Donepezil improved the clinical state and quality of life in moderate-to-severe Alzheimer disease

Feldman H, Gauthier S, Hecker J, et al., and the Donepezil MSAD Study Investigators Group. **A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease.** Neurology. 2001 Aug 28;57:613-20.

QUESTION

In patients with moderate-to-severe Alzheimer disease (AD), does donepezil improve global function, cognition, and behavior?

DESIGN

Randomized {allocation concealed*}†, blinded {participants, clinicians, data collectors, outcome assessors, data analysts}†,* placebo-controlled trial with 24-week follow-up.

SETTING

32 sites: 22 in Canada, 6 in Australia, and 4 in France.

PATIENTS

290 patients (mean age 74 y, 61% women) who had moderate-to-severe AD with a screening standardized Mini-Mental State Examination (sMMSE) score of 5 to 17 and a Functional Assessment Staging Test score ≤ 6 at baseline. (291 patients were randomized; 1 patient withdrew before the trial began.) Exclusion criteria included need for total nursing care; cause for dementia other than AD; and the presence of a complicating delirium, depression, or other concurrent diagnosis that might interfere with study participation. 85% of patients completed the study.

INTERVENTION

144 patients were allocated to donepezil (10 mg/d, decreased to 5 mg/d if necessary) and 146 patients to placebo for 24 weeks.

MAIN OUTCOME MEASURES

Global assessment of change at weeks 4, 8, 12, 18, and 24 using the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC). Secondary outcome measures included cognition (sMMSE), function (Disability Assessment for Dementia [DAD]), behavioral and neuropsychiatric symptoms (Neuropsychiatric Inventory [NPI]), and adverse effects.

MAIN RESULTS

The groups differed on CIBIC scores at all visits, favoring the donepezil group (mean difference in change from baseline at week 24, 0.54; $P < 0.001$). At week 24, more patients were rated as improved or not changed in the donepezil group than in the placebo group ($P < 0.001$) (Table). Donepezil led to greater improvement than did placebo in cognition (mean difference in change from baseline sMMSE score at wk 24, 1.79; $P < 0.001$), functional measures (mean difference in decline in DAD score at wk 24, 8.23; $P < 0.001$), and behavioral and neuropsychiatric symptoms (mean difference in change from baseline NPI score at wk 24, 5.64; $P < 0.001$). The groups did not differ in incidence of adverse effects (Table).

CONCLUSION

In patients with moderate-to-severe Alzheimer disease, donepezil improved global function, cognition, and behavior.

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*See Glossary.

†Information provided by author.

Donepezil vs placebo for moderate-to-severe Alzheimer disease‡

Outcomes at 24 wk	Donepezil	Placebo	RBI (95% CI)	NNT (CI)
Improvement or no change on CIBIC	63%	42%	50% (20 to 90)	5 (4 to 11)
			RRI (CI)	NNH (CI)
Adverse effects	83%	80%	3.9% (–6.9 to 16)	Not significant

‡CIBIC = Clinician's Interview-Based Impression of Change with caregiver input. Other abbreviations defined in Glossary; RBI, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY

The study by Feldman and colleagues is the first published investigation of the effectiveness of a cholinesterase inhibitor (ChEI) in the treatment of moderate-to-severe AD outside the nursing home setting. Tariot and colleagues (1) studied donepezil in a nursing-home population of mildly to severely demented patients and reported modest improvement in cognitive function over 24 weeks. Feldman and colleagues report a well-designed and well-executed clinical trial. Their findings suggest that donepezil may be as effective in the more advanced stages of AD as in the early and middle stages. The average benefit is modest but consistent across several measures of cognition, global improvement, function, and neuropsychiatric symptoms.

Feldman and colleagues' study further complicates the dilemma faced by clinicians in prescribing ChEIs. Clinicians who regularly prescribe them for patients with mild-to-moderate AD could justifiably extend their prescribing practice to patients in the community who have AD and severe cognitive dysfunction. Although some clinicians may choose to await confirmatory studies, the quality, size, and patient selection criteria of the study by Feldman and colleagues inspires confidence in the generalizability of the results. However, this study does not address key questions about duration of therapy, identification of clinical responders and nonresponders, cost-effectiveness of treatment, or effect on patient and caregiver quality of life. Some clinicians may legitimately not prescribe ChEIs until these critical issues are addressed. A compromise between 2 extreme approaches (i.e., treat all patients with AD living in the community and treat none until we know more) is to give patients a trial of medication, measure cognitive and behavioral changes periodically, and continue medication as long as improvement or stability persists (2). This compromise, although attractive, may not be practical in clinical settings in which careful, reliable, time-consuming measurements of cognitive and functional status are difficult to achieve routinely.

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References

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2. **Press D, Alexander M.** UpToDate, 2001. (CD-ROM or online at http://www.uptodate.com.)

