CLINICAL CAPSULES

Deaths Reported in Donepezil Trial

Eleven of 648 patients died while taking donepezil (Aricept) in a trial of the drug for the treatment of vascular dementia, according to preliminary study results announced by Eisai Co. Ltd., the drug's maker. None of the 326 patients taking placebo during the 24-week trial died.

The multicenter, randomized, double-blind study was conducted in nine countries and enrolled only people with vascular dementia (VaD), who had no prior diagnosis of Alzheimer's disease.

Those patients taking donepezil showed improvement on measures of cognition, compared with those on placebo, but there was no benefit observed on global function, the trial's other primary measure.

An analysis of adverse events data revealed that the mortality rate of 1.7% for the donepezil treatment group in this trial was consistent with that observed in a combined analysis of two previous VaD studies (1.7%) and was lower than that reported in the general population of patients with vascular dementia. However, the mortality rate observed in the placebo group of this study (0%) was lower than that seen in the placebo groups in the combined analysis for the two prior VaD studies (2%), and was lower than the rate for the general VaD population.

Additional analyses of vascular events such as stroke and myocardial infarction for the three VaD trials, alone and combined, showed a statistically significant higher risk of a vascular event in the donepezil group, compared with placebo.

Adverse events in the treatment group occurred at a rate greater than 5%, and twice the rate of placebo, for abdominal pain (5.1% vs. 2.5%), anorexia (5.7% vs. 2.8%), and nausea (9.9% vs. 4.3%).

Another FDA Panel: No ADHD Black Box

The potential for certain cardiovascular and psychiatric adverse events associated with ADHD drugs should be well communicated, but not in the form of a black box warning, a Food and Drug Administration advisory panel agreed last month.

Instead, the FDA's Pediatric Advisory Committee recommended that information about reported psychiatric and cardiovascular events be included in the half-page highlights box that appears at the beginning of the label in the newly designed format for drug labels that was introduced in January.

The panel also supported the use of a medication guide, dispensed with each prescription at the pharmacy. No formal votes on these issues were taken.

In February, another panel—the FDA's Drug Safety and Risk Management Advisory Committee, which reviewed cardiovascular event reports—narrowly recommended adding a black box warning to ADHD drug labels to alert physicians and the public that cases of sudden death and nonfatal cardiovascular events have been reported in children and adults on these drugs.

At a press conference held after the meeting, Dr. Robert Temple, director of the office of medical policy at the FDA, said that the agency would quickly start working on implementing the panel's recommendations. The area of uncertainty pertains to the cardiovascular risks in adults, he added.

Atypicals Show Modest Behavior Effect

Atypical antipsychotics appear to have a modest effect on behavioral symptoms in elderly dementia patients, but the effectiveness of nonpharmacologic treatments is less clear, according to a metaanalysis presented at the annual meeting of the American Association for Geriatric Psychiatry.

Dr. Mark B. Snowden of the department of psychiatry and behavioral sciences at the University of Washington, Seattle, and his colleagues used meta-analysis techniques to compare the efficacy of nonpharmacologic treatments with that of pharmacologic therapies. The researchers identified five randomized, controlled trials of antipsychotic drugs and three randomized, controlled trials for nonpharmacologic interventions. The drug trials included four atypical drugs and one traditional antipsychotic drug.

The calculated effect size for nonpharmacologic interventions was –.088, which was not statistically significant. In comparison, the calculated effect size for pharmacologic interventions was –.23, which "would be considered small to modest at best," Dr. Snowden said. "In this instance, the finding was consistent enough across studies that it is statistically significant."

Only the pharmacologic studies provided data on the number of patients whose condition did or didn't improve. Those studies yielded a statistically significant mean odds ratio of 1.87; thus, patients had an 87% chance of improving with treatment. The researchers also calculated the benefit-to-harm ratio for antipsychotic treatment. "For every 14 people who got a drug and improved, you would expect one excess death," Dr. Snowden said.

The FDA has issued a public health advisory about increased mortality associated with off-label use of atypical antipsychotics among elderly patients.

—From staff reports