Donepezil 23 mg

An empty suit

David S. Knopman, MD

Summary

Donepezil 10 mg/day has been a modestly successful therapeutic agent for the palliative treatment of Alzheimer disease dementia. In 2011, seeking greater efficacy and an extension of the Aricept brand, a 23-mg formulation of donepezil was introduced. A large-scale trial, organized by Eisai, the sponsor, failed to show superiority in their primary analyses of donepezil 23 mg/day in patients with moderate to severe Alzheimer disease dementia vs 10 mg, but the published report used post hoc analyses to claim "statistically significant benefits." There was greater than a 3 times higher rate of gastrointestinal side effects with 23 mg of donepezil compared to 10 mg. Thus, not only does donepezil 23 mg/day increase the likelihood of unacceptable gastrointestinal side effects, it provides no clinical benefits. Aricept 23 mg is about 10 times more costly per pill than donepezil 10 mg.

The discovery of a cholinergic deficit in the brains of patients with Alzheimer disease (AD),[1] the subsequent successful clinical trials,[2] and the marketing of the cholinesterase inhibitor donepezil were important hallmarks in the quest for treatments for AD. Donepezil, especially at the 5 mg dose, but at 10 mg as well, was remarkably well-tolerated and had a very low and avoidable risk of serious adverse events. Even now in 2012, donepezil and 2 drugs that are also cholinomimetic, rivastigmine and galantamine, together with memantine, whose mechanism of action is unclear, remain the only drugs approved for the treatment of AD dementia. There are no drugs approved for the treatment of mild cognitive impairment due to AD.

From its introduction, critics questioned the clinical value of donepezil 10 mg/day. They noted that the benefits of the medication were very modest and frank improvement, rare. Stabilization of symptoms was inferred from the clinical trial results. Of the clinical trials of donepezil, one in particular demonstrated the strengths and limitations of donepezil 10 mg most transparently. This trial, published in *Neurology*® in 2001,[3] used a novel design in which an individually tailored threshold for functional decline was defined prior to randomization for each subject. A survival analysis demonstrated that donepezil was superior to placebo in maintaining daily function, with 51% of donepezil-treated subjects maintaining function compared to only 37% of placebo-treated subjects. A trial, not designed by the sponsor, used another novel

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design,[4] in which subjects on donepezil, memantine, or both were continued or withdrawn from therapy. After 1 year, patients who received ongoing donepezil therapy had 1.9 point higher Mini-Mental State Examination scores compared to those who were withdrawn.

Over the years, there has been a belief that the 10 mg dose of donepezil might not be as high as could be tolerated by most patients, and more importantly, that additional benefits might be found with higher doses of donepezil. To my knowledge, no studies of doses higher than 10 mg were ever published, or even if higher-dose studies were ever carried out. Given the dearth of effective therapies for AD dementia, pursuing evaluations of higher doses of donepezil seemed worthwhile.

The sponsors of Aricept developed a higher-dose formulation of Aricept, 23 mg, and carried out a large clinical trial comparing the 23-mg dose to the 10-mg dose. The development of the larger dose coincided with the expiration of the patent protection for Aricept 10 mg. On its face, the choice of 23 mg as the dose rather than 20 mg is curious. The question for neurologists and other physicians who prescribe cholinesterase inhibitors is whether donepezil 23 mg per day is more effective than 10 mg per day.

The answer is "no." The sponsors of Aricept published the head-to-head comparison of Aricept 10 mg vs Aricept 23 mg in *Clinical Therapeutics*.[5] In the Methods section, the statistical analysis plan states that the study was powered to find a significant difference between treatment groups on the Severe Impairment Battery (SIB)[6] and the Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC+).[7] However, the results showed that while donepezil 23 mg was superior to donepezil 10 mg by 2.2 points ($p < 0.001$) on the SIB, group differences on the CIBIC+ were not significant. Unfortunately, a key tenet of clinical trial analysis was ignored in this report. When the statistical analysis plan of the clinical trial declares end points at the beginning of the trial, and then the trial fails to meet those goals, the trial is considered negative. Such a standard is not legalistic or nitpicking; instead it recognizes that post hoc selection of results is almost always biased and erroneous.[8] Moreover, the rate of gastrointestinal side effects was over 3 times higher (21%) in the first month in the group receiving donepezil 23 mg compared to the group receiving donepezil 10 mg (5.9%). Some of these issues as well as questions about the regulatory process that enabled the marketing of Aricept 23 mg were discussed in *Neurology Today*, volume 11, issue 14, July 21, 2011.

The fact that there was no detectable clinical benefit as measured by the CIBIC+ was not a flaw in the instrument, but rather a predictable result of the miniscule effects of the higher dose of donepezil on daily functioning. The amount of change on the SIB (2.2 points) is so slight that it would have no impact on daily functioning. The SIB is an instrument that is largely unknown to most practitioners. It is a mental status examination for moderately severely impaired patients with AD dementia. The CIBIC+ is a purposely insensitive instrument, meant to detect clinically relevant effects, in order to guard against approval of a drug that had a statistically significant effect on a neuropsychological test but that had no meaning or value to the patient, family, or physician. In the case of Aricept 23 mg, the dual outcome measure methodology worked: compared to Aricept 10 mg, the physicians in the trial could not tell a difference between the 2 doses, even though the objective test yielded a "statistically significant result." By way of comparison, when the SIB and CIBIC+ were used together in clinical trials with memantine vs memantine plus donepezil,[9] and in the memantine monotherapy trial,[10] the

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difference between memantine and placebo on the SIB was 3.4 points in the former and 5.7 points in the latter trial, and the CIBIC+ was positive in both cases.

Despite the lack of added value and the unfavorable side effect profile, the Food and Drug Administration approved the marketing of Aricept 23 mg. The cost of Aricept 23 mg is $7.74 per pill while the cost of donepezil 10 mg is $0.79 per pill (Mayo Clinic Pharmacy, personal communication, July 10, 2012). If 23 mg of donepezil is no more effective than 10 mg and costs 10 time more per day, why would anyone prescribe it? Despite our desire to exhaust all possible alternatives for our patients, Aricept 23 mg offers no benefit.

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