Hallucinations a Concern

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pensed with each prescription at the pharmacy, as another way to communicate these risks as well as the benefits of the drugs in simple language to parents and caregivers. No formal votes on these issues were taken.

In February, a different 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. That panel also agreed that a medication guide should be provided with ADHD drug prescriptions, informing people about potential cardiovascular risks—including sudden death—that have been reported in children on these drugs.

"We did feel there was an important message about improving communication about certain adverse events that were seen both in controlled data and adverse event data, but did not feel that they rose to the level of a black box," Pediatric Advisory Committee chair Dr. Robert Nelson said after the meeting.

Dr. Nelson, of the department of anesthesia and critical care medicine at the Children's Hospital of Philadelphia, pointed out that these comments applied to children in whom the data on the effectiveness of ADHD drugs were strong.

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 pertained to the cardiovascular risks in adults, he added, noting "we still have to come to grips with" some of the recommendations made at the February meeting.

The issues the pediatric panel agreed should be communicated were reports of psychosis or mania, which included hallucinations; reports of aggression that can emerge with treatment, which they agreed should be distinguished from the aggression that can be a symptom of ADHD and can respond to treatment; and reports of cardiovascular events associated with the drugs. Hallucinations were considered a particular problem: There were several reports of children who described visual and tactile hallucinations of insects, snakes, or worms.

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The panel did not believe there was a clear sign of a suicidality link with the drugs other than atomoxetine (Strattera), which has a black box warning about suicidality because of findings in controlled clinical trials. There were also four reports of suicidality in patients on modafinil, which is under review and is not approved. These reports were difficult to evaluate because of the high background rate of suicide in the adolescent population.

Overall, the panel was not concerned about cardiovascular risks in the general pediatric population, except for patients with underlying heart disease. They made a distinction between the cardiovascular risks of these drugs in pediatric patients with known underlying heart disease, who they agreed could be treated with one of these drugs only in a controlled research environment.

The difficult problem is that some of the sudden deaths reported in children on ADHD medications were in children with an unidentified underlying heart defect. But the panel generally agreed that it would not be cost effective to provide screening with EKGs and echocardiography to all children for unidentified heart disease.

Instead, they described signs and symptoms that could heighten a physician's suspicion to do a work-up, such as chest pain (especially with exercise) and a family history of arrhythmias. They also recommended that families and children should be educated about possible signs and symptoms that might be a sign of cardiovascular events, such as shortness of breath and chest pain—especially if these symptoms occur with exercise—and that families be urged to report any of these symptoms to their physician immediately.

The pediatric cardiologist on the panel, Dr. John Moore, of Mattel Children's Hospital at UCLA, Los Angeles, said he believed that in the general population of children without a heart condition, these drugs are well tolerated. But the two categories of children who may be at a heightened cardiovascular risk—those with a known heart condition ("structural or otherwise") or with cardiomyopathy, and those with undiagnosed heart disease—should be included in the label.

Those with known conditions are probably at risk for sudden death if they are put on these drugs, and most practitioners have avoided treating them for ADHD, although the prevalence of ADHD in this population may be fairly high. These patients "may be a population that should be specifically studied in a very controlled way," he said.

From 1992 to February 2005, there were 11 pediatric sudden deaths in people aged 18 years and younger on methylphenidate reported to the FDA's system; 13 in young people on amphetamine and dextroamphetamine; and 3 on atomoxetine. Among these cases, risk factors or autopsy findings included bicuspid valve abnormalities, cardiac hypertrophy, idiopathic hypertrophic subaortic stenosis, unexplained increase in or toxic amphetamine level, and a heart murmur.

Nonfatal cardiovascular or cerebrovascular serious adverse events reported in 1999-2003 included 18 for amphetamine and 8 for methylphenidate; the adverse events included cases of syncope, chest pain/MI, strokes, dyspnea, and arrhythmias. Cases of arrhythmias, syncope, and other nonfatal cardiovascular events have also been reported to the FDA for atomoxetine, and are currently being reviewed.

There also have been postmarketing reports and reports in the literature of psychosis or mania, particularly hallucinations—as well as reports of aggression or violent behavior—in patients on ADHD drugs. In the cases of psychosis or mania, about one-third to one-half of cases improved once the drug was stopped, according to the FDA. ■

FDA Panel: Modafinil Is Not Safe for Treating ADHD in Teens

BY ALICIA AULT
Associate Editor, Practice Trends

Gaithersburg, Md. — A Food and Drug Administration advisory committee said modafinil is not safe for treating ADHD in children and adolescents by a 12-1 vote, although committee members unanimously agreed the drug was effective for that indication.

At a meeting of the FDA's Psychopharmacologic Drugs Advisory Committee, the panel members were mainly concerned about modafinil's potential to cause Stevens-Johnson syndrome (SJS). The severe rash, which is often due to a hypersensitivity reaction to a drug, can be fatal in up to 5% of cases, according to Dr. Michael E. Bigby of the dermatology department at Harvard Medical School, Boston, and consultant to the panel.

Among 933 children and adolescents exposed to the drug during trials, there were 12 cases that could have been definite erythema multiforme (EM) or SJS, early prodromal EM or SJS, or suggestive of prodromal EM or SJS—a rate of 1.29%, said Dr. Glenn B. Mannheim, a medical reviewer in the FDA's division of psychiatry products.

The panel's discussion focused on one case that seemed most likely to be SJS—indicating a 1 in 1,000 risk. But they were not certain that was the true risk.

Dr. Bigby and Dr. Mannheim said more cases could occur once modafinil (Provigil) is more widely used—even though there have been no reports of SJS in the 36,000 children who were prescribed the drug off-label in 2002-2005.

Given the trial data and the assumption that modafinil could capture 10% of the market for children under age 19 (based on other stimulants' sales), there could be 500-3,250 cases of EM or SJS, and 25-488 deaths, said Dr. Mannheim.

The dichotomy between the postmarketing experience and the trial data prompted the FDA to seek its advisers' input, said Dr. Robert J. Temple, director of the FDA's office of medical policy.

The FDA usually follows the advice of its panels.

The FDA has received six reports of serious skin reactions in adults, said Dr. Mannheim.

"I'd like to see an opportunity for the company to come back with additional data. That will give us additional assurance that this case was a fluke," said panel chair Dr. Wayne K. Goodman, chair of the department of psychiatry at the University of Florida, Gainesville.

The committee said modafinil's manufacturer, Cephalon Inc., should conduct a 3,000-patient, open-label study to further clarify the risk of SJS.

After the meeting, Dr. Thomas Laughren, director of the FDA's division of psychiatry products, told reporters that if a case turns up in such a study, "then they have a problem."

It was not clear why children had higher rates of skin-related adverse events than adults, but Dr. Mannheim noted that lab tests indicated that they had a 7-16 times higher area under the curve ratio of modafinil sulfone, a metabolite. The levels could not be explained by higher milligram-per-kilogram dosing, he said.

In two of the three phase III studies, children were given a flexible dose with weekly titration (170 mg, 255 mg, 340 mg, or 425 mg). In the third study they were given a fixed dose, with those under 30 kg receiving 340 mg daily, and those over 30 kg receiving 425 mg daily.

The primary outcome was the total score on the school ADHD rating scale. In all three trials, children taking modafinil had a more significant drop in scores than those taking placebo. The total score for modafinil recipients—just over 20—was close to the normative score for a 10-year-old male, according to a Cephalon statement.

Panelists did not dispute the drug's efficacy, although many said it would not be a first-line choice.

Lesley Russell, Cephalon's senior vice president of worldwide clinical research, said modafinil offers clinicians an alternative, especially when children don't respond to other marketed drugs.

But Dr. Temple said that even though it's plausible that modafinil might work in nonresponsive children, the company had not proved that.

"The mere fact that people given a second drug respond after failing to respond to the first tells you nothing at all," he said.

According to a company statement, modafinil may be less addictive and less apt to be diverted because it does not offer a "high" to recreational users. Jeffrey L. Vaught, executive vice president of research and development at Cephalon, said the drug is not water soluble and is not stable at high heat, which makes it difficult to crush for injection or smoking. Studies have shown that modafinil does not activate reward centers in the brain, and that it does not cause release of dopamine in vitro or in vivo.

The Drug Enforcement Administration has deemed modafinil a schedule IV drug; other stimulants used to treat ADHD, such as Ritalin, are schedule II.

Despite potential advantages, the panel did not want modafinil to be marketed for children yet.

"I think we did err on the side of consumer protection," said Dr. Goodman. ■