

Donepezil did not reduce the rate of institutionalisation or disability in people with mild to moderate Alzheimer's disease










AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* 2004;**363**:2105–15.



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Q What is the effect of donepezil in people with mild to moderate Alzheimer's disease?

METHODS

	Design: Randomised controlled trial.
	Allocation: Concealed.
	Blinding: Double blinded.
	Follow up period: 60 weeks (data from 114 and 166 weeks not reported—see notes).
	Setting: 22 hospitals in the UK; October 1998 to September 2001.
	Patients: 565 people (median age 75 years, range 46–93 years) with mild to moderate Alzheimer's disease (DSM-IV). Main exclusion criteria: living in an institution, no regular carer, contraindications against donepezil, or already receiving cholinesterase inhibitors.
	Intervention: Run-in treatment: donepezil (5 mg/day) or placebo for 12 weeks. Long term treatment: donepezil (5 or 10 mg/day) or placebo for 48 weeks. (The intervention continued with a 6 week washout; then two rounds of donepezil (5 or 10 mg/day) or placebo for 48 weeks followed by 4 weeks washout; however, these results not reported due to high dropout rate).
	Outcomes: Entry into institutional care; progression of disability (Bristol Activities of Daily Living (BADLS)).
	Patient follow up: 75% for placebo, 76% donepezil (see notes) at 60 weeks.

MAIN RESULTS

At 60 weeks, there were no significant differences between donepezil and placebo in institutionalisation rates or progression to disability in people with mild to moderate Alzheimer's disease (see <http://www.ebmentalhealth.com/supplemental> for table). There were no significant differences in institutionalisation rates between the 10 mg and 5 mg donepezil groups (10 mg v 5 mg: 37 v 44, $p = 0.7$).

CONCLUSIONS

Donepezil does not delay time to institutionalization or progression to disability in people with mild to moderate Alzheimer's.

NOTES

See <http://www.ebmentalhealth.com/supplemental> for notes. In addition, the AD2000 authors dispute this interpretation—see <http://www.ebmentalhealth.com/supplemental> for their response.

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Commentary

The superiority, typically in cognition, of donepezil, and other cholinesterase inhibitors (ChEIs) to placebo has been confirmed in a systematic review.¹ Meta-analysis has shown ChEIs to have a modest beneficial impact on neuropsychiatric and functional outcomes (approximately 0.1 SD) in patients with mild to moderate AD that relative to placebo.² In a more recent report donepezil significantly improved neuropsychiatric symptoms ($p < 0.05$ for all domains of the NPI) relative to placebo in AD patients.³ A meta-analysis of 16 RCTs of ChEIs ($n = 7954$) demonstrated that the NNT was 7 (95% CI 6 to 9) for stabilisation or better, 12 (95% CI 9 to 16) for minimal improvement or better, and 42 (95% CI 26 to 114) for marked improvement.⁴ A Cochrane Review confirmed clinical efficacy of donepezil.⁵ Why could AD2000 not demonstrate these benefits?

In the AD2000 trial, donepezil benefit was demonstrated over the first two years of the study for both cognition (95% CI 0.5 to 1.2 MMSE points; $p < 0.0001$) and functionality (95% CI 0.5 to 1.6 BADLS points; $p < 0.0001$) despite a six week washout after 48 weeks of therapy, submaximal dosing, and a remarkable attrition rate. 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. Clinical trials with withdrawal periods indicate that withdrawal and reinitiation of ChEIs may result in loss of benefit that cannot be regained.⁶ The washout periods in this study certainly produced a gyration of MMSE data, and may have produced less robust results and inadvertently demonstrated the expected loss of benefits associated with interrupting therapy. This is not a regimen that would be practiced clinically, and represents a substantial flaw in establishing the validity that would be required for a study to overturn the collected evidence to date. The AD2000 primary endpoint (nursing home admission) was an insensitive and overly ambitious outcome measure at an inappropriate stage (the majority of subjects were classified as having mild dementia) of disease progression for many of the participants, and is an inappropriate parameter to gauge drug efficacy. Another interpretation of this portion of the data (equally inappropriate) is that at the end of year one, before interrupting medication and before attrition, donepezil provided a non-significant RRR of 35.7% for entry to institutional care ($p = 0.15$).

Although the laudable aim was to do a large, independent, and definitive trial, this has not been achieved for a number of design related and practical reasons. In fact, however, the results of AD2000 are not qualitatively different from, and do not invalidate, previous studies.

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