Dementia

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## **Abstract**

[Dementia](https://www.sciencedirect.com/topics/medicine-and-dentistry/dementia) is an umbrella term for a number of progressive, [organic brain diseases](https://www.sciencedirect.com/topics/medicine-and-dentistry/organic-brain-syndrome) that affect approximately 850,000 people in the UK. Most [neurodegenerative diseases](https://www.sciencedirect.com/topics/medicine-and-dentistry/degenerative-disease) leading to dementia are characterized by processes that result in the aberrant polymerisation of proteins. A small proportion of individuals with these diseases develop dementia as a direct result of mutations or polymorphisms in genes influencing these processes. The most common cause of dementia is Alzheimer's disease. Other important causes include [vascular dementia](https://www.sciencedirect.com/topics/medicine-and-dentistry/vascular-dementia), [dementia with Lewy bodies](https://www.sciencedirect.com/topics/medicine-and-dentistry/diffuse-lewy-body-disease) and fronto-temporal dementia. The management of dementia largely focuses on helping patients and families to cope with increasing care needs as the disease progresses, and with the emergence of troublesome neuropsychiatric symptoms. Current pharmacological treatments are based on the neurochemical changes that are found in these diseases. [Cholinesterase inhibitors](https://www.sciencedirect.com/topics/medicine-and-dentistry/acetylcholinesterase-inhibitor) and N-methyl-D-aspartate receptor antagonists offer some help in ameliorating the inevitable cognitive decline found in Alzheimer's disease. However, the treatment of neuropsychiatric symptoms in dementia is still largely empirical and is hampered by either limited efficacy or troublesome adverse effects.

## **Keywords**

Alzheimer's disease

cognitive deficits

dementia

fronto-temporal dementia

dementia with Lewy bodies

vascular dementia

**Key points**

•Dementia is an umbrella term encompassing a range of organic brain diseases

•A large number of rare genetic polymorphisms affecting [cholesterol metabolism](https://www.sciencedirect.com/topics/medicine-and-dentistry/cholesterol-metabolism) and inflammatory pathways have been identified as risk factors for the development of late-onset Alzheimer's disease

•Early advice regarding lasting power of attorney, financial aid and local support networks for carers is an essential part of management

•Cholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonists have an important role in the [treatment of Alzheimer's disease](https://www.sciencedirect.com/topics/medicine-and-dentistry/treatment-of-alzheimers-disease)

•The drug treatment of neuropsychiatric symptoms is empirical but should follow the maxim ‘start low, go slow’

## **Definition**

[Dementia](https://www.sciencedirect.com/topics/medicine-and-dentistry/dementia) is an umbrella term for a range of progressive [organic brain diseases](https://www.sciencedirect.com/topics/medicine-and-dentistry/organic-brain-syndrome) characterised by problems with [short-term memory](https://www.sciencedirect.com/topics/medicine-and-dentistry/short-term-memory) and other [cognitive deficits](https://www.sciencedirect.com/topics/medicine-and-dentistry/cognitive-defect).

## **Epidemiology**

In 2014 it was estimated that there were some 850,000 people with [dementia](https://www.sciencedirect.com/topics/medicine-and-dentistry/dementia) in the UK.[1](https://www.sciencedirect.com/science/article/pii/S1357303916301670" \l "bib1) The main risk factor for dementia is age, with prevalence increasing exponentially after 60 years of age to around 20% at age 85 years. However, the incidence of dementia in the UK may now be reducing, possibly as a result of improved prevention of vascular disease and higher levels of education.

## **Aetiology**

The aetiology of [dementia](https://www.sciencedirect.com/topics/medicine-and-dentistry/dementia) is determined by the underlying causative disease. Most [neurodegenerative diseases](https://www.sciencedirect.com/topics/medicine-and-dentistry/degenerative-disease) that lead to dementia are often characterised by processes resulting in the aberrant polymerisation of proteins. A proportion of subjects with these diseases develop dementia as a direct result of mutations or polymorphisms in genes influencing these processes.

### **Alzheimer's disease (AD)**

Apart from increasing age, the strongest risk factor for AD is a positive family history, amounting to an approximately threefold higher risk in the first-degree relatives of patients with AD. Direct support for a genetic component to AD comes from the recognition that a small number of patients develop early onset AD (<65 years old) in an [autosomal dominant](https://www.sciencedirect.com/topics/medicine-and-dentistry/autosomal-dominant-inheritance) pattern.

To date, a number of mutations in three genes (amyloid precursor protein, [presenilin 1](https://www.sciencedirect.com/topics/medicine-and-dentistry/presenilin-1) and presenilin 2) have been described that lead to early-onset AD. These mutations have the same effect, which is the increased production of a longer version of [β-amyloid peptide](https://www.sciencedirect.com/topics/medicine-and-dentistry/amyloid-beta-protein) (42 amino acids compared with normal 40 amino acids); this aggregates to form a condensed core of [amyloid](https://www.sciencedirect.com/topics/medicine-and-dentistry/amyloid) protein that becomes surrounded by degenerating [neurites](https://www.sciencedirect.com/topics/medicine-and-dentistry/neurite). These relatively large extracellular structures are known as amyloid plaques and are a characteristic feature of both late-onset and inherited AD.

The amyloid cascade hypothesis postulates that β-amyloid peptide is the underlying cause of all the other neuropathological features of both late-onset and inherited AD. These include the formation of intracellular tangles made up of hyperphosphorylated [tau](https://www.sciencedirect.com/topics/medicine-and-dentistry/tau) protein, neuroinflammation, widespread neurochemical changes (including loss of [acetylcholine](https://www.sciencedirect.com/topics/medicine-and-dentistry/acetylcholine) and impaired glutamatergic neurotransmission) and ultimately neuronal cell death.

In late-onset AD genetic inheritance is largely the result of the common polymorphism apolipoprotein E ɛ4. Prevalence studies suggest that the presence of one copy of the [apolipoprotein E](https://www.sciencedirect.com/topics/medicine-and-dentistry/apolipoprotein-e) ɛ4 allele is associated with a threefold increased risk of developing late-onset AD, although possession of the apolipoprotein E ɛ4 allele is neither a necessary nor sufficient condition for the development of AD. However, large [genome-wide association studies](https://www.sciencedirect.com/topics/medicine-and-dentistry/genome-wide-association-study) have shown that, in addition to apolipoprotein E ɛ4, a large number of very rare [genetic polymorphisms](https://www.sciencedirect.com/topics/medicine-and-dentistry/genetic-polymorphism) involved in cholesterol and inflammatory processes are also appreciable risk factors for developing late-onset AD. One of these rarer polymorphisms is in TREM2 (triggering receptor expressed on myeloid cells 2), which causes a threefold increase in risk of late-onset AD. TREM2 is highly expressed on microglial cells and might play a role in regulating inflammatory processes in the brain. There is thus a growing body of evidence from animal, clinical and epidemiological studies that inflammation may play a key role in the aetiology and progression of late-onset AD.

Studies investigating environmental risk factors provide support for possible associations with [head injury](https://www.sciencedirect.com/topics/medicine-and-dentistry/closed-head-injury), a family history of depressive illness, mid-life hypertension, [diabetes](https://www.sciencedirect.com/topics/medicine-and-dentistry/diabetes-mellitus) and obesity, and for a possible inverse association with long-term non-steroidal anti-inflammatory use and years of education.

### **Vascular dementia (VaD)**

VaD usually develops from the cumulative effect of multiple [cerebral infarctions](https://www.sciencedirect.com/topics/medicine-and-dentistry/brain-infarction) (multi-infarct dementia) with an accumulating loss of neurons or axons. Less commonly, dementia can arise from single focal lesions or from widespread subcortical [ischaemia](https://www.sciencedirect.com/topics/medicine-and-dentistry/ischemia) affecting the white matter. A rare form of VaD, [CADASIL](https://www.sciencedirect.com/topics/medicine-and-dentistry/cadasil-syndrome) (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), has been found to be caused by inheritance of mutations in the NOTCH3 (neurogenic locus notch homolog protein 3) gene. However, most cases of VaD are sporadic and associated with the same risk factors as stroke and heart disease, i.e. hypertension, smoking, diabetes mellitus and [hypercholesterolaemia](https://www.sciencedirect.com/topics/medicine-and-dentistry/hypercholesterolemia).

### **Dementia with Lewy bodies (DLB)**

Individuals with DLB have [Lewy bodies](https://www.sciencedirect.com/topics/medicine-and-dentistry/lewy-body) in both cortical and subcortical regions. Lewy bodies are intracellular structures composed primarily of [α-synuclein](https://www.sciencedirect.com/topics/medicine-and-dentistry/alpha-synuclein) and [ubiquitin](https://www.sciencedirect.com/topics/medicine-and-dentistry/ubiquitin). Patients with DLB also have a variable burden of [amyloid plaque](https://www.sciencedirect.com/topics/medicine-and-dentistry/amyloid-plaque) pathology and, to a lesser extent, tau pathology. Like AD, DLB shows widespread [neuronal degeneration](https://www.sciencedirect.com/topics/medicine-and-dentistry/nerve-cell-degeneration). However, unlike AD, there is also neuronal loss in the [substantia nigra](https://www.sciencedirect.com/topics/medicine-and-dentistry/substantia-nigra) in DLB.

### **Fronto-temporal dementia (FTD)**

FTD is characterised by focal [cerebral atrophy](https://www.sciencedirect.com/topics/medicine-and-dentistry/cerebral-atrophy), principally involving the frontal, anterior parietal and temporal regions. All the variable clinical and pathological phenotypes share, to a greater or lesser degree, a non-Alzheimer-type histological profile. Approximately 25–50% of FTD is familial, making the genetic contribution to these diseases substantial. Three major [genetic loci](https://www.sciencedirect.com/topics/medicine-and-dentistry/gene-locus) have been identified, two situated on [chromosome 17](https://www.sciencedirect.com/topics/medicine-and-dentistry/chromosome-17), one linked to the tau gene and the other linked to [progranulin](https://www.sciencedirect.com/topics/medicine-and-dentistry/progranulin) and one loci on chromosome 9 linked to RNA regulation.

## **Diagnosis**

The diagnosis of [dementia](https://www.sciencedirect.com/topics/medicine-and-dentistry/dementia) largely depends on obtaining a good clinical history from the patient and a close informant. Physical examination should assess for [cardiovascular risk factors](https://www.sciencedirect.com/topics/medicine-and-dentistry/cardiovascular-risk), focal [neurological signs](https://www.sciencedirect.com/topics/medicine-and-dentistry/neurologic-disease) and [parkinsonism](https://www.sciencedirect.com/topics/medicine-and-dentistry/parkinsonism). Blood tests should be performed to exclude any reversible metabolic causes of [cognitive impairment](https://www.sciencedirect.com/topics/medicine-and-dentistry/cognitive-defect), such as vitamin B12 deficiency and hypothyroidism. The major differential diagnoses are [delirium](https://www.sciencedirect.com/topics/medicine-and-dentistry/delirium), [mild cognitive impairment](https://www.sciencedirect.com/topics/medicine-and-dentistry/mild-cognitive-impairment) and depressive illness. Delirium should always be considered when the presentation is acute.

### **Clinical features**

There are a large number of causes of [dementia](https://www.sciencedirect.com/topics/medicine-and-dentistry/dementia) ([Table 1](https://www.sciencedirect.com/science/article/pii/S1357303916301670#tbl1)), the most common being AD (approximately 60% all causes), [VaD](https://www.sciencedirect.com/topics/medicine-and-dentistry/vascular-dementia) (20%), DLB (5%) and FTD (2%). Importantly, although they are considered as discrete entities, these diseases are not mutually exclusive, and mixed pathologies are common.

[Short-term memory](https://www.sciencedirect.com/topics/medicine-and-dentistry/short-term-memory) impairment is usually the presenting complaint for AD, with patients having difficulty learning new information, such as names, shopping lists and details of conversations. Later on in the disease, [remote memories](https://www.sciencedirect.com/topics/medicine-and-dentistry/long-term-memory) are also affected. Other [cognitive deficits](https://www.sciencedirect.com/topics/medicine-and-dentistry/cognitive-defect) include [aphasia](https://www.sciencedirect.com/topics/medicine-and-dentistry/aphasia), [apraxia](https://www.sciencedirect.com/topics/medicine-and-dentistry/apraxia), [agnosia](https://www.sciencedirect.com/topics/medicine-and-dentistry/agnosia) and executive deficits. The onset of memory problems in AD is usually insidious and gradually progressive. In contrast, cognitive changes in VaD are classically of sudden onset with a stepwise progression, although a gradual decline with increasing cerebrovascular burden is perhaps more common in clinical practice.

Individuals with DLB and FTD may not have prominent memory difficulties in the early stages of the disease. Marked fluctuations in alertness and cognition, with visual hallucinations, motor symptoms of parkinsonism and REM (rapid eye movement) sleep behaviour disorder, are characteristic of DLB. When the onset of dementia occurs greater than one year after the onset of parkinsonism, a diagnosis of Parkinson’s disease dementia is made rather than DLB, although there is much overlap in clinical presentation. Individuals with FTD can present with one or more of several subtypes. Behavioural variant FTD is characterised by marked changes in personality, loss of inhibition, emotional blunting, and decline in social and personal conduct. Language variant FTD, also termed Primary Progressive Aphasia (PPA), encompasses the clinical syndromes of primary non-fluent aphasia (effortful, non-fluent speech with agrammatism), semantic dementia (fluent speech with anomia and impaired comprehension), and logopenic progressive aphasia (paucity of speech with anomia).

Neuropsychiatric symptoms are common in all subtypes of dementia, particularly as the dementia progresses. Mood symptoms including depression and [apathy](https://www.sciencedirect.com/topics/medicine-and-dentistry/apathy) are common in all dementias, and are particularly resistant to pharmacological treatment. Vivid, well-formed [visual hallucinations](https://www.sciencedirect.com/topics/medicine-and-dentistry/visual-hallucination), often of small people or children, are characteristic of DLB. Marked changes in personality are characteristic of behavioural variant FTD. All dementias can lead to agitation and aggression, mostly in severe disease. (see also Clinical assessment and investigation in psychiatry and Clinical assessment in [*old age psychiatry*](https://www.sciencedirect.com/topics/medicine-and-dentistry/psychogeriatrics) on pp 630–637 and pp 641–645 of this issue, respectively).

### **Investigations**

In persistent cognitive decline cognitive tests such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA), can be used to determine whether the degree of cognitive change is sufficient to make a diagnosis of dementia (see Table 5 of Clinical assessment and investigation in psychiatry on pp 630–637 of this issue). If there is uncertainty, more disease-specific [neuropsychological tests](https://www.sciencedirect.com/topics/medicine-and-dentistry/neuropsychological-test), for example tests of [frontal lobe](https://www.sciencedirect.com/topics/medicine-and-dentistry/frontal-lobe) executive functioning, can be beneficial, and a repeat examination several months later may be warranted.

Once a diagnosis of dementia has been determined, the specific cause needs to be established. Progress is being made in the development of specific biomarkers for the diagnosis, and even prediction, of AD; this includes [positron emission tomography](https://www.sciencedirect.com/topics/medicine-and-dentistry/positron-emission-tomography) (PET) imaging and [cerebrospinal fluid](https://www.sciencedirect.com/topics/medicine-and-dentistry/cerebrospinal-fluid) tests for [amyloid](https://www.sciencedirect.com/topics/medicine-and-dentistry/amyloid) and [tau](https://www.sciencedirect.com/topics/medicine-and-dentistry/tau) burden. However, AD is still diagnosed after other dementing illnesses or other conditions associated with memory impairment ([Table 2](https://www.sciencedirect.com/science/article/pii/S1357303916301670#tbl2)) have been excluded. A [computed tomography](https://www.sciencedirect.com/topics/medicine-and-dentistry/computer-assisted-tomography) (CT) or [magnetic resonance imaging](https://www.sciencedirect.com/topics/medicine-and-dentistry/magnetic-resonance-imaging) (MRI) [brain scan](https://www.sciencedirect.com/topics/medicine-and-dentistry/brain-scintiscanning) can help differentiate AD from VaD and other potentially treatable causes of dementia. A single-photon emission CT (SPECT) perfusion scan examining frontal and anterior [temporal lobe](https://www.sciencedirect.com/topics/medicine-and-dentistry/temporal-lobe) perfusion can be helpful in establishing the diagnosis of FTD, and a [dopamine transporter](https://www.sciencedirect.com/topics/medicine-and-dentistry/dopamine-transporter) scan (FP-CIT) ([Figure 1](https://www.sciencedirect.com/science/article/pii/S1357303916301670#fig1)) in determining the presence of DLB.

It is increasingly clear that there is a need for earlier diagnosis of dementia, as well as the development of new diagnostic criteria including the recognition of prodromal states of dementia such as mild cognitive impairment.

## **Management**

Initial assessment by a non-specialist should include an assessment of how the memory problem is impacting on the person's everyday life and ideally an objective cognitive assessment such as the MMSE. Early referral to a specialist team is key for early diagnosis and treatment. A holistic approach to management is important, considering physical co-morbidities such as pain and sensory impairment as factors that may worsen cognitive symptoms. Cessation of medicines that may cause cognitive impairment, such as anticholinergic drugs, should also be considered.

Management of dementia is largely focused on helping patients and families to cope with patients' increased dependence as the disease progresses and with the emergence of troublesome neuropsychiatric symptoms, such as agitation, [apathy](https://www.sciencedirect.com/topics/medicine-and-dentistry/apathy), psychosis or depression. However, despite improved public awareness of [dementia](https://www.sciencedirect.com/topics/medicine-and-dentistry/dementia), particularly AD, there is still great stigma attached to these diseases, and this can prevent some carers requesting help. The National Institute for Health and Clinical Excellence (NICE) recommend a range of interventions that promote cognition, independence and wellbeing, including group cognitive stimulation, reminiscence therapy and occupational therapy. Carers should be educated in using [reassurance](https://www.sciencedirect.com/topics/medicine-and-dentistry/reassurance) and redirection as techniques to help manage behavioural symptoms.

Patients with dementia are at risk of financial and physical abuse, including neglect. Therefore early advice regarding financial benefits, lasting power of attorney, adult social care and signposting to local support networks is essential. Commonly used approaches include community psychiatric nurse and domiciliary support, day care and respite care. Institutional care is usually reserved for patients with more severe physical or persistent neuropsychiatric symptoms. Robust risk and capacity assessments are necessary in all cases, particularly when assessing whether an individual with dementia is unable to remain at home safely due to risks of self-neglect or vulnerability.

### **Drug treatments**

Current treatment options for the [cognitive deficits](https://www.sciencedirect.com/topics/medicine-and-dentistry/cognitive-defect) seen in AD consist of [acetylcholinesterase inhibitors](https://www.sciencedirect.com/topics/medicine-and-dentistry/acetylcholinesterase-inhibitor), which increase the amount of available [acetylcholine](https://www.sciencedirect.com/topics/medicine-and-dentistry/acetylcholine) in the brain, and N-methyl-D-aspartate receptor antagonists, which modify glutamatergic neurotransmission.[2](https://www.sciencedirect.com/science/article/pii/S1357303916301670" \l "bib2) In the UK, these treatments currently include [donepezil](https://www.sciencedirect.com/topics/medicine-and-dentistry/donepezil), [rivastigmine](https://www.sciencedirect.com/topics/medicine-and-dentistry/rivastigmine) and [galantamine](https://www.sciencedirect.com/topics/medicine-and-dentistry/galantamine) for patients with mild to moderate Alzheimer’s disease, with the addition of, or replacement with, [memantine](https://www.sciencedirect.com/topics/medicine-and-dentistry/memantine) for patients with moderate to severe disease. These drugs are supported by NICE[3](https://www.sciencedirect.com/science/article/pii/S1357303916301670" \l "bib3) and appear to temporarily delay [cognitive deterioration](https://www.sciencedirect.com/topics/medicine-and-dentistry/mental-deterioration) as well as treating behavioural symptoms. NICE also supports use of donepezil or rivastigmine in people with mild to moderate dementia with Lewy bodies. However, these drugs are not effective for either VaD or FTD.

In [dementia](https://www.sciencedirect.com/topics/medicine-and-dentistry/dementia), the use of specific drugs for the pharmacological treatment of neuropsychiatric symptoms is still largely empirical and is based on the treatment of psychiatric illness in a younger population and the avoidance of drugs with marked [anticholinergic](https://www.sciencedirect.com/topics/medicine-and-dentistry/parasympatholytic) properties. Thus, the treatment of depressive symptoms is with non-tricyclic antidepressants, for example [selective serotonin reuptake inhibitors](https://www.sciencedirect.com/topics/medicine-and-dentistry/selective-serotonin-reuptake-inhibitor). However, there is little supportive evidence for their use.[4](https://www.sciencedirect.com/science/article/pii/S1357303916301670" \l "bib4)

The treatment of psychotic symptoms is with a second-generation or ‘atypical’ antipsychotic such as [risperidone](https://www.sciencedirect.com/topics/medicine-and-dentistry/risperidone). For aggressive symptoms in dementia, the pharmacological treatment options include second-generation [antipsychotics](https://www.sciencedirect.com/topics/medicine-and-dentistry/typical-antipsychotic), non-tricyclic antidepressants or, in resistant cases, [anticonvulsants](https://www.sciencedirect.com/topics/medicine-and-dentistry/anticonvulsant) (e.g. carbamazepine). Agitated behaviours in AD are treated with second-generation antipsychotics, non-tricyclic antidepressants or, in resistant cases, short-acting [benzodiazepines](https://www.sciencedirect.com/topics/medicine-and-dentistry/benzodiazepine), but only for a short period of time. However, the use of first- and second-generation antipsychotic medication has been shown to be associated with marked extrapyramidal adverse effects, increased stroke risk and increased mortality in patients with dementia, so should be avoided if possible or be used for only short periods (up to 6 weeks).[5](https://www.sciencedirect.com/science/article/pii/S1357303916301670" \l "bib5) Patients with DLB are particularly sensitive to antipsychotics as they can develop severe [parkinsonism](https://www.sciencedirect.com/topics/medicine-and-dentistry/parkinsonism) and sedation, so it is best to avoid their use.

Overall, treatment responses vary markedly, and in practice the choice of one drug class over another is more limited by the emergence of treatment-specific adverse effects than clear efficacy of one drug over another. It is often difficult to determine in advance the amount of medication needed, and the best treatment advice is to start with [low doses](https://www.sciencedirect.com/topics/medicine-and-dentistry/low-drug-dose) (one-quarter to one-half the adult dosage) and titrate slowly upwards until a treatment response occurs. Not all patients respond, so after trying different approaches, a partial response with institutionalised care may be the only realistic alternative.

**Causes of** [**dementia**](https://www.sciencedirect.com/topics/medicine-and-dentistry/dementia)

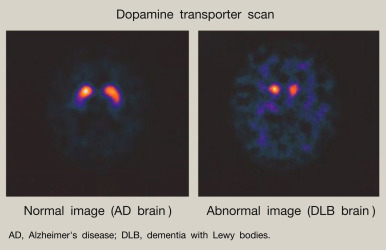
|  |
| --- |
| •Alzheimer's disease  •Vascular dementia  •Dementia with Lewy bodies  •Fronto-temporal dementia  •Parkinson's disease  •Alcohol  •Huntington's disease  •Creutzfeldt–Jacob disease  •HIV  •Multiple sclerosis  •Neurosyphilis  •Normal-pressure hydrocephalus  •Chronic subdural haematoma  •Cerebral tumours  •Hypothyroidism  •Progressive supranuclear palsy  •Tuberculosis  •Wilson's disease |

**Table 1**

**The differential diagnosis of late-onset AD**

|  |
| --- |
| **Other conditions associated with memory loss**  •Age-associated mild memory impairment  •Mild cognitive impairment  •Depression  **Other common dementing illnesses**  •VaD  •DLB  •FTD  **Potentially treatable but rarer causes**  •Vitamin B12 and folate deficiencies  •Normal-pressure hydrocephalus  •Hypothyroidism  •Neurosyphilis |

**Table 2**



**Figure 1**

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