

## PRACTICAL PSYCHOPHARMACOLOGY

## Combo Therapy Is the Rule in Pediatric Bipolar

Even the experts say it's a tough call to diagnose a child—particularly a young child—with bipolar disorder, making for enigmatic medication decisions in the pediatric population.

"It's always difficult, and the diagnosis is the most important thing before beginning treatment," said Dr. Kiki Chang, founder and director of the Pediatric Bipolar Disorders Program at Stanford (Calif.) University.

"It's a diagnosis I've been looking at for the better part of 35 years, and I still find it very hard," agreed Dr. Gabrielle Carlson, professor of psychiatry and behavioral science at the State University of New York at Stony Brook. When it comes to very young children—under the age of 10—"you get into really dicey territory."

The problem is that diagnostic criteria for bipolar I, bipolar II, and bipolar disorder not otherwise specified in the DSM-IV were developed based on research in adults and may be exceedingly difficult to apply to children.

It's been said that all normal 4-year-olds look a bit bipolar, with wild mood swings, euphoria, racing thoughts, grandiosity, periods of extreme creative and physical energy, reports of monsters under their beds, and a seemingly reduced need for sleep (by parental report).

Clinical experience and many longitudinal studies do point to profoundly troubled behavior in some children that does have a flavor of bipolar disorder, and many of these children do go on to have unequivocal bipolar disorder in adulthood.

In the most recently published report from Dr. Barbara Geller's group at Washington University, St. Louis, 44% of young adults identified in childhood with bipolar I disorder symptoms had a manic episode after the age of 18, a rate 13-44 times higher than in the general population (*Arch. Gen. Psychiatry* 2008;65:1125-33).

However, community diagnoses are notoriously fallible, illustrated by the fact that half of the children referred to the Pediatric Bipolar Disorders Program at Stanford do not have the disease. Often, they prove to have unipolar depression marked by irritability. Or pervasive developmental disorder. Or autism, Dr. Chang said.

Significant language impairment and developmental delays complicated the diagnosis of one of Dr. Carlson's patients who, at age 5, nearly got killed running alongside cars because he thought he could run faster than anyone else. He jumped out of a tree, and displayed other examples of "clearly grandiose" behavior. When he was 7, she asked him about chasing traffic and he said, "I was little at the time." The tree? "I never did that again," he said. Later, he boasted he could swim across Long Island Sound—a claim he later traced to his grandfather's musing that he could "swim like a fish."

By age 10, it was clear that child's diagnosis was autism. "He always had interesting ways of putting the world together. But he wasn't delusional when pressed," said Dr. Carlson.

Being precise about a diagnosis in children with unusual, shocking, and/or harmful behaviors would make little difference if medication management was the same whether a child has bipolar disorder or one of the many differential diagnoses masquerading as bipolar disorder, such as depression, attention-deficit/hyperactivity disorder (ADHD), pervasive developmental disorder, anxiety disorders, Tourette syndrome, or the autism spectrum disorders. But it's not.

"The question of diagnosis makes a



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DR. CARLSON

big difference," Dr. Carlson said. In the case of "diagnostic ambiguity" between severe ADHD and bipolar disorder, she chooses to treat the ADHD first, unless there are clear signs of mania.

One advantage of treating ADHD with stimulants is their quick action, sometimes providing rapid evidence of improvement. Plus, their use over many years in multiple clinical trials in children provides reassurance of their safety and guidance about dosing.

It can be difficult to start on a conservative course of action in the face of extreme behavior and symptoms, but Dr. Carlson remembers the lesson she learned from an adolescent who had been unsuccessfully treated with anticonvulsants and atypical antipsychotics for 5 years.

So frightening were the child's early meltdowns that the mother and a community psychiatrist feared that stimulant medication would be contraindicated, with the potential of making a "nightmare" situation worse. But after years of treatment, the youth's symptoms worsened and he was hospitalized. She decided to taper his medications and try traditional stimulants for ADHD, along with time-outs and consistent behavior-modification strategies. "He responded very nicely," she said. "What was heartwarming was how proud he was that he had control of himself. The mother told me, 'I was able to be a regular mom.'"

Dr. Chang also favors treating ADHD when the diagnosis tends to lean that way (and doesn't include frank mania). He starts with standard doses of short-acting methylphenidate, even when one or more parents has a history of bipolar disorder.

Whereas experts once believed that stimulants would "tip" most children with undiagnosed bipolar disorder into manic episodes, the consensus now is that this is a rare occurrence and fairly easily managed, he said. "Just stop the stimulants."

An alternative therapy for ADHD symptoms might be atomoxetine (Strattera), a hydrochloride salt, which Dr.

Chang considers if stimulants aggravate hyperactive behavior.

If a traditional therapy for ADHD reduces symptoms, both specialists said they feel comfortable in closely monitoring a child through adolescence, when more typical symptoms of bipolar disorder may emerge.

In looking at studies of patients under the age of 10, Dr. Carlson today sees few data to support the use of "powerful, fat-making antipsychotics" for the rest of the child's life (assuming the child proves to have bipolar disorder). She believes there is support in the literature for the short-term use of atypical antipsychotics for management of aggression associated with many diagnoses, however.

Of note, an international review of five longitudinal studies of the children of parents with bipolar disorder found little evidence of classically defined mania in prepubertal children (*J. Can. Acad. Child Adolesc. Psychiatry* 2009;18:200-5).

In the study by Dr. Anne Duffy of Dalhousie University in Halifax, Nova Scotia, children who went on to develop mood disorders seemed to follow a fairly predictable course leading to a first activated episode in adolescence or early adulthood—nonspecific anxiety and sleep problems in childhood, then mood swings in adolescence, with depressive episodes predating mania by several years.

Dr. Chang said while prepubertal mania has been described, it is likely less common than postpubertal mania, "and harder to diagnose given the natural neurodevelopmental propensity of young children to rapidly cycle with their moods."

Many experts have called for an evaluation of what symptoms constitute a diagnosis of bipolar disorder in children, rather than trying to shade adult-oriented symptoms to fit children. A precise definition would tailor subjects enrolled in clinical trials so that findings would be meaningful and applicable to the children seen in clinical practice, hopefully pointing the way to an evidence-based approach to pharmacotherapy.

In the meantime, treatment guidelines developed by an expert consensus panel that included Dr. Carlson and Dr. Chang offer diagnostic support and provide algorithms for treatment of bipolar I disorder with or without psychosis in children and adolescents (*J. Amer. Acad. Child Adolesc. Psychiatry* 2005;44:213-35).

A practice parameter with 11 specific recommendations also offers comprehensive guidance to clinicians (*J. Am. Acad. Child Adolesc. Psychiatry* 2007; 46:107-25).

Dr. Carlson and Dr. Chang describe personal prescribing patterns that conform to these guidelines, most often selecting lithium or another mood stabilizer or an atypical antipsychotic as first-line monotherapy, but sometimes recommending combination therapy.

Lithium, valproate, aripiprazole, and quetiapine all figure prominently in his initial treatment strategies, with queti-

apine edging out the others if sleep regulation is a particular problem.

A child presenting with rather classic euphoric mania might make Dr. Chang prescribe lithium first, whereas a more chronic picture of predominantly irritable mania or a mixed state would make him lean toward an atypical antipsychotic.

Depression remains a challenge in youthful populations as well as in adults, and Dr. Chang is generally reluctant to prescribe selective serotonin reuptake inhibitors if there is a reasonable suspicion that the child has bipolar disorder.

"We stay away from them if at all possible," concerned that they may precipitate a manic episode.

He might consider lamotrigine for a child who is already overweight, dosing it very cautiously at first, especially in smaller children, and being cognizant of the risk of a severe rash. He also now considers adding metformin to the regimen of any child or adolescent who gains considerable weight on the atypicals.

Dr. Carlson cited the same sorts of considerations. Atypical antipsychotics, for example, might be her treatment of choice for a child whose most concerning symptoms are aggression and emotional lability, because these drugs tend to ameliorate these symptoms regardless of whether the ultimate diagnosis is bipolar disorder.

Most children with bipolar disorder end up requiring combination therapy for their symptoms, plus occasional agents to manage side effects.

As the regimens grow more complex, the already limited evidence base shrinks to nearly nil, Dr. Chang said. Side effect patterns in children are also poorly understood. "Cognitive side effects have not really been studied at all. We don't have much evidence to guide us, and compared with adults, the cognitive piece is really important," he said.

When the adult literature suggests a problematic cognitive picture, as in the case of topiramate, Dr. Chang tends to avoid prescribing that drug.

Both clinicians emphasized the need to address the child's environment within the context of his or her symptoms, incorporating psychotherapeutic and educational interventions in any treatment strategy. "Medication in the absence of the others [interventions] is rarely successful," Dr. Chang said.

Dr. Carlson reported that she is a consultant for many of the pharmaceutical companies conducting research into bipolar disorder and ADHD and is currently participating in a study of lamotrigine (GlaxoSmithKline). Dr. Chang said he has received research or grant support from, or served on the speakers bureau for, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly & Co., Otsuka America Pharmaceutical Inc., and GlaxoSmithKline. ■

By Betsy Bates. Share your thoughts and suggestions at [cpnews@elsevier.com](mailto:cpnews@elsevier.com).