Panel: Modafinil Not Safe for ADHD in Teens

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GAITHERSBURG, MD. — A Food and Drug Administration advisory committee declared that 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 that 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.

Quetiapine Has Efficacy for Adolescent Mania

Quetiapine was at least as effective as divalproex in alleviating manic symptoms in adolescents in a randomized, double-blind pilot study, wrote Dr. Melissa P. DelBello and her colleagues at the University of Cincinnati, Ohio.

The 28-day pilot study of 50 adolescents aged 12-18 years was the first known to directly compare an atypical antipsychotic with an antiepileptic in adolescents with mania, the researchers noted (J. Am. Acad. Child Adolesc. Psychiatry 2006;45:305-13). The study was supported by a grant from AstraZeneca Pharmaceuticals, which markets quetiapine (Seroquel), and is one of the many companies from which Dr. DelBello has received research funding.

The adolescents who received quetiapine started with a 100-mg dose on the first day, which was increased to 400 mg by days 4-7, up to a maximum of 600 mg/day. Those who received divalproex started with a 20-mg/kg dose on the first day, which was increased to achieve serum valproic acid levels of 80-120 µg/mL. At the end of the study, the mean doses were 412 mg/day to 422 mg/day in the quetiapine group, and a valproic acid level of 101 µg/mL in the divalproex group.

Overall, patients in both groups showed statistically significant improvements in their scores on the Young Mania Rating Scale at the end of the study. The response was quicker among the quetiapine patients, compared with divalproex patients, and the overall response rate on the Clinical Global Impressions–Bipolar Version–Improvement scale was significantly greater in the quetiapine group than in the divalproex group (72% vs. 40%).

—Heidi Splete

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. ■