Editorial

What now for Alzheimer's disease? An epidemiological evaluation of the AD2000 trial

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In recent years, acetylcholinesterase inhibitors have been approved for the treatment of Alzheimer's disease. This has been mainly on the strength of many randomised placebo-controlled trials showing a statistically significant improvement in cognitive, functional and behavioural scores mainly at 12 and 24 weeks.[1,2,3] The questions now are whether this statistical difference translates into a clinically meaningful difference and whether treatment is cost-effective. The AD2000 trial[4] sheds light on this question.

This placebo-controlled trial of donepezil was not sponsored by a drug company. The trial has many strengths as it:

- is the only trial to look at end points beyond one year
- focuses primarily on clinical end points such as time to institutionalisation or progression to disability
- includes measures of caregiver burden (as a secondary outcome)
- enrolled a broader spectrum of patients than those typically included in trials sponsored by drug companies.

In this issue…

Knowledge about new drugs is usually limited to the experience of the carefully selected patients who participated in the clinical trials. A drug which satisfies short-term criteria of safety and efficacy may be less effective in the long term. The editorial by John Attia and Peter Schofield suggests that any benefits of donepezil may not be sustained, while Jeffrey Post and Mark Kelly say that cardiovascular diseasemay be emerging as a long-term adverse effect of antiretroviral therapy.

To improve our knowledge of drug safety it is important to report adverse events, particularly to new drugs. Kerri Mackay explains what happens to your reports of adverse reactions.

Amiodarone is a drug with many possible adverse reactions. Terry Campbell therefore advises on how to minimise the risk of serious adverse effects.

The drawbacks of the trial were that recruitment was slower and smaller than planned (566 versus 3000 patients). It had a complex design (multiple treatment phases and washout periods) and a large withdrawal rate. This makes a true intention-to-treat analysis difficult, however, the overall effect of these factors is to bias away from the null, that is to overstate the effect size. With this caveat in mind, the results show:

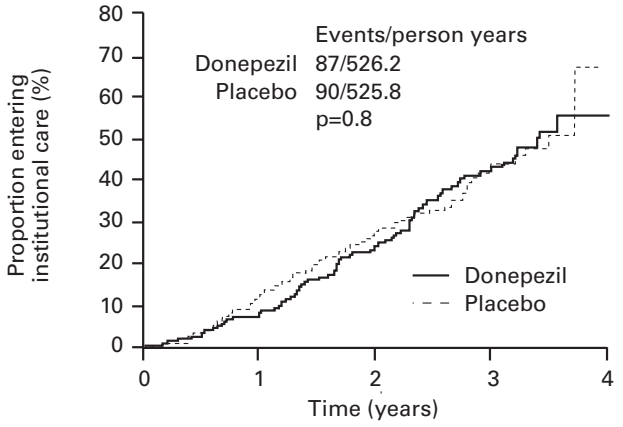
- A difference in the 30-point mini-mental state examination of 0.8 points (95% CI 0.5–1.2*) between the treatment and placebo groups at two years. This is about half the treatment effect previously seen at one year in other trials (1.8 points, 95% CI 0.5–3.2).
- No difference in institutionalisation (RR=0.97†, 95% CI 0.72–1.3) over 114 weeks. This conflicts with a previous drug company-sponsored trial indicating a significant delay in nursing home placement of about 21 months.[5] However, the sponsored trial was a non-randomised, open-label study with large potential for selection bias. The survival curves for AD2000 seem to indicate some gap at one year (Fig. 1), a potential 2–3 month delay in institutionalisation. This is consistent with many studies showing a 2–3 month delay in symptomatic progression, however this is not sustained and the overall rates at two years are similar.
- No difference in progression to disability (RR=1.02, 95% CI 0.72–1.45) over 114 weeks.
- There was a statistical difference in the functional score (as measured on the Bristol activities of daily living scale, BADLS) of about 1 point, out of a total of 60. Like the statistical difference in the mini-mental state examination, this difference was present by 24 weeks, but there was no further divergence (or convergence) of the curves with continued treatment. Neither of these score differences met previous, externally set criteria for clinical significance.
- There was no difference in behavioural and psychological symptoms as measured by the neuropsychiatric inventory.

* CI confidence interval

† RR relative risk

Fig. 1

Entry to institutional care



Number at risk

Donepezil	282	212	134	57	1
Placebo	283	209	135	60	0

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- Importantly, there was no significant difference in the carer's psychological morbidity score as measured by the General Health Questionnaire (GHQ-30). Treatment made no significant difference to the amount of time the caregiver had to spend with the patient.
- The mean annual cost per patient resident in the community was higher in the donepezil group than placebo by £500 (approx. A$1180). This increased cost was mainly due to the donepezil group requiring more hospital and home visits.

So what can we say in summary? This trial once again highlights the importance of independent trials that enrol a representative patient population. Previous work shows that industry-sponsored studies tend to have more favourable results than non-industry studies.[6,7] This may be a consequence of inclusion and exclusion criteria that are very tightly defined and implemented. After the initial wave of favourable, mainly company-sponsored, results using cognitive and behavioural scales, AD2000 suggests that these changes in scores do not translate into clinically important or cost-effective changes. It is also evident that most of the relative improvement in scores occurs in the first six months. Prolonged use does not continue to improve scores, although it is unclear whether this is needed to maintain the benefit or if stopping will accelerate the patient's decline.

References

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Dr Schofield has received honoraria from Pfizer for lectures and consultancy.

Note

While this article was under review, another study looking at the effect of donepezil and vitamin E on cognitive impairment was published with three-year outcomes (Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379-88). The results of this study are very similar to those of the AD2000 trial, that is, although there may be some mild protective effect at one year, this is not sustained at longer time points.