Should we forget about using acetylcholinesterase inhibitors in Alzheimer's disease?

Introduction

In November 2006, the National Institute for Health and Clinical Excellence (NICE) finally published *Dementia: supporting people with dementia and their carers in health and social care*.[1] The NICE guidance specified that the three acetylcholinesterase (AChE) inhibitors: donepezil, galantamine and rivastigmine, which were previously recommended for mild and moderate Alzheimer's disease (AD) are now only recommended as options for patients with moderate conditions, that is defined by a Mini Mental State Examination (MMSE) score of between 10 and 20 points.[1]

This guidance provoked an unprecedented degree of controversy and extensive media coverage, which resulted in a recent High Court judicial review lodged by the pharmaceutical company Eisai with support from Pfizer and the Alzheimer's Society. A report in the general press[2] argued that this guidance left the majority of sufferers with mild (21 to 26 points) or more severe dementia (<10 points) who number 700,000 not eligible for treatment. In Scotland the Scottish Intercollegiate Guidelines Network (SIGN) *Guideline 86* on the management of patients with dementia states that the age and severity of Alzheimer's disease should not be contraindications to the use of donepezil.[3] This could potentially rekindle the 'post-code lottery' debate within health care.

The High Court ruling on August 10 2007 rejected the main allegations that NICE had behaved 'irrationally and unlawfully' in its decision-making and that its processes were 'procedurally flawed'. However, the media reported that Mrs Justice Dobbs ruled that the MMSE, upon which NICE defines the severity of the condition, was discriminatory to patients with other disabilities or language difficulties.[4] Andrew Dillon, chief executive of NICE, is reported as saying: 'The ruling strengthens NICE by endorsing our approach to evaluating drugs. Our guidance stands and the drugs continue to be recommended only for people with moderate Alzheimer's disease, but the court has asked us to clarify guidance when it is used for certain groups.'[4] He promised to re-issue the guidance to ensure that it was 'crystal clear'.[4]

Dementia is by its nature difficult to diagnose and quantify. This is emphasised by a Canadian study[5] in which 1879 patients suspected of suffering from dementia had a full neurological examination and were assessed according to a range of established diagnostic systems. Depending on the diagnostic criteria used there was a 10-fold difference in prevalence from 3.1% (ICD-10) to 29% (DSM III).[5]

The logic of using AChE inhibitors, which increase cholinergic activity in the brain, largely stems from the analysis of post-mortem brain of AD patients. These reveal a selective loss of cholinergic nerves in the basal forebrain, reduced choline acetyltransferase activity (which results in a decreased synthesis of acetylcholine) in the hippocampus, and a decrease in nicotinic receptor density in the cortex. The pharmacology of these drugs suggests that they should be relatively ineffective in patients with advanced neurodegeneration.

Assessment of clinical effectiveness

AChE inhibitors were first introduced in 1997 and evidence of their clinical effectiveness indicates that these drugs consistently produce small gains in the scores on cognitive and global scales of some patients with mild to moderate AD. Indeed the *British National Formulary* states that up to half of patients will show a slower rate of cognitive decline.[6] A number of different rating scales have been used within AD clinical trials and these fall into four main groups: cognitive tests, clinicians' global impressions of change, behavioural ratings and functional assessments.

Because cognitive impairment is a major symptom of AD, the vast majority of randomised controlled trials (RCT's) use various measures of cognitive function as an endpoint when assessing the clinical efficacy of these drugs. However, it is unclear how any effects on cognitive enhancement have genuine effects on patient-oriented outcomes, such as quality of life (QoL) for the patient and carers, behavioural effects and delay in admission to nursing home care in the longer term. The real impact on the QoL of people with Alzheimer's (and their relatives) is therefore very difficult to assess.

A cognitive scale that is most commonly used in assessing the efficacy of these drugs in RCTs is the Alzheimer Disease Assessment Scale (ADAS-cog). This consists of 11 items that assess cognitive function, such as memory and orientation. A score of between 0 and 70 is possible on the ADAS-cog where 0 means the patient has made no errors at all and where 70 means that the patient is profoundly demented.

NICE has examined all three AChE inhibitors in depth,[7] but in this article we will concentrate on the data for donepezil. In terms of cognitive outcomes in mild to moderate disease, NICE considered 13 published RCT's and two systematic reviews

There are practical difficulties in using these AchE inhibitors in [AD] patients with moderate disease because once they have started taking them, it is difficult to withdraw therapy from patients when their disease progresses.

that met their inclusion criteria. Six showed a significant improvement in cognitive function when assessed using the ADAS-cog scale. A meta-analysis of three of these trials with comparable data over a period of 12–24 weeks demonstrated a significant weighted mean difference of -2.51 in the ADAS-cog score for 5mg donepezil daily and -3.01 for a 10mg donepezil daily dose.

The MMSE is a simpler and easier assessment tool. It is mainly used to aid diagnosis and it is recommended by NICE as one of the criteria for the grading of AD and the initiation of treatment. It has also been used in RCT's that showed a beneficial increase in score of 1.3 for 10mg daily of donepezil.[7]

NICE considered seven RCT's assessing global change.[7] One of the instruments used — the Clinicians Global Impression of Change (CGIC) scale — is an attempt to assess clinically meaningful changes based on interviews using a much looser seven-point assessment of change. In the CGIC scale 1 equates to very much improved and 7 to being very much worse. Using this measure, donepezil also shows a significant improvement from baseline.[7]

The effect of donepezil on function and quality of life is much less clear-cut. The NICE technology appraisal[7] reports no significant differences have been found when measuring rates of institutionalisation or progression of disability over periods up to three years. Three studies reported QoL outcomes and showed variable results: one showing an improvement, one showing a worsening and one showing no change.[7]

In terms of behaviour, this was assessed using the neuropsychiatric inventory (NPI) in four RCTs. This is a structured interview of the carer assessing 13 behaviours. Donepezil showed a small statistically significant effect in improving or limiting deterioration in the short term.[7]

Sub-group analysis — responders and non-responders

In total, 15% of the Caucasian population with AD are carriers of defective cytochrome P450 2D6 (CYP2D6), which is potentially responsible for therapeutic failures when receiving AChE inhibitors.[8] Indeed the AD population exhibits a higher genetic variation than the general population.[8] In addition, it has been shown that the therapeutic response in AD is genotype-specific, with carriers of the apolipoprotein (APO)-E allele, *APOE-4/4*, being the worst responders.[8]

© Joseph Jean Rolland Dubé/ istockphoto

In terms of responders verses non-responders, a re-analysis, by the MRC Biostatistics Unit, of the manufacturer's intention to treat — last observation carried forward (ITT-LOCF) was undertaken on data from five RCTs.[7] This analysis revealed that 39% of people taking donepezil were classified as responders compared with 22% who were taking placebo.[7] (The analysis was carried out using the definition of a responder taken from the NICE Technology appraisal guidance number 19. This is that the patient has stable or improved cognition AND has shown improvement in EITHER the global clinical measure OR the functional measure OR the behavioural measure 5–6 months after starting treatment.[9])

In the sub-group analysis of responders, the change from baseline using ADAS-cog was now increased to -6.26. Although this change appears relatively large, the placebo change in a corresponding group of responders was also large at -5.27.[7] Using an alternative definition of responder (no change or improvement on the ADAScog scale)[7] the manufacturers reported a response rate of 63% compared with a placebo rate of 41% with an absolute change of -5.82 on the ADAS-Cog scale.[7] Further sub-group analysis demonstrated that the maximum cognitive benefit (-3.94 on the ADAS-Cog scale) was derived in patients who had moderate Alzheimer's (MMSE 15–20), compared to -2.03 in milder (MMSE ≥ 21) disease.[7]

Other AChE inhibitors showed similar degrees of efficacy. The typical side-effects of AChE inhibitors are predictable from their pharmacology and mainly involve gastrointestinal side-effects, such as nausea and vomiting. All potential adverse effects are of concern in the elderly, but because the drugs work by selectively inhibiting the central, rather than the peripheral AChE's the incidence of side-effects is low and comparable with placebo.[10]

Cochrane review

A 2006 Cochrane review[11] of AChE inhibitors drew similar conclusions to NICE with regard to efficacy and stated: 'The three cholinesterase inhibitors are efficacious for mild to moderate Alzheimer's disease. Despite the slight variations in the mode of action of the three cholinesterase inhibitors there is no evidence of any differences between them with respect to efficacy. The evidence from one large trial shows fewer adverse events associated with donepezil compared with rivastigmine.'

The drugs produced improvements in cognitive function — on average of -2.7 points in the midrange of the 70-point ADAS-Cog scale. Study clinicians rated global clinical state more positively in treated patients.[11] Benefits of treatment were also seen on measures of activities of daily living and behaviour. None of the treatment effects were large. The effects were similar for patients with moderate-to-mild dementia and severe dementia, although there is very little evidence —

coming from only two trials. In addition more patients left AChE inhibitor treatment groups (29%) on account of adverse events than left the placebo groups (18%).[11]

A study that was excluded from this Cochrane review was the AD2000 study.[12] The trial was excluded because it was considered to be underpowered and because patients were randomised on two occasions. AD2000 was a 556-patient, NHS-funded study of donepezil, with the primary endpoints as entry to institutional care and progression of disability as measured by the loss of 2 of 4 basic activities on the Bristol Activities of Daily Living Scale (BADLS).[12] Secondary endpoints involved an assessment of cognitive function using MMSE. The trial failed to show any delay in admission to nursing homes, progression of disability, carer psychopathology, formal care costs, unpaid caregiver time, serious adverse events or deaths. There was a statistically significant improvement in cognitive function, but it was only a fraction of a point (0.8) on the MMSE rating and not considered to be clinically significant.[12]

Two small audits[13,14] of AChE inhibitors use in practice highlighted the difficulties in assessing these drugs for AD. Although they were too small for any firm conclusions to be drawn it was observed that it is difficult to attempt to stop treatment, and that withdrawal resulted in rapid deterioration in 40% of patients[13] and death in 20% of patients.[13] They also highlighted the difficulty in defining a response to treatment.

Cost-effectiveness.

Twenty-one published economic evaluations of the three AChE inhibitors and memantine were available to the NICE Appraisal Committee.[7] All four manufacturers also submitted their own economic evaluations. Further analyses were undertaken by NICE. Both the economic model and the manufacturers' models — when re-evaluated using the Assessment Group's assumptions on costs and utilities — put the AChE inhibitors outside the range of cost-effectiveness that might usually be considered appropriate for the NHS.[7] The costs per quality-adjusted life year gained (CQG) were £97,000, £82,000 and £70,000 for donepezil, galantamine and rivastigmine, respectively.

However, after further discussion and including such factors as benefits to carers and behavioural functions, and focusing on a sub-group of moderate suffers, NICE finally approved the use of these drugs for patients with moderate cognitive impairment (MMSE 10-20).[1]

Summary

On a population basis, AChE inhibitors provide small but consistent gains on cognitive and global scores in AD. However, there is no consistent and reliable evidence for any patient-oriented outcome, such as delayed time to nursing homes, QoL or behaviour, and little evidence for the long-term effectiveness of these drugs. In this regard perhaps we should forget these classes of drugs for AD. Nevertheless, there is evidence that certain patients will benefit and the decision NICE has made takes this into account.

There are practical difficulties in restricting these AchE inhibitors in patients with moderate disease because once they have started taking them it is difficult to withdraw therapy from patients when their disease progresses. It is also extremely difficult to carry out high quality research in this area, particularly when considering patient-oriented outcomes and more work is needs to be done. Thus, many questions remain to be addressed. For example:

1. What exactly is dementia and how should it be diagnosed effectively? It is clear that failing to make an accurate diagnosis of AD can markedly influence our ability to ascertain the efficacy of interventions.
2. What is a clinically useful outcome in terms of a cognitive score? How long does the effect of an AchE inhibitor really last? Is this related to patient-oriented outcomes?
3. In the future will we be able to optimise treatment by using pharmacogenomic or pharmacogenetic techniques to identify non-responders? ✣

Dr Paul F Grassby, director of clinical studies, School of Chemical Sciences and Pharmacy, UEA, Norwich

Series editors: Jonathan Underhill, National Prescribing Centre, Liverpool, UK,

Scott Pegler, principal pharmacist, medicines information manager, Morriston Hospital, Swansea NHS Trust, UK

John Bane, medicine information/clinical trial pharmacist, Pharmacy Dept, Sheffield Childrens NHS Foundation Trust, Sheffield, UK

References

1. National Institute for Health and Clinical Excellence, and Social Care Institute for Excellence. *Dementia: supporting people with dementia and their carers in health and social care. NICE clinical guidance 42.* November 2006.
2. Fortson D (Markets editor). Have a Nice day? Pfizer in court clash with British drug authority. *The Independent (London)* 13 May 2007.
3. Scottish Intercollegiate Guidelines Network. *Management of patients with dementia. A national clinical guideline. Guideline 86.* February 2006.
4. Curtis P (Health correspondent). Judge upholds restriction on Alzheimer's drug. *The Guardian (London)* 11 August 2007.
5. Erikinjuntti T, Østbye T, Steenhuis R, Hachinski V. The effect of different diagnostic criteria on the prevalence of dementia. *New Eng J Med* 1997; **337:** 1667–74.
6. British National Formulary (53rd Edition) page 270. BMJ and RPS publishing, 2007.
7. National Institute for Health and Clinical Excellence. *Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease.* NICE technology appraisal guidance 111. London, November 2006.
8. Cecabelos R. Pharmacogenomics and therapeutic prospects in Alzheimer's disease. *Expert Opin Pharmacother* 2005; **6(12):** 1967–87.
9. National Institute for Health and Clinical Excellence. *Guidance on the use of Donepezil, rivastigmine and galantamine for the treatment of Alzheimer's disease. Technology Appraisal Guidance 19.* January 2001.
10. Jackson S *et al.* The safety and tolerability of donepezil in patients with Alzheimer's disease. *Br J Clin Pharmacol* 2004; **58(S1):** 1–8.
11. Birks J. *Cholinesterase inhibitors for Alzheimer's disease.* Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD005593. DOI: .1002/14651858.CD005593.
12. AD 2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double blind trial. *Lancet* 2004; **363:** 2105–15.
13. Simpson S *et al.* Naturalistic audit of NICE criteria for the use of cholinesterase inhibitors. *Psychiat Bull* 2005; **29:** 410–12.
14. Larner AJ. Cholinesterase inhibitor use at a cognitive function clinic. *Prog Neurol Psychiatr* 2004; **8(4):** 14-20.