Published in final edited form as:
Curr Opin Pediatr. 2008 October ; 20(5): 560–565. doi:10.1097/MOP.0b013e32830fe3d2.

Pediatric Bipolar Disorder: Recognition in Primary Care

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Abstract

Purpose of Review—Bipolar disorder (BPD) is increasingly diagnosed in youth in both outpatient and inpatient settings. Research on BPD in youth has also increased dramatically; this paper summarizes issues of clinical relevance in primary care, advancements in the past year, and areas where more research is needed.

Recent Findings—Key issues and new developments are summarized in the following areas: epidemiology and relevance; assessment and differential diagnosis; patient and family decision support; shared decision making and triage; treatment; and monitoring and collaboration with mental health professionals. Recent practice guidelines have important implications for diagnosis and treatment.

Summary—Early-onset BPD appears to have a more severe course and more comorbidity than later life onset, as well as longer delays in treatment-seeking. Affected children show differences in cognitive functioning and neuroanatomy compared to the general population. Assessment of BPD in children needs to be comprehensive and longitudinal, as diagnosis remains a debated topic. Medications are a primary part of treatment, but more double-blind, placebo controlled trials are needed. Psychosocial adjunctive treatment is important. Children with a family history of BPD are at-risk for impaired functioning and psychopathology; high-risk studies will increase our understanding of the onset and course of BPD.

Keywords

bipolar disorder; children; diagnosis; treatment; recognition

Introduction

Epidemiological studies suggest striking increases in rates of youth diagnosed with BPD in both office-based settings [1*] and hospitals [2]. Research on BPD in youth has also increased dramatically; this paper summarizes: 1) epidemiology and relevance; 2) assessment and differential diagnosis; 3) patient and family decision support; 4) shared decision making and triage; 5) treatment; and 6) monitoring and collaboration with mental health professionals, with special emphasis on advancements of the past year.

Epidemiology and Relevance

The diagnosis of BPD in youth continues to be hotly debated [3,4,5**]. Two recent studies indicate greatly increased rates of diagnosis in outpatients [1*] and inpatients [2]. Several possible reasons for this change in diagnostic practice are offered. For outpatients, delays in

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treatment-seeking and less clinical and public awareness of BPD led to underdiagnosis in the past [1*]. For inpatients, increases in diagnoses may reflect frequent rehospitalizations of BPD patients; improved detection with increasing knowledge of BPD; or "upcoding" behavioral problems to BPD to secure reimbursement from insurance companies [2].

Several subtypes of BPD exist, including Bipolar I Disorder (BP-I), Bipolar II Disorder (BP-II), Bipolar Disorder-Not Otherwise Specified (BP-NOS), and Cyclothymic Disorder. BP-I consists of one or more manic episodes (typically in association longitudinally with depression), BP-II consists of depressive and hypomanic episodes, and BP-NOS includes disorders with bipolar features not meeting criteria for BP-I or BP-II. Cyclothymic Disorder consists of hypomanic episodes and depressive symptoms not meeting criteria for a major depressive episode [6]. Definitions for each of these appear below. Work is underway to clarify boundaries between these bipolar spectrum disorders (BPSD). In a sample of 217 children and adolescents with BPSD, patients with BP-I (35.9%) more likely experienced elated mood and psychotic symptoms [7*]. Youth with BP-II (44.7%) were more likely to report depression, were less severely impaired, and had the highest co-occurrence with anxiety disorders. BP-NOS subjects (19.4%) had an earlier onset, irritable mood, an episodic course, and more frequent comorbidity with attention-deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD).

Assessment and Differential Diagnosis

A manic episode is "a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)," accompanied by three of more of the following symptoms: inflated self-esteem, decreased need for sleep, more talkative than usual, flight of ideas or racing thoughts, distractibility, increase in goal-directed activity, and excessive involvement in dangerous activities that have a high potential for dangerous consequences [6, p. 362]. A hypomanic episode is "a distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least four days," accompanied by at least three of the symptoms of mania listed above [6, p. 368].

A major depressive episode consists of five or more of the following symptoms during the same two-week period: depressed mood, markedly diminished interest or pleasure in activities, significant weight loss or gain or a decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to concentrate or indecisiveness, and recurrent thoughts of death or suicidality [6].

Chang [8] argues that pediatric BPD (strictly defined BP-I and BP-II) is continuous with adult forms of the disorder. Similar symptoms in children and adults (taking developmental differences into account), childhood-onset reported in adults with BPD, family studies, and biological characteristics provide compelling evidence for this position [8]. However, youth frequently do not meet strictly defined criteria of BP-I and BP-II, presenting instead with severe mood dysregulation and features indicative of BPD.

Recommendations for the assessment of BPD in youth include use of screening questionnaires, DSM-IV-TR criteria, and caution in applying the diagnosis to preschoolers [5**]. BP-II is frequently underdiagnosed in youth who present with major depressive disorder (MDD), to avoid this mistake, a longitudinal, lifetime history must be gathered [9*].

Comorbidity

Further complicating diagnosis is the frequent occurrence of comorbidity. In a sample of 147 Turkish children with ADHD, children with comorbid BPD (8.2%) had higher rates of ODD,

panic disorder, a family history of BPD, and more problems on the Child Behavior Checklist (CBCL) and Young Mania Rating Scale (YMRS) than children with ADHD and no BPD [10]. Conduct problems are also common. Over half of adolescent inpatients with BPD had a least one offense prior to hospitalization, most commonly, larceny-theft, domestic violence, and drug law violations [11*]. Offenders were more likely to be older at first treatment and sexually active in the past month than non-offenders, who were more likely to have used stimulants and to have an anxiety disorder [11*]. Adults who reported conduct problems in childhood were 2.6 to 3.5 times more likely to have BP-II compared to those who did not report such problems, even after controlling for socio-economic status [12].

Sex differences

No sex differences in rates of BPSD or in bipolar subtypes were noted in 387 youth diagnosed with BPSD [13]. Males were more likely to present in a manic state while females were more likely to present in a depressed state. There were no sex differences in mixed mood states [13].

Cognitive function

Children with BPD show impairments in cognitive flexibility, or the ability to adapt to changing circumstances in the environment, compared to healthy controls [14]. They are also less adept than healthy controls in identifying emotionally intense happy and sad faces [15]. Children with BPD and a comorbid anxiety disorder (BPD+ANX) demonstrated a bias toward threatening faces, while children with BPD and no comorbid anxiety disorder (BPD-ANX) and controls demonstrated no such bias [16**], suggesting BPD+ANX and BPD-ANX may have different pathophysiologies and thus require different treatment approaches [16**].

Neuroanatomy

Magnetic resonance imaging (MRI) scans of orbitofrontal cortex (OFC) regions in14 youth diagnosed with BPD and 20 healthy controls demonstrate significant gender interactions [17*]. Females with BPD had larger gray matter volumes in left, lateral, and left lateral OFC regions compared to female controls, and showed a significant trend for larger volumes in the right lateral and medial left regions of the OFC. Males with BPD had significantly smaller gray matter volumes in the medial, right medial, and right lateral OFC regions compared to male controls [17*].

Family history

Youth with early-onset BPD tend to have higher percentages of first-degree relatives with various mental and emotional disorders than adolescents with later-onset BPD [18*]. Youth with a more classical BPD presentation are more likely to have parents with a BPD diagnosis, compared to youth with severe mood dysregulation but no diagnosed BPSD [19]. Children of parents with BPD have more social impairment [20] and higher parent-rated and child-rated irritability compared to control children, even after adjusting for child psychopathology, suggesting a possible genetic link between BPD and irritability in offspring [21].

Onset

Sleep and anxiety disorders, and ADHDhave been identified as antecedent conditions in those who eventually develop BPD [22**]. Stressful life events often trigger episode onset, particularly for those at-risk youth noted to be high in “emotionality,” a particular temperamental profile that suggests sensitivity to stressful life events [23*]. Frequent “ups and downs,” anxious or depressive episodes, disruptive behavior disorders, symptoms potentially indicating mania (e.g., signs of irritability, elated mood, racing thoughts) positive family

history, and lower overall functioning are all common in the prodrome of youth who develop BPSD [24,25].

Screening questionnaires

No simple screen or self-report measure is a substitute for careful clinical interview. Researchers have evaluated various instruments to identify BPD in youth, including the CBCL [26,27,28] and Child Bipolar Questionnaire (CBQ) [29]. The CBCL is unlikely to provide much specific guidance for the diagnosis of BPD, since profiles are variable and do not correlate with BPD diagnosis from semi-structured interviews [28]. The CBQ's dimensional approach may be useful for genetic studies of BPD [29]. Although scales may be helpful for early screening and supplemental information, cross-sectional assessments of a child's symptoms are inadequate for diagnosis.

Differential diagnosis

Not all irritability or "mood swings" result in a diagnosis of BPSD. Irritability and psychomotor agitation are to children's mental health what fever is to children's physical health. They are indicators of a problem, but do not equate to any particular diagnosis; rather, they can reflect developmental, behavioral, anxiety, mood or psychotic disorders—in other words, the gamut of children's emotional and behavioral disorders. Critical to the diagnosis of a BPSD is the temporal clustering of symptoms previously described accompanied by clear impairment in functioning.

Summary

Findings discussed above suggest clinicians must gather a thorough, integrative history that embeds a lifetime history of mood symptoms and episodes in the context of the child's pre- and perinatal history, developmental, family, medical, social, academic, and treatment history. Comorbid disorders are common, and complicate diagnosis. Sex differences do not appear in rates of BSPD, but girls and boys may present in different mood states. Children with BPD may present with differences in cognitive function and neuroanatomy. It is essential to assess family history when considering a BPSD diagnosis.

Five questions the primary care physician should remember are: 1) are there sustained periods of time (e.g., more than an hour or two in a day) when the child becomes too silly or giddy for hours at a time with no explanation (including paradoxical reaction to medications)?; 2) are there sustained periods of time (e.g., more than an hour or two in a day) when the child has *extreme* bouts of irritability, not in keeping with his usual temperament?; 3) during the same period of time when the child's mood becomes too high or too intensely irritable, does the child sleep far less than usual? 4) during this same period of time, does the child seem to be "going too fast"—pressured speech, racing thoughts, or clearly reckless behavior/exhibiting out-of-character poor judgment? 5) is there a family history of BPD (or depression in both sides of the family)?

Patient and Family Decision Support

It is critical that families be taught and empowered to play an active role in their child's treatment. Likewise, children must be educated to understand and manage their symptoms. Primary care physicians can utilize the treatment guidelines summarized below to provide care, information and support to youth with BSD and their families.

Longitudinal course

It is critical for patients and families to understand that BPSD appear to be lifelong conditions with symptoms that wax and wane over time. Age of onset is relatively evenly divided across

childhood (14%), adolescence (36%), early adulthood (32%), and late adulthood (19%) [30]. Paradoxically, individuals with childhood-onset BPD had longer delays from disorder onset to treatment (approximately 16 years) than those with onset later in life. Childhood and adolescent onset is related to more episodes, comorbid disorders, rapid cycling, and more severe mania and depression [30]. Childhood-onset BPD more commonly includes irritability, conduct problems, and higher rates of comorbidity; adolescent-onset BPD has higher rates of psychotic symptoms [31]. Individuals with early-onset are more likely to be female, experience more psychotic symptoms, and have greater comorbidity, a more severe illness, and a longer time to first treatment [32]. It is worth noting that some youth who present with a major depressive disorder will go on to develop a course later in life consistent with BPD. The risk of a depressed youth eventually developing BPD may be increased in those suffering from psychotic depression, who experience rapid onset or offset of their depression, and who develop symptoms of mania or hypomania when treated with antidepressant medication.

Treatment adherence

Treatment adherence is often low in this population [33**], complicating clinical outcome. A proactive discussion with patient and family of the risks of nonadherence in a chronic disorder such as BPD is advisable. Twelve months post-hospitalization for 71 adolescents with BPD, only 35% of the adolescents reported full medication adherence. Comorbid ADHD, anxiety, and disruptive behavior disorders, nonadherence to medications, and lower socioeconomic status were predictors of poor recovery [33**].

Shared Decision Making and Triage

Parents are often reluctant to have their child try medications recommended for BPSD—mood stabilizers and/or atypical antipsychotic medication, as these drugs carry with them significant risk for adverse events. It is critical that parents and children be appraised of means to monitor their: 1) moods and treatment response via mood charting; 2) side effects so they can, in conjunction with their physician, determine whether the total dose, distribution of dose, or type of medicine require modification. If possible, referral to a child and adolescent psychiatrist is recommended, although this is not realistic or adequately timely in all communities. Thus, medication recommendations appear below which primary care physicians can use to initiate treatment.

Treatment

Medications and adjunctive psychoeducational psychotherapy have demonstrated efficacy in treating BPD.

Medications

Medications are an essential first step in treating children with BPD [5**,34,35]. Guidelines are available for treating children with BP-I [5**]. Ideally, children should begin treatment with medication approved by the Food and Drug Administration (FDA) for BPD. Only lithium was FDA approved for children when existing treatment guidelines were published; subsequently, risperidone and aripiprazole have also been approved for BPD youth. Most children will require ongoing medication therapy to manage their disorder and to prevent relapse, drawing a balance between maximizing symptom relief and minimizing untoward side effects [5**]. Medications should be monitored for a sufficient length of time (e.g., six to eight weeks for mood stabilizers) to determine effectiveness. Judicious use of polypharmacy, both to treat the BPD as well as comorbid conditions, is often necessary [5**], yet poorly studied. A decision-making strategy regarding when to augment, switch, or continue a medication for a child with BPD is available [36] that is based on expert consensus. There is a dire need for

more double-blind, placebo controlled trials, and studies of treating the depressed phase of BPD, comorbidities, and relapse-prevention [35,37].

Three open-label prospective studies found aripiprazole [38], ziprasidone [39] and omega-3 fatty acids [40] to be associated with clinically significant improvement in BPD youth. Adolescents with BP-I experienced improved health-related quality of life following trials with either divalproex or quetiapine [41]. A single-blind trial found quetiapine to be effective in adolescents at high-risk for developing BP-I [42]. High-risk was defined as youth diagnosed with BP-NOS, dysthymia, BP-II, cyclothymia, or MDD, all of whom had a first degree relative with BPD [42]. However, another high-risk treatment study that employed a double-blind, placebo controlled methodology found that treatment with divalproex sodium for up to five years did not lead to significant symptom improvement compared to placebo for offspring of parents with BPD and who had diagnoses of BPD-NOS or cyclothymia [43**].

Psychotherapy

Adjunctive psychoeducational psychotherapy teaches families about the symptoms of BPD as well as its biopsychosocial management, which includes improving family problem solving and communication skills in order to better manage symptoms. Psychoeducational psychotherapy has demonstrated efficacy in treating BPSD, both acutely [44] and as maintenance treatment [45**]. Additionally, family-based psychoeducational psychotherapy results in reduced variance in the number of medications taken from pre- to post-treatment, suggesting this treatment helps parents become better consumers of mental health care, in particular, medication management [46]. Physicians should recommend therapy for families of children with BPD, to help inform and empower families and maintain treatment gains. Collaboration between the family, prescribing physician and therapist is an important part of care.

Monitoring and Collaboration

Treatment for children with BPD requires ongoing monitoring and collaboration.

Monitoring

Baseline and periodic laboratory assessments are needed to ensure safety when prescribing medications to children with BPD. These are described below.

Before prescribing lithium, obtain complete blood cell counts, thyroid function tests, urinalysis, blood urea nitrogen, creatinine, serum calcium levels, and a pregnancy test, if appropriate. Once the patient is stabilized on an appropriate dosage of lithium, lithium levels, renal and thyroid function and urinalysis should be monitored on an ongoing basis [5**].

Prior to prescribing valproate, obtain liver function tests, complete blood cell counts, and a pregnancy test, if appropriate. Continuous monitoring of serum drug levels, hepatic and hematological indices are in order once the patient is stabilized [5**].

Before prescribing atypical antipsychotics, obtain a baseline body mass index, waist circumference, blood pressure, fasting glucose levels, and a fasting lipid panel. Monitor body mass index, blood pressure, fasting glucose levels, and lipids continuously during treatment. Specific antipsychotic agents may have varying requirements [5**].

We know little about long-term effects of medications often prescribed for children with BPD. Additionally, short-term side effects (e.g., weight gain and cognitive side effects) must be carefully monitored. Once a patient is stabilized on an appropriate dosage of a medication, maintenance treatment should continue with the goal of relapse prevention. Ongoing

monitoring for symptom recurrence, including suicide risk and to improve functioning at home, school, and with peers is important.

Collaboration

In general, referral to a specialist is recommended; however, even when a referral is readily available, collaborative care with the specialist may be required to monitor potential adverse events. Referral to a mental health professional may not always be feasible or acceptable to the patient and family.

Conclusion

In summary, knowledge of BPD in children is rapidly increasing. Assessments must be longitudinal and comprehensive. As BPD often manifests early and is most likely a lifetime condition, patient and family support is crucial to give families the skills to manage the disorder. While medications are an essential treatment component, more randomized, placebo-controlled trials are needed, especially for combination treatments. Adjunctive psychosocial treatments are crucial. When prescribing medications, baseline laboratory assessments and careful periodic monitoring of side effects is necessary. Referral and/or collaboration with a mental health specialist is strongly recommended.

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