Long term donepezil did not delay institutionalisation or progression to disability in patients with 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.

Clinical impact ratings GP/FP/Primary care ★★★★★★☆ IM/Ambulatory care ★★★★★☆☆ Neurology ★★★★★★☆ Geriatrics ★★★★★★☆

Q In patients with Alzheimer's disease (AD), does donepezil delay entry to institutional care or progression of disability?

METHODS

Design: randomised controlled trial (AD2000 study).

Allocation: {concealed*}†.

Blinding: blinded {patients, healthcare providers, data collectors, and outcome assessors}†.*

Follow up period: 3 years.

Setting: 22 hospitals in the UK.

Patients: 566 patients (59% women, median age 75–76 y) who were referred to memory clinics with a suspected *DSM-IV* diagnosis of dementia of Alzheimer type, with or without coexisting vascular dementia; had a regular carer; lived in the community; were not taking a cholinesterase inhibitor; and had no contraindications to donepezil.

Intervention: during a 12 week run in period, patients were allocated to donepezil, 5 mg/day (n = 283), or placebo (n = 283). 511 patients completed this run in period, and 486 were re-randomised to donepezil, 5 or 10 mg/day (n = 242), or placebo (n = 244) for 48 weeks. After a 6 week no-treatment washout, patients could continue with the same treatment for another 48 weeks if judged appropriate; this process could be repeated as long as judged to be appropriate.

Outcomes: entry to institutional care (ie, residential, nursing, or National Health Service continuing care), progression of disability (loss of 2 of 4 basic activities on the Bristol Activities of Daily Living Scale [BADLS] or 6 of 11 instrumental activities on the BADLS), and health resource costs.

Patient follow up: all patients included in time to event analysis (log rank) with censoring of data.

*See glossary.
†Information provided by author.

MAIN RESULTS

Patients in the donepezil and placebo groups did not differ for rates of institutionalisation at 1 year (9% *v* 14%, p = 0.15) or 3 years (42% *v* 44%, p = 0.4). At a median follow up of 2 years, the relative risk for entering institutional care was 0.97 (95% CI 0.72 to 1.30). The groups did not differ for progression of disability at 1 year (13% *v* 19%, p = 0.3) or 3 years (55% *v* 53%, p = 0.9). The relative risk for progression of disability was 1.02 (CI 0.72 to 1.45). The mean annual cost per patient resident in the community (for 11 formal health and social services) did not significantly differ between the donepezil and placebo groups (£2842 *v* £2344, p = 0.16)

CONCLUSION

In patients with Alzheimer's disease, long term treatment with donepezil did not delay entry to institutional care or progression of disability.

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Commentary

Previous trials of donepezil have reported cognitive benefits and varying functional benefits.[1 2 3 4] The AD2000 study also found an initial improvement in cognition but no difference in progression of disability. More novel, they found that donepezil was not cost effective and did not reduce the risk of institutionalisation. Unlike previous studies that have not extended past 1 year, the authors followed up participants for 3 years. Longer duration of follow up is important when examining treatment benefits for Alzheimer's disease, a disorder that results in gradual progressive decline over several years. The study patients were also more representative of older AD patients typically seen in clinical practice in that approximately 50% had comorbidities. Donepezil is not without adverse effects and should be used cautiously in older patients with comorbidity. Although not statistically significant, the 13 excess deaths in the donepezil group are worrisome.

The study enrolled 566 patients, which is dramatically fewer than the initial target of 3000. Thus, the study may not have had adequate power to detect differences in several outcomes. The rather broad confidence intervals suggest that donepezil could be associated with a 30–45% increase or a 28% decrease in risk of the primary outcomes. Given the lack of evidence of long term benefits and cost effectiveness, the decision to use donepezil requires careful consideration by clinicians, patients, and caregivers.

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