Donepezil — a major breakthrough in the treatment of Alzheimer’s disease

The acetylcholinesterase inhibitor Donepezil had a major impact on the lives of patients with Alzheimer’s disease but right from the start there were budgetary concerns. In this month’s “Landmark drugs” article, Jenny Bryan looks at donepezil and the future of it and other AChE inhibitors.

Launched in the UK in 1997, the Alzheimer's disease treatment donepezil (Aricept) is among the youngest drugs in this “Landmark drugs” series. But, in the next few months, donepezil and the two newer acetylcholinesterase (AChE) inhibitors galantamine and rivastigmine look set to celebrate a landmark for which the Alzheimer’s community has campaigned for many years.

With the expected blessing of the National Institute for Health and Clinical Excellence, all three drugs will move into routine use for patients with mild Alzheimer’s disease, in addition to those with moderate disease.

Clive Ballard, director of research for the Alzheimer’s Society and professor of age-related disorders at King’s College London/Institute of Psychiatry, explains that the lack of effective treatment before the AChE inhibitors became available and the huge publicity that preceded donepezil’s launch raised budgetary concerns about the cost of treating the waiting Alzheimer population.

“Dementia affects about three quarters of a million people, most of whom have Alzheimer’s disease. So, although the new drugs weren’t very expensive, public expectations were so high that the regulators were concerned about the cost implications of Alzheimer’s disease,” he says.

As a result, local policies were introduced from the start that restricted prescribing of donepezil. Pre-NICE, the Standing Medical Advisory Committee recommended that donepezil should be initiated and supervised by a specialist experienced in dementia, that benefits should be assessed at 12 weeks and that treatment should only be continued for patients with evidence of benefit. In 2001, NICE supported the use of AChE inhibitors for mild to moderate Alzheimer’s but, in its 2006 update, treatment was restricted only to those with moderate disease.

Professor Ballard explains that, although there have been no major new AChE inhibitor trials since the 2006 decision, the revised health economic analysis used in the 2010 update supports use of the drugs in milder disease. “The previous economic model was almost entirely based on the cost of admission to care homes. As long-term care is a much more distant prospect for people with mild dementia than with moderate disease, it was much harder to demonstrate beneficial effects of the drugs in mild disease. The model for the new update takes account of the impact of treatment on transition between stages of Alzheimer’s disease and the associated costs, and recognises the benefits of treatment within this scenario,” says Professor Ballard.

A chance discovery

Donepezil was discovered in the Japanese laboratories of Eisai Co Ltd. A research programme started in 1983 looked for derivatives of tacrine, the first AChE inhibitor to be licensed, but whose use was severely limited by poor oral bioavailability and liver toxicity. By inhibiting the effects of...
cholinesterase inhibitors in breaking down acetylcholine, AChE inhibitors prolong the action of this important neurotransmitter, synthesis of which is known to be reduced in Alzheimer’s disease.

Eisai failed to develop a non-toxic tacrine derivative, but random screening threw up an N-benzylpiperazine derivative with anti-AChE activity in rat brain. The initial compound was weak but, from the approximately 700 derivatives that were synthesised, the imandone derivative donepezil struck the right balance of anti-AChE activity and duration of action.1

Clinical studies started in 1989, but did not initially show clear efficacy.1 However, 12-week, phase III placebo-controlled trials showed that donepezil significantly improved cognitive subscales of Alzheimer’s assessment scales and mini mental state examination (MMSE) tests.2,3 In the years since these early trials, many more studies have been reported and, in its 2009 update of earlier guidance, NICE reviewed data from 13 published randomised controlled trials (RCTs) covering a total of over 4,000 patients.4 Small but significant improvements in cognition were seen, together with trends in MMSE scores, but the majority of studies were of six months’ duration. Longer-term follow up of one to two years has suggested that some benefits are maintained but most data come from open label extensions of earlier trials and are, therefore, difficult to interpret.

One UK study of 486 patients with mild-to-moderate Alzheimer’s investigated the effects of long-term treatment with donepezil or placebo for up to three years.5 Patients taking donepezil had significantly higher cognition and functionality scores at two years than those taking placebo, and some differences in institutionalisation were seen at one year (9 per cent donepezil versus 14 per cent placebo). But this latter difference was not statistically significant (P=0.15) and not sustained at three years (42 per cent donepezil versus 44 per cent placebo, respectively, P=0.4). Results for the other primary outcome (progression of disability) showed little difference at one year and no benefit at three years.

The reality of treatment
AChE inhibitor treatment is not a panacea, but it is the best that’s currently available, Professor Ballard believes. “Treatment probably improves cognition by about the same amount that a patient would be expected to decline over six months. Given that life expectancy is about four to five years from diagnosis, it’s not a miracle drug but the effect is better than no treatment,” he says.

Although it has proved impossible to predict which patients will do best with AChE inhibitor treatment, Professor Ballard explains that about two thirds of Alzheimer’s patients will have some benefit from treatment, with about 10 per cent getting a lot of benefit. But, he adds, the only way to find out if a patient is benefiting is to do a six-month trial of treatment and, even then, improvement at six months does not predict long-term effects.

“We probably aren’t getting many patients staying on treatment for more than two years because, by that stage, it’s difficult to see if they are still benefiting,” he says.

Comparing drugs
Like donepezil, both rivastigmine and galantamine also prolong the effects of acetylcholine by preventing its breakdown by cholinesterase enzymes. But, unlike donepezil, which is selective for acetylcholinesterase alone, rivastigmine inhibits both butrylcholinesterase and acetylcholinesterase. Galantamine is a weaker AChE inhibitor but has additional activity in modulating nicotinic cholinergic receptors, leading to an increase in acetylcholine release.

There has been little head-to-head research on the drugs and, in its most recent deliberations, NICE concluded that only one comparative RCT was of sufficient quality for inclusion.6 In this comparison of donepezil and rivastigmine, there were no significant differences for cognitive or behavioural outcomes at two years, although functional and global outcomes were significantly better for rivastigmine. In its new guidance, NICE is expected to recommend use of the AChE inhibitor with the lowest acquisition cost, while taking account of the adverse event profile for each drug.

“In it’s hard to make any definitive recommendations for one drug rather than another on the basis of efficacy, but patients do vary in how well they tolerate each agent. So it’s useful that a patient who doesn’t tolerate one drug may well be fine on another,” Professor Ballard points out.

Impact on Alzheimer’s services
The greatest impact of donepezil and the other AChE inhibitors has been on the development of services for people with Alzheimer’s, says Professor Ballard. He explains that, since their introduction, there have been huge developments in memory clinics that, in turn, have improved the overall management of Alzheimer’s.

“Before the arrival of these drugs, there were very few memory clinics, and they were involved mainly in clinical trials. Now, there are many more and they are predominantly involved in diagnosis and implementation of care pathways for patients, including the use of drugs where appropriate,” says Professor Ballard.

Many patients are diagnosed earlier than previously, so steps are taken more quickly to support them at home.

“The focus is on home support and care in the community, so patients are staying in their homes longer. But it’s hard to say how much of that is due to better drugs for Alzheimer’s disease and how much is due to the policy of better home support,” Professor Ballard adds.

The next generation of drugs
A new generation of Alzheimer’s treatments is in development. These are targeting the underlying abnormalities of amyloid protein deposition in plaques and formation of neurofibrillary tangles.

But Professor Ballard points out that it took 20 years for the science underlying the development of AChE to bear fruit, and the next generation of drugs, which are based on research carried out in the late 1980s and early 1990s, is likely to have a similar gestation period.

He predicts that they are unlikely to replace the cholinesterase inhibitors because they work through different mechanisms.

Professor Ballard says: “The new agents would be used in the earliest stages of Alzheimer’s to try to protect the nerves, while the cholinesterase inhibitors would continue to address the cholinergic deficit later in the disease. There’s no suggestion that cholinesterase inhibitors will be made redundant. Instead, the drugs will be used to complement each other and hopefully get the best possible effect for patients.”

References