Hallucinations a Concern

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

BY ALICIA AULT

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 hyper-sensitivity 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 pro-dromal 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 (Provig-il) 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 500-1,250 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 problem was a fluke,” said panel chair Dr. Wayne K. Goodman, chairman of the department of psychiatry at the University of Florida, Gainesville.

The panel did not want to have the drug’s marketing license revoked because it does not cause release of dopamine in vitro or in vivo. 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 get a second drug response 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 of-fer 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 sta-ble at high heat, which makes it difficult to crush for injection or smoking. Studies have shown that modafinil does not acti-vate 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, while other stimulants used to treat ADHD, such as Ritalin, are schedule II.

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

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From 1992-2000, 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 dextroamphetamine, and 20 on amphetamine. 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 cerebrovascu-lar events associated with the drugs. There have been no reports of SJS in the pediatric population, except for patients with underlying heart disease. They made a distinction between the cardiovascular risk of these drugs in pediatric patients with known underlying heart disease, and those with undiagnosed heart disease. Those with a known heart condition (“structur-al or otherwise”) or with cardiomyopathy, and those with undiagnosed heart disease—should be included in the label.

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 they could not be sure that they would not be 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.

There were several reports of children who described visual and tactile hallucinations of insects, snakes, or worms. These children reported seeing insects, snakes, or other strange objects, as another way to communicate concerns 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 communica-tion about certain adverse events that were seen both in controlled data and adverse events that they rose to the level of a black box,” Pediatric Ad-visory Committee chair Dr. Robert Nel-sohn said after the meeting.

At a press conference held after the meeting, Dr. Robert Temple, director of the office of medical policy at the FDA, said the agency would quickly start working on implementing the panel’s rec-ommendations. 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 recom-mendations 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 distin-guished from the ag-gression that can be a symptom of ADHD and can respond to treatment; and reports of cardiovascu-lar events associated with the drugs. Hallucinations were con-sidered a particular problem: There were several reports of children who described visual and tactile hallucinations of insects, snakes, or worms.

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 sui-cidality 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. There were reports difficult to evaluate be-cause of the high background rate of sui-cide 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 risk of these drugs in pediatric patients with known underlying heart disease, and those agreed could be treated with one of these drugs only in a controlled research environment.

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