Pediatric SSRI Use Means Intense Monitoring

BY SHERRY BOSCHERT
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SAN DIEGO — Vigilantly monitor depressed children and adolescents during the first month of selective serotonin reuptake inhibitor therapy—especially during the first 10 days, David Sack, M.D., said at a psychopharmacology congress sponsored by the Neuroscience Education Institute.

See the patient face-to-face at least weekly during that first month, and make sure that someone is monitoring the patient between visits. "It isn't enough to begin monitoring them when they show up at the office" for follow-up, said Dr. Sack of White Plains, N.Y.

Selective serotonin reuptake inhibitors (SSRIs) lack consistent data showing effectiveness in treating depression in children and adolescents, and metaanalyses of pediatric SSRI use show a slight but consistently significant increased risk of suicidal behavior with the drugs. The Food and Drug Administration's recent addition of a black box warning to labeling for SSRIs notes the risks of antidepressants in children.

An informal poll of several hundred physicians at the meeting showed that about half routinely schedule 1-week follow-ups after starting SSRIs in depressed children and adolescents. The first and second weeks "are very high-risk periods. If we're going to treat children with SSRIs, then we're going to have to modify the way we follow them up," he said.

See the patient face-to-face at least weekly during that first month, and make sure that someone is monitoring the patient between visits.

Studies of depressed adults treated with SSRIs suggest that the risk of suicidal behavior is four times higher in the first 7 days, compared with other times in the first 90 days. In the first month of treatment, the risk of suicidal behavior is three times higher than in the following 60 days.

Vigilant monitoring during these high-risk periods is a challenge for most medical practices. "As hard as it is for a psychiatrist to maintain contact in the first week, it's even more difficult for many pediatric practices," Dr. Sack noted.

Front-office nurses or other personnel may not have the knowledge to assess over the phone whether a patient has had a change in behavior. "We have a lot of work to do in terms of our training and understanding to make this a reality in practice," he said.

Patients with a history of prior suicide attempt or previous antidepressant therapy failure are at increased risk for suicidal behavior on SSRIs.

Before starting SSRI therapy in a child or adolescent, rule out bipolar disorder as much as possible. Give verbal and written information to families about the lack of consistent benefit with SSRIs in depressed pediatric patients and the apparent increase in risk of suicidal ideation. Respect a family's decision if they refuse SSRI therapy for the patient, Dr. Sack instructed.

Families should be told to contact the physician's office if they see changes suggesting suicidal thinking or behavior. "They need to know that changes in hopelessness or suicidal ideation are an emergency," he said.

The need to change dosages or drugs should be a sentinel for increased risk, he added. Pay special attention about 3-4 weeks after starting therapy, which is when most switches occur.

Use the weekly visits and monitoring in between to look for and respond to signs of suicidality, and to avoid a lawsuit in the event that something goes wrong, write down everything done to monitor the patient, Dr. Sack said.

None of the pediatric trials individually showed an increased risk of suicidality. Only when the data were pooled did that risk emerge. Pooled estimates suggest up to a doubling of risk for suicidal ideation in children on SSRIs, compared with placebo.

Only one out of five placebo-controlled studies of SSRIs in children and adolescents showed efficacy in treating depression, but that may be attributable to the studies' designs, Dr. Sack said. A separate 2004 study suggested that every 1% increase in adolescent use of SSRIs for major depression decreases the suicide rate by 0.23 per 100,000 adolescents. ■

SSRI Use Tied to Reports of Neonatal Withdrawal Symptoms

BY ELIZABETH MECHCATIE
Senior Writer

International reports of withdrawal symptoms in 93 newborns whose mothers had taken selective serotonin reuptake inhibitors during pregnancy raise concerns about a possible causal relationship between such symptoms and drugs in this class, particularly paroxetine, according to authors of a study that identified these cases.

Nearly two-thirds (64) of these cases were seen in babies whose mothers had taken paroxetine (Paxil), which the authors concluded should not be used in pregnancy, "or, if used, should be given at the lowest effective dose."

The use of other SSRIs "should be carefully monitored and new cases promptly communicated to the pharmacovigilance systems," wrote Emilio Sanz, M.D., professor of clinical pharmacology at the University of La Laguna (Spain), and associates (Lancet 2005;365:482-7).

When asked to comment on the study, two experts on drug therapy during pregnancy disagreed with the authors' conclusions, which they said fail to balance the risks and benefits of these drugs in pregnant women with depression.

Gideon Koren, M.D., director of the Motherisk Program, a teratogen information service at the Hospital for Sick Children, Toronto, said that while the identification of these cases in an international database was commendable, he took issue with the conclusion that paroxetine should not be used in pregnancy. This recommendation is not based on an appropriate risk-benefit analysis, he said, and it does not take into account the increased risk of maternal morbidity associated with untreated maternal depression, which is the strongest predictor of postpartum depression.

Moreover, the authors fail to take into account a study published last year, which found that in a large Swedish database, the association between paroxetine and these symptoms was no greater than with other SSRIs, added Dr. Koren, who said he has no financial ties to manufacturers of antidepressants.

He noted that neonatal withdrawal symptoms are self-limited and that the syndrome has "a very benign course," which also was not discussed by the authors. He and his associates at Motherisk have conducted many prospective case-control studies on the effects of different drugs in pregnancy. One of the studies, published in 2002, found a significantly higher rate of neonatal withdrawal symptoms in newborns exposed to paroxetine in the third trimester, compared with unexposed controls.

Lee Cohen, M.D., director of the perinatal psychiatry program at Massachusetts General Hospital, Boston, emphasized that while an appropriate level of vigilance is warranted in neonates who have been exposed to SSRIs in the third trimester, the cases in the study represent spontaneous reports, not controlled data.

They are "not a clap of thunder" but represent another data set that is starting to suggest that there is some association between SSRI exposure and risk for perinatal syndrome, Dr. Cohen said in an interview.

What complicates the situation is that use of these drugs in the general population and in pregnant women is significant, but the incidence of these symptoms is probably extremely small. There are no controlled data available that can be used to reliably estimate the prevalence of these symptoms in pregnant women on antidepressants, added Dr. Cohen, who is a consultant to manufacturers of several antidepressants.

What concerns him most, Dr. Cohen said, is that the study could not only lead to a reduction in antidepressant use during the peripartum period, but could affect a woman's willingness to take medication she may need at other points during pregnancy. The study also could affect the clinicians' willingness to prescribe therapy when needed during pregnancy.

The study, published last month, involved a search for reports of cases in the WHO adverse drug reaction database, where spontaneous reports of suspected adverse drug reactions are sent from centers in 81 countries. The first case, which was associated with fluoxetine, was reported in 1995. As of November 2003, 93 suspected cases of SSRI-associated neonatal withdrawal syndrome had been reported. In 73 of those cases, no concomitant medications were reported or the concomitant medications were thought to be unrelated to the symptoms.

For 10 of the remaining 20 cases, an association with the SSRIs was considered "doubtful," because of the concomitant use of medications that included antipsychotics or other drugs for which an association with neonatal withdrawal symptoms have not been clearly established. Another 10 were considered as "probably not" associated with SSRIs, because concomitant medications included drugs like opioids or tricyclics, according to the authors.

The most common neurological symptoms reported were nervousness, abnormal crying, tremors, and hypertonia. Other symptoms included digestive symptoms (vomiting, feeding disorders, or diarrhea), and respiratory symptoms (including two cases of respiratory depression). There were 13 cases of neonatal convulsions—11 listed as neonatal convulsions and 2 as grand mal convulsions.

Of the 93 cases, 64 were associated with exposure to paroxetine, followed by 14 associated with fluoxetine (Prozac), 9 with sertraline (Zoloft), and 7 with citalopram (Celexa). Information on doses and duration of treatment during pregnancy were reported in a minority of cases.

The pharmacokinetic differences between SSRIs "could partly explain their different withdrawal effects," they said.

For about a decade, there have been reports of withdrawal symptoms in newborns exposed in the third trimester to SSRIs. Symptoms have included irritability, abnormal crying, and difficulty feeding.

Acknowledging these reports, the Food and Drug Administration last year required manufacturers to add information to the labels of SSRIs and selective norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, on clinical findings in newborns exposed to these drugs late in the third trimester, including respiratory distress, jitteriness, irritability, hypoglycemia, feeding difficulties, and constant crying.

A spokesperson for Paxil manufacturer GlaxoSmithKline said the company had no statement on the Lancet report but pointed out that the FDA required this label change for all SSRIs and SNRIs. ■