Intended for healthcare professionals

Clinical Review

Alzheimer's disease

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This article has a correction. Please see:

- Errata - April 01, 2009

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Summary points

People with mild cognitive impairment are up to 15 times more likely to develop Alzheimer's disease than those with normal cognition

Memory loss is a presenting symptom in most people who develop Alzheimer's disease

The cause of Alzheimer's disease is unknown, but genetic and environmental risk factors have been implicated

Cholinesterase inhibitors are safe and effective and can be prescribed for people in the moderate stages of Alzheimer's disease

Antipsychotic drugs reduce agitation but are linked with an increased risk of mortality and impair cognition

Evidence is growing that some strategies are successful at preventing Alzheimer's disease

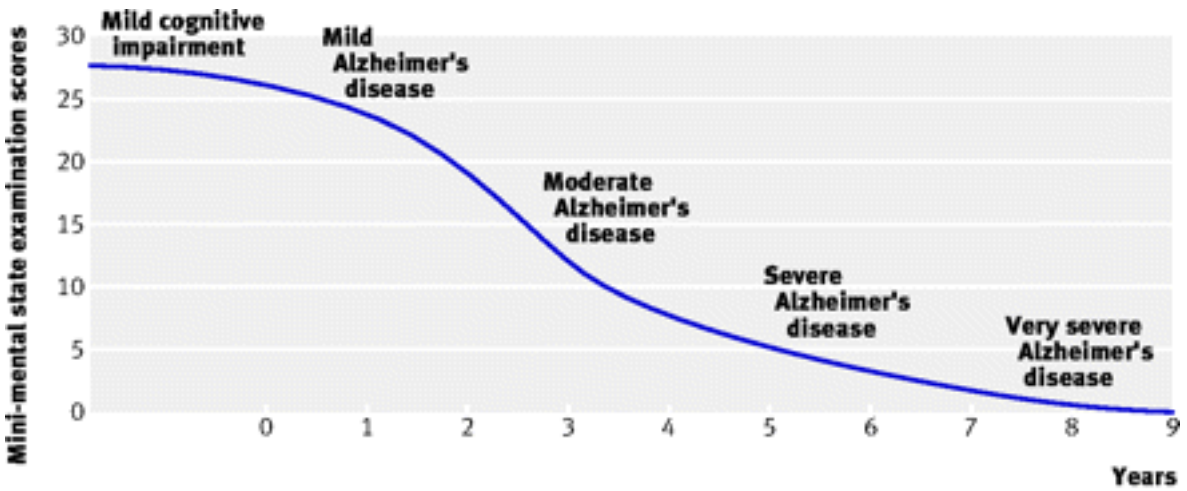
In this, the second of two review articles about dementia, we focus on Alzheimer's disease, which is the most common cause of dementia. Dementia is a clinical syndrome characterised by a cluster of symptoms and

signs manifested by difficulties in memory, disturbances in language, psychological and psychiatric changes, and impairments in activities of daily living. Alzheimer's disease is a specific disease that affects about 6% of the population aged over 65 and increases in incidence with age.[1]

Patients with Alzheimer's disease are often identified and managed in primary care, where they may present diagnostic and management challenges. The benefits of early investigation and diagnosis of Alzheimer's disease include instigation of pharmacological symptomatic treatments and initiation of psychosocial support, plus treatment of comorbid conditions. Here we review the diagnosis and medical management of Alzheimer's disease, relying where possible on evidence from randomised controlled trials.

What is Alzheimer's disease?

Alzheimer's disease is a chronic progressive neurodegenerative disorder characterised by three primary groups of symptoms. The first group (cognitive dysfunction) includes memory loss, language difficulties, and executive dysfunction (that is, loss of higher level planning and intellectual coordination skills). The second group comprises psychiatric symptoms and behavioural disturbances—for example, depression, hallucinations, delusions, agitation—collectively termed non-cognitive symptoms.[2] The third group comprises difficulties with performing activities of daily living (deemed "instrumental" for more complex activities such as driving and shopping and "basic" for dressing and eating unaided). The symptoms of Alzheimer's disease progress from mild symptoms of memory loss to very severe dementia (figure⇓). Increasingly, the coexistence of vascular disease and Alzheimer's disease is being recognised clinically, pathologically, and epidemiologically.[4]



Mild cognitive impairment: Complaints of memory loss, intact activities of daily living, no evidence of Alzheimer's disease
Mild Alzheimer's disease: Forgetfulness, short term memory loss, repetitive questions, hobbies, interests lost, impaired activities of daily living
Moderate Alzheimer's disease: Progression of cognitive deficits, dysexecutive syndrome, further impaired activities of daily living, transitions in care, emergence of behavioural and psychological symptoms of dementia
Severe Alzheimer's disease: Agitation, altered sleep patterns, assistance required in dressing, feeding, bathing, established behavioural and psychological symptoms of dementia
Very severe Alzheimer's disease: Bedbound, no speech, incontinent, basic psychomotor skills lost

Symptom progression in Alzheimer's disease. Adapted from Feldman et al[3]

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What is the relation between normal ageing and Alzheimer's disease?

Population studies of ageing and cognition suggest that impairment in multiple cognitive domains is observable several years before a clinical diagnosis of Alzheimer's disease is made.[5] This observed cognitive dysfunction is not qualitatively different from that seen in normal ageing, suggesting continuity rather than discontinuity in the shift from normal ageing to preclinical dementia.[6] Global cognitive deterioration, affecting memory and other aspects of cognitive functioning (verbal ability, visuospatial skills, attention, and perceptual speed), is almost always a presenting symptom.[w1] There is considerable overlap in cognitive performance between normal ageing and this stable phase,[w2] and little evidence exists as yet that these changes are detectable in clinical encounters. A person with symptoms of Alzheimer's disease is about 30% more likely to display the clinical features of dementia if they have coexisting symptoms of vascular disease.[4]

What is the benefit of identifying mild cognitive impairment?

Longitudinal studies suggest that cognitive impairments in this early stage may remain relatively constant for several years.[w3] This phase corresponds to the clinical concept of mild cognitive impairment, in which the individual has subjective symptoms (predominantly of memory loss) and measurable cognitive deficits but without notable impairment in defined activities of everyday life (box 1). Controversy surrounds the concept of mild cognitive impairment: is it really an identifiable precursor ripe for preventive interventions, or is it merely medicalising normal ageing? The debate continues, but prospective studies have shown that people with amnestic mild cognitive impairment (the form characterised by memory loss) are up to 15 times more likely to have developed dementia at follow-up,[w4] suggesting it may be a precursor to Alzheimer's disease .

Box 1 Criteria for diagnosing mild cognitive impairment[w4]

- Memory complaints, preferably corroborated by an informant
- Impaired memory function for age and education
- Preserved general cognitive function
- Intact activities of daily living
- No evidence of dementia

Currently, stringent tests of episodic memory are the best neuropsychological predictors of subsequent conversion from mild cognitive impairment to Alzheimer's disease at group level. Imaging techniques can identify early brain changes, both structural and metabolic, but no single technique if used as a screening test can accurately identify individuals with mild cognitive impairment who will subsequently develop Alzheimer's disease or other dementias.[7] A combination of neuropsychological testing and neuroimaging improves the diagnostic accuracy of predicting cognitive decline in people in this phase compared with that achieved with either modality alone.[8] However, the tools for identifying the early changes of Alzheimer's disease are outpacing the therapeutic options, so the usefulness of such early "preclinical" diagnosis remains uncertain.[w5]

The stable phase of mild cognitive impairment ends with a detectable decline in cognitive function, lasting two to five years, in which semantic memory (the store of facts and general knowledge) and implicit memory (the non-conscious influence of past experience on subsequent performance) also becomes degraded.[9] Trial evidence shows that early recognition of cognitive impairment and clinical assessment and management at

this point delays the subsequent need for nursing home care and reduces the risk of misdiagnosis and inappropriate management.[w5]

How does Alzheimer's disease present?

Memory loss is universal and is the first symptom in the vast majority of cases. The gradual onset of memory loss means that it may (understandably) be misattributed to normal ageing and is often recognised only in retrospect as the onset of Alzheimer's disease. The onset is insidious, emerging with mild loss of memory and difficulty with word finding, symptoms that are common in everyday life to varying degrees. It is only when the symptoms interfere significantly with social and work activities, or are recognised by others, who sense they are progressing, that suspicion of a dementia is justified. Emotional changes are common, major depression occurs in 24-32% of cases, anxiety in 17-27%, apathy in up to 41%, and delusions in 23%.**10**

How do we diagnose and assess Alzheimer's disease?

The clinical diagnosis of Alzheimer's disease follows a logical sequence: the history should include information from an informant; a mental state assessment should include a validated cognitive function test; and the physical examination should focus on vascular and neurological signs supplemented by investigations. Assessment of dementia involves a two step process. Firstly, it is important to distinguish dementia syndromes from other conditions that can mimic them, such as depression, delirium, and mild cognitive impairment. Secondly, once dementia syndrome is recognised, the diagnosis of a subtype is important because it may determine the kind of treatment possible. Current criteria for the main causes of dementia (Alzheimer's disease,**11 12** vascular dementia,**13 14** and Lewy body dementia**15**) are well summarised by Dubois.**12**

For cognitive screening in general practice, the clock test is popular because of its non-confrontational nature and because the normal drawing of a clock more or less excludes the presence of important cognitive impairment. However, the rules for scoring the tests can be quite complex and using a solitary cognitive test to screen for the presence of a dementia syndrome does not do justice to the wide variety of symptoms that make up the clinical syndrome of dementia. Activities of daily living are assessed alongside cognition, but there is less consistency in the assessment instruments used.

What is the cause of Alzheimer's disease?

The cause of Alzheimer's disease is unknown, but case-control studies have linked several risk factors with the disease including age, family history, apolipoprotein (Apo) E4 status, head injury, depression, hypertension, diabetes, high cholesterol, atrial fibrillation, presence of cerebral emboli, and low physical and cognitive activity (box 2). Some risk factors are potentially modifiable.

Box 2 Risk factors for Alzheimer's disease[w6]

Sociodemographic[w7]

- Age: increasing age
- Sex: no consistent evidence
- National and ethnic profile: some evidence of regional variations

Familial and genetic factors[w8 w9]

- Family history: 3.5-fold increase in risk when a first degree relative is affected
- Diseases causing mutations: on chromosomes 1, 14, and 21 (see later in the article)
- ApoE genotype
- Down's syndrome: everyone eventually develops the neuropathological features of Alzheimer's disease
- Premorbid cognitive reserves: longer education and higher intelligence are protective

Medical history and treatments[w10]

- Head injuries: anti-inflammatory drugs are associated with a reduction in risk
- Oestrogen replacement: no consistent evidence
- Vascular risk factors: hypertension, diabetes, homocysteine, and cholesterol are all implicated
- Depression: associated with Alzheimer's disease
- Herpes simplex: a risk factor, possibly mediated by the presence of ApoE e4

Habits[w11]

- Alcohol: drinking wine is protective
- Smoking: no consistent evidence
- Diet: no consistent evidence (including for aluminium)
- Occupational and recreation factors: no consistent evidence

Neuritic (or senile) plaques and neurofibrillary tangles are the primary histological features of Alzheimer's disease; the presence of phosphorylated tau is the hallmark of the former, and the deposition of the insoluble protein amyloid denotes the latter. Both have been correlated with the severity of the clinical features of the dementia syndrome (as has synaptic density, a measure of neuronal loss).[w12 w13]

What is the genetic contribution to Alzheimer's disease?

Familial aggregation of Alzheimer's disease has been known for some 75 years, and the risk for first degree relatives of people with the disease is estimated at 10-40% higher than in unrelated people.[w14] Twin studies have found that concordance is higher in monozygotic twins than in dizygotic twins, indicating the presence of a genetic component, although the modest concordance levels in monozygotic twins (who share 100% genetic material) would suggest that environmental factors are at play as well.[w15]

Mutations have been described in three genes: the amyloid precursor protein, presenilin 1, and presenilin 2, on chromosomes 21, 14, and 1 respectively. For late onset Alzheimer's disease, the only known genetic risk factor is ApoE, located on chromosome 19. Three gene forms exist (ApoE e2, ApoE e3, and ApoE e4), with

possession of one e4 allele being associated with a threefold risk for the development of Alzheimer's disease, whereas those with the homozygous condition have an eightfold risk.[w16] The importance of environmental factors is confirmed by the fact that the strongest association is not true across all races and 50% of white patients with Alzheimer's disease do not carry an e4 allele.

What treatments work for Alzheimer's disease?

Although we focus here on treatments for Alzheimer's disease, many psychosocial interventions are appropriate for the clinical syndrome of dementia regardless of its cause. As most psychosocial interventions and some drug treatments are for symptomatic benefit they do not rely for their efficacy on modifying the underlying pathophysiology. For example, the treatment of depression in dementia is essentially the same whether the dementia results from Alzheimer's disease or vascular dementia, alone or in combination.

In clinical practice, non-drug interventions should be tried first[w17] especially when symptoms are neither causing distress nor placing a person at risk to themselves or others.**16** Therapeutic interventions that are tailored to the individual and establish a good rapport with the person with dementia and their carers are essential. Continuity of clinical care may also be important because it permits a complex appreciation of individuals. For example, a person's own awareness of changes in their cognitive function is associated with better treatment outcomes after cognitive rehabilitation, but awareness can be difficult to assess as individuals with Alzheimer's disease may deny problems in one context but report awareness of them in another.[w18] General practitioners are well placed to have this understanding of their patients, and collaboration between specialists and general practitioners in the care of people with Alzheimer's disease is essential.

Pharmacotherapy

Cholinesterase inhibitors are the mainstay of drug treatment for Alzheimer's disease (box 3).**17** They inhibit cholinesterase, which breaks down acetylcholine, raising the level of the neurotransmitter and resulting in symptom modification. Controversy emerged after guidance from the National Institute for Health and Clinical Excellence (NICE) recommended that cholinesterase inhibitors should be used only to treat moderate Alzheimer's disease and not mild or severe disease.[w17] Underpinning this guideline is a cost effectiveness analyses by NICE that suggested that cholinesterase inhibitors are beneficial only for people with dementia whose scores on the (30 point) mini-mental state examination are between 10 and 20.[w17] The NICE dementia guidelines point out the unreliability of the mini-mental state examination and advocate treatment based on clinical assessment of "significant impairment."[w17] This latter criterion is the one that clinicians will find more useful. Uptake of dementia drugs in the United Kingdom is lower than in other European countries.**18** [w19]

Box 3 Drug treatments for Alzheimer's disease

Cholinesterase inhibitors (for moderate disease)

- Donepezil 5-10 mg
- Rivastigmine 6-12 mg
- Galantamine 8-24 mg

Glutamatergic partial antagonist* (for moderately severe disease)

- Memantine 10-20 mg
- *Not recommended by the National Institute for Health and Clinical Excellence

Cochrane reviews show that cholinesterase inhibitors have a moderate but worthwhile symptom modifying effect in a substantial minority of people with Alzheimer's disease and are generally well tolerated.[w20] The difference between active treatment and placebo on core measures of cognitive function is about three points on a 70 point scale over six months. This equates approximately to the decline expected over the same period. About 10% more people taking the active drug responded compared with those taking the placebo. Core efficacy is essentially the same for the drugs, with choice determined on the basis of familiarity by the clinician, "once daily" dosing (all three cholinesterase inhibitors are available in patch form), and ability to manipulate the dose (rivastigmine). Since April 2004 all English primary care trusts have been required by the national service framework for older people (2001) to have a shared-care protocol in place for prescribing and monitoring use of cholinesterase inhibitors in general practice and specialist settings.

Memantine is a glutamatergic partial antagonist that some trials have found effective in people with more severe dementia, but its use in the UK National Health Service is restricted to those involved in clinical trials of this drug (see NICE's technology appraisal at www.nice.org.uk/TA111).

Amnesia and activities of daily living

Non-drug approaches are not effective in modifying memory loss, although memory retraining techniques can offer support and improve wellbeing in people with mild dementia.[w21] Both cholinesterase inhibitors and memantine produce modest but identifiable improvements in activities of daily living.**17** Patients and their carers often report that improvements in activities of daily living make the biggest positive impact on their lives.[w20]

How can behavioural and psychological difficulties be managed?

General assessment

If a person with dementia develops distressing symptoms or challenging behaviour, an assessment to identify modifiable factors that may influence behaviour (such as depression, adverse effects of drugs, individual biography, and psychosocial or physical environmental factors) is important. A physical examination may, for example, discover a source of pain that underlies challenging behaviour. Environmental and psychosocial factors that may increase the likelihood of challenging behaviour include overcrowding, poor communication between the person and staff, lack of privacy, lack of activities, conflicts between staff and carers, and inadequate attention from staff.[w17]

The sequence of events is often more important than phenomenology in determining causation. For example, did a change happen after an alteration in medication, moving rooms in a nursing home, or even a change in staffing? The management of behavioural disturbance is closely linked to the underlying cause and is generally independent of the type of dementia.

Agitation

Environmental factors play a role in the genesis and maintenance of agitation, and non-drug approaches are important first line treatments. Advice on behavioural management and support for carers is essential, and when symptoms are mild and the environment supportive this is usually sufficient to manage the situation.

Non-drug approaches that have been used with benefit include aromatherapy, bright light therapy, music or dance, massage, pet therapy, and multisensory stimulation.[w17]

Although antipsychotic drugs consistently reduce agitated behaviour, concerns have been expressed recently over the safety of both the older (such as haloperidol) and second generation (such as risperidone, olanzapine, and quetiapine) antipsychotics[19] in terms of an increased risk of stroke and mortality[20] and a detrimental effect on cognition.[w22] Antipsychotic drugs have long been used to treat problem behaviours such as sexual disinhibition, wandering (often associated with agitation), swearing, and shouting. Other sedatives may be effective, as may β blockers, benzodiazepines, and carbamazepine.[w23] The evidence for efficacy is patchy, with few well described methodologically sound randomised controlled trials.

Drug treatment should be used with great caution, if at all, and general practitioners caring for patients with dementia should seek specialist advice about the management of behaviour and psychological symptoms in dementia. Recent trials using the cholinesterase inhibitor donepezil have shown conflicting results in its ability to improve behavioural problems[21] [w24] while rivastigmine may be beneficial in reducing behavioural symptoms in Lewy body dementia.[15]

Depression

Exercise may help reduce the symptoms of depression, and randomised controlled trials support the use of antidepressants. Newer selective serotonin reuptake inhibitors are the preferred class, rather than the older tricyclic agents, which have troublesome side effects.[w24]

Psychosis

Second generation antipsychotic drugs have been more extensively studied in prospective randomised controlled trials than the older tricyclics, but evidence has accumulated to show they have the same side effect profile and increased mortality rate as first generation antipsychotics, and both have been shown to be associated with more rapid cognitive decline.[22] Although the second generation antipsychotics reduce agitation, probably independently of a sedative effect, they seem to have little specific benefit on psychosis. Concerns over the safety of second generation antipsychotics led to a warning about their use for people with agitation in dementia, but their licence still allows for the treatment of psychosis. The NICE dementia guidelines recommend that if drug treatment is used, it should be at the lowest effective dose. The guidelines advise caution if using drugs to control behaviour, particularly if the person has been restrained, because of the risks of loss of consciousness instead of sedation, over-sedation with loss of alertness, and damage to the relationship between the person with dementia, their carers, and the care team.

Carers' needs

Loss of function and psychological and behavioural symptoms in people with Alzheimer's disease are sources of stress and a burden for carers. Some interventions reduce psychological morbidity in carers and help people with dementia stay at home longer; programmes that involve both the patients and their families and are more intensive and modified to carers' needs may be more successful.[23]

The PREVENT trial found significant improvements in care processes and outcomes for both people with dementia (increased prescribing of cholinesterase inhibitors and antidepressant drugs and fewer behavioural and psychological symptoms) and family carers (improved depression scores and higher carer satisfaction ratings).[24] Multicomponent interventions that included, for example, educational sessions, group support, and practical training were the most successful interventions for both people with dementia and their family carers.[23] [w25]

Is prevention of Alzheimer's disease possible?

Evidence is growing that some interventions may delay the onset of Alzheimer's disease. Predicting the onset of dementia is possible (table⇓). Prevention is a complex area: interventions with single agents (such as antihypertensive drugs or statins) are unlikely to result in a large scale reduction because many risk factors are involved and intervention studies would therefore be complex to design and execute. Whether interventions affect the core biological mechanisms of Alzheimer's disease or are mediated through reduction of vascular risk factors is unclear. For example, statins not only reduce cholesterol but also have, for example, antithrombotic and anti-inflammatory actions. Ageing and family history (genetic) factors are traditionally regarded as non-modifiable risk factors, but that view may be challenged by the avoidance of the effects of chronological ageing by lifestyle interventions and perhaps ultimately by gene therapy. Public interest in the possibility of preventing Alzheimer's disease is high (box 4).

> Newly developed scoring system based on mid-life vascular and non-vascular characteristics that predicts risk of dementia over 20 years. Adapted from Kivipelto et al[w26]
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Box 4 Seven signposts for a "brain healthy" lifestyle [w27]

- Keep your brain active
- Eat healthily
- Be physically active
- Manage your blood pressure, blood cholesterol, blood sugar, and weight
- Participate in social activities
- Avoid tobacco smoke and drink alcohol only in moderation
- Protect your head from injury

Conclusion

The ageing of populations in industrialised and developing countries makes Alzheimer's disease everybody's business. It requires all practitioners working with older patients to understand the insidious onset, main features, and impact of dementia and to be aware of the range of responses available.

Sources and selection criteria

We searched Medline and Pubmed from 2006 to September 2008, previous work having been summarised in the joint dementia guideline published by NICE and the Social Care Institute for Excellence in 2006. We searched the Cochrane database (2008 version) for randomised controlled trials for drug treatment and psychosocial interventions and used our own knowledge of the literature and selected authoritative reviews to supplement these sources.

Tips for the non-specialist

- History from a knowledgeable informant is as useful in the diagnosis of Alzheimer's disease as a direct interview with the patient

- Take care when discussing Alzheimer's disease or dementia—many people have seen a relative with a disease and will have their own preconception, often profoundly negative, of what the disease is

- It is always worth doing a physical assessment and routine blood tests in people with Alzheimer's disease—coexisting, easily treatable illness may be found

Additional educational resources

- Burns A, O'Brien J. Clinical practice with anti-dementia drugs: a consensus statement from British Association for Psychopharmacology. *J Psychopharmacol* 2006;20:732-55.

- Alzheimer's Society. *Dementia in the community: management strategies for primary care.* London: AS, 2006.

- Alzheimer's Australia. *Mind your mind: a user's guide to dementia risk reduction*. www.alzheimers.org.au/upload/MYM_book_lowres.pdf

Notes

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Footnotes

- Clinical Review, doi:10.1136/bmj.b75

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Modifiable Predictors of Dementia in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis
Claudia Cooper et al., American Journal of Psychiatry

Nonclassical Properties of Nonlocal Coherent Photon- Added Two-Mode Circular State
WANG Zhong-Jie et al., Journal of Sichuan University (Natural Science Edition)

Comprehensive Evaluation Model of Users’ Satisfaction Based on Gray Relational Analysis and AHP
CHEN Wei-Peng et al., Journal of Sichuan University (Natural Science Edition)

Yes No

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