Monitor Children on Antidepressants, FDA Urges

BY NANCY WALSH
New York Bureau

New York — Now that all antidepressants carry a black box warning regarding pediatric suicidality, physicians who treat children with depression need to institute closer monitoring and pay careful attention to informed consent, Bruce Waslick, M.D., said at a psychopharmacology update sponsored by the American Academy of Child and Adolescent Psychiatry.

In response to analyses identifying an increased risk of suicide during the early weeks of antidepressant treatment, the Food and Drug Administration recommends that children and adolescents be actively monitored for worsening of depression, response to treatment, and emergence of suicidality.

"I am not trying to dissuade you from using antidepressants," said Dr. Waslick of the division of child psychiatry at Columbia University, New York.

The importance of pharmacotherapy was highlighted by findings from the Treatment for Adolescents With Depression Study (TADS), which showed that cognitive-behavioral therapy plus fluoxetine was superior to either modality alone. (See box.)

"You will need to make a risk-benefit calculation and try to give patients and parents some understanding about the safety concerns. Try to give them a rational view of the available evidence and take their preferences into account," he said.

"Based on my experience with TADS and from an objective reading of the literature, I do think antidepressants have a role in the treatment of kids with depression," Dr. Waslick said.

The FDA's black box decision followed a year of controversy and media attention that left fluoxetine the sole antidepressant with a pediatric indication for major depressive disorders. That decision, in turn, has left clinicians without clear guidance on several issues, such as what to do if an adequate trial of fluoxetine is unsuccessful.

There also are no clear guidelines on medicolegal issues and physician liability, but closer monitoring during the initial phase of treatment is key. According to the FDA, patients should be seen weekly for the first 4 weeks, biweekly for the next 4 weeks, and then monthly or as clinical need dictates.

Informed consent is very important. "I don't know if it will protect you regarding liability issues, but I think it's the right thing to do," he said.

Besides the black box warning, the FDA plans to send letters to parents. "I've seen a draft of the letter, and it emphasizes the risks and doesn't talk too much about the benefits," Dr. Waslick said. "This is black box plus."

After the initial reports of potential suicidality associated with paroxetine (Paxil), the FDA requested that all manufacturers of selective serotonin reuptake inhibitors and atypical antidepressants go through their data to find suicide-related events in both active treatment and placebo patients. Companies were asked to prepare vignettes about these events, detailing the circumstances and outcome, so that FDA officials might determine whether they were indeed drug related and see if there was some way of assessing risk.

The initial analysis of these data, done by chief FDA scientist Andrew Mosholder, M.D., found 109 "possibly suicide-related" events in 4,100 subjects. Twice as many events were reported in patients taking the active drug than in those taking placebo.

In February 2004, a public hearing was held on antidepressant safety but Dr. Mosholder was not permitted to present his data. When word of the FDA's action was leaked to the media, a firestorm resulted, with charges that dangers were being suppressed, leading to congressional investigations.

The FDA's position was that the initial analysis was unreliable and that investigations were ongoing. In an attempt to have the data analyzed in a blinded fashion, FDA officials contracted with a group of independent suicide experts from Columbia University to undertake a more definitive analysis.

The Columbia panel analyzed the suicide events in two ways: when reported as an adverse event/serious adverse event, and according to scores on suicide items on depression questionnaires.

Presenting its findings in September 2004, the panel concluded that there was what Dr. Waslick called a "low-magnitude, low-frequency suicide [ideation or behavior] signal" in the adverse events/serious adverse events data set. However, evaluation of the systematically collected rating scale scores found no evidence of a suicide signal, he said.

Despite that discrepancy, the FDA concluded that no antidepressant is completely risk free and determined that all the drugs—even the older tricyclics and MAO inhibitors—would carry the black box warning.

"I have been using these drugs for 15 years and always assumed any suicidality was a result of the underlying disease," Dr. Waslick said. "But the FDA has concluded that this adverse event signal is evidence that a relationship exists between antidepressant treatment and emergent suicidality," he said.

Nonetheless, adolescent suicide rates have been falling in the past decade. "Widespread use of antidepressants doesn't seem to be leading to an epidemic of completed suicides. Whether the falling suicide rate is actually related to the benefits of antidepressant medication—and there's some supportive evidence suggesting that might be the case—we don't know yet. Keep following this story," he said. ■

Fluoxetine and CBT Are Teamed Up

The Treatment for Adolescents With Depression Study (TADS) was a multicenter, randomized trial comparing treatment with fluoxetine alone, cognitive-behavioral therapy (CBT) alone, the two combined, and placebo. In the initial 12-week phase of the trial, the response rate for patients in the combination group was 71%, and for the fluoxetine alone group it was 61% (JAMA 2004;292:807-20).

The 43% response rate in the CBT alone group did not differ significantly from the placebo response rate of 35%, said Dr. Waslick, who was an investigator for the trial.

Longer-term data from TADS have yet to be analyzed, but the emerging message is that the combination of medication and CBT is best. This finding was particularly important for the most severely ill patients in the study, who clearly needed medication to get better, he said.

The trial was funded by the National Institute of Mental Health and has a degree of credibility not necessarily shared by all industry-funded trials, which typically have been done under the condition of pediatric exclusivity.

This incentive provides drug companies with a 6-month extension on their patent if they undertake studies of the agent in pediatric populations, but they are under no obligation to publish their findings. Examination of industry-generated data on antidepressants—some of which came out only under the Freedom of Information Act—has found that, aside from fluoxetine, the evidence of their efficacy in children is "underwhelming," Dr. Waslick said.

Dextromethorphan Abuse Now 'Rampant' Among Teens

BY TIMOTHY F. KIRN
Sacramento Bureau

Incline Village, Nev. — A 14-year-old intoxicated and confused girl is brought into the emergency department by her parents. She has nystagmus and is extremely ataxic. One of her friends reports that she may have taken some "skittles."

What are "skittles"? How about "red hots"? "Triple C"?

All are street names for Coricidin, the dextromethorphan-containing cough and cold medication that has become one of the more frequent reasons for calls to poison control centers over the past few years, Steven R. Offerman, M.D., said at an annual emergency medicine meeting sponsored by the University of California, Davis.

"It is just rampant now," said Dr. Offerman in the toxicology division of the department of emergency medicine at the University of California, Davis. "We're seeing this in poison control all the time."

Between 2000 and 2003, the number of calls to poison control centers nationwide involving abuse or misuse of dextromethorphan by teenagers has roughly doubled, to 3,271 calls in 2003, according to the American Association of Poison Control Centers. Although there are several products that contain dextromethorphan, almost 90% of the calls involve Coricidin.

The reason that product is so popular has to do with the fact that it comes in gelatin tablets, Dr. Offerman said.

Dextromethorphan was first approved in 1958 and was introduced as a replacement for codeine in cough medications. The first product, Romilar, came in tablet form. Its abuse potential was quickly discovered, and in the 1970s Romilar tablets were taken out of the over-the-counter market. New products put dextromethorphan into cough syrups intentionally designed with a bad taste to discourage abuse.

In the 1990s, however, several products reintroduced it in tablet form.

The high that teens get from dextromethorphan is described as an LSD-like, hallucinogenic high. Dextromethorphan is a prodrug converted to the d-isomer of levorphanol, a semisynthetic morphine derivative, which noncompetitively antagonizes *N*-methyl-D-aspartate (NMDA) receptors, and possibly also affects serotonin receptors.

Teens who are in the know talk about using specific dosages to reach different "plateaus": the first, a mild stimulant effect (100-200 mg); the second, intoxication with mild hallucinations (200-400 mg); the third and most sought after, an "out of the body" experience (300-600 mg, or 14-16 Coricidin HBP Cough/Cold tablets, each of which contains 30 mg dextromethorphan hydrobromide).

At doses above 600 mg, individuals become fully dissociated, the fourth plateau.

Web sites contain recipes for making dextromethorphan cough syrups more palatable, and give instructions on how to extract it from Sucrets lozenges, Dr. Offerman said.

Treatment of an overdose requires supportive care, but it is also a good idea to consider decontamination with activated charcoal, Dr. Offerman advised. Many of the products also contain an antihistamine, which delays gastric emptying.

Dr. Offerman said he recommends giving charcoal all the way up to 6 hours after ingestion.

Physicians also need to be aware that many of the dextromethorphan-containing products may also contain large amounts of other active ingredients, particularly acetaminophen.

Drug toxicology screens do not specifically test for dextromethorphan, but the drug can cross-react with the test for phencyclidine (PCP).

Some reports have suggested naloxone is effective in reversing dextromethorphan. But there also have been reports that naloxone does not work, Dr. Offerman said. ■