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Drug treatments for Alzheimer’s disease

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This article discusses the development and progress of treatment for Alzheimer’s disease. Medical treatments have not changed since the late 1990s and have limited effects. They treat the symptoms patients experience but do not reverse the effects or repair neurological damage caused by Alzheimer’s disease.

Keywords: Alzheimer’s disease/Dementia/Drug therapy

No new drugs have been approved to treat Alzheimer’s disease since the late 1990s; this article discusses the problems this poses and the efficacy of these drugs...

...and the implications for future treatment.

In the mid-1990s, drugs became available that improved cognitive function in Alzheimer’s disease (AD), leading to a sense of optimism that finally something could be done to help people with the disease. However, the treatments have limited efficacy (Langtot et al., 2003) and no new drugs have been licensed for over 10 years.

The promise of improvements in cognitive functioning has helped reduce the negativity around the diagnosis and management of Alzheimer’s, contributed to more people being diagnosed early and changed the direction of service development. However, the availability of these drugs may have resulted in AD treatment being prioritised over that for other forms of dementia and over the later stages of dementia, where the drugs are less useful (Pelosi et al., 2006). Many memory clinics provide a different, less supportive pathway for people with other types of dementia, particularly vascular.

More recently, national dementia strategies have increased the emphasis on early recognition and diagnosis of dementia, leading to these drugs being more widely prescribed.

**Drugs licensed for Alzheimer’s**

The first drug licensed for the treatment of the cognitive symptoms of AD in the UK was the cholinesterase inhibitor donepezil (Aricept), which was licensed in 1997. Donepezil was closely followed by two more cholinesterase inhibitors, rivastigmine (Exelon) and galantamine (Reminyl).

These drugs were developed based on the theory that cognitive deficits associated with AD are due to reduced production of acetylcholine, a neurotransmitter. Cholinesterase inhibitors work by slowing down the breakdown of acetylcholine, leading to higher levels in the brain (Fig 1).

Memantine (Ebixa), an N-methyl-D-aspartate (NMDA) receptor antagonist, was approved in 2002 for the treatment of more severe AD. It appears to work through a different neural pathway, by blocking glutamate receptors, preventing excessive levels of glutamate from further damaging brain cells (Fig 2).

**Guidelines**

When these drugs were first made available, many areas were reluctant to fund them as the benefits were thought not to justify the cost.

Reviewing the evidence for the use of cognitive enhancers, the National Institute for Health and Care Excellence (2006) found little difference between cholinesterase inhibitors and recommended they were used only in the treatment of...
moderate AD. NICE did not recommend the use of memantine other than in research.

However, an updated guideline recommended donepezil, galantamine and rivastigmine for mild as well as moderate AD; memantine was recommended for moderate AD in people unable to take cholinesterase inhibitors, and as an option for severe AD (NICE, 2011).

A Cochrane review concluded that, despite slight variations in the actions of the different cholinesterase inhibitors, there was no evidence of any differences in efficacy (Birks, 2006). The drugs do differ in how and when they are administered; for example, rivastigmine can be given by a skin patch that is changed once a day or as an oral suspension as an alternative to twice-daily tablets for people who have difficulty swallowing. Galantamine is usually prescribed twice daily though there is now a modified-release form, which is taken once a day. Donepezil has a longer half-life, so is given only once daily.

How effective is ongoing treatment?

There are no clear guidelines on how long cholinesterase inhibitors should be continued as well as a lack of any long-term trials. Statements from NICE and other sources tend to rely on cognitive testing (NICE, 2011), but the benefits of treatment should be based on quality of life, which is more difficult to measure.

Although medication is less likely to be of benefit when impairments are more advanced, discontinuing treatment has been linked with a decline in mental state (Rainer et al, 2001).

A Cochrane review concluded that memantine has a definite but small beneficial effect after six months in later-stage AD, but no effect in mild to moderate disease (McShane et al, 2006).

While cognitive enhancers have led to improvements that can be measured in cognitive testing, their benefits in terms of global functioning are less clear. There is evidence of improvements in general functioning and behaviour as well as in cognitive benefits in some patients, but it is difficult to predict who will respond in this way, and average improvements tend to be small (Raina et al, 2008). Claims that cognitive enhancers lead to later admission into institutional care have not been consistent (AD2000 Collaborative Group, 2004).

Ongoing studies are looking into the effects of combining treatments. Early evidence shows no convincing benefit of combining memantine with a cholinesterase inhibitor (Howard et al, 2012). Cholinesterase inhibitors may also be useful in the management of dementia associated with Parkinson’s disease. Although only rivastigmine is licensed for this purpose, the benefits are likely to be due to the class effect of this group of drugs, so donepezil and galantamine are...
likely to have similar effects. Similarly, anecdotal evidence suggests cholinesterase inhibitors reduce some symptoms associated with Lewy body disease, such as hallucinations, although this use is unlicensed.

Various other drugs and supplements have been assessed as possible treatments for AD, including gingko biloba, indomethacin, vitamins E and B12, folic acid, selegiline and metrifonate; there is no convincing evidence of benefit for any of them.

To date, licensed treatments for AD treat only symptoms; they can help with the cognitive, behavioural and functional aspects of the condition but do not alter the disease process. The evidence that treatments also help with other symptoms associated with AD, including aggressive or agitated behaviour and hallucinations, is inconsistent, although there appears to be little doubt in clinical practice that some patients show benefit.

NICE (2011) recommends that treatment with cognitive enhancers should be started by a specialist, but does not define what this means. At present this is usually a psychiatrist, and it takes place almost entirely in secondary care. This may need to be reviewed due to increasing numbers of people being diagnosed with AD and a rising number of older people.

As these drugs are coming off licence, cheaper generic production is likely to reduce costs, so the benefits are more likely to outweigh financial implications.

**Side-effects**

Although cholinesterase inhibitors are largely well tolerated, they have a range of side-effects. Some, such as restlessness and gastrointestinal symptoms, are largely transient; others, such as syncope, agitation, insomnia, bradycardia, persistent rhinitis and muscle cramps, can be more debilitating and lead to the medication being stopped.

Gill et al (2009) reviewed the risk these drugs pose in relation to more serious effects such as syncope, bradycardia, the need for pacemaker insertion and hip fracture. Although these are uncommon events, the authors suggest that as these drugs provide only a modest benefit, practitioners should think carefully about whether the benefits outweigh the risks before prescribing them. Some authorities advocate the use of ECGs before prescribing; however, a review of the evidence concluded this was of no benefit (Rowland et al, 2007).

Memantine has generally been found to be well tolerated, although reported side-effects include agitation, hypertension, headaches and constipation.

**Future treatment**

The drugs available for the treatment of AD are of limited clinical benefit and more effective treatments that change the course of the illness are needed. Research focuses largely on two areas:

- Reducing the amount of abnormal amyloid in the brain (which leads to amyloid plaques);
- Reducing the deposition of tau protein, which is a substantial part of the neurofibrillary tangles also seen in the illness.

In theory, statins might be useful in slowing down the progress of AD. However, research has shown no benefits in cognitive impairment despite some changes in amyloid deposition (McGuinness et al, 2013). There have been some suggestions that statins might delay or prevent the onset of AD, but the evidence is unclear (McGuinness et al, 2009).

One promising line of research was the use of monoclonal antibody bapineuzumab, which reduces the amount of abnormal amyloid in the brain. However, two large trials were aborted in 2012 due to participants already having substantial damage that could not be reversed.

Future studies are likely to involve patients in the early stages of the disease. In 2008, optimistic claims were made on a website not subject to peer review following a trial of Rember, a derivative of the dye methylene blue. At the time of writing, there have been no reports in peer-reviewed journals, but phase 3 trials in frontotemporal dementia are about to start.

More recently, there have been promising results from the use of an intravenous immunoglobulin (Relkin et al, 2009), but trials have been small. If this does prove to be effective, the logistics of giving this intravenous treatment will present a major challenge.

**Conclusion**

For any breakthrough in the treatment of AD, disease-modifying drugs are needed. However, the biological causes that lead to neuronal loss in AD are not fully understood. We also lack an understanding of when the disease process starts, who will develop it, and how it will progress in different people.

Further research is also needed into the relationships between normal cognitive ageing, mild cognitive impairment and AD. The process that causes cognitive impairment in AD is likely to start years or even decades before deficits are noticed.

Effective treatments will therefore depend on being able to recognise people at high risk. While genetic studies may help with this, particularly in cases where dementia develops at an early age, the development of this type of pre-emptive treatment relies on recognition of detectable biomarkers (Galimberti and Scarpini, 2013; Dubois et al, 2010). NT

**References**


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