

Understanding Alzheimer's disease

It has been 100 years since the features of Alzheimer's disease were first described. Since then our understanding of it has increased but there is still no cure. In this article, Alan Worsley and Andrew Husband outline how the disease is currently managed



Depending on the severity of the dementia, people with Alzheimer's disease may not be able to recognise themselves

Alzheimer's disease (AD) is a chronic neurodegenerative disorder and the fourth leading cause of death in developed countries after heart disease, cancer and stroke. This disease is the leading cause of dementia in the elderly — incidence in 60–64 year olds is approximately 1 per cent but this increases to 40 per cent in those aged 85 and over.¹ The symptoms of AD were first identified by the German psychiatrist Emil Kraepelin in individuals between the ages of 45 and 65 years. These include progressive memory loss and cognitive functional decline. In the later stages of the disease, patients become unable to perform activities of daily living (eg, brushing teeth, tying shoe laces, etc). Such inactivity results in reduced musculature and is likely to lead to residential care. Most patients also experience behavioural (eg, sleeplessness, aggression and apathy) and psychiatric (eg, delusions and hallucinations) problems.

Various risk factors have been suggested for AD (see Panel 1). Although not all have good supporting evidence, pharmacists could advise on risk reduction measures, such as giving up smoking.

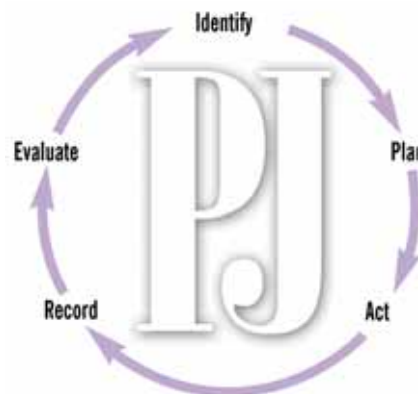
Diagnosis

Diagnosis must be made in a specialist clinic and requires a combination of taking a medical history, observation and assessing intellectual function and memory. Assessment usually includes a mini mental state examination (MMSE). This tool was discussed in a CPD article on dementia (*PJ*, 11 November, p579–82). Other assessment tools for AD include the Alzheimer's disease assessment scale (ADAS) and the Blessed test of information, memory and concentration.

The ADAS scale comprises a cognitive and non-cognitive portion. It takes about 45 minutes to perform. The cognitive portion (ADAS-Cog), covers a large range of cogni-

Panel 1: Risk factors for Alzheimer's disease

- Increasing age
- Being female
- Family history
- Head injury
- Parkinsonism
- Hypothyroidism
- Exposure to dietary aluminium
- Cardiovascular disease
- Smoking
- High alcohol intake



Identify knowledge gaps

1. What are the biochemicals involved in Alzheimer's disease?
2. What are the treatments available for Alzheimer's disease and what is the latest NICE guidance on treatment?
3. What advice could you give on preventing Alzheimer's disease?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "common disease states" and (see appendix 4 of "Plan and record").

tive areas, including memory and language. The non-cognitive portion investigates psychosis, agitation and depression. ADAS-Cog is probably the most widely used cognitive assessment instrument for clinical trials of drugs for dementia in the US. It is also used in Japan and Europe.

Specialists can only make a probable diagnosis — an absolute diagnosis requires autopsy to confirm the presence of distinct microscopic features in the brain. However, clinicians with expertise in memory loss are able to diagnose AD to within 80–90 per cent accuracy. Neuroimaging can support a diagnosis.

Depending on the symptoms, the disease can be categorised as mild, moderate or severe (see Panel 2, p644). Initially, the only sign of AD may be mild forgetfulness which can go unnoticed. People often get more forgetful with age. However, if the disease is present, memory loss increases and is accompanied by other symptoms which cause people to seek medical advice.

Average survival from the time of diagnosis is eight to 10 years. AD is a progressive disorder so an early diagnosis is important to allow the care of the patient to be planned. This includes aspects such as modifying the patient's

Panel 2: Severity of dementia in Alzheimer's disease

Mild Symptoms may be so slight that they are not noticed by relatives. Patients tend to be less energetic and slightly "forgetful" (MMSE score 21–26).

Moderate Signs include aphasia, memory loss and difficulty with language (eg, problems with reading or writing) but patients may still manage daily activities (MMSE score 10–20).

Severe Patients have difficulty performing daily tasks, such as brushing their teeth or tying shoe laces. Patients may fail to recognise friends and family (MMSE score < 10).

Case Mrs AA is an 80-year-old widow brought to her GP surgery by her daughter, who says that her mother becomes regularly confused during telephone conversations. Her friends at bingo say that she has difficulty "doing the cards" and has memory lapses. Mrs AA scored 22 in a MMSE. She was able to recall one of three objects after five minutes. She was unable to draw a clock and also did not know the date.

home environment and lifestyle, and investigating care options. Home modifications can range from making sure there are emergency numbers near the telephone and replacing everyday objects with those designed for people with motor skill deficiencies, to using more calendars, clocks and labels (to improve orientation to time) and fitting a downstairs bathroom. Lifestyle modifications can include wearing an identity bracelet and getting into a regular routine in terms of meals, exercise, personal hygiene and medicines — having a routine means that the patient does not have to think about what to do next and can prolong his or her independence. Moreover, early diagnosis allows the patient to take part in the planning of his or her own care (eg, patients may want to document their wishes) and everyone involved to learn about the disease.

Pathology

AD has both microscopic and biochemical features.

Microscopy The distinct microscopic features of AD were first described by Kraepelin's research assistant, Alois Alzheimer in 1906, on examining brain tissue in autopsy. As described in a previous article (*PJ*, 11 November, p580), AD is associated with the presence of amyloid plaques (due to the accumulation of beta-amyloid protein) and neurofibrillary tangles (due to hyperphosphorylation of tau proteins). These features result in neuronal death in the cortical and subcortical brain regions.

Biochemistry The oldest hypothesis associated with AD is the cholinergic hypothesis. This attributes declining memory and learning ability to a deficit of acetylcholine, with impaired attention due to excesses of excitatory amino acids, the main one being glutamate. Various inflammatory pathways have also been implicated in AD. It has been proposed that prostaglandin pathways and cytokines (interleukin-1, IL-6 and TNF-alpha) are associated with neuronal damage.

Acetylcholine Acetylcholine is a neurotransmitter that effects cognition by acting on cholinergic receptors. The central nervous sys-

Panel 3: Global clinical state

A patient's "global clinical state" is the impression he or she gives a clinician (in terms of cognitive and non-cognitive functioning; ie, global functioning). This can be assessed using the clinical global impression of change scale. This is a three-part scale that looks at the severity of illness, improvement and drug efficacy.

tem contains two known types of cholinesterase enzyme, acetylcholinesterase and butyrylcholinesterase, both of which are involved in the degradation of acetylcholine in normal and diseased brains. As AD progresses and cholinergic neurones degenerate, there is a decrease in acetylcholine levels — the activity of acetylcholine decreases by 30–45 per cent. And, in direct response to the reduction, levels of acetylcholinesterase also decline. However, butyrylcholinesterase activity increases by 40–90 per cent. Current AD therapy attempts to prevent the breakdown of acetylcholine by inhibiting cholinesterases.

Glutamate Glutamate is the major excitatory neurotransmitter of the CNS. Disturbances in L-glutamate biochemistry may be responsible for the pathogenic mechanisms of AD. L-Glutamate is also associated with learning processes. One of the key glutamate receptors is called NMDA, named after its selective ligand N-methyl-D-aspartate. Once glutamate binds to an NMDA receptor, calcium ion channels are opened in the neurone, causing excitation. Developed NMDA antagonists are deemed neuroprotective because they prevent glutamate activity before it can overstimulate neurones. Overstimulation causes damage.

Treatment

Four drugs are approved for the treatment of dementia of AD in the UK: donepezil, galantamine, rivastigmine and memantine. The first three are cholinesterase inhibitors and memantine is an NMDA receptor antagonist. All of these drugs must be started under specialist care.

The use of cholinesterase inhibitors in AD is based on the cholinergic hypothesis. It is presumed that these drugs prolong the duration of released acetylcholine in synapses. Donepezil and galantamine are specifically active on acetylcholinesterase, whereas rivastigmine acts also on butyrylcholinesterase. The most common side effects are cholinergic, namely, nausea, vomiting, diarrhoea and anorexia. These can be a particular problem because many patients with AD lose weight. However, tolerance to these adverse effects normally develops. To prevent side effects dose titration is required on starting therapy and retitration may be advisable if drug therapy is substantially interrupted.

Donepezil and galantamine are metabolised by cytochrome P450, CYP2D6 and CYP3A4, respectively, and could potentially interact with cytochrome P450 inhibitors, such as fluoxetine and paroxetine, exacerbating cholinergic side effects.

The efficacy of these three cholinesterase inhibitors has been studied in more than 30 randomised controlled trials, with a mean duration of three to six months. Most of these trials have demonstrated a modest improvement in cognitive symptoms, with mean improvements of 1.4 points in the MMSE and 2.7 points on the ADAS-Cog.¹ Some studies demonstrate a beneficial effect for up to two years after starting treatment. There are no

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Panel 4: NICE guidance update

This month, the National Institute for Health and Clinical Excellence issued a review of its guidance on the use of donepezil, rivastigmine and galantamine in patients with Alzheimer's disease. This states that these drugs should only be made available for people with moderate AD and that treatment should only continue if the patient's MMSE score remained above 10 at six-monthly check-ups. NICE previously cited "limited and largely inconclusive evidence on outcomes that are important to carers, such as quality of life and time to admission to a nursing home" for this decision, which met with opposition from groups such as the Royal College of Psychiatrists.

The guidance means that patients with newly diagnosed AD are unlikely to be prescribed anticholinesterases on the NHS unless they meet the NICE criteria. Patients being treated with these drugs before the guidance was published may still be prescribed them even if they do not meet the criteria. However, according to joint guidance from NICE and the Social Care Institute for Excellence, published this week, these drugs can also be offered to patients if non-cognitive symptoms are causing significant distress and other treatments have not worked or are not suitable.

Current annual costs for these drugs range from £800 to £1,000 per patient.

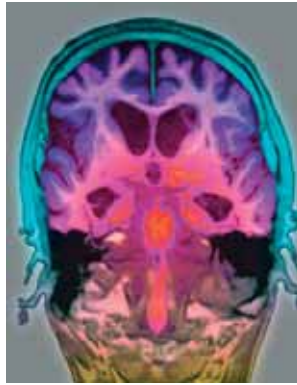
studies of longer periods of medication but most patients can expect that, in time, they will stop responding to treatment as the disease progresses. If tolerance develops, some prescribers recommend a "drug holiday" (eg, the drug is stopped for six weeks and then started again, by retitration).

Patients who are prescribed drugs for AD should be reassessed two to four months after reaching a maintenance dose. European guidelines suggest that drugs used to treat AD should be assessed by monitoring symptom improvement in three domains: cognition, activities of daily living and overall clinical response.

Donepezil A recent Cochrane review identified 24 clinical trials with over 5,000 patients treated with donepezil for six to 12 months. Patients in 20 trials had mild to moderate disease, in two trials moderate to severe disease and in two trials severe disease. People with mild, moderate or severe dementia treated for 12, 24 or 52 weeks with donepezil experienced benefits in cognitive function, activities of daily living and behaviour. Study clinicians rated global clinical state (see Panel 3) more positively in treated patients, and measured fewer declines in measures of disease severity. Donepezil has demonstrated in the short term (six months) a beneficial effect on mood and behaviour.

Galantamine Originally isolated from a species of snowdrop, galantamine was approved for use in the UK in 2000 for mild to moderate dementia in AD. It is a reversible inhibitor of acetylcholinesterase and enhances the action of acetylcholine at nicotinic receptors. To date, galantamine has, in six published RCTs, shown some benefit in improving cognitive function and global state. These effects are dose-dependent with higher doses demonstrating greater effects. The published trials demonstrated mixed effects on mood and behaviour.

Reports have been made suggesting that regulatory authorities have been reviewing data that suggested that galantamine was associated with increased mortality among patients with mild cognitive impairment.²



Alzheimer's disease causes loss of brain mass, seen here as four enlarged ventricles and deep indentations around the brain

Sovereign/ISM/Science Photo Library

Blood test latest

Last month, researchers at King's College, London, announced that they had found two biochemical markers for Alzheimer's disease. Patients with the disease have elevated blood levels of two proteins (complement factor H and α -2-macroglobulin).

This discovery could finally lead to a blood test that can be used to diagnose the disease and measure disease progression.

Further details are available at www.iop.kcl.ac.uk

Rivastigmine In theory, rivastigmine has a therapeutic advantage over donepezil and galantamine because of its action on butyrylcholinesterase. To date, however, the clinical significance of this dual mode of action has not been demonstrated. Rivastigmine does not depend on cytochrome P450 metabolism and thus has less potential for drug interactions. To date, four published RCTs have demonstrated that rivastigmine improves cognitive and global outcomes. This effect may be dose-related. There were no reported improvements in behaviour and mood.¹

Rivastigmine is also licensed to treat dementia in Parkinson's disease.

Memantine Memantine has been licensed for use in AD in Europe for over 10 years. Of the four drugs available in the UK, it is the only one to be licensed to treat moderate to severe AD. Memantine acts as an uncompetitive NMDA antagonist and so stabilises neuronal membranes.

Three studies in the past 15 years have demonstrated in over 800 patients with moderate to severe AD that doses of memantine 10 to 20mg daily for three to six months have improved patients behavioural and overall global impressions of change.³

According to the National Institute for Health and Clinical Excellence, cholinesterase inhibitors for AD should only be used in patients with moderate AD and be continued only if the MMSE score does not fall below 10 (see Panel 4 for guidance issued this month). In addition, NICE says that memantine should only be used as part of clinical studies. However, access to such studies can be difficult. Information on ongoing trials within the UK is available from the Alzheimer's Society.

There are no guidelines to recommend one drug over the others but prescribing considerations include compliance issues. For example, only donepezil and modified-release galantamine can be taken once a day.

Other treatments Other treatments for AD that have been tried include selegiline, vitamin E and *Ginkgo biloba*. The monoamine oxidase B inhibitor selegiline is not licensed for use in AD but it has been prescribed. There have been reports of increased MAOB in the brains of patients with AD, and MAOB inhibition was suggested to be effective in reducing oxidative stress and consequent lipid peroxidation and neuronal damage. However, according to a recent Cochrane review no clear benefit with selegiline has been established.

The major investigation into the use of vitamin E in AD is the AD co-operative study, which examined the use of selegiline 10mg *od* or 1,000iu vitamin E *bd*, or both. Authors established that, after adjusting for differences between patient groups, there was insufficient evidence to support the use of Vitamin E in AD.⁴

Dried extract of *Ginkgo biloba* (Egb 761) has been approved in Germany for the treat-

ment of dementia. Clinical trials have shown that Egb 761 (a formulation of 24 per cent Ginkgo leaf extract) taken three times daily produced a modest improvement in cognitive scores, but not in global state.⁵ Further studies are required.

Future treatments With our increased understanding of the pathways involved in AD, several future treatments are being studied.

Flurbiprofen R-Flurbiprofen is currently included in clinical trials for the treatment of AD. The R-enantiomer does not inhibit either cyclo-oxygenase-1 or COX-2 enzymes. While demonstrating no COX activity, R-flurbiprofen at a dose of 400 to 800mg twice daily has been shown to reduce levels of beta-amyloid protein. Phase II clinical trials are in progress.

Cytokine therapy In response to recent findings that TNF-alpha is associated with neuronal damage, etanercept has been administered as an intrathecal dose at 25–50mg weekly for six months to 15 participants with mild to severe AD. Patients have demonstrated improvements in MMSE and ADAS-Cog.

Paclitaxel The use of paclitaxel, the microtubular binding drug primarily used in ovarian cancer, has been considered in AD patients. In a similar way to the tau protein, paclitaxel has demonstrated some effects on the stabilisation of microtubules within the neurone, and it is hoped that it may be used as a future treatment for AD, despite the fact that it does not cross the blood-brain barrier.

Xaliproden Xaliproden (SR57746A), a non-peptide drug that mimics nerve growth factor, is currently undergoing clinical trials for AD.

Tramiprosate Tramiprosate (Alzhemed) selectively binds to soluble beta-amyloid protein and thus interferes with its abnormal accumulation of this protein and consequences such as plaque formation. In a double blind trial 42 patients, who had previously received cholinesterase inhibitors, were given tramiprosate 150mg *bd* for 36 months. Levels of cerebrospinal fluid beta-amyloid protein were reduced and declines in MMSE scores were described as being modest (five points over three years). Tramiprosate is still in developmental stages.

Behavioural and psychiatric problems Nearly all patients with dementia will develop changes in behaviour and personality (eg, agitation, aggression and wandering), generally in the later stages. Psychotic features associated with dementia may be present in as many as 75 per cent of patients.

The acetylcholinesterase inhibitors have been associated with a reduction in behavioural disturbances in patients with AD. However, some patients may not achieve satisfactory levels of control with these agents alone. The recommended strategy for behav-

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Make sure you know what to advise if a patient misses a dose of a cholinesterase inhibitor (see patient information leaflets). What if seven doses are missed?
2. Practice explaining a dose titration in simple language.
3. People with AD can have all sorts of eating problems (weight loss is common in advanced dementia). In addition, there have been many items in the media regarding how some foods (eg, fish and folate-rich foods) can help prevent dementia. Research this with a colleague and form and opinion on the advice you would give.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

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our disorders in AD is sequential monotherapy. Once treatment has been initiated, reassessment should be performed at three- to six-month intervals. Behavioural disturbances can be assessed with scales like the behavioural pathology in Alzheimer's disease scale (BEHAVE-AD).

The first-line treatment for psychotic symptoms in AD patients is an atypical antipsychotic. These are associated with fewer extrapyramidal effects than conventional antipsychotics. Atypical antipsychotics should be initiated at the lowest effective dose and titrated weekly. Carers and physicians should be aware of the development of dystonias and dyskinesias. Dosing in the evening with once daily atypical antipsychotics can help patients who have problems sleeping. Although atypical antipsychotics are first line, haloperidol has been used to get initial control of behavioural disorders. It should be used at low doses for short periods (days), after which a patient should be transferred to an atypical antipsychotic.

Anticonvulsants such as carbamazepine are recommended as second-line treatments when patients fail to respond to antipsychotics. Short-term trials have shown that anticonvulsants are well tolerated and effective.

Antidepressants (usually selective serotonin reuptake inhibitors) and anxiolytics are also prescribed. Small studies have demonstrated beneficial effects with trazodone and citalopram. See also Panel 4, p645.

Conclusion

One of the most useful things pharmacists can do in terms of AD is make sure they understand the disease and the available treatments so that they can provide support for patients and carers.

The summaries of product characteristics for all four drugs licensed for AD specify that therapy should only be started if a carer is available to monitor the patient's medication regularly, and it is often the carer whom the pharmacist will deal with. However, in the early stages of the disease, pharmacists may have contact with patients. It is important, in such situations, for pharmacists to make sure that they give explanations in simple language and, if giving instructions on how to take medicines, simplify them by breaking them down into steps.

In addition to explaining treatments to patients and their carers, pharmacists can also offer advice on compliance aids and strategies. For example, the patient could use a weekly medicine organiser with a built in alarm or he or she could put a note in the bathroom or kitchen as a reminder to take medicines. Finally, an awareness of non-drug management strategies, such as keeping a regular routine, can also be useful information for pharmacists to pass on.

Resource

A range of practical factsheets about dementia is available on the Alzheimer's Society website www.alzheimers.org.uk