Is donepezil effective for treating Alzheimer's disease?

Leah S. Steele, MD, CCFP Richard H. Glazier, MD, MPH, CCFP

Rogers SL, Doody RS, Mohs R, Friedhoff LT, the Donepezil Study Group. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. ***Arch Intern Med*** **1998;158:1021-31.**

Research question

Donepezil (Aricept) is the first drug approved by Health Canada's Health Protection Branch for symptomatic treatment of early- to intermediate-stage Alzheimer's disease (AD).[1] Donepezil is a cholinesterase inhibitor that reduces the catabolism of acetylcholine in the cerebral cortex. Is donepezil safe and effective for treating mild to moderate Alzheimer's disease?

Type of article and design

Randomized, double-blind, placebo-controlled trial.

Relevance to family physicians

Alzheimer's disease is the most common cause of dementia worldwide. In 1991, the Canadian Study of Health and Aging found the prevalence of dementia in people older than 85 was 28.5%; AD comprised 64% of these cases of dementia.[1] The social costs of AD are enormous. They include direct costs, such as fees for physicians and hospital services, and indirect costs, such as loss of productivity of patients and their caregivers. A recent cost analysis estimated the annual cost of AD per patient ranged from $9540 for mild disease to $36 800 for severe disease.[2] As family physicians, we have all seen the devastating emotional effect that AD can have on patients and their families. Treatments that attempt to reduce the burden of illness of AD should be of great interest to family physicians, policy makers, patients, and families.

Critical Appraisal reviews important articles in the literature relevant to family physicians. Reviews are by family physicians, not experts on the topics. They assess not only the strength of the studies but the "bottom line" clinical importance for family practice. We invite you to comment on the reviews, suggest articles for review, or become a reviewer. Contact Coordinator, Michael Evans, by e-mail **michael.evans@utoronto.ca** or by fax (416) 603-5821.

Overview of study and outcomes

Four hundred sixty-eight ambulatory patients aged 50 years and older with established diagnoses of mild to moderate AD were considered for the study. Eligible patients had Mini Mental State Examination (MMSE) scores between 10 and 26 and Clinical Dementia Rating (CDR) scores of 1 or 2 (mild or moderate dementia). Patients with any other notable neurologic or psychiatric diagnoses, including depression and substance abuse, were excluded. Patients with serious comorbidities, such as type 1 diabetes; chronic obstructive pulmonary disease; asthma; cancer; B_{12} or folate deficiency; or uncontrolled gastrointestinal, renal, hepatic, endocrine, cardiovascular, or hematologic disease, were also ineligible.

Patients were randomized to receive 5 mg of donepezil, 10 mg of donepezil, or placebo daily for 12 weeks. This course was followed by a 3-week washout period. Patients were assessed at baseline and every 3 weeks. Other medications that affect the central nervous system were prohibited. Outcomes were rated on several scales (**Table 1**). Primary outcomes of interest in this study were patients' performance on two measures: the ADAS-cog, a scale that measures cognition, and the CIBIC-plus, a global scale that measures clinical impression of change in function as perceived by clinicians and caregivers. Because global function is a more patient-oriented measure than cognition, clinicians might find results of the CIBIC-plus scale more relevant to patient care.

Secondary outcomes included scores on another cognitive scale (MMSE), another measure of function (CDR), and a quality of life scale (QofL). Serum levels of donepezil, red blood cell acetylcholinesterase activity, and adverse events were also measured.

Drs Steele *and* **Glazier** *practise at St Michael's Hospital and teach in the Department of Family and Community Medicine at the University of Toronto.*

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Table 1. Dementia measurement instruments

The **Alzheimer's Disease Assessment Scale-cognitive subscale** (ADAS-cog) is an 11-item standardized scale that examines aspects of cognitive performance including memory, orientation, attention, reasoning, language, and praxis. The score ranges from 0 to 70, with higher scores indicating greater cognitive impairment.
The **Clinician's Interview-Based Impression of Change scale with information from caregivers** (CIBIC-plus) rates change in four areas of patients' function (general, cognitive, behavioural, and activities of daily living), based on clinicians' and caregivers' impressions of change. The score ranges from 1 to 7 (1 indicates marked improvement, 4 no change, 7 marked worsening). We could not ascertain the validity and reliability of the scale.
The **Mini Mental State Examination** (MMSE) is a familiar 30-point psychometric test that evaluates cognition.
The **Clinical Dementia Rating—sum of boxes** (CDR-sb) is a global scale that assesses six domains of patient function: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.
The **Quality of Life** (QofLp) test is a seven-item patient-rated scale that evaluates patients' perceptions of their well-being. This scale has not been validated for patients with AD

Results

Of the 468 patients enrolled, 56 (12%) withdrew. More than half of those who withdrew were in the 10-mg donepezil group. At end point, ADAS-cog scores were statistically significantly different for both the 5-mg dose (2.5 points favouring donepezil) and the 10-mg dose (3.1 points favouring donepezil) compared with placebo. The same was true of CIBIC-plus scores with 0.3 points favouring donepezil in the 5-mg group and 0.4 points favouring donepezil in the 10-mg group. The proportion of patients demonstrating clinical improvement at end point (CIBIC-plus score of 1, 2, or 3) was 38% in the 10-mg group, 32% in the 5-mg group, and 18% in the placebo group.

For secondary outcomes, there was a statistically significant dose-response relationship in MMSE scores. Mean drug-placebo differences at end point were 1.0 point and 1.3 points favouring donepezil for the 5-mg and 10-mg groups, respectively. In the 10-mg group, CDR scores showed a non-significant trend toward benefit of treatment. Results of the QofL assessment were variable: significant improvement in the placebo and 5-mg groups, but significant worsening in the 10-mg group.

Adverse events that were significantly more common with donepezil were nausea, insomnia, and diarrhea. Three serious adverse events were possibly related to treatment (a gastric ulcer; a transient ischemic attack; and an episode of aphasia, tremor, and diaphoresis). Treatment had no clinically significant effects on vital signs, hematologic tests, or biochemistry. The withdrawal rate for adverse events was 2%, 4%, and 10% for the placebo, 5-mg, and 10-mg groups, respectively.

Analysis of methodology

This was a well-designed, double-blind, randomized controlled trial. Treatment and control groups were similar in demographic charactenstics and known prognostic factors. An intention-to-treat analysis provided added protection against bias due to patient withdrawals. Prohibiting concomitant medication with CNS effects and adequate double-blinding protected against contamination (the control group getting the treatment) and cointervention (either group getting an additional effective intervention). Wherever possible, clinicians assessing outcomes were also blinded to results of the other relevant measures. These methodologic strengths make us reasonably confident that the results of this trial are valid. We can conclude that donepezil is effective in improving scores on cognitive and global function assessments.

How does the study fit into existing research? Results are consistent with results of two other randomized controlled trials by the same authors that looked at the efficacy and safety of donepezil during 12-week and 24-week periods.[3,4] All three studies showed modest improvements in cognition and function scores; none showed significant improvement in quality of life or activities of daily living. We found only one methodologically weak trial that looked at the long-term safety and efficacy of donepezil.[5]

Application to clinical practice

While the statistical significance of donepezil's efficacy has been established, the clinical significance is uncertain. How important is a 3-point change in the ADAS-cog scale or a 0.4-point improvement on the CIBIC-plus scale? A Food and Drug Administration consensus statement has suggested that improvement on the ADAS-cog scale must be 4 or more to be considered clinically significant.[2] If we accept this cutoff, the 3-point change seen in this study is not clinically relevant to patients. Clinicians familiar with the MMSE will note that a 1.3-point change is very small.

While the mean improvement in cognition might not be clinically significant, some people might have a more marked improvement that is clinically important. In this study, 48% to 57% of patients receiving treatment improved their ADAS-cog scores by at least 4 points. Interestingly, almost a third (29%) of the placebo group showed the same degree of improvement. (Was this the Hawthorne effect, ie, the tendency for subjects to change their behaviour because they are under scrutiny? One person we discussed this with said they would have the same results with a cup of coffee!)

What about the 0.4-point improvement on the CIBIC-plus scale? The clinical significance of this result is not straightforward either. On the CIBIC-plus scale, 4 indicates no change. In this study, mean CIBIC-plus scores were 3.8 (very slight improvement) in the 10-mg group and 4.2 (very slight worsening) in the placebo group—not very impressive. Donepezil looks better, however, when we compare the treatment groups: 38% of patients in the 10-mg group demonstrated clinical improvement at end point compared with 18% in the placebo group—rather more impressive. We can reconcile this apparent disparity by interpreting the results to say that a large proportion of patients with AD will improve with donepezil, but the degree of improvement is likely to be small.

Because the clinical benefit of the drug is small, a close look at the risks associated with treatment is warranted. Nausea, vomiting, and diarrhea were common side effects in 10% to 20% of subjects. The authors said these symptoms tended to be mild and transient. For every 12 patients treated with 10-mg doses of donepezil, one patient discontinued the drug because of side effects. Helping patients to think better does not necessarily help them to feel better.

Both the risks and benefits of the medication could prove different in practice than they seemed in the context of a controlled clinical trial. In other words, we do not know whether these results can be generalized to patients in a typical family practice, since the patients enrolled in this study were healthy apart from their dementia.

Other questions remain about how we tell whether the drug is actually working and "worth it." It will be difficult to tell in clinical practice whether the medication is "working" for our patients without having scores on some of the many scales used in this trial. Donepezil costs patients about $150 each month, a considerable amount that might be better spent on community programs and supportive care. Although donepezil works for some people, it seems impossible to predict who will respond. Can we justify giving donepezil to all patients with AD?

Bottom line

The number of patients needed to treat with 10 mg of donepezil to show improvement in one patient was five in this trial. Improvements in global functioning and results of psychometric tests of cognition were extremely modest. Seven patients had to be treated with 5 mg of donepezil to have one patient achieve this modest benefit. For every 12 patients treated, one patient discontinued treatment due to adverse effects. No evidence to date indicates that donepezil improves the quality of life of patients with AD, nor is there any good evidence of the long-term efficacy and safety of donepezil.

Because some patients might have significant clinical improvement and because it is impossible to predict who will respond, physicians might want to consider a 9- to 12-week trial of donepezil to gauge individual response based on scores on standardized scales. Clinicians who use informal methods of measurement should be mindful of the large placebo effect in these types of trials. If no significant clinical improvement is noted after the trial period, there is little reason to continue the drug. Further research on which patients are most likely to improve and which aspects of functioning are most likely to be affected would be welcomed. ✤

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