses of the seven galantamine trials included 2,046 patients treated with galantamine and 1,343 treated with placebo (follow up from 3 to 6 months). Forty-three percent of those randomised to galantamine and 44% randomised to placebo had MMSE scores in the mild dementia range. The effect size for ADAS-Cog favouring galantamine amongst patients with MMSE scores in the

mild dementia range (n=938) was statistically significant (MD 2.40, 95% CI 1.69 to 3.11), but smaller than that for those with MMSE scores in the moderate range (n=1215) (MD 4.10, 95% CI 3.39 to 4.81).

The rivastigmine re-analyses included 1,916 patients from four trials with 26 weeks of follow up. All patients had mild or moderate AD measured by both ADAS-Cog and MMSE. Forty-seven percent of those randomised to rivastigmine and 49% of those randomised to placebo had MMSE scores in the mild dementia range. There was a statistically significant effect of rivastigmine treatment on ADAS-Cog for all degrees of MMSE severity; mild (n=734) (MD 1.20, 95% CI 0.52 to 1.88), moderate (n=557) (MD 3.70, 95% CI 2.61 to 4.79) and moderately severe (n=232) (MD 5.00, 95% CI 3.17 to 6.83).

The reviewers noted, on meta-analysing treatment effects by disease severity subgroups across the three different AChEIs, there was remarkable homogeneity of effects between drugs within sub-groups; for mild MMSE severity (pooled MD 1.86, 95% CI 0.83 to 2.89), moderate (MD 3.98, 95% CI 3.22 to 4.74), and moderately severe (MD 5.44, 95% CI 3.94 to 6.94).

Conclusion
The first NICE guidelines for anti-dementia drugs recommended the use of the three AChEIs – donepezil, galantamine and rivastigmine – for patients with Alzheimer's disease of moderate severity only. Memantine was recommended for use only in the treatment of people with moderate to severe Alzheimer's disease. Published evidence, and that made available to the authors of the Cochrane systematic reviews, indicated similar efficacy for each of the three AChEIs for mild to moderate AD. The subsequent industry submissions to the NICE appraisal committee, reviewed by the MRC Biostatistics Unit, do provide convincing evidence of their efficacy for people with mild dementia, with effect sizes of the order of one to two points on the ADAS-Cog. These effect sizes were smaller than those seen for moderately severe dementia, and the MRC Biostatistics Unit reviewers concluded that the treatment benefit for all three drugs probably increases with disease severity. This may be explained by more deterioration among those with more severe dementia in the placebo group, rather than lesser degrees of improvement in the treatment group. The review group also flagged up the unanswered question of whether the size of the treatment effect among drug 'responders' varied by dementia severity. With this new evidence, NICE has now revised its guidelines to support of the use of donepezil, galantamine and rivastigmine for patients with mild as well as moderate dementia. Memantine was still recommended only for use amongst those with moderate to severe dementia.

In summary, there is now robust evidence to support the efficacy of AChE inhibitors in the early stages dementia. Given that manufacturer sponsored trials have been of relatively short duration (typically 12 to 24 weeks), there is still uncertainty as to the long-term benefits

of treatment. Of particular interest is the question of whether early initiation and persistent use these drugs may be associated with better long-term outcomes, than delayed treatment (an obvious consequence of late diagnosis). Evidence relating to this question is reviewed in Chapter 5.

Antidepressants

Background

Depression is a common problem in old age, with a particularly high prevalence among people with dementia. In a recent study the prevalence of depression in those with very mild AD (CDR=0.5) was 32.1%, and 39.6% in mild AD (CDR=1)[14]. The prevalence of major depression tends to decrease with increasing dementia severity[15;16]. Depression in dementia has been associated with decrease in quality of life, increased need for institutionalisation, greater health care utilisation, higher mortality rates and increase caregiver burden[17].

Results

The Cochrane Database includes a review on antidepressants for treating depression in dementia[18], with content assessed up to April 2005 and including seven trials with 1,140 participants. One of these included older people with and without dementia, and did not present findings stratified by dementia status, hence is not considered further[19]. One trial recruited participants meeting DSM-IV criteria for major or minor depression, the others DSM major depression only. Inclusion criteria for three trials was an MMSE score of 10 or over[20-22], and in one other was 11 to 28[23], hence results would be applicable to those with mild to moderate dementia. One trial recruited those with MMSE scores of 25 or lower, hence including some participants with severe dementia[24]. Mean MMSE score at baseline varied between 15.4 and 23.2. Neither the review nor any of the individual trials provided results stratified by dementia severity. Only two trials tested the efficacy of SSRI antidepressants[20;25], which are currently most widely used. Others assessed a tetracyclic antidepressant, maprotiline[26], tricyclic antidepressants, clomipramine[21] and imipramine[27], and a monoamine oxidase inhibitor, moclobemide[28]. Results from only four trials[20;21;29;30] could be subject to meta-analysis since inadequate information was provided in two others[31;32]. These indicated no overall effect of antidepressant treatment on Hamilton Depression Rating Scale scores (pooled MD -0.93, 95% CI -3.27 to 1.41), or cognitive function (MMSE pooled MD -0.53, 95% CI -3.61 to 2.56). There was no significant difference in drop-outs between active and placebo groups, but adverse effects were significantly more common in those randomised to antidepressants. Most of the trials were of moderate to poor methodological quality. The one trial with sound methodology[20] did show apparent clinical benefit of sertraline, an SSRI antidepressant. In the sertraline-treated group 9 patients (38%) were full responders and 11 (46%) were partial responders compared with 3

(20%) and 4 (15%), respectively, in the placebo-treated group (p=0.007), with a standardised mean difference (effect size) of 0.68 for the Cornell Scale for Depression in Dementia and an SMD of 0.51 for the Hamilton Depression Rating Scale. This was, however, a single small trial (n=44). As with other trials, results were not stratified by dementia severity.

Our supplementary search identified three further relevant trials[33-35]. Two described the results of the DIADS-2 trial, assessing the efficacy of sertraline for the treatment of depression in mild to moderate AD (MMSE scores 10-26) with outcomes assessed after 12[36] and 24 weeks[37]. One hundred and thirty-one participants from five U.S. medical centres were randomised to double-blinded treatment with sertraline (n=67) or placebo (n=64). Results were not stratified by dementia severity in any phase. At 12 weeks there were no statistically significant differences in Clinical Global Impression of Change, or change in Cornell Scale for Depression in Dementia (CSDD) scores[38]. There was a non-statistically significant trend towards remission favouring those randomised to sertraline (OR 2.06, 95% CI 0.84-5.04, p=0.11). Sertraline-treated patients experienced more adverse events, notably gastrointestinal and respiratory, than placebo-treated patients. Results at 24 weeks failed to show any delayed treatment effect[39]. The authors concluded that sertraline may not be indicated for the treatment of depression in AD. The third publication relates to the SADD trial, a multi-centre double-blind placebo-controlled RCT of the clinical and cost effectiveness of two classes of antidepressants, and, more specifically, mirtazapine and sertraline, from baseline to 3 months (13 weeks) and 9 months (39 weeks) enabling estimation of short and long-term impacts of these antidepressants among patients with AD and at least moderately severe depression of more than four weeks duration. Patients were recruited with any severity of AD; mean MMSE scores varied between 17.6 and 18.5 by randomisation group. Decreases in depression scores (CSDD) at 13 weeks did not differ between 111 controls and 107 participants allocated to receive sertraline (mean difference 1.17, 95% CI -0.23 to 2.58) or mirtazapine (MD 0.01, 95% CI -1.37 to 1.38). These null findings persisted to 39 weeks. Fewer controls had adverse reactions (29/111, 26%) than did participants in the sertraline group (46/107, 43%) or the mirtazapine group (44/108, 41%).

Conclusion

The authors of the Cochrane review concluded that despite widespread prescription of antidepressants for depression in dementia, the evidence to support this practice was weak. They acknowledged that this conclusion was based on a few trials with small sample sizes, mainly investigating classes of antidepressants not often used in clinical practice. The authors highlighted the need for more definitive research to clarify efficacy. In the light of recent evidence from larger, better designed and reported trials of antidepressants from the classes more commonly used nowadays to treat depression in dementia (Selective Serotonin Reuptake Inhibitor

– SSRI and Noradrenaline and Selective Serotonin Antidepressant – NASSA) it is now possible to strengthen the conclusions of the earlier Cochrane systematic review and meta-analysis. There is evidence that these drugs lack efficacy for the treatment of depression in dementia, while being associated with significant adverse effects. They should therefore no longer be considered as the first line of treatment. Reasons for the apparent treatment resistance of depression in dementia are unclear, but there may be a biological basis. It is also unclear at what point in the trajectory of the development of dementia (from cognitive ageing to MCI to early stage dementia) the drugs lose their efficacy. The SADD trial was the only trial to date to test for treatment effect modification by dementia severity, and serotonin and mirtazapine were equally ineffective at all levels of severity. However, even that large trial was not powered specifically to detect clinically significant treatment benefits among those with mild dementia.

Pharmacological interventions – treatments with disease modifying potential

Hormone Replacement Therapy

Background
Women tend to show a higher incidence of dementia and AD than men, and it has been suggested that post-menopausal decline in oestrogen production may play a role in that process. Animal and in vivo cell studies have suggested that oestrogens can have beneficial effects on brain structures including those related to memory, such as the hippocampus and basal cholinergic forebrain[40]. There appear to be a variety of mechanisms involved in this process, including anti-amyloidgenic effects, antioxidant effects, dendritic sprouting and effects on various neurotransmitters involved in cognitive function[40;41]. Several prospective epidemiological studies have shown an apparent protective effect of oestrogen replacement therapy (ERT) or combined oestrogen and progestogen replacement therapy (hormone replacement therapy – HRT) on the incidence of dementia. However, the one prevention trial to be conducted showed that randomisation to HRT was associated with an increased risk of dementia onset[42;43].

Results
We identified a Cochrane systematic review of hormone replacement therapy to maintain cognitive function in women with dementia published in 2009, with content assessed as up-to-date on 8 April 2008[44].

Seven trials including 351 women with dementia were analysed. All but one trial recruited only women with AD dementia subtype. According to the review, participants were in general considered to have mild to moderate dementia (MMSE scores between 10 and 28). In one study recruitment was restricted to those with early age-onset mild AD[45]. Different drugs were used in different studies (conjugated equine oestrogen (CEE) at different doses with or without progestogens, and transdermal

oestradiol), limiting the potential to meta-analyse results across trials.

There was evidence for a small net increase in MMSE favouring active treatment after 2 months at the lower (0.625 mg) dose of CEE (pooled MD 1.28, 95% CI 0.26 to 2.30) but not at the higher dose of 1.25 mg (0.65, 95% CI -0.20 to 1.50). However, the effects were not maintained at 3, 6 or 12 months. Neither were there any statistically significant short nor longer term effects observed on the ADAS-Cog. Moreover, meta-analysed results from two trials of CEE suggested worse overall outcomes on the Clinical Dementia Rating from one to 12 months of follow-up (weighted MD 0.35, 95% CI 0.01 to 0.69).

Conclusion
The authors of the review conclude that HRT or ERT for cognitive improvement or maintenance is not indicated for postmenopausal women with dementia. It should also be noted that there are significant concerns regarding safety, and that these compounds are now only recommended for short term treatment of perimenopausal symptoms. A large scale prevention trial, the Women's Health Initiative in the USA, had to be stopped early because of an unexpected increased risk in cardiovascular disease outcomes[44], but not before sufficient data was collected to suggest also an increased incidence of dementia in the early years after initiating treatment[42].

Micronutrients

Background
Micronutrient deficiencies are relatively common among older people, due to insufficient dietary intake, inefficient absorption, or both. Low levels of Vitamin B_{12} and folate (folic acid) are associated with high blood levels of the amino acid homocysteine, which has been linked with the risk of arterial disease, dementia and Alzheimer's disease. Vitamin E is another dietary compound, with antioxidant properties. Evidence that free radicals may contribute to the pathological processes of Alzheimer's disease (AD) has led to interest in the use of Vitamin E in its prevention and treatment.

Results
We identified three relevant reviews each covering the treatment of dementia as well as the use of these compounds in healthy older people; on folate with or without B_{12}[46] published in 2009 and with review content assessed as up-to-date on 21 July 2008; on B_{12}[47] published in 2009 with review content assessed as up-to-date on 23 January 2006; and on Vitamin E[48] published in 2008 with review content assessed as up-to-date on 15 January 2007.

VITAMIN B_{12}
Three trials were identified. Two trials included those with dementia and low B_{12} blood levels[49;50]. One evaluated oral supplementation with one month follow-up (n=31)[51] and the other used B_{12} injections with 5 months of follow up (n=11)[50]. One much larger trial (n=140) recruited those aged 75 and over with B_{12} deficiency regardless

of cognitive function[52]; at baseline 40 participants had a MMSE score below 25 and the mean MMSE was 26.5 points. There was no evidence from any of the trials of any benefits of treatment on cognitive function. However, the two treatment trials of those with dementia were underpowered to detect anything other than very large effects[50;53]. For the third trial[54], results were not presented for the subgroup of participants with cognitive impairment. The authors of the review considered the evidence to be 'insufficient' meaning that efficacy was neither demonstrated nor excluded.

FOLATE

Two trials were identified that recruited patients with dementia, 41 patients with AD from Scotland[55], and 11 patients with varying subtypes of dementia and MMSE scores between 16 and 27[56]. A further UK trial included 149 participants; 95 had dementia (AD or mixed AD/VaD) and the remainder cognitive impairment no dementia[57]. Combined treatment with 2mg folate and B_{12} had a significant effect on reducing serum homocysteine levels[58]. However, no such effect was seen with 1mg daily folate supplementation alone[59]. In the Clarke trial there was no effect of folate 2mg combined with B_{12} on MMSE (MD 0.39, 95% CI -0.43 to 1.21) or ADAS-Cog (change from baseline at 12 weeks MD 0.41, 95% CI -1.25 to 2.07). The only outcome for which pooling was possible, across two trials, was the effect of folate with or without B_{12} on MMSE for cognitive impairment and dementia (pooled MD 0.30, 95% CI -0.45 to 1.05). In the Connelly trial, while there was no effect of folate 1mg on MMSE -0.13 [-1.96, 1.70] there was a significant net benefit on Instrumental Activities of Daily Living 2.67 [0.25, 5.09], but not social behaviour. Those randomised to folate were much more likely to be considered as 'treatment responders' to cholinesterase inhibitors (OR 4.06, 95% CI 1.22 to 13.53).

The authors of the review conclude that there is insufficient evidence to conclude either way on the possible benefits or harms of folic acid. This is probably justified, although the evidence on cognitive impairment does seem conclusively negative. The findings of a possible positive interaction with acetylcholinesterase inhibitor medication requires replication[60]. For healthy older people, in the same review, possible cognitive benefits were identified in just one trial of those with elevated homocysteine levels; it may be that people with dementia with raised homocysteine may also be more likely to benefit.

VITAMIN E

One trial was identified that recruited people with dementia[61], 341 patients with a diagnosis of probable AD of moderate severity (CDR of two), from 23 centres in the USA. The trial had a factorial design trial in which patients were randomised to Vitamin E (2000 IU total daily) only, selegiline only, the two drugs combined, or placebo. The primary outcome was the survival time to any one of four endpoints: death, institutionalisation, progression to CDR severe (3.0) or change in loss of activities of daily living. Secondary outcomes were

change in ADAS-Cog and MMSE, but since these were assessed on the basis of change between baseline and last follow-up with no fixed endpoint, these were not assessed in the Cochrane review. The Cochrane reviewers only compared the vitamin E and placebo groups, to avoid confounding. In so doing they confirmed the findings from the original analysis of a statistically significant reduction in the main endpoint (progression) with an OR of 0.49, 95% CI 0.25 to 0.96, but a statistically significant increase in falls – OR 3.09, 95% CI 1.07 to 8.62 (RR 0.70, p=0.08). The effect size for the main endpoint was similar to the survival analysis conducted by the trial investigators once baseline differences in MMSE scores had been accounted for (HR 0.47, p=0.001)[61]. The authors of the Cochrane review conclude that there is no evidence of efficacy of Vitamin E in the treatment of people with AD, but that more research is needed to identify the role of Vitamin E, if any, in the management of cognitive impairment.

OTHER NUTRIENT INTERVENTIONS

One further relevant study was identified in our own updated search[62], a pilot randomised controlled trial of a 'medical food' (Souvenaid®) in 225 drug-naïve patients with mild AD. The rationale for this approach was that a combination of nutrients (in the case of Souvenaid, eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], phospholipids, choline, uridine monophosphate, Vitamins E, C, B_6 and B_{12}, selenium and folic acid) might be required synergistically to increase brain levels of phosphatide molecules that comprise the bulk of brain synaptic membranes. At 12 weeks, significant improvement was noted in the delayed verbal recall task in the treatment group compared with control (p=0.02). However, there was no change and no significant difference in other relevant outcomes; ADAS-Cog, Clinician Interview Based Impression of Change, activities of daily living, or quality of life. Compliance was excellent (95%) and the product was reported to be well tolerated. The trial was sponsored by Danone Research – Centre for Specialised Nutrition (part of Groupe Danone – the manufacturers of Souvenaid), who were involved in study design, data collection and analysis. Alpha-Plus Medical Communications Limited were involved in drafting and editing the manuscript.

Conclusion

There is, as yet, no evidence to recommend the use of nutritional supplementation at any stage of dementia. Given the strong theoretical basis for intervention in this area, it is under-researched, with relatively few trials, some of which are small and underpowered. The combined micronutrient supplementation approach used in the Souvenaid trial requires further investigation, in particular regarding the longer term effects of sustained supplementation from the earliest stage of AD.

Treatment of cardiovascular disease and management of cardiovascular risk factors

Background

Despite occasional negative findings from large prospective studies[63;64], the accumulated evidence for a causal role for cardiovascular risk factors (CVRF) and cardiovascular disease (CVD) in the aetiology of dementia and AD is very strong. In short[65-67] and longer latency[68;69] incidence studies, smoking increases the risk for Alzheimer's disease. Diabetes is also a risk factor[70], and in longer term cohort studies midlife hypertension[71;72] and hypercholesterolaemia[72] are associated with AD onset in later life. Those with high cardiovascular risk scores (incorporating hypertension, diabetes, hypercholesterolaemia and smoking) have an increased risk for dementia incidence whether exposure is measured in midlife[69] or a few years before dementia onset[67]. Recent studies report associations between metabolic syndrome and incident cognitive decline[73], and insulin resistance and impaired executive function[74]. These findings have led to the hypothesis that atherosclerosis and AD are linked disease processes[75], with several common underlying factors (the APOE e4 gene, hypertension, increased fat intake and obesity, raised cholesterol, diabetes, the metabolic syndrome, smoking and systemic inflammation).

Consideration of underlying mechanisms has suggested some specific pharmacotherapeutic approaches. Microvascular mechanisms for β-amyloid clearance could be modified by endothelial changes from hypertension[76] and some antihypertensive drugs such as calcium channel blockers[77] or angiotensin-converting enzyme inhibitors could interact with β-amyloid trafficking[78]. Statins are a class of drugs that act by reducing the formation and entry of low density lipoprotein cholesterol (LDL) into the circulation and upregulate LDL receptor activity, thus lowering LDL cholesterol and triglycerides and increasing high density lipoprotein (HDL) cholesterol. Studies have shown that treatment with lowering cholesterol drugs reduces the production of β-amyloid, which in turn has been linked to neuroprotective effects in patients with AD.

Results

We identified a Cochrane systematic review of statins for the treatment of dementia. Our own search identified a further trial of a multi-faceted 'vascular care' intervention for patients with mild AD from the Netherlands.

STATINS
The Cochrane systematic review of statins for the treatment of dementia, published in 2010 with review content assessed as up-to-date on 2 March 2009[79]. Three trials were identified with 748 participants, age range 50-90 years, all of whom had a diagnosis of probable or possible AD. The evidence base is dominated by the LEADe trial (n=614, MMSE scores 13-25), with two much smaller trials ADCLT n=63 MMSE 12-28, n=44 MMSE 12-26). Most patients were taking a cholinesterase inhibitor. Treatment, with atovastatin in

two trials and simvastatin in the other, achieved more than 50% reduction in LDL cholesterol in all three trials. There was no evidence, after pooling across the three trials, for any effect of statin treatment on either ADAS-Cog (pooled random effects MD -1.12, 95% CI -3.99 to 1.75) or MMSE (pooled random effects MD -1.53, 95% CI -3.28 to 0.21). It was noted that there was some evidence from one small trial (ADCLT 2005) that patients on statins maintained better cognitive function if serum cholesterol was high at baseline, MMSE was higher at baseline or if they had an apolipoprotein E4 allele present. However, these were post hoc subgroup analyses, and would require independent confirmation in larger hypothesis driven trials.

COMPREHENSIVE 'VASCULAR CARE'
One hundred and thirty patients with mild AD and cerebrovascular lesions on neuroimaging were randomised to a 'vascular care' secondary preventive intervention or treatment as usual in neurological or geriatric secondary care clinics in ten Dutch hospitals. The vascular care intervention comprised evidence-based treatment for hypercholesterolaemia and hypertension, prescription of aspirin, folic acid and pyridoxine, attention to smoking cessation, losing weight, and taking physical exercise at three-monthly follow-up visits. Over a two-year follow-up period the intervention had no impact on subsequent disability, cognitive decline, institutionalisation or costs[80].

Conclusion

The authors of the Cochrane review conclude that there is insufficient evidence to recommend statins for the treatment of dementia. One large trial in this area has yet to report[81]. We did not identify any trials of the treatment of hypertension among people with dementia. However, optimal control of hypertension was a component of the Dutch vascular care intervention, together with correction of dyslipidaemia and attention to behavioural risk factors for cardiovascular disease, with no benefits noted for any relevant clinical outcomes. One of the complicating factors for interventions in this area is that there is a body of evidence to suggest that while hypertension, hypercholesterolaemia and obesity in midlife are associated with an increased risk for the later onset of dementia, blood pressure levels[71], cholesterol[82] and body mass index[83] tend to fall progressively prior to the onset of the disease. Hence people with dementia tend to have lower blood pressure levels, cholesterol and body mass than others. In principle, therefore, early primary prevention may be the more effective intervention. Preventive trials of statins[84], and antihypertensive treatment[85], do not seem to lower the incidence of dementia when initiated in older people, but there have been no long-term trials from midlife onwards. For people with dementia, it should be noted that for statins there was no evidence for any adverse effect on cognitive function, and their use for the treatment of dyslipidaemia is probably indicated, as for those without dementia, to prevent stroke and coronary heart disease. Although there is no specific evidence for their safety or efficacy in

people with dementia, the same advice probably holds true for antihypertensive treatment, which is at least not associated with cognitive decline in healthy older people[86]. Attention to cardiovascular risk factors remains part of current good practice guidelines for dementia care[87].

Non-steroidal anti-inflammatory drugs (NSAIDs)

Background

Non-steroidal anti-inflammatory drugs may attenuate the effects of modulators of inflammation that have been implicated in the pathogenesis of Alzheimer's disease.

Results

We identified two Cochrane systematic reviews, one for ibuprofen for the treatment of AD[88] and one for indomethacin for the treatment of AD[89]. The review for ibuprofen (review content assessed as up-to-date on 5 May 2008) failed to identify any relevant trials. Our supplementary search identified one recently completed trial, of ibuprofen 400mg twice daily accompanied with esomeprazole for gastroprotection, versus placebo[90]. One hundred and thirty-two patients with MMSE scores of 16-25 and CDR questionable to mild dementia were randomised of whom fifty-one patients (77%) in the ibuprofen arm and 46 (70%) in the placebo arm completed the protocol. At one-year follow-up there was no difference between the two groups in ADAS-Cog worsening (MD 0.1, 95% CI -2.7 to 2.9). There was also no difference seen in secondary outcomes; MMSE, CDR, Basic and Instrumental Activities of Daily Living scales, and Neuropsychiatric Inventory (NPI). The trial did demonstrate that the treatment was well-tolerated when covered with gastroprotection.

Only one trial was identified in the indomethacin review: a six-month, double-blind, placebo-controlled study testing the efficacy of indomethacin for people with mild to moderate AD, and MMSE scores of 16 or greater[91]. Forty-four patients were randomised to indomethacin 100-150mg or placebo, but only 14 in each arm completed the trial. At six month follow-up there was a marginally statistically significant difference in percentage change on ADAS-Cog favouring the indomethacin arm (MD 14.7%, 95% CI 0.1% to 29.3%) and a marginally statistically non-significant difference in percentage change on MMSE also favouring the active treatment arm (MD 12.5%, 95% CI -0.3% to 25.3%). The dropout rate was higher in the indomethacin group (10/24) than in the control group (6/20), and gastrointestinal adverse events were more prevalent in the treatment group (5/24 compared with 1/20 in control group), although neither of these differences were statistically significant. The review authors concluded that there is no evidence of difference between indomethacin and placebo, due to their reservations regarding the use of percentage change rather than absolute change scores. Regardless of these methodological limitations, concerns regarding adverse events, particularly gastrointestinal bleeding,

would counsel against any recommendation to use indomethacin based upon such slender evidence.

Conclusion

Surprisingly few treatment trials have been conducted into the efficacy of NSAIDs in dementia. The early indomethacin trial could be regarded as providing some proof of concept that these agents may have a role in modifying the course of AD. Indomethacin is a classical NSAID with both a particularly potent anti-inflammatory effect and a particularly high incidence of side effects for old people. The more recent ibuprofen trial showed that newer generation NSAIDs were well-tolerated if used with gastroprotection. There was no evidence for a beneficial effect on cognition or other global outcomes but the trial was underpowered and cannot, by itself, definitively exclude clinically significant treatment benefits. Recent evidence that CR1 (encoding the complement component receptor[1]), a gene involved in regulation of inflammation is associated with AD[92], may lead to increased interest in exploring safe and effective prevention and treatment opportunities[93]. The possibility of different treatment effects with greater effectiveness among those who are ApoE epsilon4 carriers has been mooted, but with very little supportive evidence to date.

Gingko biloba

Background

The use of the leaf extract from the maidenhair tree, gingko biloba, has been hypothesised to benefit people with AD and vascular dementia. The active components are thought to be flavonoids, terpenoids and terpene lactones which supposedly have a positive effect on cerebral blood flow, on the neurotransmitter systems, have anti-oxidant properties, and an anti-amyloid aggregation effect[94].

Results

We found a Cochrane review on gingko biloba for the treatment of cognitive impairment and dementia, with review content assessed as up-to-date on 25 March 2008[95]. The review summarises a large and complex literature; 36 trials were included but most were small and of duration less than three months. One of the significant limitations is that the authors did not distinguish between effects on AD and other forms of dementia, and cognitive impairment. Earlier studies had used a variety of ill-defined inclusion criteria, such as organic brain syndrome and cerebrovascular insufficiency. In later versions of the review, a subgroup analysis was carried out on efficacy among people with AD based on data from four trials (958 participants), two of which recruited only patients with AD and two of which reported outcomes for this subgroup. In the AD subgroup analysis there was no evidence of efficacy on ADAS-Cog scores, but a significant difference in favour of ginkgo biloba for the low dose (MD -4.30, 95% CI -5.34 to -3.26) and high dose (MD -1.30, 95% CI -2.29 to -0.31) on another brief test of memory and orientation: the Syndrom Kurz Test. No effect was noted on ADL, but there was a significant effect on clinical global outcome

at 24 weeks at the higher dose (181/249 showing clinical improvement compared with 154/253, OR 1.79, 95% CI 1.21 to 2.65), but not for the lower dose.

Two subsequent systematic reviews have focussed upon evidence of efficacy for those with AD[96] and all forms of dementia[97]. The AD review was carried out by researchers from the Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany with no conflicts of interest reported. The dementia review was carried out by independent researchers from the Institute for Social Medicine, Epidemiology and Health Economics at the Charité University in Berlin, but the review was funded via an unrestricted grant from the makers of standardised gingko extract, EGb 761®, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany. The review of gingko as a treatment for AD identified six contributing trials with mean or median MMSE scores (where reported) between 21 and 23 points for three trials, and around 18 for one other. Effect sizes were highly heterogeneous between studies for both ADL and cognitive outcomes at both low dose (120mg daily) and high dose (240mg daily). However, at the higher dose gingko was generally favoured, with statistically significant effects on both ADL and cognition, in three of the four trials that tested high dose gingko against placebo. Given the high degree of heterogeneity in study findings the authors chose not to report pooled estimates. The review of gingko as a treatment for all forms of dementia identified nine trials using the standardized gingko extract and included 2,372 patients in total. Despite again observing high degrees of heterogeneity between studies, the authors did report pooled effect sizes (standardised mean differences – SMD). The SMDs for change scores for cognition were in favour of ginkgo compared to placebo (SMD -0.58, 95% CI -1.14 to -0.01), but did not show a statistically significant difference from placebo for activities in daily living (SMD -0.32, 95% CI -0.66 to 0.03). For the Alzheimer subgroup, the SMDs for cognition outcomes (SMD -0.63, 95% CI -1.16 to -0.10) and for ADL (SMD = -0.44, 95% CI -0.77 to -0.12) were larger than for the whole group of dementias with statistical superiority for ginkgo.

All three reviews are in agreement that ginkgo seems to be safe and well tolerated, with no significant differences between gingko biloba and placebo in drop outs or adverse events.

Conclusion
Recent reviews, focussing on studies carried out on people with AD and other forms of dementia, indicate possible positive treatment benefits for gingko biloba on cognition and activities of daily living, at least at the higher dose of 240mg daily. Of concern is the high degree of statistical heterogeneity in the size of the treatment effect between studies, and the lack of clear evidence that the quite modest effects observed are clinically meaningful. From the point of view of the focus of our report, while most of the dementia trials focussed upon those with mild to moderate dementia, there is no evidence regarding efficacy specifically in people with mild or early stage dementia. In the view of the Cochrane review authors, further trials are unlikely now that AChE inhibitors are an established treatment and 'researchers in dementia and cognitive impairment will probably give priority to more consistently promising forms of treatment'. Conversely, the authors of the manufacturer sponsored review have argued for head-to-head comparisons to compare the relative effectiveness of gingko biloba and acetylcholinesterase inhibitors for different dementia subgroups. A more realistic and potentially useful design, given the contrasting modes of action, might be a trial of gingko among participants already taking AChE inhibitors.

Non-pharmacological interventions – for the person with dementia

Strategies to support and enhance cognitive function

Background
Five therapies are in relatively common use – cognitive training, cognitive rehabilitation, cognitive stimulation, reality orientation and reminiscence therapy. There is some degree of overlap between them. Cognitive training involves guided practice on a set of standard tasks designed to reflect particular cognitive functions such as memory, attention or problem-solving. Cognitive rehabilitation is a more individualised approach to helping people with cognitive impairments and their family caregivers, in which the emphasis is on enhancing residual cognitive skills and coping with deficits. Cognitive stimulation targets cognitive and social function, through reality orientation, activities, games and discussions, prioritising information-processing rather than knowledge. It is capable of being administered by professional therapists to groups of people with dementia (typically in a nursing home or residential care setting) or by carers who have been trained in the technique. Reality orientation, generally included under the umbrella of cognitive stimulation, aims to improve the quality of life through presentation of orientation and memory information. Reminiscence therapy involves the discussion of past activities, events and experiences with another person or a group of people.

Results
COGNITIVE REHABILITATION & COGNITIVE TRAINING
We searched the Cochrane database and found one review on cognitive rehabilitation and cognitive training for early-stage AD and vascular dementia, with review content assessed as up-to-date on 17 September 2006[98].

Nine trials of cognitive training were identified. Individual and group approaches were used, and some interventions involved carers. Most were conducted on people with mild to moderate dementia, with no stratification of results by dementia severity. Two trials focussed specifically on mild dementia[99;100]. Eight of the nine studies contributed at least one outcome measure, and no significant positive effects of cognitive training

Table 2

Author, publication year	Intervention	Additional intervention provided to all participants	Duration	Inclusion criteria	Mean MMSE treatment/ control
Bottino et al 2005[103]	Described as cognitive rehabilitation, but closer to CS/RO	rivastigmine	5 months	Mild dementia	22.3
Breuil et al 1994[104]	Cognitive stimulation		5 weeks	Dementia – MMSE >=10 (mild to moderate)	21.5
Chapman et al 2004 (abstract only)[115]	Cognitive-communication program	donepezil	12 months	MMSE 12-28 (mild to moderate)	No data
Ferrario et al 1991 (abstract only)[116]	Reality orientation		24 weeks		No data
Hanley et al 1981[117]	Classroom reality orientation		12 weeks	Long-stay hospital patients (n=41) 7% mild 27% moderate 66% grave Residential care home (n=16) 20% mild 55% moderate 25% grave	No data
Niu et al 2010[118]	Cognitive stimulation (reality orientation, fluency, overlapping, and photo-story learning tasks)	Stable dose of an AChEI	10 weeks	Chinese older adults with mild to moderate AD (n=32)	T 16.9 (3.0) C 17.3 (3.2)
Onder et al 2005[111]	Long-term, home-based programme of reality orientation	donepezil	25 weeks	Mild (n=77) to moderate (n=60) dementia (MMSE 14-27)	T 20.2 (3.3) C 19.9 (3.0)
Requena et al 2006[119]	Factoral design – 1. CS and donepezil 2. Donepezil only 3. CS only 4. No treatment		Up to 2 years	Mild to moderate dementia – attendees at a day centre	group 1 23.0 group 2 21.2 group 3 19.4 group 4 19.4
Spector et al 2001[120]	Reality orientation		7 weeks	Dementia	T 11.5 (4.4) C 15.5 (4.4)
Spector et al 2003[112]	Cognitive stimulation/ reality orientation		7 weeks	Mild to moderate dementia (MMSE 10-24)	T 14.2 (3.9) C 14.8 (3.8)
Wallis et al 1983[121]	Reality orientation vs diversional occupational therapy		3 months	Long-stay hospital patients with dementia	No data

Numbers treatment/ control	Result
T 6 C 7	Mean differences (MD) MMSE 2.26 MWU test p=0.047 ADAS-Cog -1.74 MWU test p=0.092
T 29 C 27	MMSE MD 2.1 (0.5-3.7)
T 26 C 28	Positive effect on discourse and functional abilities
T 13 C 6	Significant improvement in mental ability measured by the CAPE
T 28 C 29	Significant changes in orientation, but not in memory, concentration or behaviour. Clinical significance unclear
T 16 C 16	MMSE MD 1.00 (p=0.004).
T 79 C 77	Mean differences Overall MMSE 1.3 (1.2-1.4) ADAS-Cog 2.9 (2.6-3.2) Mild dementia MMSE 2.1 ADAS-Cog 3.6 Moderate dementia MMSE 1.5 ADAS-Cog 3.6 No interaction between severity and treatment
group 1 – 14 group 2 – 20 group 3 – 14 group 4 – 30	Cognitive function was better maintained in those randomised to CS alone or CS+donepezil, compared with no treatment. Significant improvements in MMSE and ADAS-Cog over year 1 declining to baseline by end of year 2.
T 17 C 10	Mean differences MMSE 3.1 (p=0.08) ADAS-Cog 5.3 (p=0.4)
T 115 C 86	Mean differences MMSE 1.1 (0.6-2.3) ADAS-Cog 2.4 (0.6-4.1)
T 10 C 9	Modest and statistically significant improvement in cognition (Royal College of Physicians Mental Scale for the Elderly) seen in both groups with no significant between group differences observed.

were observed overall on cognitive function, subjective memory impairment or carer rated impairment. There were also no significant negative effects. One of the trials focussing on mild dementia (44 patients with mild AD all stabilised on cholinesterase inhibitors[101]) did demonstrate improved cognitive performance relative to controls who received a similar amount of less structured 'mental stimulation', but only for the cognitive tasks that were similar to those used in training. Gains in recall of face-name associations, orientation, cognitive processing speed and specific functional tasks were present post-intervention and at a 3-month follow-up.

No trials of cognitive rehabilitation were identified in the Cochrane review. However, this more individualised therapy has shown promise in uncontrolled case reports and series[102], and in one small pilot RCT in Brazil[103]. When we contacted the authors of the Cochrane review they identified one further trial, which they had conducted, testing the efficacy of goal oriented cognitive rehabilitation in 69 participants with early-stage dementia, randomised to cognitive rehabilitation, relaxation therapy or no treatment[104]. The intervention was delivered weekly for 8 weeks and re-assessed at 6 months. Each session was 1 hour long and individualised (personal goals) to the person. There was a significant effect favouring the cognitive rehabilitation intervention group for the main outcomes of goal performance and satisfaction with large effect sizes in comparison to the relaxation and no treatment groups. At 6-month follow-up, the cognitive rehabilitation group subjectively rated their memory performance more positively than the no treatment group. Changes in the cognitive rehabilitation group were supported by functional magnetic resonance imaging data for a subset of participants showing significant effects of intervention on activation during encoding and recognition while undertaking a face-name association task.

COGNITIVE STIMULATION & REALITY ORIENTATION
We searched the Cochrane database for reviews on cognitive stimulation and found a review at the protocol stage entitled '*Cognitive stimulation to improve cognitive functioning in people with dementia*' which also includes reality orientation (the protocol for a review on reality orientation for dementia was permanently withdrawn so it could be included in the new protocol). The authors sent us the list of 15 studies under consideration for inclusion. We excluded five of these from further consideration for the purposes of our review, two because they recruited only participants with moderate to severe dementia[105;106] and three because they referred to trials that were controlled but not randomised[107-109]. We identified one further trial[110] from our own search. The characteristics of the 11 retained studies (eight accessed in full text form and three as abstracts) are summarised in Table 2. The trials are generally small or very small in size, with 743 participants randomised in all. Most of the trials recruited patients with mild to moderate dementia. Only in one of these[111] have results presented separately for those with mild dementia (n=77).

The evidence overall for the efficacy of cognitive stimulation is consistently positive. All of the available 11 trials suggest statistically and clinically significant treatment effects, although little information is available for the three trials published as abstracts only. Efficacy has been demonstrated for group interventions by professionals[112] and when administered one-to-one by carers[111]. The effect sizes associated with the intervention, for the ADAS-Cog and the MMSE, are similar to those seen for acetylcholinesterase inhibitor drugs[112], and are apparent for mild as well as moderate dementia[111]. There does also seem to be evidence of efficacy over and above AChE inhibitor medication effects[103;111;113].

REMINISCENCE THERAPY

We found a Cochrane review on reminiscence therapy[122] which included five trials, but only 4, with a total of 144 participants, had extractable data[123-125]. The only study which, according to the Cochrane review, included patients with mild to moderate dementia is an unpublished PhD thesis[125] that included 17 care home residents randomised to two groups, one receiving life review intervention and the comparison group receiving no treatment. At 4 and 6 weeks, reminiscence intervention was associated with significant improvements in cognition (standardised mean difference 0.5, z=2.31, p=0.02). We did not identify any further trials of reminiscence therapy in our own updated search. Although the Cochrane review meta-analysis of four trials of reminiscence therapy indicated some evidence for short-term improvement in cognition and mood, and reduction in carer strain, limitations in the evidence base were highlighted. The trials had small sample sizes, and some were of low quality. The types of intervention varied considerably across studies.

Conclusion

The evidence suggests that it is possible to produce short-term improvements in cognitive function and/or reduce cognitive decline in people with dementia using non-pharmacological approaches. The strongest evidence by far for efficacy relates to interventions applying principles of cognitive stimulation and/or reality orientation. The interventions can be quite intensive of therapist time, but the optimal dose, duration and mode of administration have yet to be determined. Use of trained carers as therapists or co-therapists is an attractive and potentially cost-effective approach. Cost-effectiveness data are required to support the wider scaling up of this therapeutic technique. There is evidence to suggest that structured cognitive training is ineffective and this approach cannot be recommended. However, the more individualised cognitive rehabilitation has shown some promising results, particularly with patient-centred outcomes such as goal performance and satisfaction. There is very limited evidence for any beneficial effects of reminiscence therapy in the treatment of dementia, particularly for those in the early stages of the disease.

Psychological and psychosocial interventions

Background

Previous research has drawn attention to adverse psychological reactions to confirmation of a diagnosis of dementia (Chapter 1). These may be self-limiting but might also be ameliorated by counselling and support. Support groups have been widely adopted. Evidence-based psychological treatments for depression and anxiety in older people include cognitive behavioural therapy (addressing maladaptive thoughts and beliefs about the self, the world and the future, and their links to behaviour) and behavioural therapy (focusing on behavioural change to improve mood). A needs assessment for people with early stage AD in the US identified a particularly strong preference for practical advice (legal and financial counselling), as well as emotional support and peer support[126].

Results

PSYCHOLOGICAL TREATMENTS

We found no systematic reviews of behavioural and/or psychological therapies for people with dementia, and no trials of either individual cognitive behavioural therapy (CBT) or individual counselling. Our complementary search identified one very small randomised controlled trial of a multi-modal intervention that included group CBT, along with Taiji exercises and support groups for people with early stage AD[127]. Outcomes (cognitive functioning, physical functioning, depression, and self-esteem) were assessed at 20 weeks and after the full 40 weeks of the intervention. At 20 weeks, the treatment group (n=24) performed better than the control group (n=19, receiving educational programs) on mental ability and self-esteem, with gains in balance also being evident. We also identified a trial testing the effectiveness of behavioural treatments applied by the caregiver in reducing levels of depression symptoms in depressed AD patients[128]. Participants had a mean MMSE score of 16.5 suggesting mild to moderate dementia severity. Seventy-two participants were randomly assigned to two treatment conditions, one focussing on increasing pleasant events (n=23), the other problem-solving issues of concern (n=19), compared two control groups, typical care (n=10), and wait list (n=20). All depression outcomes favoured the treatment groups to a statistically significant degree. Standardised mean differences indicated a 4 to 5 point net benefit on the Hamilton Depression Rating Scale, and a 4 point net benefit on the Cornell Scale for Depression in Dementia. Clinically significant improvement was observed in 50% (pleasant events) and 68% (problem-solving) versus 20% in the two control groups.

SUPPORT GROUPS

No Cochrane reviews were found on support groups for people with dementia. The US Alzheimer's Association review included eight publications describing seven studies assessing the effects of support group participation on outcomes for patients in the early stages of dementia. Studies varied in format, content, program

goals and quality of information described. Most articles were descriptive accounts of newly implemented support groups with conclusions based on observation or qualitative analysis. There were no trials, either controlled or randomised.

1   Zarit et al 2004 – 10-session support program that included 23 dyads of patients and their caregivers. The main goal of the program was to empower care partners to problem solve and plan for the future. MMSE scores for most participants were 25 or higher. Results showed positive ratings of program's content, a beneficial shared experience, and increased social support[129].

2   Morrissey 2006 – a reflective account of 8 patient-caregiver dyads following a recent dementia diagnosis attending an adapted version of an Alzheimer's Café. The Cafés are informal environments were people with dementia and their caregiver can exchange ideas with other people with dementia while increasing social interactions thus reducing isolation and improving self-esteem, living skills and insight[130].

3   Mason et al 2005 – aimed to investigate the mutual support processes that occur in dementia support groups and how members perceive the groups. Eleven participants from two support groups were included. MMSE scores ranged from 19 to 29 (mean 24). In a qualitative analysis, participants identified benefits as well as negative aspects[131].

4   Snyder et al 1995 – a qualitative analysis of an 8-session support group that included 15 participants. Four positive themes were identified: purposefulness, gratification, belonging, and surviving. Negative themes identified were helplessness, devaluation, and unpredictability[132].

5   Yale 1991 – 13 patients in the early disease stages entered an 8 week educational/emotional support group or a 'usual-care' control group. Reports of the group's benefits were positive (decreased feelings of isolation, opportunity to exchange ideas), but no differences were found in quantitative outcome measures[133].

6   LaBarge et al 1995, 1998 – describes a newly formed support group program (8 sessions) targeting people with AD aimed to provide opportunities to share thoughts and feelings. Ten mildly to moderately impaired persons were included. Open ended questions and observations by group facilitators were used to evaluate program outcomes. Findings suggest that persons with early stage AD are aware of their deficits and the changes that accompany the disease[134;135].

7   Morhardt & Menne 2001 – a qualitative study of 6 face-to-face interviews carried out with AD patients and their caregivers. All participants had attended support groups[136].

Our new search identified one randomised controlled trial comparing a 9-session structured early-stage dementia support group program (n=96) to a wait-list control group (n=46)[137]. Mean MMSE score for the intervention group was 23.2 (4.7) and for the control group was 24.0 (3.8). The support group program focused on coping with memory problems, daily living, self-esteem, relationship, health, legal and financial concerns. Main outcomes were quality of life (QOL), mood, communication, stress, self-efficacy, and assessment of memory-related behaviour problems. Intervention participants report significant improvement in QOL, whereas wait-list reported decreased QOL (β=1.74, p<0.001), R^2=0.05, effect size d=0.44. Similar results were found for depressive symptoms.

LEGAL AND FINANCIAL ADVICE
We did not find any Cochrane reviews, or trials, of interventions providing legal and financial advice for people with early stage dementia.

Conclusion
The evidence base for the effectiveness of psychological and psychosocial interventions for people in the early stages of dementia (CBT, individual counselling, support groups) is remarkably limited. This is surprising given the extensive literature on psychological and psychosocial interventions for caregivers, and the recognition that people with dementia are prone to adverse psychological reactions post-diagnosis, and are generally at high risk of depression and anxiety.

We were only able to identify three randomised controlled trials. It may be that the benefits of some of these approaches (for example support groups) appeared to many to be almost self-evident. However, while evidence from several uncontrolled observational evaluations and qualitative research suggests that well-designed support groups for people in the early stage of dementia are generally appreciated and thought to be beneficial by participants, some negative perceptions were reported from some users. It is important to be clear about their safety (lack of harm), efficacy and cost-effectiveness. Such evaluations need to be conducted through well-designed randomised controlled trials.

At present, it is not possible to make clear, evidence-based recommendations on the use of psychosocial interventions in early stage dementia. Behavioural treatments seem very promising, and have the advantage of engaging the caregiver as co-therapist, potentially increasing their sense of efficacy. While one randomised controlled trial of support groups provides evidence of efficacy on key patient-centred outcomes, more confirmatory research is required to clarify the benefits of support groups in relation to other services, benefit to caregivers, evaluation of effective components, and optimal length of programs. The US Alzheimer's Association review highlights the termination of support at the end of the formal group sessions as a drawback, since, with earlier diagnosis, persons may remain in the early stage of AD for up to five years, hence probably requiring ongoing support programs[138]. Recent clarification of the apparent ineffectiveness of

antidepressant treatment may stimulate more trials of non-pharmacological interventions, including supportive counselling and the feasibility and effectiveness of cognitive behavioural therapy.

Physical exercise

Background

In several longitudinal cohort studies higher levels of baseline physical activity are associated with lower risks of developing dementia[139]. As well as primary prevention, this has raised interest in the potential benefits of exercise and activity programs in slowing the progression of dementia. Dementia is strongly associated with physically frailty, with significantly impaired mobility[140]. Possible benefits of physical activity, including increased lower-limb strength, and improved exercise endurance, might help maintain physical function and performance of basic activities of daily living.

Results

We identified a Cochrane review on physical activity programs for people with dementia[141]. This was unsatisfactory for our purposes, since only four trials were identified, three of which focused on late stage or severe dementia. The quality of the trials was reported to be poor, and only two had data in a suitable form for analysis[142;143]. The authors concluded that there was insufficient evidence of benefit to make any recommendation with respect to physical activity programs in dementia.

A more recent systematic review of the effects of physical activity on strength, balance, mobility and ADL performance in older people with dementia identified 10 randomised controlled trials (all of poor methodological quality) and six non-randomised trials[144]. There was little overlap with the Cochrane review – only one of the trials was included, and two listed as excluded from the Cochrane review. Overall the review concluded that

a) there was evidence that people with all levels of severity of dementia could take part in physical activity interventions, with generally high participation and low drop-out rates.

b) physical activity interventions in older people with dementia lead to an improvement in physical performance with the largest improvements on gait speed, functional mobility, balance and endurance seen after multicomponent interventions, and not after progressive resistance training alone. The largest improvements in physical functioning were found after interventions with the largest training volume.

Although the authors of the review concluded that there was evidence for efficacy of physical activity interventions for all severities of dementia, it was clear that most of the constituent trials recruited people with moderate to severe dementia. Two very small trials had recruited participants with predominately mild/early stage dementia. Santana-Rosa et al[145] randomised 16 people with dementia to an exercise group three times a week for 12 weeks with individualised joint mobility, resistance

and coordination exercises (n=8, mean MMSE 20.1) or care as usual (n=8, mean MMSE 19.9). There were large and statistically significant net benefits on the timed get up and go test (Cohens d 2.37, p<0.001), 2 minute step test (0.58, 0.002), sit-to-stand test (3.14, p<0.001) and Barthel ADL scale (5.06, p<0.001). Steinberg et al[146] randomised 27 people with dementia to a 12 week exercise group with different aerobic, strength and balance exercises (n=14, mean MMSE 20.1) or a home safety review control group (n=13, mean MMSE 15.5). There were no statistically significant benefits identified for gait speed, Yale Physical Activity Survey or sit-to-stand test.

We identified one further randomised controlled trial of potential relevance, excluded from the systematic reviews since this was a multimodal intervention of home based exercise training combined with teaching caregivers behavioural management techniques[147]. The latter component had previously been shown to be efficacious in the treatment of depression in dementia (see above)[148]. The exercise intervention included aerobic/endurance activities, strength, balance and flexibility training. Twelve one hour sessions were conducted at home over 11 weeks, involving the caregiver as co-therapist. The intention seems to have been to maintain the exercise program beyond the duration of the intervention. One hundred and fifty-three people with AD were randomised to the intervention (n=68, mean MMSE 17.6) or a routine medical care control group (n=77, mean MMSE 15.9). Mean duration of dementia symptoms was 4.3 years. At three months follow-up those randomised to the intervention group were nearly three times more likely to take at least one hour of exercise per week (OR 2.8, 95% CI 1.3-6.4), and to have fewer days of restricted activity (3.1, 95% CI 1.1-9.0). Treatment effects favouring the intervention group were also noted for depression at three month and two year follow-up.

Conclusion

There is evidence to suggest that people with dementia can participate in physical activity programs. There is suggestive evidence that, for people with dementia in general, physical activity programs can be efficacious in improving physical function and endurance, and, possibly, in limiting impairment in activities of daily living. There is insufficient evidence to recommend physical activity programs specifically for people with mild dementia, although one very small trial does suggest that large benefits might be achieved from an intensive high dose program. There is a need for more high quality randomised controlled trials in this area, in particular assessing the longer term benefits of people with early stage dementia initiating and maintaining increases in physical activity.

Non-pharmacological interventions – caregiver focussed interventions

Background

Caregiver focused interventions include: psychoeducational interventions, often including components of carer training; psychological therapies such as cognitive behavioural therapy (CBT), and counselling; carer support; and respite care. Many interventions combine several of these elements.

Results

There are several systematic reviews and meta-analyses;[149-153] all of the constituent trials were conducted in high income countries, and many were non-randomised[149]. Outcomes studied include carer strain, depression and subjective wellbeing; behaviour disturbance and mood in the care recipient; and institutionalisation. Most carer-focused interventions seemed to reduce carer strain and depression, CBT having the largest impact on depression[149]. Psychoeducational interventions seem to require the active participation of the carer (for example, in role-playing activities) to be effective[149].

A more recent systematic review of the efficacy of nonpharmacological therapies in Alzheimer's disease[154] provides evidence specifically from parallel group randomised controlled trials to support the effectiveness of high dose multicomponent caregiver interventions in delaying institutionalisation, improving caregiver mood and well-being. In addition, caregiver education interventions that also included problem-solving or attention to coping skills were effective in improving caregiver mood. However, there is doubt as to the extent to which this evidence-base is relevant to caregivers of people with mild or early stage dementia.

Two of the three trials of the effect of caregiver interventions on institutionalisation recruited care recipients with mild through to severe dementia; in one the median MMSE score ranging from 11 to 15 by randomisation group[155], in the other only 30% of those with male caregivers and 33% of those with female caregivers had mild dementia[156]. However, in the second of these trials treatment had the greatest effect on risk of placement for patients who had mild dementia at entry into the trial (Hazard Ratio 0.18, 95% CI 0.04-0.77)[156].

For the trials of caregiver education and coping skills (individual sessions) and multi-component interventions, care recipients were recruited with all degrees of dementia severity but mean or median MMSE scores in the range of 10-15 points indicated a preponderance of moderate to severe cases. This is largely a by-product of inclusion criteria that are designed to identify those experiencing a significant burden of care; for example in the REACH family of trials (for which median MMSE scores were 13-14 points)[157] care recipients must have at least one limitation in basic activities of daily living or two dependencies in instrumental activities of daily living[158]. For the caregiver education and coping skills group session interventions, no information was made

available on the severity of dementia among care recipients. This was probably because of the method of recruitment, typically through Alzheimer's associations or by advertisements, hence the only contact was with the caregiver and the care recipient was not directly assessed. Entry criteria typically include the duration of care, burden of care and level of psychological strain.

The only interventions for which there was evidence for a benefit for caregiver quality of life were multicomponent interventions involving both the caregiver and the person with dementia, based on comprehensive assessment, environment modifications and continuous caregiver counselling and support[159;160]. Unusually these interventions seemed to be evaluated principally among those with mild dementia; in one trial the entry criteria were mild to moderate dementia, and the mean MMSE score was 19 points in each arm[159]. In the other, 80% of the care recipients were described as being at the early (ambulatory) stage of dementia with low to moderate levels of impairments in activities of daily living, and the mean MMSE score was 17 points[160].

Conclusion

There is evidence that caregiver psychosocial interventions, particularly those that include multiple interactive components, can be beneficial in improving caregiver mood and quality of life, and in delaying institutionalisation. Caregiver multicomponent interventions (including elements of training, support, enhanced coping and respite) have typically targeted caregivers who are already actively engaged in substantial practical caregiving tasks, and who may be experiencing psychological strain as a result. This would not be a typical scenario for family members of most people in the early stages of dementia. Nevertheless, there is evidence that such interventions when started relatively early in the disease course may be especially effective in delaying institutionalisation[156] (see also Chapter 5). In the US, family members of those with early stage dementia did identify needs for education, advice and support. These included: educational information on the disease, and on research and clinical trials, emotional support (including peer-to-peer programs), and practical advice on employment, disability benefits, financial and legal issues. There is little if any literature evaluating programs specifically tailored to the needs of family members of those with early stage dementia.

Non-pharmacological interventions – focussed on both the caregiver and the person with dementia

Case management

Background

Fragmentation of dementia care contributes to increase the burden to caregivers, affects people with dementia and is likely to increase costs[161;162]. Case management seems a potential alternative to improve care and to reduce costs. The Case Management Society of America (CMSA) describes case management as "a collaborative

process of assessment, planning, facilitation and advocacy for options to meet an individual's health need through communication and available resources to promote quality cost-effective outcomes"[163].

In a recent systematic review of the effectiveness of case management on health care costs and resource utilisation[164], case management interventions were operationalised as

"any intervention involving interaction between a case manager and patient-caregiving dyads and providing continuity and advocacy over time, support, information about community services, care and disease evolution, financial and legal advice. The case manager could also reduce fragmentation among services, monitor medication to avoid adverse reaction and give advice on behavioural management strategies tailored to the needs of patients and families".

Results

The authors of the systematic review identified 12 randomised controlled trials, all conducted in high income countries, eight in the US. For the majority of trials, patients with all levels of dementia severity were eligible for inclusion. Case managers were either nurses or social workers. Duration of the intervention ranged from 6 months to 3 years in most trials. No formal meta-analyses were conducted due to heterogeneity. Narrative summaries were stratified according to the methodological quality of the trials. Of the six trials rated as 'good quality', four reported a positive impact on institutionalisation delay. Three RCTs included economic evaluations with none identifying a net cost-benefit of the intervention. In the one high quality economic evaluation (of the US Medicare Alzheimer's disease demonstration on Medicare expenditures (MADDE)), after three years the cost savings on Medicare part A and part B expenditures did not compensate the case management program costs. Four RCTs included an evaluation of the effect of case management upon hospitalisation rates or emergency visits, with no evidence of positive impact favouring the case management group.

Only one of the trials included in the review, conducted in Canada, specifically targeted people with 'early stage dementia'[165]. The treatment group (n=37) had a mean MMSE score of 22.7 (range 11-28) and the control group (n=38) a mean of 22.8 (range 13-29), suggesting predominately mild dementia, but with some people with dementia of moderate severity also included. The intervention comprised case management, occupational therapy, in home and residential respite care, home care and a psychiatric consultation. After six months caregiver burden was significantly lower in the intervention group. The authors present data indicating a potential benefit for reduced institutionalisation limited to those with more severe dementia at baseline (MMSE scores <= 23). Over 18 months, this subgroup of patients remained in the community an average of 53 days longer if allocated to the intervention. However, no tests of statistical significance were presented for the main effect or

interaction by severity. A similar finding was presented in a trial conducted in Finland of systematic, comprehensive support by a dementia family care coordinator[166]. In this trial, people with all severities of dementia were recruited, and survival plots suggest a progressively greater benefit of the intervention on delayed institutionalisation from mild to moderate to severe dementia. Again, there were no tests for statistical significance of this interaction, and with 78 participants with mild dementia, 62 with moderate dementia and 60 with severe dementia, the analysis would have been greatly underpowered. By contrast, in Mittelman's much larger US trial[156], also included in this case management review, the benefits of the caregiver intervention on institutionalisation were greater for those with mild to moderate dementia at baseline than for those with severe dementia. This issue is considered in more detail in Chapter 5 (Do some interventions work better when applied earlier in the disease course?).

Our own literature search identified one further recent trial of case management in early stage dementia, published since the period covered by the systematic review[167]. This was a 12-month randomised controlled trial carried out in the primary care settings in Netherlands to test the effectiveness of case management among older adults with early symptoms of dementia and their caregivers. Patients were randomised to case management by district nurses specialising in geriatric care (n=54) or usual care (n=45), comprising a diversity of health care and welfare services. The nurses were described as having a coordinating function consisting of assessment, giving advice and information, planning, organising collaboration, and monitoring of care. Outcomes were measured at 6 and 12 months. Intention to treat analyses using linear mixed models revealed no differences in the course over time between the two groups on caregiver's sense of competence, quality of life, depressive symptoms or burden, or upon patient's quality of life. Apart from case management, no differences were found in health care utilisation between the two groups. The authors acknowledge that the intervention may have lacked sufficient intensity and duration, and that poor intervention fidelity may have contributed to the null findings.

Conclusion

There is evidence to suggest that case management may be efficacious in delaying institutionalisation in people with dementia. It should be noted that there is some overlap between the interventions and studies considered in this section and the 'intensive multi-component' caregiver interventions considered above. There is no evidence that this approach can increase the efficiency with which health services are used (reducing hospitalisations or emergency care), and, at best, the economic impact on health care costs seems to be cost-neutral. Nevertheless, the fairly consistent effect on delaying institutionalisation would suggest that there may be overall societal cost benefits. It is unclear from the current literature what might be the optimal time in

the disease process for introducing a case coordinator; at the time of diagnosis, or later in the process as more complex needs for medical, psychiatric and social care arise, and the informal care demands increase. Future research is needed to evaluate case management approaches tailored to the different stages of dementia, assessing outcomes appropriate to disease stage, and evaluating the longer term impacts of the intervention when commenced in the early stages.

Overall summary and conclusions

We found strong evidence (multiple RCTs) that acetylcholinesterase inhibitors (for cognitive function, functional impairment), and cognitive stimulation (for cognitive function) are effective interventions in mild dementia. We found strong evidence (multiple RCTs) that gingko biloba (for cognitive function), caregiver multicomponent interventions and case management (for carer mood and institutionalisation of the person with dementia) are effective interventions in mild to moderate dementia although their value for people with mild dementia, and their carers, has not been specifically quantified. We found some evidence (single RCTs only) that support groups for people with dementia (for quality of life and depression), behavioural treatment (for depression) and cognitive rehabilitation (for goal performance, satisfaction and subjective memory impairment) may be helpful in early-stage dementia. We found suggestive evidence from multiple RCTs that physical activity interventions may improve physical function and limit impairment in activities of daily living in people with dementia; however, the evidence is limited and equivocal for people with mild dementia.

We found no evidence to support the use of antidepressants for depression in mild dementia, or for the use of HRT, micronutrient supplementation, non-steroidal anti-inflammatory drugs, statins or comprehensive vascular care in mild dementia, for dementia related outcomes. However, good practice guidelines advocate testing for and correcting B_{12} and folate deficiency, and attending to cardiovascular risk factors and optimising medical management of cardiovascular disease. There is insufficient evidence to recommend the use of reminiscence therapy or cognitive training in mild dementia, and individual CBT and counselling has not been evaluated for people with mild dementia.

It is clear that very few interventions have been evaluated specifically for efficacy in mild or early stage dementia. Neither are people with mild dementia excluded from the evidence base; mild to moderate dementia was widely used as an inclusion criterion for the trials assessed in this review, with somewhere between a third and a half of participants typically falling into the mild dementia severity category. When the results of such trials have not been stratified by dementia severity, it is not entirely safe to conclude either that the intervention lacks efficacy for those with mild dementia when the overall results are null, or that the intervention will be efficacious when the

overall results are positive. A trial that focuses entirely on those with mild or early stage dementia will generally be more definitive than one in which results have been presented separately for this subgroup, since it is more likely to be adequately powered, with a sufficiently large sample size to detect clinically significant treatment effects.

Trial participants are generally recruited from patient populations, and, as we have seen, people with dementia have tended to present late for care. This probably explains the lack of focus upon those with mild dementia in much of the research conducted to date. It is also clear that there has been a trend in recent years towards trials of interventions among those with mild or early stage dementia. Our search for such trials published since 2005 yielded 17 publications including protocols, most of which were published in the last three years. Eight were trials of evaluations of potential disease modifying agents, where the rationale would presumably have been that early intervention is likely to show greater benefit. It also seems that, as people are increasingly presenting in the early stages of dementia, there is growing interest in how best to support and treat them from early diagnosis onwards. Seven of the trials would have fallen into this category.

Most current recommendations for early stage management are based upon expert opinion, and observational data. A recent systematic review of mainly qualitative studies from high income countries identified good practice for disclosing dementia diagnosis. This should include: preparation; integrating family members; exploring the patient's perspective; disclosing the diagnosis; responding to patient reactions; focusing on quality of life and well-being; planning for the future; and communicating effectively[168]. The person assessed should be asked if they, and/or others, wish to be told the diagnosis. If so, they should be given information about the signs, symptoms and course of dementia, available treatments, care and support services.

Careful consideration should be given to providing the right amount and type of information, at the right time, to both the person with dementia and their family members. More evidence is required on optimal and effective modalities of psychosocial support and psychotherapies for people with early stage dementia, particularly given the evidence of profound psychological reactions in the immediate aftermath of diagnosis (see Chapter 2), and the apparent ineffectiveness of antidepressant drugs for depression in dementia. Support groups, behavioural therapy and cognitive behavioural therapy all show some signs of promise, but in each case with evidence limited to single RCTs conducted in the US. In the US, people with early stage dementia expressed an interest in peer support, provided by other people in the early stages of the disease, but the need for practical advice and information was accorded greater priority than that for emotional support[126] (Chapter 1). Spouses and other family members may also benefit from education and support in the early stages of the disease, but again there

is little evidence from clinical trials to guide which specific approaches should be used, and when. It seems that education to enhance coping skills and problem solving capacity may be particularly effective for carers who are already experiencing psychological strain[154], with the implication that these strategies, and the more intensive multicomponent / case management interventions could be kept in reserve and offered in a timely fashion as care burden increases. On the other hand, it has also been suggested that counselling, support and homecare, when accessed early, may allow carers to anticipate and plan ahead for how they will manage increasing care demands, and to introduce routines that may be helpful later in the disease course[169]. There is evidence that the circumstances surrounding assumption of the caregiving role appear to have long term implications for key outcomes, including caregiver wellbeing and institutionalisation[170].

If the purpose of early diagnosis is to provide access to evidence-based interventions, then the strongest current recommendation is that acetylcholinesterase inhibitors should be offered to people with mild AD. Cognitive stimulation may also prove to be effective therapy for people with early stage dementia, either complementing treatment with AChEIs or as the main therapy to support cognitive function in those who do not meet evidence-based criteria for AChEIs. This therapy, although relatively simple to deliver, is not routinely available in most services. Caregiver education, training and support also seems to be particularly effective in delaying or avoiding institutionalisation. In the next two chapters,

we examine whether there is any evidence for a critical window of therapeutic opportunity, early in the disease course for these interventions (Chapter 5), and whether early diagnosis coupled with early implementation of these interventions can help to control the societal costs arising from dementia (Chapter 6).

István Kappéter, who has Lewy Body dementia, Budapest, Hungary

The best known Hungarian dementia specialist advised (in a TV program made by the Hungarian Academy of Sciences) everyone who notices memory problems in themselves or their loved-ones to keep it quiet, not to tell anyone, so they don't become socially stigmatized. Those in Hungary who probably have Lewy Body or Alzheimer's type of dementia rarely get cholinesterase inhibitors. Most Hungarian doctors, psychiatrists and even neurologists I know, when asked to examine someone for thinking disorders, say they don't see serious problems. According to Professor Konrad Beyreuther, they had the same troubles in Germany 20 years ago, but it has gotten a lot better since.

The most important factor in getting over these prejudices and getting people to be open about their condition is to find ways to promote reasonably optimistic approaches to dementia.

People whose cognitive impairment started in their adulthood, especially if they have Lewy Body or Alzheimer's dementia are still able to work – they can still be worth their salary to the employers, if they get work that is easy and not humiliating – in the first stage of their disease. This would be good for everyone – for them, their families, and all humankind.

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CHAPTER 5

Do some interventions work better when applied earlier in the disease course?

In the previous two chapters, we have reviewed evidence of benefits associated with early diagnosis (Chapter 3) and evidence for effective interventions for those with early stage dementia (Chapter 4). Another related question is whether, for some interventions and some outcomes, there may be a critical period of intervention in the early stage of the disease.

Despite an age difference of more than 90 years, Marie-Thérèse and Frederica had a good time painting a kite together. AMPA, the Monegasque Association for Research on Alzheimer's Disease, and the Speranza – Albert II day care centre for Alzheimer's patients in Monaco, have organised intergenerational paint workshops. The children and their older partners were free to express their artistic talents to decorate one hundred kites. The project promotes intergenerational health care, support work and public awareness.

The question is whether the intervention is only effective in early stage dementia, or is more effective when administered earlier rather than later in the disease course. As was discussed in Chapter 2, this is critically important when justifying increased efforts, and increased expenditure on advancing the time at which dementia is typically diagnosed (see figure 1 on page 11).

We did not implement any specific new search strategies, but reviewed all of the publications identified through the extensive searches described in Chapter 3 and Chapter 4, with respect to their potential relevance to the question for this Chapter. We found four studies with at least some bearing on this issue, two of which referred to the effect of antidementia drugs and two relating to caregiver intervention and support.

Antidementia drugs

A large naturalistic open label Phase IV trial of donepezil, funded by the manufacturers of the drug, was carried out in multiple clinical centres in Spain[1]. Participants were recently diagnosed with AD, and had not previously received treatment with any AChEIs. Of the 403 people with dementia, 152 were considered to have mild dementia at study baseline (MMSE>=21) and 251 moderate dementia (MMSE<21). Patients with moderate dementia were 1.5 years older on average than those with mild dementia. No information was provided on duration of symptoms prior to diagnosis and treatment. The authors report a general trend, over six months on treatment with donepezil, towards deterioration in cognitive test scores among those with moderate dementia and improvement among those with mild dementia. In the moderate dementia group there was statistically significant deterioration in MMSE language item scores and memory alteration test (M@T) semantic memory and temporal orientation scores. In the mild dementia group there was significant improvement in MMSE memory item scores and M@T temporal orientation. Differences in the change scores between the two groups were statistically significant, in favour of the mild dementia group, for MMSE memory and language and M@T semantic memory and temporal orientation. Scores on the Alzheimer's disease functional assessment and change scale (ADFACS) indicated functional deterioration for both groups, but to a lesser extent for mild compared with moderate dementia. This study illustrates one of the main limitations of non-randomised open-label trials and pharmacosurveillance studies; without a placebo control group, it is impossible to know whether the group differences in cognitive change scores were accounted for by differential responsiveness to donepezil, or different trajectories of decline in mild and moderate dementia, regardless of treatment. It is difficult to track cognitive change precisely with only a baseline and six month follow-up assessment. Multiple follow-up cognitive assessments over a longer period would have permitted control for baseline cognitive status while comparing subsequent

trajectories. Finally, one cannot assume that all of the scales used had arithmetical properties, that is, for example, that a two point deterioration in MMSE from 19 to 17 for a patient with moderate dementia would be equivalent to a two point deterioration from 24 to 22 for a patient with mild dementia.

Another large observational study addressed more indirectly the question of whether earlier treatment with antidementia drugs (donepezil, galantamine, rivastigmine and/or memantine) influences the course of cognitive decline[2]. In the US Baylor College of Medicine longitudinal database, prior duration of symptoms is assessed for each new patient visit using a validated structured assessment. At subsequent follow-ups cognitive function is assessed using a standard battery of tests, and use of medication recorded. The authors developed a 'persistency index' defined as the proportion of the total duration of the illness (from first onset of symptoms) for which a patient has been taking antidementia drugs. After controlling exposure to antidementia drugs before contact with the service, estimated cognitive decline rate prior to first visit, gender, education, age, and the severity of disease at baseline, higher persistency scores were associated with lesser decline in MMSE (P <0.0001), Clinical Dementia Rating Sum of Boxes score (P <0.001), instrumental activities of daily living (P <0.0001), and a Physical Self-Maintenance Scale (P <0.05). In a further analysis, presented at International Conference on Alzheimer's Disease (ICAD) 2008, higher persistency scores were also reported to be independently associated with survival[3]. When compared with the quarter with the highest persistency, the relative risk for death in the quarter with the lowest persistency was 2.4, 95% CI 1.7-3.5. Logically, one would presume that the persistency index would tend to be higher for those patients who started antidementia drugs earlier in the disease course, and that hence this exposure would be to some extent a proxy for early intervention. However, no data was presented on the association between the persistency index and symptom duration at the time of initiation of treatment, and the effect of earlier intervention per se was not assessed. The better outcome for those with a higher persistency index could be explained by a critical early stage for effective intervention, or a cumulative effect of the drugs, or both.

Caregiver interventions

The Medicare Alzheimer's Disease Demonstration Evaluation (MADDE) was a large multi-centre US randomised controlled trial of case management, conducted in the 1990s, comprising assessment of the needs of caregivers and care recipients and implementation of care plans that included a range of community-based services largely reimbursed by Medicare. There was no effect of this intervention on time to nursing home placement for care recipients[4]. In a subsequent analysis, the entire trial sample, comprising 4,176 caregiver / care recipient dyads who had survived to first follow-up at six months, was used

as an observational cohort to assess factors associated with time to institutionalisation[5]. The researchers tested a priori hypotheses that the effects of receipt of in-home help (personal care and companion services) and adult day care (respite) would be modified by duration of care. These services accounted for 80% of community-based long-term care used by participants in the MADDE trial. The hypotheses were partly supported. Use of both services was associated with delayed institutionalisation; however, the effect of in-home help but not respite day care was greater among those who had more recently taken on a caregiving role[5]. Also, the effects of in-home care in delaying institutionalisation were greater among those with higher MMSE scores, and hence earlier disease stage at recruitment[5].

In Mittelman's trial of caregiver counselling and support, initial analysis on the first 208 trial participants, recruited between 1987 and 1990 and followed up to 1995, indicated a median institutionalisation delay of 329 days associated with the intervention[6]. A subsequent long-term follow-up analysis, based upon data from the full trial cohort of 406 carer/care recipient dyads recruited between 1987 and 1997 and followed up to mid-2005, indicated a median institutionalisation delay of 557 days[7]. In the first publication, data was presented that suggested a strong and statistically significant interaction between dementia stage at the time of entry into the trial, and the effect of the intervention on institutionalisation. While the overall hazard ratio was 0.65 (95% CI 0.45 to 0.94), indicating a one-third risk reduction for those who had received the intervention, treatment had the greatest effect on risk of placement for patients with mild dementia (HR 0.18, 95% CI 0.04 to 0.77) or moderate dementia (HR 0.38, 95% CI, 0.17 to 0.82), compared with those with severe (HR 0.78, 95% CI, 0.53 to 1.15) or very severe dementia (HR 1.62, 95% CI, 0.70 to 3.76)[6]. The intervention by dementia severity interaction was supported by a test of statistical significance (p=0.04). Unfortunately, this interaction analysis was not presented in the second updated publication, so it is unclear whether this apparent differential effect of caregiver intervention persisted over the longer-term[7].

Two trials of case management[8;9] (an intervention with considerable overlap to that pioneered by Mittelman), which were presented in the previous Chapter, provide a somewhat contrasting picture. In each of these trials, there was a trend towards the intervention having the greatest effect on reducing risk for institutionalisation among those with more severe dementia at baseline, with apparently negligible effects among those with mild dementia. However, in neither of these publications was there a test for statistical significance of the observed interaction. Given the very small sample sizes, it seems quite likely that this could have been accounted for by chance.

Conclusion

There is limited evidence, from two studies, to support the hypothesis that early intervention with antidementia drugs may be associated with more favourable cognitive outcomes. The evidence provided by the US Baylor College of Medicine study[2] is much the more compelling. The 6 months follow-up period in the Spanish study[1] is similar to that of most RCTs, and the evidence presented is contradicted by the much stronger evidence from the pooled meta-analysis of RCT data on effect sizes by dementia severity presented in Chapter 4 (page 35). In the randomised controlled trials, across the three different AChEIs, there was remarkable homogeneity of effects between drugs within sub-groups with larger effects seen for more severe dementia; for mild MMSE severity (pooled MD 1.86, 95% CI 0.83 to 2.89), moderate (MD 3.98, 95% CI 3.22 to 4.74) and moderately severe (MD 5.44, 95% CI 3.94 to 6.94). The unique feature of the Baylor College of Medicine dataset is the long follow-up period, a mean of 3 years, range 0.8-13.4, unprecedented for a randomised controlled trial. It is conceivable that the initial treatment response to AChEIs is greater for people with more severe dementia, but the overall long-term course of cognitive decline is more favourable among people who commence treatment with AChEIs earlier in the disease course, and then persist with that treatment.

There is also limited evidence, from one trial[7] and one observational data analysis[5], that early intervention with caregiver counselling and support, or homecare, may be more effective in delaying or avoiding institutionalisation of the person with dementia. Mittelman's finding, while robust in itself, requires confirmation in other similar randomised controlled trials, particularly given that a trend in the opposite direction has been suggested in two trials of case management. A possible explanation for this discrepancy is that the follow-up period in Mittelman's New York trial report was up to 8 years, compared with just 18 months[8] and two years[9] in the two case management studies. A longer follow-up might be required in order to detect the full benefit of the caregiver intervention for people with mild dementia, who may only be at substantial risk of moving into a care home after several years of disease progression. It is plausible that counselling, support and homecare, when accessed earlier, allow carers to adapt better to increasing care demands, and to make more effective advanced plans for coping with those demands[5]. Advice and emotional support may be particularly helpful in the early stages. Research suggests that the circumstances in which the informal caregiver assumes that role may have long term implications on key outcomes[10].

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CHAPTER 6

Spending to save – the economic case for earlier diagnosis and intervention

The economic costs of dementia are enormous. In last year's World Alzheimer Report, we estimated that worldwide costs were US$604 billion per year in 2010. These 'societal' costs included the costs of unpaid care provided by family members and others (sometimes referred to as indirect costs), the direct costs of medical care and the direct costs of social care provided by community services, residential care homes and nursing homes.

Since there are only nine residents in most of the Japanese group homes, there is no institutional cooking. Preparation of meals is done by the staff, with assistance from some of the residents who are able to help and wish to do so. At this group home in Kyoto, everyone did something to participate, whether it was laying out the plates and chopsticks or checking on all the dishes to be served, as was the case of the man here, a former chef.

Background

The economic costs of dementia are enormous. In last year's World Alzheimer Report[1], we estimated that worldwide these amounted to US$604 billion per year in 2010. These 'societal' costs included

1 the costs of unpaid care provided by family members and others (sometimes referred to as indirect costs),

2 the direct costs of medical care,

3 the direct costs of social care provided by community services, residential care homes and nursing homes.

Worldwide, the costs of medical care for people with dementia currently account for around 16% of total costs, since uptake is low, and investigations and interventions are not very cost intensive. In low and middle income countries the indirect costs of carer time predominate, since community care services and residential care are rarely available. In high income countries the direct costs of social care and the indirect costs of family care are similar, each accounting for around 40% of total costs. In these settings, the costs of institutional care account for a large proportion of direct social care costs, since, according to some estimates, between one third to one half of people with dementia live in care homes[2].

Globally, numbers of people with dementia are set to double every twenty years, from 36 million in 2010 to 115 million in 2050[3]. Given patterns of demographic ageing, it is likely that the largest increases will be among frail, older people with more severe dementia, who for those reasons, and because they are more likely to be widowed, are most likely to require residential or nursing home care[2]. Governments are already focused upon the need to manage, and if possible contain, these costs. In a report published last year, Standard & Poor's the credit rating agency identified global ageing to be the dominant threat to global economic stability, suggesting that for high income countries, without sweeping changes to age-related public spending, sovereign debt will soon become unsustainable[4].

The UK National Audit Office, in its 2007 report 'Improving services and support for people with dementia'[5], recommended to parliament an 'invest to save' approach, asserting that earlier diagnosis and intervention could reduce costs for both families and the taxpayer by delaying entry to care homes. This delay was hypothesised as possible through the prevention of harm and crises from early rather than late or no diagnosis, by providing support, respite and psychological therapies to carers to prevent or treat psychological stress. It might also be achieved by slowing the progression of the disease. As one of the participants in a focus group conducted for the report opined:

> "Make the system more cost-effective by giving carers the correct levels of support and they will be able to manage at home for longer – in the long term it would save the Government money. Otherwise it's a sticking plaster on an open wound."

The National Audit Office report includes the statement that "Experts and the Department (Department of Health, the Government Ministry) agree that early diagnosis and intervention in dementia is cost-effective"[5]. What then are the economic arguments to support early dementia diagnosis, coupled with earlier intervention?

The methodologies

Health economists use economic analyses to inform decisions about resource allocation and prioritisation. In a cost-effectiveness analysis the aim is to estimate the ratio of the incremental costs associated with an intervention per unit net benefit (often assessed as a Quality Adjusted Life Year, or QALY). Hence, how much does it cost, through the application of the intervention, to produce one QALY? In a cost comparison analysis the costs of the intervention and all other relevant costs (that might be reduced or increased by the intervention) are computed and summed, and compared between groups receiving and not receiving the intervention. Ideally, the comparison is effected using a randomised controlled trial design. If overall costs are lower in the intervention group, then this option is considered to be 'dominant' and the economic arguments favouring the introduction of the intervention are then clearly very strong. If the costs are greater in the intervention group then it may also be important to consider the ratio of incremental costs and benefits through a cost-effectiveness analysis.

As we have seen, there have to date been no randomised controlled trials of earlier against later diagnosis and intervention, and such studies would be both ethically and practically complex. There are trials of the effectiveness of pharmacological and psychosocial interventions, some of which have been carried out in early stage dementia (see Chapter 4). Most of these are trials of individual interventions, as opposed to multiple effective components combined into 'packages of care'. Most trials, particularly of pharmacological interventions (e.g. acetylcholinesterase inhibitors and memantine) have been of short duration.

Given these limitations, health economists have recently applied sophisticated modelling techniques to integrate the best available information on:

• The potential for bringing forward the time at which diagnosis is made

• The effectiveness of pharmacological and psychosocial interventions on long term disease course, and institutionalisation

• The likely impact of these interventions on costs

As with all economic modelling exercises, the outcome is often critically dependent upon the assumptions, which should be made explicit. Certain key parameters are varied across a range of plausible values in 'sensitivity analyses' in order to quantify the likely degree of uncertainty in the estimates.

The evidence

We identified three economic analyses that had attempted to model the impact of implementing earlier diagnosis on future costs health and social care system and/or societal costs.

1. Researchers from the University of Wisconsin[6] conducted a Monte Carlo cost-benefit analysis, based on estimates of parameters available in the medical literature, which suggests that the early identification and treatment of AD have the potential to result in large, positive net social benefits as well as positive net savings for states and the federal government.

The cost of early identification of one patient with AD was estimated at approximately US$4000, from the results of a universal primary care screening and diagnosis program of all attendees aged 65 years and over[7], taking into account both the misclassification rate and the relatively low uptake of diagnostic referrals. Each patient in two imaginary cohorts, one screened and diagnosed early and the other later reflecting current norms, was assigned a random annual cognitive decline (MMSE score), drawn from an appropriate distribution. Patients' MMSE scores were used to determine the probability that they would enter institutional care in the next interval of time, taking into account also their age, sex and the presence of a spouse carer. The researchers examined the impact of two evidence-based interventions applied early in the early diagnosis cohort; pharmacological treatment with acetylcholinesterase inhibitors, and carer education, training and support; separately and in combination. The pharmacological intervention was assumed to modify the rate of cognitive decline, either by reducing the proportion of 'rapid decliners' and increasing the proportion of 'slow decliners', or in an alternative model, by reducing the mean annual decline from 3.5 to 1.5 points per annum. The benefits of caregiver intervention were identified from Mittelman's US trial of an enhanced counselling intervention, comprising individual and family sessions, support groups and telephone contacts initiated by carers[8]. The initial counselling required 24 hours of therapist time, with an average of 9 hours per year of supportive contact subsequently. In the trial there was a 28% reduction in the risk of institutionalisation for those randomised to receive the intervention (adjusted Hazard Ratio 0.72, 95% CI 0.54 to 0.96), translating into an average delay of about 1.5 years of nursing home admission. The model also took into account the greater benefits of the carer intervention associated with earlier as opposed to later uptake[8], the possible increased use of services among those receiving the caregiver intervention, and reduced caregiver depression. In the model, acetylcholinesterase inhibitor drugs were assumed to reduce rates of institutionalisation by reducing cognitive decline, while the benefits of caregiver intervention were assumed to apply at every level of MMSE score. Therefore the effects of the two interventions on institutionalisation were assumed to be synergistic. In a broader analysis of costs and benefits from a societal perspective, impacts of the interventions were also computed upon unpaid 'informal' care inputs, and upon patient and carer utility weighted quality of life, linking these parameters to the patient's MMSE level, and the presence or absence of depression in the carer. QALYs were valued at between US$93,500 and US$187,000. The counterfactual scenario against which early diagnosis and intervention was compared was intended to reflect current 'usual practice'. Based on retrospective data from AD patients diagnosed in memory clinics and the Medicare Current Beneficiary Survey, it was assumed that AD patients not detected at early stages of the disease would present for diagnosis at an MMSE score of 19, after which they would have a 25% chance of receiving drug treatment.

In this modelling exercise, the net benefit was positive (that is, the benefits of early identification and intervention exceeded costs) under most assumptions and for each of the interventions. However, the net benefits were highest when cases were identified at earlier stages, i.e. an MMSE score of 28, and when drug therapy was combined with a caregiver intervention program. The net societal benefits (which included impacts on unpaid informal care and carer quality of life) were greater than the net benefits from a federal or state fiscal perspective, which focussed on direct costs of formal social and medical care, and institutionalisation incurred by those branches of government. However, the net benefit computed from direct costs alone remained positive even when the cost of screening to achieve early diagnosis was accounted for. The authors estimated that even if the State of Wisconsin paid all costs of implementing an early identification and caregiver intervention protocol not covered by the federal government, the combined

John du Preez, who has dementia, South Africa

I went through a denial phase at first and then I decided to read up more about this sickness. The more I read, the more I despaired at first. Then I decided to fight the disease and try to stay healthy until a drug is found to delay the sickness from going over to the second phase. I strongly recommend that all persons who start to suspect that they may have Alzheimer's and persons whose parent is showing tendencies of severe short-term memory loss to undergo diagnosis.

intervention would yield overall savings to the state of US$10,000 per diagnosed patient.

2. The second economic analysis was carried out by researchers from the United BioSource Corporation, a consulting research firm, commissioned by Eisai Ltd, the manufacturers of donepezil[9]. The scenario tested in this case was the early diagnosis of dementia effected by indicated screening of all those presenting in primary care with subjective memory impairment, and commencing treatment with donepezil for those that met NICE guidelines of a MMSE score of between 10 and 26. Those meeting dementia diagnostic criteria but with a MMSE score of greater than 26 were assumed to have regular reviews with treatment commencing when the score fell within the range specified by the guidelines. This was compared with two counterfactuals; one in which there was no screening program for earlier diagnosis and no treatment, and the other, reflecting current practice, in which there was no screening program, but in which diagnosis was assumed to occur on average three years after first symptoms, and treatment to commence at that time. The approach used in this modelling exercise was 'discrete event simulation', a more flexible, but also more complex, decision modelling tool that tends under most scenarios to deliver similar results to Markov chain modelling. In the model developed by the authors, the estimated treatment effect of donepezil on annual rate of change in MMSE score, estimated from seven randomised controlled trials and two open-label extension studies, was 6.2 MMSE points per year over the first 20 weeks of treatment and 2.5 points per year for the remainder of the first year on treatment. After the first year, continued treatment was assumed to have no further effect on cognitive decline and therefore the rate of disease progression was the same as that for untreated patients; however, the previous treatment gains were maintained. Premature treatment discontinuation was allowed for in the model, conditional upon its major predictors. The incremental cost of the screening program was estimated at £4,803 (US$7,700) per patient diagnosed, accounting for primary and secondary care inputs, and investigations, but assumed 100% sensitivity for the screening procedure. The model considered the impact of the intervention upon direct costs (the cost of the intervention, other health care costs, community social care and institutionalisation), indirect costs (informal caregiver time) and carer and patient health utilities, conditioned upon MMSE score, behavioural symptoms and institutionalisation status.

In this modelling exercise, the net benefit was again positive (that is, the benefits of early identification and intervention with donepezil exceeded costs) under most assumptions. In the base case model, the net benefit in direct costs was £3,593 (US$5,750) per patient, and in indirect costs was £4,148 (US$6,650), giving a total net benefit of £7,741 (US$12,400). Varying many of the parameters simultaneously in a probabilistic sensitivity analysis resulted in incremental cost-effectiveness ratios below the £30,000 per QALY cost-effectiveness threshold adopted by NICE in the United Kingdom, in 70% to 90% of replications.

3. The third economic analysis[10] assessed the possible cost-effectiveness of nationwide introduction, in England, of the Croydon Memory Service model[11] for early diagnosis and intervention in dementia. The costs that were calculated included those relating to the diagnostic process (other than investigations), imparting the diagnosis to the family and the care and the support needed following diagnosis. Costs of pharmacological treatments were not considered. Allowance was made, however, for induced downstream service needs from existing community health and social care services for people with dementia. The only benefit considered was reduced institutionalisation. Additional costs for the memory service were estimated at £95 million (US$150 million) per year nationally, with an additional £70 million (US$110 million) per year for dementia care health service downstream costs and £55 million (US$90 million) per year for social care. Total costs were therefore £220 million (US$350 million) per year. No attempt was made to model directly the impact of the introduction of such services on institutionalisation. However, it was demonstrated that if a 10% reduction in transitions into care homes was achieved 10 years after introduction of the new service, then costs and savings to society would be roughly balanced. The costs would, by then, be around £265 million (US$425 million), while the savings would be £120 million (US$190 million) in public expenditure on health and social care and £125 million (US$200 million) in private expenditure for those not eligible for publicly funded care. The authors point out that very modest QALY savings associated with early diagnosis and intervention could bridge the gap and result in a net benefit associated with the nationwide introduction of the service.

Conclusion

Economic analyses are most compelling when based on outcomes directly observed in randomised controlled trials. In the case of early diagnosis and intervention for dementia, this would involve service level innovations and the application of complex packages of care. Such an evaluation could only be feasibly be carried out in a cluster randomised controlled trial, with primary care centres or health districts rather than patients as the unit of randomisation. Long-term follow-up would be required in order to capture the full downstream costs as well as the potential benefits. Secular changes in 'treatment as usual' would be an additional complicating factor, as awareness in the population and service provision improved beyond the experimental intervention. For all of these reasons, economic evaluations carried out to date have been limited to modelling exercises using the best available observational data on the likely impact of early diagnosis and intervention on downstream outcomes and costs. Economic analyses are only as robust as the

data upon which they are based and the assumptions that informed them.

The economic analysis based upon a hypothetical scaling up of the Croydon Memory Service model to cover the whole of England demonstrates that the cost of introducing such services is probably relatively modest, and that this might be recouped over a few years, given a modest (10%) reduction in the proportion of people with dementia moving into care homes. The approach was conservative in that most costs but not all benefits were considered. However, the evidence that the introduction of memory services of this type can lead to earlier diagnosis is indirect (the evaluation of the Croydon Memory Service estimated a 63% increase in diagnoses by specialist services, with 77% of referrals to the new memory service comprising those in the early stages of dementia). While there was no direct modelling of the processes by which earlier diagnosis might lead to delayed institutionalisation, the modest assumptions seem reasonable based upon the substantial effects of caregiver interventions on this outcome[8].

The two other cost-benefit analyses provide slightly more direct evidence of the potential economic benefits associated with earlier diagnosis and intervention. Both analyses have generated realistic costs for earlier identification based upon the introduction of wider screening programs in primary care. These are fairly substantial; the estimates are of a similar order of magnitude; US$4,000[6] and US$7,700[9] ; although the latter is based upon indicated screening of those with complaints of memory impairment and the former upon universal screening of all attendees aged 65 years and over. As we saw in Chapter 2, it is unclear from previous trials whether such initiatives alone would be sufficient to increase numbers of newly diagnosed patients[12]. More intensive practice-based educational programs may be required, and these may need to be sustained[13]. The costs may be higher than those estimated in the modelling exercises. The modelling of the net effects of acetylcholinesterase inhibitor treatment on cognitive function are much more sophisticated and satisfactory in the economic analysis commissioned by Eisai than in the independent US analysis, which was flawed in assuming that patients prescribed these drugs would remain on them for life, and would continue to experience slower cognitive decline than those not taking the drug throughout this period. However, although the manufacturer sponsored model was the more conservative, both studies found that the drug intervention was dominant; that is, that there was a net economic benefit associated with its earlier introduction. The validity of the Eisai disease and intervention models was largely accepted by the UK National Institute for Health and Clinical Excellence (NICE) in their 2011 revised guidance recommending that donepezil, together with galantamine and rivastigmine, now be considered as cost effective treatments for mild as well as moderately severe dementia[14]. The NICE assessment group's model, although using different

data sources and somewhat different assumptions, reached similar conclusions. However, as noted by NICE, an important imponderable is that there has been no direct demonstration that acetylcholinesterase inhibitor drugs do delay institutionalisation. This is currently absolutely critical to the economic argument for early diagnosis and intervention. The problem is that most of the drug trials have been of 6 to 12 months duration and institutionalisation has not been considered as an outcome of interest. The exception is the AD2000 long-term trial of donepezil, in which there was no effect on institutionalisation rates over three years (Relative Risk 0.97; 95% CI 0.72-1.30; p=0.8)[15], but this study is widely considered to be underpowered for this outcome and hence perhaps few inferences can be drawn from this negative finding. Both economic models[6;9] rely upon the robust findings of clinical effectiveness of acetylcholinesterase inhibitor drugs on MMSE scores and the assumption that for those patients whose scores have declined less as a result of this treatment, their risk of institutionalisation will be the same as if they recorded a similar MMSE score without the benefit of treatment. This assumption may not hold true since there is no evidence that the acetylcholinesterase inhibitor treatments modify the underlying disease pathology or course. If it is this rather than MMSE score that most directly influences risk of institutionalisation, then the expected benefits of the drug treatment (from the model, a one to two month average delay in institutionalisation) may not be realised.

The beneficial effects of caregiver interventions upon institutionalisation rates have been much more robustly and directly demonstrated. In addition to the long-term Mittelman trial, used in the US economic modelling analysis, a systematic review of 10 RCTs has indicated a 40% reduction in the pooled odds of institutionalisation[16]; the effective interventions were structured, intensive and multicomponent, offering a choice of services and supports to carers[16;17]. The Mittelman trial suggested a greater benefit as regards institutionalisation when the interventions were commenced earlier in the disease course[8]. The difference in predicted time to placement between those receiving and not receiving the caregiver intervention was 557 days. Much of the intervention's beneficial effect on placement appeared to be mediated via improvements in caregivers' satisfaction with social support, response to behavioural problems, and amelioration in depression symptoms. One of the strengths, therefore, of the US economic analysis[6] was that it considered the economic effects of these potentially potent carer interventions separately and when offered together with treatment with an acetylcholinesterase inhibitor. Each were associated with net economic benefits, with a larger combined effect. However, this may have been an artefact of the assumptions in the model regarding mode of action on institutionalisation risk – a definitive trial would require a 2 x 2 randomisation design; carer intervention alone

versus acetylcholinesterase inhibitor alone versus both combined versus neither.

In conclusion, the economic arguments in favour of early diagnosis and early intervention are strong, but not yet completely unassailable. The evidence, partly of necessity, is somewhat indirect and circumstantial, and several untested assumptions are quite critical to the case for there being a net benefit. On the other hand, the failure of most trials to include adequate assessment of the impact of the intervention on quality of life of people with dementia and their carers may have led to a substantial underestimate of the net benefits, were these to have been measured and weighed in the balance with the fiscal costs and benefits. These direct costs tend to be given more weight than wider societal benefits by governments and other health and social care purchasers.

The need for further research

It is clear that much implementation research is required in an effort to reduce the treatment gap. This will involve, as part of the experimental designs, some individuals being assigned to arms that make it more likely that they will receive early diagnosis and intervention than others. Hopefully, such trials will include a broader range of potentially effective interventions (see Chapter 4) including, for example cognitive stimulation, and a case management care approach, in addition to AChEIs and caregiver interventions as indicated. This will provide a pragmatic opportunity to assess the potential cost-benefit ratio of earlier diagnosis and implementation of packages of care in a framework that is more realistically representative of routine practice.

We should also not neglect the opportunity to use routine practice data to assess the clinical and economic benefits of earlier diagnosis and treatment. As described in Chapter 3, patients do present at different stages of the disease, and with careful study design and analysis, this does create potential opportunities to evaluate the impact of earlier versus later diagnosis and intervention on subsequent course and outcome (including costs and benefits), once stage at presentation has been unlinked from stage at inception into the clinical cohort.

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CHAPTER 7

Conclusions and recommendations – a call for action

Assuming that 60% of people with dementia living in high income countries, and 90% of those living in low and middle income countries have yet to receive a diagnosis, it is possible that up to 28 million of the world's 36 million people with dementia do not receive evidence-based treatment and care. The new evidence collated and presented in this World Alzheimer Report 2011 exposes this as a gross neglect, and a tragic missed opportunity to secure better outcomes for people with dementia, their families, and society.

Claudia Beyer-Feldman, formerly Director of the Munich Alzheimer's Association, loves this photograph of a couple going home after a Memory Clinic session in Nice, France. She comments: "An umbrella protects us from the rain. It's important that we create an virtual umbrella for those who receive an Alzheimer's diagnosis – an umbrella made of confirmation, love, care and true friendship."

We have shown that it is possible to promote earlier diagnosis, that there are many effective interventions for people in the early stages of dementia, that some interventions may be more effective when applied earlier in the disease course, and that, at least in high income country settings such as the US and UK, early diagnosis coupled with early intervention is cost-effective – governments could and should invest to save.

1 There is evidence that earlier diagnosis can be achieved through a) practice-based educational programs in primary care, b) the introduction of accessible diagnostic and early stage dementia care services (memory clinics) and c) promoting effective interaction between different components of the health system.

Recommendations

- All primary care services should have basic competency in indicated screening for dementia, making and imparting a provisional dementia diagnosis (including exclusion of reversible causes), initial management (providing information and support, optimising medical care) and referral.

- Practice based registers should be maintained in order to audit diagnostic activity, and to promote shared care with specialist services.

- In resource-poor settings with limited or no access to specialist dementia diagnostic and care services, the WHO mhGAP evidence-based intervention guide should be scaled up across primary care services.

- Where feasible, national networks of specialist diagnostic centres should be established, to which primary care centres could then refer all those identified with probable dementia for diagnostic confirmation.

- In complex health systems, explicit recommendations should be made regarding the roles of primary care, memory clinics and community care services in dementia diagnosis, early stage and continuing care.

2 There is, as yet, no unequivocal evidence that earlier diagnosis is associated with better outcomes for people with dementia and their carers, but there is a marked lack of observational research data from population studies and clinical cohorts from which to draw conclusions.

Recommendations

- More observational research should urgently be commissioned and conducted, in particular making use of data routinely collected by

clinical services at the time of diagnosis and in subsequent follow-ups.

- Population-based surveys of dementia prevalence should routinely ascertain where and when a formal diagnosis has been made, and what dementia-specific services have been received.

3 It is a myth that there is no point in early diagnosis, since 'nothing can be done'. In fact, there are a range of evidence-based early interventions that are effective in improving cognitive function, treating depression, improving caregiver mood, and delaying institutionalisation.

- Acetylcholinesterase inhibitors and cognitive stimulation may enhance cognitive function in people with mild Alzheimer's disease, and these interventions should therefore be routinely offered.

- Gingko biloba cannot be recommended as a first line treatment for Alzheimer's disease, but could be considered for non-responders to acetylcholinesterase inhibitors, and for those with other subtypes of dementia. Cognitive stimulation may also be effective across dementia subtypes.

- People with early stage dementia may benefit from participation in peer support groups, and individual behavioural therapy programs should be considered to treat depression.

- Consideration should be given to developing physical activity programs although the benefits for people with mild dementia are uncertain.

- High quality caregiver education, training and support interventions should be offered to carers in a timely fashion as care demands increase; their use is associated with improved carer mood, and delayed institutionalisation of the person with dementia.

Recommendations

- The availability of effective interventions should be actively publicised to health and social care professionals through training, and to the public through population health promotion and primary and secondary healthcare and social care facilities.

- Purchasers and providers of dementia care services should ensure that these evidence-based interventions are made available, as indicated, to people in the early stage of dementia. This will involve commissioning early

stage dementia services, securing appropriate financing, and providing training and support to staff.

- Implementation and uptake should be monitored through regular service audits.
- More randomised controlled trials are required to promote evidence-based intervention in early stage dementia. Priorities include:
  - Testing drug interventions earlier in the course of dementia, over longer periods of time, and in larger and more diverse populations
  - The efficacy, and optimal targeting, duration and type of psychological intervention or support for those who have recently received a diagnosis of dementia
  - The efficacy of psychological interventions (cognitive behavioural therapy, behavioural therapy, supportive psychotherapy) for depression and anxiety in early stage dementia
  - The efficacy, including longer-term benefits, of sustained physical activity programs for people with early stage dementia
  - The efficacy, including longer-term benefits, of sustained comprehensive micronutrient and essential fatty acid supplementation for people with early stage dementia
  - The optimal timing of effective caregiver intervention, including more nuanced stepped care models for introducing and escalating provision of information, education, training and support from the time of diagnosis through early- to mid-stage dementia

4 **There is evidence from economic modelling that the cost of an earlier dementia diagnosis and the downstream costs of providing evidence-based treatment may be more than offset by the cost savings accrued from the benefits of a) anti-dementia drugs and caregiver interventions, and b) delayed institutionalisation and enhanced quality of life for people with dementia and their carers.**

Recommendations

- Current economic models are to some extent specific to the health system context (UK and US) for which they were generated. Policymakers need evidence of the real-world costs and benefits of scaling up earlier diagnosis and early-stage dementia care services, specific to the setting in which the economic evidence is to be applied.
- Commissioning of such studies, whether based on observational data or cluster-randomised controlled trials, should be prioritised by stakeholders committed to evidence-based advocacy, and by governments for evidence-based policymaking.

Francisco Antonio Guerrero Andújar, who has dementia, and his wife Ana Sylvia Frias de Guerrero, Dominican Republic

After his diagnosis five years ago, I really could not understand the magnitude of what was ahead of us – I never imagined how things would change.

My husband's mother and many of his family members suffered from dementia, but our relationship was not close enough for me to realize how this diagnosis would impact our lives.

I like to know a lot about things I have to deal with and I felt lost because I didn't know about this, until somebody told about the Dominican Alzheimer's Association. I joined them and I started to understand how this illness was going to change our lives, our plans.

What I miss the most is my independence and I know that if he could understand how dependent he is on me it would be the very same thing he would miss as he was also quite independent. Only my faith in God and my constant prayers to have the patience, the humility and wisdom to handle this is what has permitted me to care for him with all the love and respect that he deserves.

Alzheimer's Disease International

Alzheimer's Disease International (ADI) is the international federation of Alzheimer associations throughout the world. Each of our 76 members is a non-profit Alzheimer association supporting people with dementia and their families.

ADI's vision is an improved quality of life for people with dementia and their families throughout the world. ADI aims to build and strengthen Alzheimer associations and raise awareness about dementia worldwide. Stronger Alzheimer associations are better able to meet the needs of people with dementia and their carers.

What we do

- Support the development and activities of our member associations around the world.

- Encourage the creation of new Alzheimer associations in countries where there is no organization.

- Bring Alzheimer organizations together to share and learn from each other.

- Raise public and political awareness of dementia.

- Stimulate research into the prevalence and impact of Alzheimer's disease and dementia around the world.

Key activities

- Raising global awareness through World Alzheimer's Day™ (21 September every year).

- Providing Alzheimer associations with training in running a non-profit organization through our Alzheimer University programme.

- Hosting an international conference where staff and volunteers from Alzheimer associations meet each other as well as medical and care professionals, researchers, people with dementia and their carers.

- Disseminating reliable and accurate information through our website and publications.

- Supporting the 10/66 Dementia Research Group's work on the prevalence and impact of dementia in developing countries.

ADI is based in London and is registered as a non-profit organization in the USA. ADI was founded in 1984 and has been in official relations with the World Health Organization since 1996. You can find out more about ADI at www.alz.co.uk.

**Alzheimer's Disease
International**