

Are there long-term benefits of donepezil in Alzheimer's disease?

Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, et al; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* 2004;363:2105-15.

Background: Second-generation cholinesterase inhibitors (donepezil, galantamine and rivastigmine) have been shown to have beneficial effects on cognitive, global and daily functioning lasting 6–12 months in patients with mild to moderate Alzheimer's disease (AD) in double-blind, randomized controlled trials (RCTs),^{1,2} with continued benefits apparent in open-label extensions over 3–4 years.³ Double-blind data concerning their long-term utility are lacking.

Design: The investigators set out to conduct a double-blind, long-term RCT of donepezil for the treatment of AD in a family practice setting, using pragmatic end points; the study was funded by a UK National Health System regional authority, free of pharmaceutical industry sponsorship. The original target of 3000 patients was revised to 566 owing to recruitment problems (the final sample was 565; 1 patient withdrew consent before treatment). The 2 primary outcomes were entry into institutional care and progression of disability (defined as loss of 2 of 4 basic or 6 of 11 instrumental activities on the Bristol Activities of Daily Living Scale [BADLS]). Secondary measures included results of other objective psychometric tests (e.g., the Mini-Mental Status Exam [MMSE]), functional ability on the BADLS, behavioural symptom and caregiver burden scales, and costs of care. Eligible patients met DSM-IV criteria for AD with or without vascular dementia, and clinicians had to be "substantially uncertain" that patients would benefit from taking donepezil. After a 12-week compliance run-in, 486 patients were randomly reas-

signed and followed up quarterly for 48 weeks. After a 6-week wash-out period, remaining patients continued for another 48 weeks. The 486 participants provided 90% power at $p < 0.05$ to detect a 6-month annual delay to entry into institutional care and an effect size of 0.3 standard deviations on the secondary measures in the intervention arm versus the placebo arm.

Results: A total of 293 patients (60%) completed the first year and 111 (23%) the second year of follow-up. At 2 years, no significant differences were found between the 2 groups in the primary outcome measures. Of the secondary measures, the mean MMSE score at 2 years was 0.8 points higher in the donepezil group than in the placebo group (95% confidence interval [CI] 0.5–1.2, $p < 0.0001$), and the mean BADLS score for functionality was 1.0 point higher in the donepezil group than in the placebo group (95% CI 0.5–1.6, $p = 0.0004$). No other measures or subgroup analyses showed significant differences. The mean annual net cost was £498 higher in the donepezil group. Serious adverse events and deaths were similar in both groups, but by 1 year, more of the patients in the donepezil group than in the placebo group discontinued treatment because of side effects (7% v. 3%).

Commentary: The main flaw of this study was that it was underpowered. The power, calculated on the basis of 486 subjects being in the final randomization for the long-term study, was undermined by a 40% dropout rate by year 1 and 77% dropout rate by year 2. Although dropout num-

bers were similar in both groups, the authors did not specify how many patients crossed over to the other treatment arm. This could be a major confounder. Furthermore, although demographic characteristics, baseline scores and comorbid diagnoses were balanced in the initial sample, no such data were given for the subjects who were eventually randomly assigned in the long-term study. Differences in baseline characteristics between the 2 final groups (e.g., pre-existing cerebrovascular disease and psychosis, which had not been excluded in order to increase sample generalizability) could have affected the outcomes.

Dosing and treatment interruptions did not accord with usual practice. The authors do not explain why subjects were washed out for 6 and 4 weeks after each 48-week treatment period. Previous trial data suggest this could attenuate response and patients might not recoup gains made on treatment. Also, the 5- and 10-mg doses were analyzed together, presumably because of sample attrition. In clinical practice, the treatment goal is 10 mg if tolerated, and 5 mg is considered suboptimal; therefore, inclusion of patients taking the lower dose may have diluted the treatment effects.

Another concern is the use of doctors' "substantial uncertainty" about drug benefit as a premise for enrolment and how this was conveyed to patients and their physicians. Setting realistic expectations — a delay of 6–12 months in disease progression, possibly longer in some cases — is important for appropriate prescription of cholinesterase inhibitors. Making doubt the basis for recruitment may have subtly biased patient selection, expectations, tolerance of side effects and dropout rates, and potentially influenced outcomes. The decision to enter into institutional care, al-

though apparently a hard end point of the study, is a complex reflection of social, cultural, caregiver and patient factors.

Practice implications: Despite this study being well intentioned, there were problems with patient recruitment and retention. As such, the calculation for statistical power was performed post-hoc; the treatment effects that the study was powered to detect based on patient enrolment were small to medium. Inadequately powered to detect more meaningful clinical differences, the study cannot be interpreted positively or negatively — absence of proof is not proof of absence. Hence, the study neither refutes

nor strengthens existing guidelines, which recommend a trial of cholinesterase inhibitors in cases of mild to moderate AD. Clearly what is needed are better measures to set expectations and evaluate outcomes, data analysis independent — as in this study — of pharmaceutical sponsors and more effective, disease-modifying interventions.

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