

## Recognition and Treatment of Pediatric Bipolar Disorder

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*Learning objectives:* After reading this issue, the participant should be able to:

- Describe the clinical symptoms of pediatric bipolar disorder (PBD).
- List the biopsychosocial risk factors for PBD.
- Discuss the psychopharmacotherapeutic and other treatment options for managing PBD.

Pediatric bipolar disorder (PBD) severely impairs a child's developmental and emotional growth. It is associated with an alarming suicide rate, school failure, aggression, engagement in high-risk behaviors such as sexual promiscuity and substance abuse, and high relapse and low recovery rates.<sup>1-3</sup> PBD is frequently misdiagnosed, resulting in inadequate management (e.g., inappropriate stimulant medication) and a worsening of the disorder.<sup>4-6</sup> Often, PBD is not recognized until late adolescence, with patients reporting long histories of related psychopathology misdiagnosed as attention deficit hyperactivity disorder (ADHD)<sup>7</sup> or a "behavior disorder" (oppositional defiant disorder [ODD] or conduct disorder [CD]).<sup>8</sup> Therefore, the first and most important step in treating these children is to accurately recognize the disorder. This article updates practitioners about empirical findings relevant to the recognition and treatment of PBD and translates these findings into "real-life practice." The article reviews these issues:

- *Phenomenology of PBD* (definition, clinical description, prodromal symptoms);

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The authors have further disclosed that the FDA has not approved the use of risperidone, olanzapine, or topiramate for bipolar disorder or aggression in children; trazodone for sleep difficulties in children; clonidine and guanfacine for bipolar disorder, aggression, hyperarousal, or attention deficit hyperactivity disorder in children; or carbamazepine for bipolar disorder in children.

- *Epidemiology* (prevalence, biologic and psychosocial risk factors, course); and
- *Treatment approaches* (psychopharmacotherapy, psychosocial therapy, clinical problem-solving model).

### Phenomenology of PBD

#### Definition of PBD

Adult criteria do not always adequately describe PBD. Table 1 lists the core clinical features for bipolar disorder across the life span as defined by DSM IV-TR criteria.<sup>9</sup> These are divided into four subgroups: bipolar I, children who have had at least one manic or mixed episode; bipolar II, children who have had at least one episode of major depression and hypomania; cyclothymia, children who have manifested alternating episodes of hypomania and subsyndromal symptoms of depression; and bipolar not otherwise specified (NOS), children who do not meet full criteria but suffer from

**Table 1. Core Features of Bipolar Disorder:  
Manic/Hypomanic Episode: DSM IV-TR Criteria**

Mood symptoms: elevated,* expansive, or irritable mood
Associated symptoms: 3 out of 7 (4 of 7 if irritable mood)
Inflated self-esteem/grandiosity*
Decreased need for sleep*
Flight of ideas/racing thoughts*
Poor judgment or hypersexuality*
Distractibility
Goal-directed activity
Talkative/pressure of speech

\*Specific symptoms of manic/hypomanic episode.

Source: Geller B, Zimmerman B, Williams M, et al: DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. *J Child Adolesc Psychopharmacol* (in press).

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symptoms of a mood disturbance and are functionally impaired. These include patients who present with severe irritability, chronic and continuous psychopathology, a lack of episodic cycling, and mixed or minimal symptoms of depression but may not manifest an elated mood or grandiosity.<sup>10</sup>

Empirical evidence indicates that there are two variants of PBD:

- Prepubertal and early adolescent onset bipolar disorder (PEA-BD); and
- Adolescent onset bipolar disorder (AO-BD).

PEA-BD (also termed atypical or juvenile bipolar disorder) and AO-BD have distinguishing presentations. Findings from phenomenologic studies in both these age groups are summarized in Tables 2 (clinical features) and 3 (comorbidity and associated factors). Studies on PEA-BD usually involve subjects under 12 years of age,<sup>11-13</sup> while those on AO-BD involve postpubertal adolescents.<sup>14-18</sup> It is important to note, however, that these studies vary widely in diagnostic assessments, sample sizes, methodology, age range, and subtypes of bipolar disorder.

The predominant clinical features of PEA-BD are irritability, rapid cycling, little inter-episode recovery, and high comorbidity with ADHD and ODD.<sup>11-13</sup> AO-BD is characterized by high rates of substance abuse, anxiety symptoms, and an episodic nature in at least a quarter of the subjects.<sup>14-18</sup> Similarities between PEA-BD and AO-BD include elated mood and mixed episodes, longer duration of episodes, and lower interepisode recovery. By comparison, adult onset bipolar disorder tends to be episodic, with shorter distinct episodes.<sup>19</sup> As opposed to PEA-BD, AO-BD often presents with classic symptoms of adult mania, including psychosis.<sup>17</sup> Thus, AO-BD

is often misdiagnosed as schizophrenia and related psychotic disorders.<sup>18</sup>

Given the high degree of comorbidity and similarity of symptoms, it is critical to distinguish PEA-BD from ADHD. Five DSM-IV criteria do not overlap with the clinical criteria for ADHD and can discriminate PEA-BD from ADHD and normal controls. They are elation, grandiosity, racing thoughts/flight of ideas, decreased need for sleep, and hypersexuality. Irritability is common in mania, depression, ADHD, and ODD, and is present in 97.9% of PEA-BD episodes and 71.6% of ADHD episodes. Elated mood and irritability coexist in up to 87% of the patients in the PEA-BD sample.<sup>11</sup>

Controversy prevails about the critical features necessary to diagnose bipolar disorder in children. Some consider elated mood and grandiosity essential in PEA-BD,<sup>2</sup> while irritability alone is acceptable to others.<sup>13,20</sup> Carlson and Kelly<sup>1</sup> highlight the importance of an episodic pattern in defining PBD. They warn against the diagnosis of mania if there is no clear change from premorbid functioning or if symptoms of irritability and aggression are explained by a lack of limit setting. The authors, however, examined psychiatrically hospitalized prepubertal children aged 5-12 years with multiple disorders and reported significantly higher Child Behavior Checklist scores on the social, thought, and aggressive behavior aspects.<sup>1</sup> Based on parents' report, four or more manic symptoms were present in 80%. These results indicate that manic symptoms must be recognized, since they are a marker for more severe psychopathology even if they do not always meet the criteria for a full episode.

Findling et al. examined children aged 5 to 17 years with bipolar I disorder and

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**Table 2. Age-Based Comparison of Prepubertal, Adolescent, and Adult Onset Bipolar Disorder**

Clinical Features	Prepubertal-Early Adolescent Onset Bipolar Disorder		Adult Onset Bipolar Disorder
	Prepubertal-Early Adolescent Onset Bipolar Disorder	Adolescent Onset Bipolar Disorder	
Age of onset (years)	7.3 ± 3.5, <sup>11</sup> 5 ± 2.6, <sup>12</sup> 4.4 ± 3.1 <sup>13</sup>	11.75 ± 2.9, <sup>14*</sup> 13.9 ± 1.56, <sup>15</sup> 14.5 ± 1.7, <sup>17</sup> 17.7 ± 1.6 <sup>18†</sup>	30
Irritable mood (%)	97.9, <sup>11</sup> 77 <sup>13</sup>	22.2, <sup>14</sup> 14.1 ± 1.7 <sup>17</sup>	100
Elated mood (%)	89.3, <sup>11</sup> 14 <sup>13</sup>	88.9 <sup>14</sup>	90
Mixed (%)	54.8, <sup>11</sup> 19.6, <sup>12</sup> 84 <sup>13</sup>	19, <sup>16</sup> 26.1 <sup>18†</sup>	16–67
Psychosis (%)	60.2, <sup>11</sup> 17.9, <sup>12</sup> 16 <sup>13</sup>	28, <sup>16</sup> 75 <sup>17</sup>	75
Suicidal behavior (%)	24.7 <sup>11</sup>	44.4, <sup>14</sup> 20 <sup>16</sup>	24–58
Duration of the episode (months)	42 ± 29 <sup>11</sup>	36.3 ± 28.9, <sup>14</sup> 1.5–4 <sup>16</sup>	4–13
Interepisode recovery (%) (or episodic)	0, <sup>12</sup> 16 <sup>13</sup>	20–50 <sup>17</sup>	75–80
Rapid cycling (%)	87.1%, <sup>11</sup> 46.4 <sup>12</sup>	10 <sup>16</sup>	20–25

\*Lewinsohn and colleagues' data were included under the adolescent onset group since the standard deviation for age of onset is wide, with their cross-section sample having a mean age of 16 years.

†Subjects limited to psychotic bipolar disorder.

**Table 3. Age-Based Comparison of Prepubertal and Adolescent Onset Bipolar Disorder**

Comorbidity and Associated Factors	Prepubertal-Early Adolescent Onset Bipolar Disorder	
	Prepubertal-Early Adolescent Onset Bipolar Disorder	Adolescent Onset Bipolar Disorder
Comorbidity (%)		
ADHD	> 75 <sup>11,12,13</sup>	11.1, <sup>14</sup> 53 <sup>17</sup>
ODD	> 75, <sup>11,13</sup> 46.4 <sup>12</sup>	5.6 <sup>14</sup>
CD	17.9, <sup>12</sup> 37 <sup>13</sup>	5.6 <sup>14</sup>
Anxiety	12.5, <sup>12</sup> 56 <sup>13</sup>	33.3, <sup>14</sup> 33 <sup>17</sup>
Substance abuse	0–17.6 <sup>12</sup>	22.2, <sup>14</sup> 9, <sup>16</sup> 40 <sup>17</sup>
PTSD	—	27, <sup>17</sup> 47.8 <sup>18*</sup>
Intelligence Quotient (WISC-III)	103.5 ± 11.5 <sup>13</sup>	83–138, <sup>16</sup> 83.9 ± 18.2 <sup>17</sup>
Special education (%)	26.8, <sup>12</sup> 14 <sup>13</sup>	53, <sup>17</sup> 27.3 <sup>18*</sup>
Functioning (CGAS)	43.3 ± 7.6, <sup>11</sup> 43 ± 7.3 <sup>13</sup>	76.3 <sup>14</sup>

ADHD: Attention deficit hyperactivity disorder; ODD: Oppositional defiant disorder; WISC-III: Wechsler's Intelligence Scale for Children; CGAS: Clinical Global Assessment Scale; CD: Conduct disorder; PTSD: Post-traumatic stress disorder.

\*Subjects limited to psychotic bipolar disorder.

found that they had an average of 5.8 out of seven DSM-IV symptoms of mania during periods of elated or irritable mood. This disorder was also found to be associated with high rates of rapid cycling (i.e., 50%–87%) with almost no interepisode recovery.<sup>11,12</sup>

While cycling is a central aspect of bipolar disorder, onset and offset are not always easy to identify in PBD. Alternatively, complex cycling involves episodes that are

very long, at times characterized by daily cycles imbedded within a prolonged episode. Ultrarapid cycling (five to 364 cycles per year) and ultradian rapid cycling (≥365 cycles per year) have also been described.<sup>2</sup> As with adults, these episodes may meet the criteria for a mixed episode if the mood shifts rapidly from elation or irritability to depression and the manic symptoms coexist with depressive symptoms for at least 4 hours each day.<sup>19</sup>

**Clinical Description of PBD Symptoms**

The clinical picture in this group can be very confusing, since normal children can be active, imaginative, boastful, and sensitive to the environment, and can “act out” periodically. Experienced clinicians, however, can differentiate the abnormal from the normal based on qualitative changes from baseline, persistence and severity of dysfunction in multiple contexts, and a typical clustering of symptoms. Grandiose statements typical of classic mania, such as, “I can run the world,” are similar to statements from a child such as, “I can run the school.” This clinical description illustrates PBD:

- **Elated mood** often manifests as being excitable, silly, giddy, and feeling invincible and “overwhelmed,” with behavior such as laughing fits and excessive joking.
- **Irritable mood** presents as being easily irritated and aggressive, throwing things, slamming doors, having difficulty transitioning from one activity to another, being hostile or acidic, kicking, screaming, and showing intense and inconsolable responses out of proportion to the psychosocial situation. The children may apologize to their parents later: “I said ‘No, no, no’ to my brain but can’t stop being mad.” Parents often say, “We are walking on eggshells.”
- **Inflated self-esteem and grandiosity** are characterized by unsupported statements such as: “I am the best baseball player in America,” “I will teach the coach how to swim; he has no clue,” “I am absolutely sure I will get an Oscar before I’m 35,” “I am going to make millions through E-trade,” and “I do not need to go to school.” As with adults, psychosis is often seen in the manic phase. Delusions of grandiosity are differentiated from bragging if the age-appropriate reality check is absent and the child acts on the delusions.
- **Decreased need for sleep** is illustrated by parents’ descriptions of their children playing, singing, or watching television into the early morning, refusing to go to bed, and still not feeling tired in the morning. Children often describe their subjective experience as feeling like an “Energizer bunny.”
- **Pressure to keep talking** is often illustrated by statements like: “My mind is like a Ferrari; a million thoughts are racing. I can’t stop it.” Parents describe these children as constantly talking, never letting others have a say, domineering, and continually seeking attention by talking to them excessively or being unable to stop entertaining at home or school.
- **Constant goal-directed activity** is illustrated by continually fiddling and making a mess at home. When parents confront the mess or spills, the children become defensive, denying that they were responsible. In our experience,

parents report this as “lying.” It takes some effort to piece together the history of these “frenzied episodes.” One child described himself as going through “crazy maniacal spells.” Another child reported: “I ran for class president and I lost, but I’m fund-raising for ’N Sync to organize a concert.” Parents may describe constant goal-directed behavior such as feeding the dog, playing chess, doing art, and fighting with siblings all in 1 hour.

- **Excessive pleasurable activities, poor judgment, and risk taking** can be described with factual details. Youngsters may call 1-900 sex lines; suddenly start dressing inappropriately; get on sexually oriented chat lines; masturbate excessively; cut, hoard, or carry pornographic pictures; simulate sexual activity with animals; use their parents’ credit cards to order sex items by mail; or pressure parents to buy expensive dresses or other items. Sexual abuse is often considered in the differential diagnosis in these poorly socialized, sexually disinhibited children. However, many families with bipolar children also have well-behaved siblings. In an ongoing phenomenologic study, only 1.1% of the PBD sample had a history of sexual abuse or overstimulation, while 43% exhibited hypersexuality,<sup>11</sup> supporting this behavior as a critical symptom in PBD.
- **Features of depression** are often described in age-specific terms. Children may report feeling crabby, whine excessively, cry for no reason, look unhappy, spend hours in a dark room, change moods rapidly from irritable to tearful, engage in skin-pinching and self-scratching at a young age, or complain of somatic symptoms. These children often develop intense rejection sensitivity after years of negative response from others because of their prickly and cyclic behavior. Even very young, prepubertal children may report suicidal behavior, stating a desire to hang or choke themselves. This usually represents desperate attempts to regulate or escape from these affective swings. **Suicidal behavior is reported to be as high as 25% in PBD.**<sup>11</sup> In psychotic depressive episodes, mood-congruent delusions of doom, disaster, and nihilism are common. For example, one child drew pictures of a black ghost trying to take over the world.
- **Psychosis** can present as auditory or visual hallucinations, usually in addition to the mood-congruent delusions already described. Thought disorder presents as flight of ideas but becomes garbled if severe. **Psychotic features vary according to the method of reporting and may be present in 17% to 60% of PBD patients.**<sup>11–13</sup>

### Prodromal Symptoms

To determine symptoms that predict a diagnosis of PBD, Egeland et al.<sup>21</sup> coded the medical record data from first hospital admissions for bipolar disorder in an Amish population. The most frequently reported symptoms were episodic changes in mood (depressed and irritable) and anger dyscontrol, with no gender difference in symptom presentation. Many of the children were reported to be very sensitive and seemed “hyperalert” to the feelings of others. Rapid “extreme changes” from silence to bold, loud, and hostile behavior were also noted in many. Symptoms increased by 13–15 years of age, with a time interval of 9 to 12 years

between first symptoms and a documented manic episode. Chang et al.<sup>22</sup> found a similar symptom profile (i.e., increased severity of depressed and irritable mood, lack of affect modulation, and rejection sensitivity) in the offspring of bipolar patients. These prodromal symptoms may be more accurately termed “symptoms of high risk” since not all these children develop PBD.

## Epidemiology

### Prevalence

Since the concept of PBD has undergone major revision over the past several years, no large epidemiologic studies have examined the prevalence and incidence of PEA-BD as currently defined. In one community school survey of older adolescents (aged 14–18 years), the lifetime prevalence of bipolar I and bipolar II disorders was 1%.<sup>14</sup>

A U.S. study examining high-risk children found that 39% of the offspring of parents with bipolar disorder also had the disorder,<sup>23</sup> but only a 4% rate was observed in a Dutch study.<sup>24</sup> One reason suggested for this discrepancy was the higher use of stimulants and antidepressants by U.S. children, which may precipitate an otherwise-latent disorder in this high-risk group.

### Risk Factors

#### Biologic factors

No clear neuroendocrine, biochemical, genetic, or neuroimaging findings confirm or rule out PBD.

One study based on detailed interviews with parents of an outpatient population of bipolar I children or adolescents found that roughly 80% had at least one parent diagnosed with a mood disorder.<sup>12</sup> In another study, Faraone et al.<sup>25</sup> examined ADHD probands (with and without bipolar disorder), non-ADHD controls, and their first-degree biologic relatives. Relatives of ADHD probands with bipolar disorder had a risk of manifesting ADHD equal to that of relatives of ADHD probands without bipolar disorder. In contrast, relatives of ADHD probands with bipolar disorder were at a higher risk for bipolar disorder and major depression than those of the non-bipolar ADHD and control groups. Thus, the discriminant validity of bipolar disorder from ADHD needs to be examined.

Botteron et al.<sup>26</sup> attempted to identify susceptible individuals by examining eight manic patients and five controls using magnetic resonance imaging. Four manic subjects and one control subject demonstrated white matter abnormalities, while two manic patients and none of the controls had confluent subcortical hyperintensities. Such preliminary findings need replication in a larger study.

#### Psychosocial Factors

Certain psychosocial factors are relevant in PEA-BD compared with ADHD and control populations, but their exact role is unknown. They do, however, play a critical role when planning psychosocial interventions. Geller et al.<sup>27</sup> reported that more than half of those diagnosed with PEA-BD had no friends, were teased by other children, and had

poor social skills. They also had poor relationships with siblings and high-tension relationships with their parents. There was also a high degree of hostility and low warmth in maternal-child relationships, poor agreement between parents on child-rearing, and minimal problem-solving skills.

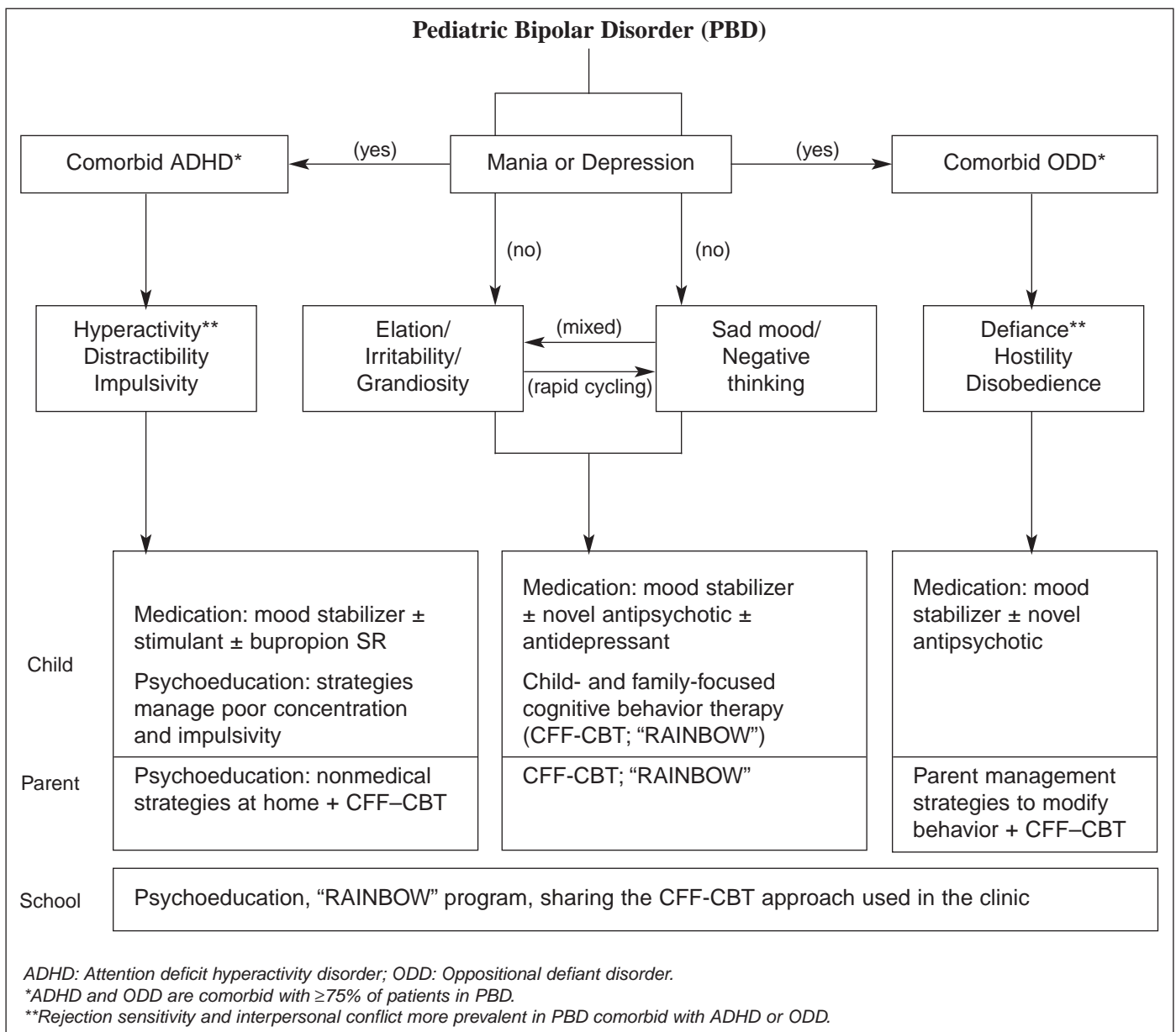
**Longitudinal Course**

A 1-year follow-up study of PEA-BD reported only a 37% recovery rate (defined by symptomatic and functional impairment). In addition, the rate of relapse after recovery was reported to be 38%.<sup>3</sup> Three explanations can be posited for this poor outcome. First, PEA-BD may be a more-severe variant of bipolar disorder, resembling poor outcome adult cases (i.e., long episode duration with high prevalence of mixed mania, psychosis, and rapid cycling).<sup>19</sup> Second, a significant number of adolescents were inadequately treated, (e.g., 50% were not on a mood stabilizer). Finally, many subjects were not in an organized treatment program, having

been recruited for a phenomenologic study from pediatric and psychiatric primary care practice settings.

Another study prospectively followed adolescents with bipolar I disorder (mean age = 16 ± 1.5 years).<sup>16</sup> The investigators observed a chronic unremitting course in only 3.7%, but 44% had one relapse or more. Covariates such as psychosis, family history of bipolar illness, duration of episodes before entering the study, age, sex, and socioeconomic class did not influence recovery.

Another study examining psychotic AO-BD (mean age = 15.3 ± 1.7 years) found that the prognosis was better than that of adolescents diagnosed with schizophrenia.<sup>17</sup> Most of these subjects were on mood stabilizers and in organized treatment programs. The disorder was more likely to be cyclical and associated with better functioning. Symptoms in these patients seemed similar to those of adult onset bipolar illness, which may not be the case in PEA-BD.



**Figure 1. Pediatric bipolar disorder treatment model.**

In a longitudinal study of ADHD children and controls, 11% had bipolar disorder at baseline in the ADHD group, and an additional 12% developed bipolar disorder by the fourth year of follow-up. Compared with controls and ADHD children without PBD, children who had both bipolar disorder and ADHD were more irritable and usually had mixed symptoms, higher scores on the Child Behavior Checklist, and a stronger family history of mood disorder.<sup>7</sup> The findings illustrate the severity of psychopathology in these comorbid cases.

## Treatment Intervention

To better understand and treat PBD, it is critical to develop a model that considers:

- The unique characteristics of PBD, especially PEA-BD (e.g., irritability, elated mood, grandiosity, and mixed and rapid cycling);
- High rates of comorbidity with ADHD and ODD;
- Developmental needs;
- Involvement of various social systems including family and school; and
- Innovative strategies to manage both the primary and associated features, such as rejection sensitivity.

We have developed and outlined one such model, depicted in Figure 1.

As with adults, the optimal treatment of PBD involves pharmacotherapy combined with various psychosocial interventions. Invariably, an effective treatment team includes a pharmacist (who may also be the psychotherapist), a psychotherapist, and a collaboration with parents or guardians, teachers and/or school counselors. The anchors in developing a treatment alliance are psychoeducation, venues for support such as the Child Bipolar Foundation (via Bpkids.org), educational materials, and local support groups.

Before definitive treatment is initiated, the baseline evaluation should include a comprehensive psychiatric evaluation; recent physical examination; complete blood count; comprehensive metabolic profile, including liver and thyroid function tests; urine pregnancy test in teenage girls; and a drug screen. A baseline ECG is recommended if treatment with lithium or clonidine is anticipated.

## Psychopharmacotherapy

The essential steps in developing rational pharmacotherapy for PBD are:

- Recognition of the disorder;
- Adequate understanding of the efficacy, safety, pharmacokinetics, and dynamics of the medication used;
- Development and testing of an algorithm based on specific hypotheses; and
- Application in the clinical setting.

We will summarize the key studies used to develop an algorithm for the pharmacologic management of this disorder that is being tested at the Pediatric Mood Disorders Clinic of the University of Illinois at Chicago.

Mood stabilizers are the first choice of medication in treating PBD. In a double-blind study, Kowatch et al.<sup>28</sup> developed effect sizes for three mood stabilizers (i.e., lithium, valproate,

and carbamazepine) used as monotherapy in the acute phase of bipolar I and II disorders, mixed or manic episodes, in children and adolescents 8–18 years of age. Response rates were measured based on  $\geq 50\%$  change from baseline score on the Young Mania Rating Scale. The effect size was found to be 1.63 for valproate, 1.06 for lithium, and 1.00 for carbamazepine. Response rates were 53% for valproate, 38% for lithium, and 38% for carbamazepine. While these results show relatively comparable response rates with all three mood stabilizers, monotherapy was clearly insufficient for adequate recovery from an acute manic or mixed episode.

In a second study, Geller et al.<sup>29</sup> administered lithium monotherapy in a double-blind, placebo-controlled design to bipolar adolescents with comorbid substance abuse. After 6 weeks of treatment, the subjects treated with lithium showed a significant decrease in their substance abuse, as well as improvement in their overall functioning.

Weller et al.<sup>30</sup> proposed the following lithium dosing strategy in the pediatric population:

- 600 mg for children weighing less than 25 kg;
- 900 mg for those 25–39 kg;
- 1,200 mg for those 40–50 kg; and
- 1,500 mg for over those 50 kg.

Dosing is then titrated based on serum lithium levels, treatment response, and tolerability. Another study reported that valproate (15–20 mg per kg body weight) was safe in a younger population.<sup>31</sup>

The literature on comorbid ADHD suggests that it can be treated safely with stimulants but only after stabilization of PBD with a mood stabilizer. This is because antidepressants and stimulants can exacerbate symptoms of mania in patients with PBD plus ADHD.<sup>5,32</sup> Further, stimulant exposure may lead to an earlier onset of bipolar disorder than in those without prior stimulant exposure.<sup>6</sup>

Combination therapy with a mood stabilizer and a novel antipsychotic is often necessary, since only a 40%–50% improvement is usually achieved with a mood stabilizer alone.<sup>28</sup> In this context, Kafantaris et al.<sup>33</sup> combined lithium and risperidone to treat acutely manic adolescents with psychotic features. This group was characterized by a first psychotic mood episode and short duration of illness. When the psychosis resolved, the antipsychotic was gradually tapered and was discontinued after 4 weeks of therapeutic lithium levels. Lithium monotherapy was then continued for another 4 weeks. While 64% improved significantly on combination therapy, only 29% of the initial responders continued to do well on lithium monotherapy. These results indicate that combination therapy should be continued longer in severe mania with psychotic features. In another study of combination therapy, valproate plus quetiapine was found to be more efficacious than valproate monotherapy in a group of hospitalized adolescents with bipolar I disorder.<sup>34</sup>

Recently, risperidone was used to treat prepubertal onset mania in an outpatient setting. While this was a naturalistic study and most patients were on other medications (including mood stabilizers and stimulants), the addition of risperidone reduced symptoms of mania, aggression, and psychosis but not ADHD.<sup>35</sup>

### Clinical Problem-Solving Model for Pharmacotherapy

After a manic or depressive episode is stabilized, the second goal is to prevent relapse. Furthermore, associated symptoms such as aggression, sleep disturbance, and comorbid psychopathology (e.g., ADHD) may require treatment with multiple medications. Determination of the type and severity of bipolar disorder is critical since:

- Severe psychotic bipolar I disorder usually requires lithium or valproate plus an antipsychotic;
- Moderate to mild bipolar I disorder or bipolar II disorder may respond to lithium or valproate alone; and
- If there is evidence of organicity, carbamazepine may be the mood stabilizer of choice.

Often, parents of children with bipolar disorder NOS are reluctant to consent to a trial with a mood stabilizer because of concern about adverse effects. In such situations, clinicians are faced with the dilemma of treating ancillary symptoms such as aggression rather than the primary mood symptoms. Often, a lower dose of a *novel antipsychotic* may be an appropriate initial step before introducing a mood stabilizer, since these agents have a lower rate of neuromotor side effects than neuroleptics. In our experience, about half the children with bipolar disorder NOS evolve to rapid cycling and bipolar I disorder, and then require the addition of a mood stabilizer. The other half respond well to an antipsychotic alone. Unfortunately, we cannot predict which course a specific patient will follow.

Once adequate mood stabilization is achieved, the clinician faces several obstacles, with different strategies needed to overcome them.

If depression is the primary symptom, *lithium* is the choice for mood stabilization. The adult literature indicates that lithium may also reduce the suicide rate associated with PBD.<sup>36</sup> In addition to a mood stabilizer, bupropion or venlafaxine may be viable additions in view of their possible decreased propensity to switch mood states in comparison with other antidepressants.<sup>37</sup>

For concurrent PBD and ADHD, a *psychostimulant* may be necessary. It is important, however, to stabilize mood symptoms before embarking on such a course. Methylphenidate (Ritalin, Concerta), dextroamphetamine (Dexedrine), or dextroamphetamine and amphetamine sulfate (Adderall, regular or extended release) are all reasonable choices. We start at low doses of methylphenidate (e.g., 10 to 15 mg) and titrate up as needed, seldom prescribing doses higher than 60 mg. Likewise, excessive doses of dextroamphetamine may trigger psychosis or mania.<sup>36</sup> *Bupropion SR* (150 mg per day) may effectively treat cognitive symptoms of ADHD (inattention and impulsivity), especially in the presence of depressed symptoms.<sup>38</sup> For excessive motoric symptoms, *clonidine* may be an appropriate choice.<sup>39</sup> Of note, emergent symptoms of inattention may be due to pharmacotherapy with a mood stabilizer or residual symptoms.

For sleep difficulties, the initial step is to prescribe the primary medication at night. If inadequate, *trazodone* (25–50 mg) or clonidine (0.05 mg qhs) may be effective

adjuncts.<sup>40</sup> Pharmacotherapy for insomnia should be time-limited, especially if using benzodiazepines or other agents that can cause habituation and rebound insomnia upon discontinuation.<sup>36</sup>

If arousal and aggression are prominent, we would maximize the dose of the mood stabilizer as tolerated and add a novel antipsychotic at low doses if necessary.<sup>35,41</sup> If there is clear but only partial response with a primary mood stabilizer plus novel antipsychotic, the addition of clonidine or *guanfacine* may be useful to reduce arousal and increased activity.<sup>39,40</sup>

Weight gain is often an issue with olanzapine, risperidone, or valproate. If significant weight gain occurs, alternative medications should be considered. Frequently, *topiramate* is used in adults to stabilize mood and reduce weight.<sup>36</sup> This raises the question of whether it can be used for a similar indication in children.<sup>42</sup> We urge caution in this regard, however, given the cognitive side effects and parathesia associated with topiramate. We also strongly recommend reviewing healthy eating habits, consulting a nutritionist, and providing information on weight management.

Breakthrough symptoms or emerging psychosis with the maximum tolerated dose of mood stabilizer may require intermittent, short adjunctive courses of a novel antipsychotic.

Since the hepatic enzyme system may not be mature in preschoolers,<sup>36</sup> lithium is the drug of choice, especially for those under age 4. Total T<sub>3</sub>, T<sub>4</sub>, free T<sub>4</sub>, and thyroid-stimulating hormone should be determined periodically as lithium causes hypothyroidism. If abnormalities occur, referral to an endocrinologist is appropriate. If gastrointestinal symptoms occur with one preparation (e.g., Synthroid), an alternative (e.g., Levothyroid) may be as effective and better tolerated.

### Psychosocial Therapy

Psychosocial interventions in the treatment of children with PBD include:

- Individual therapy with children and adolescents;
- Family therapy;
- Liaison work with the schools; and
- Group therapy or supportive therapy for children, parents, and families.

Presently, there are no proven psychosocial treatment methods for PBD. However, two National Institute of Mental Health-funded studies<sup>43,44</sup> are testing psychoeducation models, while another is focused on a collaborative problem-solving model. Fristad et al.<sup>43</sup> use a manually driven, adjunctive, multiple-family group treatment in youths aged 8 to 12 years with bipolar and depressive spectrum disorders. This method includes psychoeducation about the disorder, the role of medications, reducing self-blame, improving communication between parents and children, stress management, and helping to develop coping strategies.

Miklowitz et al.<sup>44</sup> are developing a manual for adolescents (ages 13 to 17 years) with bipolar I disorder. This is based on their success with use of a family-focused psychoeducation model in bipolar adults. The program involves psychoeducation, family problem-solving, communication

enhancement training to reduce expressed emotion, managing crises, and “relapse drill” (in which the patient rehearses coping strategies for a future relapse).

Finally, Greene<sup>45</sup> has developed a “collaborative problem-solving” model that focuses on parents as a “surrogate frontal lobe” so that children can develop appropriate skills. The main focus is to help parents avoid engaging their children when they are raging, not ask “why is he or she doing this?” or “give up passively,” but instead “let the rage pass.” Only after a rage attack subsides can the parent encourage collaborative problem-solving. This approach is controversial, since the model emphasizes “no consequences” for the rage behavior or actions related to it.

Our clinic has developed a treatment program that involves parent-and-child sessions for 8- to 12-year-olds with bipolar disorder called “child- and family-focused cognitive behavior therapy (CFF-CBT).” Central to this approach is building the youth’s self-esteem and helping all involved parties to understand that PBD is a neuropsychiatric problem of affect dysregulation, rather than willful misbehavior. Over 12 sessions, parents are trained as coaches, while engaging in parallel therapy to address their own affect regulation in dealing with their children, restructuring their thoughts regarding their effectiveness as parents, and learning to resolve interpersonal conflicts through empathy.

In this approach, both the parents and children are instructed in the use of “**RAINBOW**”:

- R = the importance of a *routine* (including sleep hygiene);
- A = *affect regulation/anger control* (including knowledge about the disorder, medication, and life charts);
- I = “*I can do it*” (positive self-statements);
- N = *no negative thoughts* (restructuring negative thinking)/living in the “now”;
- B = *be a good friend/balanced lifestyle* (also for parents);
- O = “*Oh, how can ‘we’ solve it?*” (letting the rages pass, interpersonal and situational problem-solving); and
- W = *ways to ask and get support* (build a “support tree”).

The school receives the work folder of the child documenting what has been accomplished in the individual sessions. In addition, we have a teleconference with school staff members to educate them in the use of the “RAINBOW” program.

## Conclusion

### PBD presents as two phenotypes:

- **PEA-BD, sometimes referred to as atypical or juvenile bipolar disorder; and**
- **AO-BD, which usually resembles bipolar disorder in adults.**

Characteristics of PEA-BD include chronic persistence of symptoms with poor remission rates, ultradian cycling, and a mixed picture with manic and depressive symptoms. Central features of a manic episode are elated mood, grandiosity, and irritability. While there is overlap in the diagnostic criteria for PEA-BD and ADHD, five symptoms usually differentiate the two (i.e., elated mood, grandiosity, racing thoughts/flight of ideas, hypersexuality, and sleep disturbance). ADHD and

ODD remain the most common comorbid conditions. No clear biologic or psychosocial markers identify PBD.

### The five essential steps in treatment are:

- **Initial and ongoing psychoeducation;**
- **Medication management;**
- **Psychotherapy for the child;**
- **Parent/family work; and**
- **Liaison with the school.**

We use a problem-solving treatment model of psychopharmacotherapy that initially aims to stabilize the primary disorder. It also involves managing persistent depression, aggression, ADHD, and sleep difficulties, as well as addressing adverse effects that interfere with treatment. Psychosocial treatment for parents and children is based on targeting affect dysregulation and negative thinking, teaching situational and interpersonal problem-solving skills, and helping parents teach their children the skills needed to deal with life stresses.

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1. Common clinical presentation of pediatric bipolar disorder includes:
  - A. Irritability, mixed episodes, rapid cycling, chronicity.
  - B. Aggression, psychosis, episodic follow-up.
  - C. Irritability but never elated mood.
  - D. Grandiosity and irritability, not elated mood.
2. Common comorbid conditions in pediatric bipolar disorder include:
  - A. Substance abuse disorder and generalized anxiety.
  - B. Oppositional defiant disorder and attention deficit hyperactivity disorder (ADHD).
  - C. ADHD and conduct disorder.
  - D. Autism and ADHD.
3. Stimulant use in pediatric bipolar disorder is associated with:
  - A. Improvement in both the mania and the ADHD.
  - B. Short-term recovery in mania.
  - C. Early presentation of mania but not worsening of mania.
  - D. Earlier onset of mania and worsening of mania.
4. The sequence of medicating a child who presents with bipolar disorder with mixed features of depression, oppositionality, and ADHD includes:
  - A. Mood stabilizer, small doses of stimulant if needed after stabilizing the mood.
  - B. Avoidance of stimulants, with mood stabilizers the primary choice.
  - C. Mood stabilizer and antidepressant.
  - D. Mood stabilizer and bupropion in the first step.
5. Is adolescent onset mania the same as prepubertal onset mania?
  - A. There is no clear answer, but current data suggest that they are the same.
  - B. There is no clear answer, but current data indicate that adolescent onset bipolar disorder is similar to adult onset bipolar disorder while prepubertal onset bipolar disorder is atypical.
  - C. Adolescent patients and prepubertal patients with early onset bipolar disorder can be similar and atypical.
  - D. Both B and C.
6. What would be the sequence of medicating a child who presents with bipolar I disorder and severe rage attacks with rapid cycling, no clear episodes of depression, and 50% response to the maximum tolerable dose of mood stabilizer?
  - A. Change to another mood stabilizer.
  - B. Add a small dose of novel neuroleptic.
  - C. Add another mood stabilizer.
  - D. Continue for 3 months on the current dose.
7. Familial history in pediatric bipolar disorder indicates an increased rate of:
  - A. Bipolar disorder in families.
  - B. Affective disorder in families.
  - C. Substance abuse in siblings.
  - D. ADHD in parents only.
8. Evidence indicates that the following factor(s) influence(s) prognosis in pediatric bipolar disorder:
  - A. Family history.
  - B. Family functioning.
  - C. Organized treatment program and mood stabilizers.
  - D. Mood stabilizers alone.
9. A double-blind, randomized, clinical trial indicated that:
  - A. Lithium is not effective in prepubertal mania.
  - B. Valproate, lithium, and carbamazepine are equally effective in pediatric bipolar disorder.
  - C. Valproate is superior to lithium and carbamazepine.
  - D. Valproate, lithium, and carbamazepine are equally effective in pediatric bipolar disorder, but on average, there is only a 50% response rate with monotherapy.
10. The average lag time between onset of pediatric bipolar disorder and being diagnosed is:
  - A. 5 years.
  - B. 1 year.
  - C. 10 years.
  - D. 15 years.