Depression Treatment Fraught With Challenges

Factor in safety concerns of parents; monitor patients closely during initial phase of treatment.

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NEW YORK — Now that all antidepressants carry a black box warning regarding pediatric suicidality, physicians who treat children and adolescents 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.

Adolescent suicidality rates have been falling over the last decade, but it is unclear whether this decline is tied to the benefits of antidepressants.

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," Dr. Waslick 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."

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 proved to be 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 in an effort 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 whether 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 University 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. 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, Dr. Waslick 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.

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

Nonetheless, adolescent suicide rates have been falling over the last decade. "Widespread use of antidepressants does not seem to be leading to an epidemic of completed suicides," he said. "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." ■

Lessons From TADS

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."

Suicide Attempt Associated With Risk of First Seizure

NEW ORLEANS — Suicide attempt is associated with a fourfold increase in the risk of developing a first unprovoked seizure in adults and children older than 3 years, Dale Hesdorffer, Ph.D., said at the annual meeting of the American Epilepsy Society.

Major depression is associated with almost a doubling in the risk of first unprovoked seizure, she said. "There's clearly an underlying susceptibility for all these problems," said Dr. Hesdorffer of Columbia University, New York City. "This has been shown in several studies, but we don't know what it could be. It's completely undetermined at this point."

Dr. Hesdorffer presented the results of an Icelandic population-based case-control study that compared depression and suicide attempt rates and the number of depressive symptoms in subjects with and without a first unprovoked seizure.

The study included 387 cases and 773 controls. Major depression prior to the onset of seizure occurred in 11% of cases and 6% of controls. Among the cases, 6% had made a suicide attempt, compared with only 2% of controls. The association remained significant even after controlling for age, gender, number of depressive symptoms, and alcohol intake.

—Michele G. Sullivan

Seizure Control Stems Other Problems

Controlling seizures often lessens behavioral and neuropsychological problems that are ubiquitous in children with refractory epilepsy, said Marc Boel, M.D., of University Hospitals Gasthuisberg, Leuven, Belgium.

Among 573 such children seen in his clinic, 80% showed behavioral problems, and 15% showed significant mental decline related to their epilepsy. About half of the entire group had an IQ of below 50 (Eur. J. Pediatr. Neurol. 2005;8:291-7).

Most of the children had either partial epilepsy (29%) or secondary generalized tonic-clonic epilepsy (25%). About 4% had Lennox-Gastaut syndrome. Other diagnoses included absence epilepsy, photosensitive epilepsies, tuberous sclerosis, West syndrome, severe myoclonic epilepsy of infancy, and continuous spike waves during slow-wave sleep.

The most frequent neurobehavioral disorders were pervasive developmental disorder (8%); attention-deficit hyperactivity disorder (7.5%); loss of self-esteem (9%), and self-induction of seizures (7%). Psychosis, anxiety disorders, intermittent explosive disorder, and cursive seizures were seen at lower rates.

Seizure control helps reduce those symptoms, Dr. Boel said. In 101 of the 220 children who achieved seizure control, behavioral problems disappeared or were minimized. Seizure control had only a limited effect on those patients with psychosis, pervasive developmental disorder, or attention disorders.

—Michele G. Sullivan