Antipsychotics May Boost Alzheimer's Mortality

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Antipsychotics appeared to increase the risk of death in patients with Alzheimer's disease, especially if taken for more than 12 months, in a randomized controlled trial.

Nursing home patients with Alzheimer's who continued taking the drugs for 1 year were 7% more likely to die than were those who discontinued them, and the mortality difference escalated over the 4-year study. By the end of the trial, just 26% of those taking the drugs were still alive, compared with 53% of those taking a placebo, Dr. Clive Ballard of King's College, London, and his associates wrote in the Lancet (doi:10.1016/S1474-4422[08]70295-3).

The authors did support a limited use of the drugs, particularly in patients with severe dementia-related aggression, geriatrician Karl Steinberg noted in an interview. But the risks must be carefully considered.

"The authors make it clear that in some clinical situations, the benefits of treatment seem to outweigh the risks, but it's important to obtain informed consent when we choose to utilize them," said Dr. Steinberg, who is in a group practice in Oceanside, Calif.

The findings seem to support the Omnibus Budget Reconciliation Act of 1987, which mandated gradual dose reductions of antipsychotics in nursing home residents, he added. "We need to keep in mind that the patients for whom we prescribe these medications are suffering from significant dementia and already nearing the end of life, where quality of life should be a major concern."

The trial comprised 165 nursing home residents with Alzheimer's disease (mean age 89 years). At baseline, all patients were taking an antipsychotic medication. Most (93%) were taking either risperidone or haloperidol; other agents included thioridazine, chlorpromazine, and trifluoperazine.

Patients were randomized to either continue treatment (83) or discontinue treatment by taking a placebo. Because 37 patients did not start treatment, 64 were left in each treatment group. The 12-, 24-, 36-, and 42-month survival rates were analyzed among those who began taking their study medication, regardless of whether they stopped at any time during the study.

After 12 months, those on placebo were 7% more likely to survive than were those on an active agent (70% vs. 77%); the difference was statistically significant. The disparity grew as the trial continued. At 24 months, the cumulative survival rate was 71% in the placebo group vs. 46% in the active group; at 36 months, the rate was 59% vs. 30%; and at 42 months, it was 53% vs. 26%.

Death certificates were available for 78%. More deaths of a probable vascular nature occurred in the placebo group; there was no indication that antipsychotics contribute to cerebrovascular deaths. The reasons why the biggest difference in mortality occurred after the first 12 months of the trial are unclear, the researchers wrote.

They noted that up to 60% of nursing home residents with dementia in Europe and North America receive antipsychotic medication, despite studies suggesting that the risks outweigh any possible benefit.

"There is clear evidence of a significant increase in adverse events, including parkinsonism, sedation, oedema, chest infections, accelerated cognitive decline, and cerebrovascular events in patients with Alzheimer's treated with antipsychotics," they noted. Alternative treatments include psychological management, memantine, and antidepressants, which "might be safer and effective for some neuropsychiatric symptoms."

The results confirm other evidence of a link between the drugs and increased morbidity and mortality in dementia patients, Alzheimer's researcher Marwan Sabbagh said in an interview. "This risk was the impetus for the black box warning issued by the FDA for risk associated with antipsychotic use specifically in dementia," said Dr. Sabbagh, director of clinical research at the Sun Health Research Institute, Sun City, Ariz.

"What makes this more compelling is that it is not simply an observational study. Rather, this is objective evidence in a randomized, placebo-controlled study that [Alzheimer's disease] subjects taking antipsychotics had demonstrable increases in mortality," Dr. Sabbagh said. "This should compel practitioners to employ additional caution when administering this class of medication to demented individuals."

The study was funded by the U.K. Alzheimer's Research Trust. Dr. Ballard noted financial relationships with many companies that manufacture antipsychotics and Alzheimer's medications. ■

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say about bapineuzumab is that it's not going to be a miracle therapy," he said.

A long-term follow-up study of patients enrolled in the early AN-1792 immunotherapy trial "doesn't look great for amyloid, either," he said. The AN-1792 trial was halted early, in 2002, when some patients developed encephalitis after getting the vaccine. The follow-up showed that the vaccine did clear plaques, but that clearance didn't affect cognition or survival. In fact, the authors said, "seven of the eight immunized patients who underwent postmortem assessment, including those with virtually complete plaque removal, had severe end-stage dementia before death" (Lancet 2008;372:216-23).

Dr. Hardy doesn't think that slow progress on antiamyloid drugs negates the theory's basic truth, though—at least for a subset of patients. "There's no doubt at all that the amyloid hypothesis explains the disease in families with mutations of the amyloid precursor protein and presenilin genes. A much more open debate is whether the same process is at work in the typical Alzheimer's patient."

But drug companies must target this larger population in order to create a financially successful therapy, and the lack of progress has them fidgeting, Dr. Hardy said. "Every drug company is worried now and wondering if they should widen to other therapies, including tau-targeted drugs. And to this I say, 'Yes, of course you should have other strings for your bow.'"

The essential mystery of amyloid further complicates things, Dr. Hardy said. "We don't really know if amyloid has a function. It could be that amyloid is a response to vascular damage. We all ignore the fact that amyloid deposition occurs to a large extent in the vasculature. … It could have something to do with vascular repair."

That worry also plagues Mark A. Smith, Ph.D., a professor of pathology and Alzheimer's researcher at Case Western Reserve University, Cleveland. "We have said for a long time that amyloid is doing something important in the brain. It could be acting like a vascular sealant in areas of injury. It forms structural scaffolding for blood vessels, and if you start getting rid of that scaffold, you'll see problems in the blood-brain barrier." This reaction probably caused the brain inflammation seen in the AN-1792 trial, he said.

Dr. Smith, a paid consultant for several companies investigating non–amyloid-related therapies, is among a minority of researchers who resist the amyloid theory, although the overwhelming focus on amyloid has virtually drowned out their opinion. The amyloid research momentum is so strong right now that only more high-profile failures will begin to temper it, he said.

"People still can't believe it's not working, and they're waiting for the results of the phase III vaccine trial," as well as new data on β-secretase inhibitors, theorized to reduce the buildup of plaque-forming AB-42. "At this point, the research community is so totally invested in amyloid that we need to either get something else that works or have an honest, sober, the-party's-over discussion of why amyloid-targeted therapies are failing."

Dr. Rachelle Doody, director of the Alzheimer's Disease and Memory Disorders Center at Baylor College of Medicine, Houston, has some ideas. The failure of antiamyloid drugs illustrates not a failure of the theory, but the failure of specific drugs and possibly of drug companies to follow a comprehensive and logical phase II plan, she said in an interview.

"Companies want their drug to be labeled as a disease-modifying agent as soon as possible; the implication is that it can then be priced at a higher rate. And because they are going for that, they are designing phase II trials that are long and costly but don't give them all the information they need."

An ideal future for an amyloid-based approach might be a combination of immunotherapy to break up plaques, and secretase inhibitors to prevent the formation of new ones.

Ideally, by the time any agent finishes phase II, there should be clear evidence that it is both safe and effective in the primary end point. "Neither tramiprosate nor tarenflurbil had a clear signal in phase II, and neither did bapineuzumab, although it at least had some signal. Another phase II study for bapineuzumab would have been nice to further clarify this proposed subpopulation of interest."

Companies could also modify their research track to prove first that a drug confers symptomatic benefit, and then examine its possible disease-modifying properties. That is the path Medivation Inc. is following with dimebon—the only bright note in late-stage clinical trials this year. The antihistamine, thought to boost mitochondrial function, succeeded where the antiamyloids failed, significantly improving cognition, behavior, and function in Alzheimer's patients, although it did not modify disease progression.

"Dimebon probably is a disease-modifying drug, but proving this requires long-term studies," said Dr. Doody, primary investigator on the phase II trial. "But many pharmaceutical companies fear that a drug will be priced too low if they go for symptomatic approval first."

Dr. Doody follows research on dozens of potential Alzheimer's drugs, only some of which are antiamyloids. But she agreed that these compounds grab the lion's share of attention. "The amyloid story gets articulated over and over again because a lot of people in academia feel most comfortable with a story that's already been told. But there's no a priori reason that any one of these approaches should work better than another."

In fact, rather than a one-step cure, the compounds may be best used in primary prevention, said Dr. Marwan Sabbagh, chief medical and scientific officer of Sun Health Research Institute, Sun City, Ariz. "The problem is, we may be approaching it too late," he said in an interview. "By the time you clinically manifest dementia, it might be too late for the drugs to help, even if they clear the plaques.

"The ideal future for an amyloid-based approach would probably be a combination of immunotherapy to break up existing plaques, and secretase inhibitors to prevent the formation of additional plaques," said Dr. Sabbagh, an investigator on the phase III bapineuzimab trial. Putting this to practical use will require big advancements in early detection. ■