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Letters to the Editor

Current Alzheimer's Medications: Effective Treatment Options, or Expensive Bottles of Hope?

To the Editor:

I am not a medical researcher, nor am I a medical doctor. I am, however, a spouse caregiver for my wife, who is now in moderate stages of Alzheimer disease (AD). My reading of the AD literature, my listening to other spouse caregivers, and my research on the effectiveness of current AD medications all tell me that doctors too often recommend that patients with AD continue taking ineffective “treatment medications.” Well after the time period when even the pharmaceutical manufacturers claim that their products are effective, many doctors continue to prescribe these same ineffective AD medications for their patients.

History

My wife took 2 of the most commonly prescribed AD medications: donepezil (Aricept) and memantine (Namenda). Along with galantamine (Razadyne) and rivastigmine (Exelon), these are 4 of the 5 prescription medications that have been approved by the US Food and Drug Administration (FDA) to treat people diagnosed with AD. A fifth medication, tacrine (Cognex), was also approved by the FDA, but is now rarely prescribed because of safety concerns.¹ All but memantine are termed “cholinesterase inhibitors” that “prevent the breakdown of acetylcholine, a brain chemical believed to be important for memory and thinking.”¹ Memantine works differently, by regulating glutamate, a brain chemical that, “when produced in excessive amounts, may lead to brain cell death.”¹ Each of these medications carries the possibility for side effects, such as nausea, vomiting, or diarrhea, to name a few.¹

Research

Although there is absolutely no research to indicate that any of these medications will stop or cure AD, there is *some* research to indicate that, for *some* patients, these medications *may* slow the rate of decline for a *brief* period of time. However, this research is based on only a few clinical trials of very short duration, and this research is badly flawed in 2 major respects.

The first research flaw is that the “significant positive outcomes” obtained in clinical trials cited by drug manufacturers as “evidence” of the effectiveness of their medications are usually based on results obtained on the Mini-Mental State Examination (MMSE) or Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog) tests. The MMSE, a commonly used AD screening test, is an instrument that was never designed to diagnose AD, and cognitive declines in

some people with early- to moderate-stage AD score may not be accurately measured.² The ADAS-Cog, according to 2 studies reported in 2012, is a test instrument “not subtle enough to properly track changes in the early stages of Alzheimer's.”³ A major study conducted by *Consumer Reports* in 2012⁴ concluded that the differences in scores on the ADAS-Cog for patients taking *any* of the FDA-approved medications, when compared with placebo groups, are “smaller than 4 points, which is so small, it is not considered meaningful.” *Consumer Reports* also concluded that the “small improvements” showing slower rates of decline in activities of daily living as measured by various instruments “would not be considered clinically meaningful by most doctors.”⁴

The second research flaw is that clinical trials cited as evidence of the effectiveness of these medications are few, and of very brief duration, with absolutely no data supporting any positive outcomes beyond that clinical trial duration. I would think that if any pharmaceutical manufacturer had *any* evidence of its medication having *any* positive effects beyond the duration of their brief clinical trials, that evidence would be made public ... in a heartbeat!

All had clinical trials of short duration, all of the positive effects were leveling off or slowing down by the end of the trials, and all testing was with instruments that are not necessarily the best measurements of cognitive performance.

The Web site of Ortho-McNeil Neurologics, a division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., cites only 4 randomized, double-blind, placebo-controlled clinical investigations for galantamine in patients with probable AD.⁵ Using the ADAS-Cog to assess cognitive performance, the 4 trials lasted 21, 26, 26, and 13 weeks, respectively. At the end of these short-duration trials, results had already either leveled off or begun to decline, even for the groups demonstrating initial improvement. *There is not even one study demonstrating that galantamine is effective to any degree whatsoever beyond 26 weeks.*⁵

On the Novartis Web site, one finds data from 5 clinical trials with patients with AD that lasted 12, 24, and 48 weeks using rivastigmine in oral or “patch” form, and all relied on the ADAS-Cog and MMSE to measure outcomes. All trial results show that even for the groups demonstrating improvement on the medication, declines in scores appear after 24 weeks. *There is not even one study demonstrating that rivastigmine is effective to any degree whatsoever beyond 48 weeks.*⁶

On the Eisai/Pfizer Web site, one finds data from 4 clinical trials with patients with AD taking donepezil. Two trials were for patients with mild to moderate AD, 1 for 15 weeks and 1 for 30 weeks. Two trials were for patients with moderate to severe AD, for 24 weeks in Japan and 6 months in Sweden. Once again, even for groups demonstrating improvement on this medication, declines in scores begin at or before the 24-week stage as measured by the ADAS-Cog and other instruments. *There is not even one study demonstrating that donepezil (Aricept) is effective to any degree whatsoever beyond 30 weeks.*⁷

Discussion

What do all clinical trials using cholinesterase inhibitors tell us? Very simply, we learn that of the 11 clinical trials for these 3 medications, 9 of them lasted for 26 weeks or less. We also learn that in every study, even patients showing initial evidence of improvement started to decline after 24 weeks, if not sooner.

And, finally, we learn that *there is absolutely no evidence indicating that patients continuing to take these medications beyond a very limited period of time, 1 year or less, will continue to demonstrate any positive effects these medications may have had.*

And what do we learn from clinical trials about the evidence of effectiveness of memantine? On the Forest Laboratories, Inc., Web site, 2 studies are reported, 1 lasting 24 weeks and 1 for 28 weeks. Outcomes were measured using 2 instruments, 1 to measure activities of daily living and 1 to measure cognitive function. In the 28-week study, after 4 weeks, the group receiving a placebo started to decline; the group receiving memantine showed a slight improvement for 12 weeks, and then started to decline. In the 24-week study, the treatment groups were different. One group received memantine and donepezil, whereas the other group received memantine and a placebo. After 4 weeks, the group receiving memantine and the placebo started to decline, whereas the group receiving memantine and donepezil did not show declines until the 8-week point. *There is not even one study demonstrating that memantine (Namenda), given with or without donepezil, is effective to any degree whatsoever beyond 28 weeks.*⁸

Despite there being no research to support the effectiveness of these AD medications beyond a few months, at best, many doctors continue prescribing these medications for years and years. Not only can these AD medications no longer be helping their patients, but they may actually be causing some harm. Maintaining patients on these medications long term may provide false hope to patients and their caregivers. I refer to these medications as “bottles of hope” because as I watch my wife decline, I know that the medications cannot possibly be helping anymore, if they ever did at all.

For many patients and caregivers, the high costs of AD medications present an economic hardship. Money spent on AD medications is money that might otherwise be spent on day care programs, companions, home health aides, or other services that would actually improve the quality of their lives.

Another problem with continuing to take these medications for many years may be long-term negative side effects. Negative side effects were reported to some degree in all of the short-duration clinical trials, but there are no data on long-term negative side effects. Side effects not initially apparent may surface after continuing to take these medications year after year.

Doctors must be realistic and honest with both patient and caregiver. Absent research to the contrary, doctors should recommend that their patients discontinue taking these medications after a year or 2 at the most.

The *Best Buy Drugs Report*, issued by Consumers Union in May 2012, was not given much publicity until excerpts appeared in the *Washington Post* on January 7, 2013. Consumers Union, which reviewed more than 1100 research studies and articles on AD medications, begins the recommendations section of their comprehensive 2012 report with this statement: “The medications used to treat mental decline in people with Alzheimer’s disease are not particularly effective. When compared to a placebo, most people who take one will not experience a meaningful benefit. And it is the rare person who has a significant delay in the worsening of their symptoms over time.”⁹ The recommendations page concludes with these words, “if the person taking the drugs does not show signs of improvement within three months, it is unlikely they ever will, so the drug should then be stopped.”⁹

The Research Center of the Alzheimer’s Association provides much information about treatments for AD. Their conclusion with respect to current medication is this: “On average, the five approved Alzheimer’s drugs are effective for about six–12 months for about half of the individuals who take them.”¹⁰

The National Institutes of Health also recently affirmed that these AD medications are largely ineffective beyond a limited period of time. The executive summary of its comprehensive “Alzheimer’s Disease Progress Report,” 2011–2012, concludes that the current FDA-approved AD medications “may help some people” ... but even for those it does help, it is “only for months to a couple of years.”¹¹

Conclusion

Doctors should definitely prescribe AD medications for several months and even up to a year or 2 if they or their patients or caregivers see positive effects. But doctors should not recommend that patients continue taking these medications once they are obviously ineffective. This practice must stop.

Doctors must accept that AD medications eventually become expensive “bottles of hope” that will not slow down the inevitable degenerative progression of AD. Doctors must also accept that, by continuing to prescribe these medications year after year, long after they can possibly still be helpful, they may unintentionally be doing their patients and caregivers more harm than good.

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