New Treatment Guidelines for Bipolar Children

BY CARL SHERMAN
Contributing Writer

An independent work group of 25 psychiatrists has issued the first new guidelines for the treatment of children with bipolar disorder in nearly a decade.

The consensus document arose out of a need for updated information first voiced by the Child and Adolescent Bipolar Foundation, a parent advocacy organization, said Robert Kowatch, M.D., professor of psychiatry and pediatrics at Cincinnati Children's Hospital/University of Cincinnati, who organized and chaired the project.

Bipolar management in children has changed considerably since the American Academy of Child and Adolescent Psychiatry published its 1997 Practice Parameters, but the subject remains "infused with considerable controversy, debate, and dyspepsia," Jon McClellan, M.D., of the University of Washington, Seattle, said in his accompanying commentary (J. Am. Acad. Child Adolesc. Psychiatry 2005;44:236-9).

Although the AACAP practice parameters are under revision, "we wanted something different in approach and a bit more independent," Dr. Kowatch said. The goal was a "broad-based integration of what we know in the field: educational assessment and family therapy as well as medication."

The guidelines are intended for "anyone who treats these kids, diagnostically and therapeutically"—psychologists and primary care physicians along with psychiatrists—and reflect the uncertainties surrounding the disorder, he said.

The guidelines lead clinicians through a comprehensive evaluation to differentiate manic symptoms like euphoria, grandiosity, and increase in goal-directed activity from manifestations of other disorders (notably attention-deficit hyperactivity disorder) and from normal behavior (J. Am. Acad. Child Adolesc. Psychiatry 2005;44:213-35).

"There's a lot of controversy in the field about what these kids look like. We wanted to address some of that," Dr. Kowatch said.

Confronting the difficulty of fitting kids into a diagnostic protocol that was designed for adults, the guidelines attempt "to make DSM-IV criteria developmentally appropriate," he said.

The sections on treatment include two algorithms—acute manic or mixed episodes with and without psychosis—and shorter discussions of depression, comorbid disorders, and maintenance, using a standard system of evidence levels (randomized controlled trials in children to case reports) to characterize research support.

The biggest problem in "making the guidelines is that we just don't know much about treatment for these kids," Dr. Kowatch said. "There aren't a lot of controlled data." Besides lithium, which is approved for patients down to age 12 years, pharmacotherapy is off label, he noted.

Several large clinical trials, currently underway, should sharpen the picture, he suggested.

Robert L. Hendren, D.O., director of child and adolescent psychiatry at the University of California, Davis, said the work group "did a great job in advancing the field by defining what bipolar disorder is in children and adolescents, and what algorithms to consider in treating them," Dr. Hendren said.

The result unavoidably reflects the limitations of the data. "This group thought carefully about what it is saying, but couldn't recommend whether to start with a mood stabilizer or an atypical antipsychotic; and if a mood stabilizer, they waffled between lithium and divalproex," he said, "but that's the state of the art."

He agreed with Dr. McClellan's commentary that the inclusion of brief, intense outbursts of mood and behavior dysregulation under the bipolar rubric implies a fundamental change in the definition of the illness. "There's a real controversy whether this represents bipolar I or II, or a developmental phase for some kids," he said. ■

Navigating Treatment of Bipolar Disorder in Pregnancy

BY DIANA MAHONEY
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BOSTON — Managing bipolar disorder during pregnancy requires balancing the competing risks and benefits to the woman and her fetus, said Adele Viguera, M.D.

"Pregnancy, and particularly the postpartum period, is associated with a high risk of disease recurrence for women with bipolar disorder," said Dr. Viguera, director of the perinatal and reproductive psychiatry program at Massachusetts General Hospital in Boston. Although mood-stabilizing drugs can reduce this risk, most are associated with some degree of teratogenicity.

Limited data exist to support the use in pregnancy of the mood stabilizers most commonly used to treat bipolar disorder. In addition, mood stabilizers have been shown to increase the risk of certain types of birth defects or congenital malformations in infants exposed in utero, Dr. Viguera said during a meeting on bipolar disorder sponsored by Harvard Medical School.

To minimize the possibility of fetal damage, some women choose to discontinue their mood-stabilizing regimen, which itself markedly increases the risk of disease recurrence during pregnancy as well as postpartum illness. "More than half of women who discontinue treatment before or during pregnancy relapse, most frequently in the first trimester," Dr. Viguera said.

The risks associated with treatment and treatment cessation vary considerably, depending on the nature and degree of illness and the agents used to treat it. "There is no single optimal management approach," Dr. Viguera said. "Clinical management requires ongoing assessment of maternal and fetal status, risks, and benefits."

Further complicating management is the fact that the Food and Drug Administration has not approved for use during pregnancy any of the psychotropic medications used to treat bipolar disease, because these agents diffuse across the placenta. The risk of birth defects depends on the drug used, when exposure occurs, and the duration of the exposure. It is generally understood that the highest risk to the fetus is during the first trimester, "but later exposure can also lead to malformations, behavioral effects, low birth weight, and preterm delivery," Dr. Viguera said.

Women with bipolar disorder who have been stable for many years may be able to slowly decrease their dosage and stop medication before conception. If symptoms emerge during the first trimester, these women may be able to avoid using a mood stabilizer by treating some of the more troubling symptoms, such as irritability, insomnia, and hypomania, with an antipsychotic agent such as haloperidol or perphenazine. If symptoms appear after the first trimester, the mood stabilizer can be reintroduced with less risk of congenital malformation, she said.

Among women who choose to continue a mood stabilizer during pregnancy to minimize the risk of recurrence, lithium appears to be the safest option. However, it is associated with a relatively small increased risk of a serious cardiac malformation. Valproic acid, on the other hand, is associated with a 3%-5% risk of a neural tube defect and an 8.9% risk for all anomalies vs. a baseline rate of 2%-4%.

The risk of bipolar relapse in the postpartum period is high, as is the risk for postpartum psychosis. Consequently, medication prophylaxis generally is recommended, although there is some debate on timing, Dr. Viguera said. "The goal is to maintain euthymia by reintroducing the mood stabilizer early," she said. Some studies have shown benefits to reintroducing the drug in the third trimester, and others have suggested 24-48 hours post partum. In any case, Dr. Viguera said, "the postpartum treatment plan should be addressed in advance." ■

Drugs Often Used in Pregnant Patients

Following are some drugs commonly used to treat the symptoms of bipolar disorder during pregnancy:

► **Lithium.** Although effective in only a limited number of patients, lithium is a popular treatment for bipolar disorder. Studies have shown the teratogenicity rates are much lower than previously reported. Common effects of fetal exposure are high birth weight and "floppy-baby" syndrome.

► **Valproate and carbamazepine.** These anticonvulsants are associated with major congenital malformations and carry a greater risk of birth defects than lithium. They are linked to neural tube defects, craniofacial anomalies, urogenital problems, growth retardation, microcephaly, and heart defects. Late last year, the American Epilepsy Society's pregnancy outcomes forum panel recommended that valproate should not be prescribed as first-line therapy for any indication in women of childbearing age because it significantly increases the risk of major malformations in babies exposed in utero.

► **Lamotrigine.** This anticonvulsant is associated with a low overall rate of fetal malformations, but it carries a higher rate of miscarriages and stillbirths than seen in unmedicated women. The agent also has been linked to a skin rash in babies who have different antigen characteristics than their mothers.

► **Chlorpromazine.** This first-generation antipsychotic is often used to treat mania during pregnancy. It is among the best-studied of the antipsychotics in pregnancy, and the data support its relative safety in this population. Related compounds, such as trifluoperazine and perphenazine, also may have low teratogenic risk, although they are not as well studied.

► **Lorazepam and clonazepam.** These benzodiazepines often are used to treat the anxiety, agitation, and sleep disturbances that accompany bipolar disorder. They have not been associated with significant increases in malformation rates, although chronic use of benzodiazepines during pregnancy has been linked to withdrawal symptoms in babies.

► **Olanzapine.** One of the newer atypical antipsychotics, olanzapine is used for acute mania and for prophylaxis against recurrent mania; however, data on this and the other atypical antipsychotics in pregnancy are still too sparse to make conclusions regarding their reproductive safety.

Strategies for minimizing the risks associated with these drugs include using monotherapy rather than a combination of drugs, and relying on the lowest possible effective dose, Dr. Viguera said. Folic acid supplementation—in addition to a daily prenatal vitamin—may help reduce the increased risk of neural-tube defects. Women taking anticonvulsants, in particular, should take 4 mg of supplemental folic acid per day from preconception through the first trimester.

"All women taking these medications during the first trimester should obtain a high-resolution ultrasound at 16-18 weeks to detect the presence of fetal malformations," Dr. Viguera noted. Both maternal and fetal serum drug levels should be monitored regularly.