



Pediatric bipolar disorder

Mood swings, irritability

Our challenge is to make the diagnosis early and stabilize mood so that these young patients can cope and achieve at home and in school.

are cues to this diagnosis

Robert A. Kowatch, MD

Professor of psychiatry
and pediatrics

Melissa P. DelBello, MD

Assistant professor of psychiatry
and pediatrics

University of Cincinnati Medical Center
Cincinnati Children's Hospital
Medical Center
Cincinnati, OH

Children and adolescents with bipolar disorder are often referred to psychiatrists because of disruptive behaviors at home and in school. They exhibit poor academic performance, disturbed interpersonal relationships, increased rates of substance abuse, legal difficulties, multiple hospitalizations, and high rates of suicide attempts and completions.^{1,2} Many have comorbid psychiatric problems—particularly attention-deficit/hyperactivity disorder (ADHD).

Although few studies have examined this complex diagnosis, we do know that bipolar disorder presents differently in children and adolescents than in adults. Prodromal symptoms can appear early—before kindergarten in some children. Early recognition therefore is key to effectively treating these sick and often complicated patients.

How often a clinician encounters a child or adolescent with bipolar disorder depends largely on the practice setting (*Box*).^{1,3,4} Wherever you practice, however, you can recognize and treat pediatric bipolar disorder if you keep in mind that its presentation and disease progression differ from the adult type.

Pediatric versus adult symptoms

Prodromal symptoms—such as episodes of depressed mood or hopelessness and excessive mood lability—have been detected in youths who later were diagnosed with bipolar disorder. More than one-half of 494 adult members of the Depression and Bipolar Support Alliance have reported that they first exhibited signs of bipolar illness before age 19, with distribution by age as follows:

- 5% before age 5
- 12% at ages 5 to 9
- 14% at ages 10 to 14
- 28% at ages 15 to 19.⁵

continued



Box

HOW LIKELY ARE YOU TO SEE PEDIATRIC BIPOLAR DISORDER?

Pediatric bipolar disorder is seen much more commonly in specialized psychiatric settings than in general practice.

Overall prevalence. A large, well-designed population study of mood disorders in adolescents reported a lifetime prevalence of 1% for bipolar spectrum disorders, including bipolar I, bipolar II, and cyclothymia.¹ Most adolescents in the bipolar group (84%) reported a distinct period of elevated, expansive, or irritable mood that best fit DSM-IV criteria for bipolar disorder not otherwise specified (NOS). These adolescents—who represented an overall prevalence of 5.7%—had extremely high rates of psychosocial impairment and use of mental health services, similar to those with bipolar I disorder.

In specialized settings. Bipolar disorder is seen much more frequently in specialized settings, such as a pediatric psychopharmacology clinic, than in general psychiatric practice. For example:

- Among 262 children referred consecutively to a specialty pediatric psychopharmacology clinic, 16% met DSM-III-R criteria for mania.³
- In a special education class, 8 of 12 students met DSM-III-R criteria for a bipolar disorder.⁴
- In child and adolescent psychiatry inpatient units, it is not uncommon to find 30 to 40% of patients with a bipolar disorder.

Table 1

COMMON PRESENTING SYMPTOMS OF PEDIATRIC BIPOLAR DISORDER

- Episodes of depressed mood/hopelessness
- Excessive mood lability
- Periods of increased or decreased energy
- Episodes of decreased need for sleep
- Anger dyscontrol
- Markedly irritable moods
- Frequent argumentativeness
- Bold/intrusive/demanding behaviors

In a similar study,⁶ 58 adult patients with bipolar I disorder reported an average interval of 9 to 12 years between the emergence of bipolar symptoms and the onset of a major affective disorder.

Common initial symptoms of pediatric bipolar disorder are listed in *Table 1*. Most of these symptoms occur in discrete episodes and represent a change from the child's normal functioning.

Many children and adolescents are labeled "bipolar" without careful consideration of this disorder's diagnostic complexities and subtypes. Bipolarity in young patients can be difficult to establish because of:

- variability of symptom expression, depending on the illness' context and phase
- effects of development on symptom expression
- mood and behavioral effects of psychotropic medications the patient is taking.

Pediatric bipolar patients often present with a mixed or "dysphoric" picture characterized by frequent short periods of intense mood lability and irritability rather than classic euphoric mania.^{3,7} Clinicians who evaluate children with pediatric bipolar disorders often try to fit them into the DSM-IV "rapid cycling" subtype. This subtype does not fit bipolar children very well, however, because they often lack clear episodes of mania. Rather, researchers are reporting that bipolar children cycle far more frequently than the four episodes/year in DSM-IV's diagnostic criteria:

- Continuous, daily cycling from mania or hypomania to euthymia or depression was seen in 81% of a well-defined group of pediatric bipolar patients.^{7,8}
- A high rate of rapid cycling and onset of a first manic episode at mean age 7 was reported in 90 children and adolescents (mean age 11) with bipolar I disorder.⁹

The picture that emerges from independent research groups is that multiple daily mood swings and irritability are much more common than euphoria in prepubertal children with bipolar disorder.^{8,10}

Making the diagnosis

DSM-IV's diagnostic classification system for bipolar disorders is complex, involving:

- five types of episodes (manic, hypomanic, mixed, depressed, unspecified)

continued

Table 2

**PEDIATRIC BIPOLAR DISORDER SUBTYPES:
DIAGNOSTIC CHARACTERISTICS AND ASSOCIATED FEATURES**

DSM-IV subtype	Minimum duration of manic symptoms	Depression symptoms	Cardinal features
Bipolar I	Pure mixed or manic 1 week (or hospitalization needed)	Major depressive disorder may be the first presentation of bipolar disorder, particularly in adolescents	Multiple daily mood swings with severe irritability (mood lability) Short periods of euphoria Decreased need for sleep Hypersexuality Grandiosity Racing thoughts Pressured speech
Bipolar II	Hypomania 4 days	One or more prior episodes of major depressive disorder required, each with a duration of 2 weeks	Noticeable manic symptoms that do not cause significant dysfunction or lead to hospitalization
Cyclothymia	Hypomania cycling with depressive symptoms 1 year	Hypomania cycling with depressive symptoms, without manic, mixed, or major depressive episodes (1 year, with symptom-free intervals <2 months)	Chronic, low-level mood cycling
Bipolar NOS	< 4 days of bipolar symptoms	Rapid alternation (within days) between manic and depressive symptoms without full manic, mixed, or major depressive episodes	May include hypomanic episodes (but <4 days) without intercurrent depression May also be diagnosed when clinician determines bipolar disorder is present but cannot determine whether it is primary, due to a general medical condition, or substance-induced, such as severe mood lability secondary to fetal alcohol syndrome or alcohol-related neurodevelopmental disorder

NOS: not otherwise specified



Table 3

COMPLICATING FACTORS IN PEDIATRIC BIPOLAR DISORDER

Medical conditions that may mimic bipolar mania

- Temporal lobe epilepsy
- Hyperthyroidism
- Closed or open head injury
- Multiple sclerosis
- Systemic lupus erythematosus
- Alcohol-related neurodevelopmental disorder
- Wilson’s disease (rare progressive disease caused by defective copper metabolism)

Medications that may increase mood cycling

- Tricyclic antidepressants
- Selective serotonin reuptake inhibitors
- Serotonin and norepinephrine reuptake inhibitors
- Aminophylline
- Corticosteroids
- Sympathomimetic amines, such as pseudoephedrine

- four severity levels (mild, moderate, severe without psychosis, severe with psychosis)
- and three course specifiers (with or without inter-episode recovery, seasonal pattern, rapid cycling).

DSM-IV criteria for mania—which were developed from data on adults with bipolar disorders—do not take into account developmental differences between bipolar adults and bipolar children and adolescents.

Diagnostic characteristics of the pediatric bipolar disorder subtypes are compared in *Table 2*. Generally:

- Pediatric patients with bipolar I disorder have multiple daily mood swings, a “mixed” type of episode with short periods of euphoria and longer periods of irritability, and comorbidities such as ADHD, oppositional defiant disorder, or conduct disorder.^{3,11,12}
- Bipolar II disorder presents more typically in adolescence and is usually noticed clinically as a major depressive episode. Past episodes of hypomania may have been missed unless a careful history was taken.

- Cyclothymia is difficult to diagnose because the hypomania and depressive symptoms are not as severe as in bipolar types I or II. Prospective mood charting can help the clinician diagnose cyclothymia (see “Related Resources,” p. 47).
- Bipolar disorder NOS represents the largest group of patients with bipolar symptoms. This diagnosis is made when bipolar symptoms are present but not of sufficient severity or duration to warrant a diagnosis of bipolar I, II or cyclothymia. Bipolar NOS also can be diagnosed when a bipolar disorder is secondary to a general medical condition, such as fetal alcohol syndrome or alcohol-related neurodevelopmental disorder.

Differential diagnosis. Medications and medical disorders may exacerbate or mimic pediatric bipolar symptoms (*Table 3*), so it is important to assess these potential confounds before initiating treatment. Psychiatric comorbidities also frequently complicate the presentation of pediatric bipolar disorder and its response to treatment (*Table 4*). ADHD is the most common comorbidity, with rates as high as 98% in bipolar children.^{3,13}

Outcomes

Long-term outcomes of children and adolescents with bipolar disorders have not been well studied. In the only prospective follow-up investigation of adolescent inpatients with mania, Strober et al found that most of 54 patients (96%) recovered from an index affective episode, but nearly one-half (44%) experienced one or more relapses within 5 years.¹⁴ The rate of recovery varied according to the index episode’s polarity. Recovery was faster in patients with pure mania or mixed states, and multiple relapses occurred more frequently in those with mixed or cycling episodes. Twenty percent of the patients attempted suicide.

Recently, Geller et al reported the results of the first large, prospective, follow-up study of children with bipolar disorder.¹⁵ In 89 outpatients (mean age 11) with bipolar I disorder, comprehensive assessments at baseline and at 6, 12, 18, and 24 months showed that 65% recovered from mania but 55% relapsed after recovery. Mean time to recovery was 36 weeks, and relapse occurred after a mean of 28.6 weeks. Children living with their intact biological families were twice as likely to recover as those in other living arrangements.

The poor outcomes of these bipolar children highlight the need for earlier recognition and more effective treatments.

Treating acute mania

Many psychotropic medications used to treat adults with bipolar disorders are also used for children and adolescents. To date, only two double-blind, placebo-controlled studies^{13,16} and one uncontrolled maintenance treatment study¹⁷ have examined treatment of acute mania in pediatric bipolar disorder.

Lithium is the most studied medication for pediatric bipolar disorder and the only FDA-approved medication for treating acute mania and bipolar disorder in patients ages 12 to 18. Approximately 40 to 50% of children and adolescents with bipolar disorder respond to lithium monotherapy.^{18,19}

In general, lithium should be titrated to 30 mg/kg/d in two or three divided doses; this typically produces a serum level of 0.8 to 1.2 mEq/L. Common side effects in children and adolescents include nausea, polyuria, polydipsia, tremor, acne, and weight gain. Lithium levels and thyroid function should be monitored, as in adult patients.

Only one prospective, placebo-controlled study has examined lithium use in children and adolescents with bipolar disorders. Twenty-five adolescents with comorbid bipolar and substance use disorders were treated with lithium or placebo for 6 weeks. Positive urine toxicology screens decreased significantly, and global assessment of functioning improved in 46% of those receiving lithium vs. 8% of those receiving placebo.¹³ This study demonstrated lithium's efficacy in treating bipolar adolescents with comorbid substance abuse but did not measure its effect on mood.

Risk factors for poor lithium response in children and adolescents with bipolar disorder include prepubertal onset and comorbid ADHD.²⁰

Divalproex. No placebo-controlled studies of antiepileptics in pediatric bipolar disorder have been published. Open-label studies of divalproex have reported response rates of 53 to 82% in manic adolescents.^{18,21-23} Several case reports and series have described successful use of carbamazepine as monotherapy and adjunctive treatment in children and adolescents with bipolar disorder.^{24,25}

Table 4

RATES OF COMMON COMORBIDITIES IN PEDIATRIC BIPOLAR DISORDERS

Disorder	Children (prepubertal)	Adolescents
ADHD	70 to 90%	30 to 60%
Anxiety disorders	20 to 30%	30 to 40%
Conduct disorders	20 to 30%	30 to 50%
Oppositional defiant disorder	60 to 80%	20 to 30%
Substance abuse	10%	40 to 80%
Learning disabilities	30 to 40%	30 to 40%

40 to 50% of children and adolescents with bipolar disorder respond to lithium monotherapy

One 6-week, random-assignment, prospective study compared lithium, divalproex, and carbamazepine in treating 42 acutely manic or hypomanic patients ages 8 to 18.¹⁸ In this open study, all three mood stabilizers demonstrated efficacy in treating a mixed or manic episode in youths with bipolar I or II disorder. Response rates—based on a $\geq 50\%$ improvement in Young Mania Rating Scale baseline scores—were divalproex 53%, lithium 38%, and carbamazepine 38%.

In general, divalproex is started at 20 mg/kg/d, which typically produces a serum level of 80 to 120 $\mu\text{g/ml}$. Common side effects in children include weight gain, nausea, sedation, and tremor.

A possible association between divalproex and polycystic ovary syndrome (PCOS) has been reported in women with epilepsy.²⁶ The mechanism for PCOS has been hypothesized to be obesity secondary to divalproex, resulting in elevated insulin and androgen levels. Recently, Rasgon et al²⁷ reported that epilepsy—and not the anticonvulsants used to treat it—may increase the risk of PCOS. In contrast, O'Donovan et al reported higher rates of menstrual irregularities and PCOS in women with bipolar disorder who were taking divalproex than in those who were not taking divalproex and in healthy controls.²⁸

Until we learn more about this association, clinicians



Pediatric bipolar disorder

should monitor bipolar female adolescents treated with divalproex for any signs of PCOS, which include menstrual abnormalities, hirsutism, and acne.

Carbamazepine is used widely for seizure management but less commonly than divalproex in pediatric bipolar disorder. This anticonvulsant must be titrated slowly and requires frequent monitoring of blood levels, which can be a problem in children with needle phobia.

Carbamazepine is usually titrated to 15 mg/kg/d to produce a serum level of 7 to 10 $\mu\text{g/ml}$. Its most common side effects are sedation, rash, nausea, and hyponatremia. Aplastic anemia and severe dermatologic reactions, such as Stevens-Johnson syndrome, occur uncommonly.²⁸

Atypical antipsychotics. Recent case series and open-label reports suggest that atypical antipsychotics such as clozapine,²⁹ risperidone,³⁰ olanzapine,³¹⁻³³ and quetiapine¹⁶ are effective in treating pediatric bipolar disorder. However, clinically significant weight gain may be associated with the use of olanzapine and risperidone.³⁴ Ziprasidone may increase QTc prolongation, and safety data are limited in children and adolescents. Therefore, ziprasidone should be used with caution in pediatric bipolar disorder, and ECGs should be monitored.

In the only double-blind, placebo-controlled study of an atypical antipsychotic in pediatric bipolar disorder, manic symptoms were more greatly reduced in 15 adolescents given

quetiapine plus divalproex than in 15 patients who received divalproex alone. Quetiapine was titrated to 450 mg/d across 7 days and was well-tolerated. The findings suggest that a mood stabilizer plus an atypical antipsychotic may be more effective than a mood stabilizer alone for treating adolescent mania.¹⁶

Long-term treatment

In addition to treating acute affective episodes, lithium may also help prevent recurrent affective episodes in younger patients. In the only maintenance treatment study for pediatric bipolar disorder, Strober et al prospectively evaluated 37 adolescents whose bipolar disorder had been stabilized with lithium during hospitalization.¹⁷ After 18 months of follow-up, 35% of patients had discontinued lithium, and their relapse rate was 92% (compared with 38% in patients who were lithium-compliant).

It is reasonable to maintain a child or adolescent who has had a single manic episode on mood-stabilizing treatment for several years and then—if the patient is euthymic and asymptomatic—to slowly taper the mood stabilizer(s) over several months. If mood symptoms recur, the agent(s) should be reintroduced.

If a child with bipolar disorder does not respond or only partially responds to a mood stabilizer, it may be necessary to add a second mood stabilizer or an atypical antipsychotic. A bipolar child or adolescent with psychotic symptoms should be maintained on an antipsychotic (typical or atypical) for at least 1 month, even if the psychosis has resolved.³⁵

Treatment of comorbid ADHD. Most children with bipolar disorder have comorbid ADHD, and mood stabilization is necessary prior to starting stimulant medications.³⁶ In bipolar patients, sustained-release psychostimulants may reduce rebound symptoms more effectively than immediate-release formulations. Typical dosages for a child with bipolar disorder and ADHD would be Concerta, 36 mg/d, or Adderall XR, 10 to 20 mg/d.

Psychosocial interventions

Most psychotherapeutic interventions have not been systematically studied in pediatric bipolar disorder but may be beneficial. In a recent study, Fristad et al reported the efficacy of multifamily psychoeducational group therapy for treating bipolar children and adolescents and their families.³⁷

In patients with bipolar disorder and ADHD, stabilize mood before starting stimulants

Early diagnosis is key to treating pediatric bipolar disorder. Recognizing age-related differences in symptom presentation and evolution can uncover clues to this often complicated disorder in children and adolescents. Although data are limited, mood stabilizers, atypical antipsychotics, and other interventions have shown promise in treating young bipolar patients.

BottomLine

Related resources

- ▶ Mood charts appropriate for pediatric patients.
<http://www.bpkids.org/learning/6-02.pdf>.
- ▶ Child and Adolescent Bipolar Foundation. www.cabf.org
- ▶ Findling RF, Kowatch RA, Post RM. *Pediatric bipolar disorders: a handbook for clinicians*. London, Martin Dunitz Press, 2002.
- ▶ Geller B, DelBello MP (eds). *Child and early adolescent bipolar disorder: theory, assessment, and treatment*. New York: Guilford Publications, 2002.

DRUG BRAND NAMES

Clozapine • Clozaril
 Divalproex sodium • Depakote
 Olanzapine • Zyprexa

Risperidone • Risperdal
 Quetiapine • Seroquel
 Ziprasidone • Geodon

DISCLOSURE

Dr. Kowatch receives grant support from, serves as a consultant to, or is on the speakers bureau of Novartis Pharmaceuticals Corp., Abbott Laboratories, Solvay Pharmaceuticals, Eli Lilly and Co., Janssen Pharmaceutica, GlaxoSmithKline, and AstraZeneca Pharmaceuticals.

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Other useful psychosocial tactics include:

- Minimize periods of overstimulation (for example, these patients do not do well at shopping malls).
- Maintain good sleep hygiene.
- Address medication nonadherence immediately.
- Discuss the risk of substance abuse with the patient.
- Encourage mood charting by the patient and or parent.

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