AFP Journal Club

The Story Behind the Study

Donepezil to Manage Alzheimer Disease: New vs. Standard Dosing

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Purpose

In *AFP* Journal Club, three presenters review an interesting journal article in a conversational manner. These articles involve "hot topics" that affect family physicians or "bust" commonly held medical myths. The presenters give their opinions about the clinical value of the individual study discussed. The opinions reflect the views of the presenters, not those of *AFP* or the AAFP.

This Month's Article

Farlow MR, Salloway S, Tariot PN, et al. Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: A 24-week, randomized, double-blind study. *Clin Ther.* 2010;32(7):1234-1251.

For more information on evidence-based medicine (EBM) terms, see the EBM Toolkit at http://www.aafp.org/afp/ebmtoolkit.

Alzheimer disease is devastating to the patient and the family. We all wish for a good treatment option. Donepezil (Aricept) has tried to fill this void, but does donepezil (in any dose) actually benefit patients? And, is the new dosage of 23 mg per day superior to the standard dosage of 10 mg per day?

What does this article say?

Mark: This is a randomized, double-blind, 24-week trial comparing 23 mg with 10 mg of donepezil in 1,467 patients 45 to 90 years of age. Patients had "probable" moderate to severe Alzheimer disease as defined by the DSM-IV, but were ambulatory and otherwise healthy. Those with controlled hypertension, diabetes mellitus, coronary artery disease, and hypothyroidism were eligible. Patients with other illnesses were excluded, as were patients with other neurologic diseases that can change cognition. Magnetic resonance imaging or computed tomography was performed within one year of enrollment to rule out other causes of dementia.

Qualifying patients were randomized to 23 mg or 10 mg of donepezil per day. A "double-dummy" design was used because the two drugs looked dissimilar, making blinding impossible. A double-dummy design means that there was a matching placebo for each active drug. Each participant was given two pills: one active and one placebo. Compliance was measured by counting the tablets remaining.

Outcome measures included change in cognition and global functioning as measured by the Severe Impairment Battery (SIB; scored 0 to 100) and the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) scale. Secondary end points included the severe version of the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale and the Mini-Mental State Examination (MMSE). The analysis to determine effectiveness as a function of severity of initial illness was done post hoc.

Overall, 296 of 981 patients (30.2 percent) withdrew from the higher-dose group and 87 of 486 patients (17.9 percent) withdrew from the lower-dose group. On the SIB, the 23-mg dose was superior to the 10-mg dose, *but only by two points on a 100-point scale*, *which is clinically meaningless.* There were no differences between the 23-mg and 10-mg dose when comparing the MMSE, ADCS-ADL scale, and CIBIC-Plus scale scores. The authors concluded that 23 mg per day of donepezil was associated with greater benefits in cognition compared with 10 mg per day in patients with moderate to severe Alzheimer disease.

Should we believe this study?

Mark: No—there are a couple of problems. First, the authors did four comparisons. Three were negative and only one was positive (the SIB). *And the one that was positive was only two points different on a 100-point scale*. So, although this is statistically significant, it is clinically meaningless. There is no discernible benefit for the patient or caregivers. We have seen this kind of thing before. If you remember the study of aripiprazole (Abilify) for depression, the change was three points on a ▶

60-point scale, which did not translate into anything the patients noticed.[1,2] They felt just as depressed as before the addition of aripiprazole.

The authors did do a post hoc analysis that showed a positive result on the CIBIC-Plus scale in patients with advanced Alzheimer disease. The authors rightly point out that this post hoc subgroup analysis "requires additional studies for confirmation."

Bob: Also, the drop-out rate in this study was an astounding 30 percent in the higher-dose group and 18 percent in the lower-dose group.

Adverse effects of donepezil include bradycardia, falls, nausea, diarrhea, and anorexia. In fact, a recent study demonstrated that community-dwelling older persons with dementia who are taking currently available cholinesterase inhibitors have higher rates of hospitalization for syncope, bradycardia, pacemaker insertion, and hip fractures compared with similar patients with Alzheimer disease who are not taking these medications.[3] So, the idea of increasing the dose to 23 mg, potentially resulting in more serious adverse events while achieving no clinical gain, is ill-conceived at best. Many patients living in nursing homes already battle nausea, diarrhea, and subsequent weight loss. We do not need to add to that burden.

Andrea: And why 23 mg? Why not 25 mg or 20 mg? Call me suspicious, but it is too easy to make 20 mg or 25 mg by using the current forms of donepezil.

What should the family physician do?

Mark: We should hope for a better therapy for Alzheimer disease. A systematic review shows that the number needed to treat is 12 to benefit one patient.[4] The American Academy of Family Physicians and American College of Physicians have pointed out that, overall, the average change in cognitive score using the Alzheimer Disease Assessment Scale–cognitive subscale, MMSE, and SIB with donepezil was statistically significant but not clinically important. They suggest that physicians base the decision to start a trial of therapy with a cholinesterase inhibitor or memantine (Namenda) on individualized assessment (grade: weak recommendation, moderate-quality evidence).[5]

Given these dismal results, we should be especially mindful of the adverse effects and stop the drug if weight loss, diarrhea, falls, etc., become a problem.

Andrea: If you are going to use a drug for Alzheimer disease, consider using memantine. The outcomes may not be better, but it has fewer adverse effects.

Bob: We all feel pressured to "do something" for our patients with Alzheimer disease, but sometimes nonaction is the best course. Remember, above all, do no harm.

Main Points

- The current choices for treating Alzheimer disease are poor. Do not expect any significant benefit in the majority of patients, and keep in mind that there are significant downsides, including falls, diarrhea, nausea, and anorexia.
- Remember, when you see a patient who seems to benefit from a drug, neither you nor the patient is blinded to the treatment. We all want to think our treatments work.
- If you want to give high-dose donepezil, use 25 mg of the generic instead of 23 mg of the branded drug. There is likely going to be no difference between these two doses (except cost).

EBM Points

- Something can be statistically significant, but clinically meaningless. In this study, 23 mg of donepezil was statistically better than 10 mg, but only on one of three tests, and by only two points on a 100-point scale. This is clinically imperceptible, yet it will be touted as superior by pharmaceutical companies.
- A "double-dummy" design is used when the two drugs being tested look different from each other, so that group assignment cannot be blinded. In a double-dummy design, there are matching placebos for both administered drugs (two "dummy" drugs) and every patient gets an active drug and a placebo.
- As rightly pointed out by this study's authors, post hoc and subgroup analyses should be used only to generate a new hypothesis that must be tested, and should not be used to show the harm or benefit of a therapy.

If you conduct a journal club and would like to know the next article that will be discussed, please e-mail afpjournal@georgetown.edu with "*AFP* Journal Club notification" in the subject line.

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