

## Feedback from AD2000 authors

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I am writing to express my strong concern about the serious misrepresentation of the AD2000 study<sup>1</sup> in *Evidence-Based Mental Health* emailed to me on the 9 September 2004. The *Lancet* will publish correspondence relating to the AD2000 study, on 2 October 2004, which covers some of the issues raised. A more detailed rebuttal is set out below.

The main criticism is of the high attrition rate: “only 105 patients began donepezil in the second year and 31 in the third year”. Firstly, no other study has continued placebo controlled treatment beyond one year and so AD2000 provides the only reliable evidence on efficacy of donepezil beyond one year. Secondly, just considering the second year data, AD2000 is still one of the largest studies of donepezil: 486 entered the randomisation between long term donepezil and placebo. In the first year, 34 (7%) died, 48 (10%) reached the principal endpoint of institutionalisation, and 81 (17%) were at centres that withdrew from the trial following the NICE recommendation that Alzheimer’s patients should be offered cholinesterase inhibitors. The numbers discontinuing treatment was lower in AD2000 than in any previous study with only 62 (13%) of the 486 patients randomised stopping protocol treatment in the first 48 weeks, and 67 (14%) opting not to continue into a second year of treatment. Thus, 323 patients who were alive, resident in the community, and at centres that had not withdrawn from the study were eligible for a second year of treatment (see table 1 of reference 1). Of these, 64% (105/165) of donepezil and 56% (89/158) of the placebo group remained compliant with study treatment. Of the patients starting a second year of trial treatment, only 6% (11/194) stopped taking trial medication during year 2. Fifty one patients continued treatment into a third year but three year assessments were not reported in the AD2000 paper because of the relative paucity of data at three years, mainly due to centre withdrawal following the NICE recommendation for cholinesterase use. In summary, the total on study in year two is large, and the compliance with allocated treatment is high for a long term study in an elderly frail group. It is misleading to include patients who did not complete the run-in, those who were institutionalised, dead, or censored in attrition rates. Moreover, unlike previous studies, AD2000 sought data for all patients whether or not they complied with trial treatment and, consequently, there were also fewer missing data than in any previous study—thereby minimising “dropout bias” a problem in most previous reports.

The Commentary also asks “Can the small numbers studied in year three (life table estimates) truly negate this demonstrated efficacy and that of multiple other studies? The attrition, along with the washout phases, dosing, and a study design allowing centres to drop out in favour of going open label, raise concerns about the study results”. All patients were followed up for the institutionalisation endpoint whether or not they had stopped treatment or if their centre had withdrawn from the study. The three year comparison of institutionalisation rates cited in the AD2000 report are life table estimates based on all available data, not just on patients who reached three years. The Commentary makes no mention of the sensitivity analyses in AD2000 demonstrating that the very small improvements in Bristol ADL score (below previously defined minimal worthwhile improvements) would at most result in an average avoidance of three days institutional care per patient per year. The AD2000 results thus provide statistically convincing evidence to refute the primary cost effectiveness hypothesis that donepezil use is cost neutral, as

well as ruling out minimally clinically relevant improvements in the secondary outcome measures—that is, AD2000 has not produced a false negative result.

There is also no substance in the claim that “the washout phase, dosing, and the potential bias of a design allowing subjects to drop out in favour of going open label raises concerns”. The negative findings are not explained by an irreversible loss of benefit following the washouts—for example, patients who entered a second year of treatment declined 1.45 MMSE points more in the donepezil group than in the placebo group during the preceding six week washout but then improved 2.84 MMSE points more than placebo patients after 12 weeks of retreatment. Similar post-washout recovery has been reported in other studies.[2] Results would have been little different if all patients had received 10 mg of donepezil given the small, non-significant difference between doses. All ethically conducted studies allow patients to drop out. What is important is to follow up outcome of all patients irrespective of compliance to allow proper intention-to-treat analyses. It should be noted that it was AD2000 centres that withdrew, not individual patients. All patients were censored following their centre’s withdrawal, to avoid diluting the measured treatment effect, which introduces no bias.

Finally, it also misleading to state that “another interpretation of the data is that donepezil provided a non-significant RRR of 35.7% for entry to institutional care ( $p=0.15$ )”. To emphasise a subset of the data rather than the overall result is a well recognised subgroup misinterpretation, which should have no place in an evidence-based publication.

For the reasons set out above, we believe it is wrong for *Evidence-Based Mental Health* to describe the AD2000 study as a 60 week study.

## References

1. AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer’s disease (AD2000): randomised double blind trial. *Lancet* 2004;**363**:2105–15.
2. Rogers S, Friedhoff LT. Long-term efficacy and safety of donepezil in the treatment of alzheimer’s disease: an interim analysis of the results of a us multicentre open label extension study. *Eur Neuropsychopharmacol* 1998;**8**:67–75.