Pediatric bipolar disorder: Epidemiology and pathogenesis

AUTHOR: Boris Birmaher, MD
SECTION EDITOR: David Brent, MD
DEPUTY EDITOR: David Solomon, MD

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INTRODUCTION

Bipolar disorder in children and adolescents is characterized by recurrent episodes of mania (table 1) or hypomania (table 2); in addition, episodes of major depression (table 3) usually occur [1]. The disorder severely affects normal development and psychosocial functioning and increases the risk for behavioral, academic, social, and legal problems, as well as psychosis, substance abuse, and suicide [2-4].

Multiple retrospective studies have reported that in up to 60 percent of adults with bipolar disorder, onset of mood symptoms occurred before age 20 [2,5,6]. However, pediatric bipolar disorder is often not recognized, and many youth with the disorder do not receive treatment or are treated for comorbid conditions rather than bipolar disorder [7]. A retrospective study of 88 pediatric patients with bipolar disorder found that the duration of untreated bipolar disorder, from onset of the first mood episode to first mental health contact, was nearly two years [8]. In addition, retrospective studies in adults with bipolar disorder have reported diagnostic delays of 5 to 10 years [9,10]. The longer it takes to start appropriate treatment, the worse the adult outcomes [9,10].

This topic describes the epidemiology and pathogenesis pediatric bipolar disorder. The clinical features, comorbidity, assessment, diagnosis, and treatment of bipolar disorder in children and adolescents are discussed separately.

- (See "Pediatric bipolar disorder: Clinical manifestations and course of illness".)
- (See "Pediatric bipolar disorder: Comorbidity".)
- (See "Pediatric bipolar disorder: Assessment and diagnosis".)
- (See "Pediatric bipolar disorder: Overview of choosing treatment".)
- (See "Pediatric bipolar major depression: Choosing treatment".)
- (See "Pediatric bipolar disorder and pharmacotherapy: General principles".)
- (See "Pediatric mania and second-generation antipsychotics: Efficacy, administration, and side effects".)
- (See "Pediatric bipolar disorder: Efficacy and core elements of adjunctive psychotherapy".)

TERMINOLOGY

Bipolar disorder is characterized by episodes of mania (table 1) and/or hypomania (table 2) [1]. These episodes consist of concurrent symptoms (eg, decreased need for sleep and pressured speech) that always include elevated mood or irritability and persistently increased activity or energy. The symptoms of mania/hypomania exceed what is expected for the child's developmental stage and are not better explained by other psychiatric and general medical conditions [1,2,11,12]. In mania, the symptoms last at least one week, and in hypomania at least four consecutive days.

In addition, youth with bipolar disorder usually have recurrent episodes of major depression (table 3); however, depressive episodes are not necessary for making the diagnosis [1]. In contrast to mania, major depression is marked by an overall decrease in emotion, cognition, and energy. Episodes of depression consist of concurrent symptoms (eg, fatigue and decreased concentration) that always include either depressed mood or anhedonia; the symptoms last for at least two consecutive weeks.

According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the subtypes of bipolar disorder include bipolar I disorder, bipolar II disorder, cyclothymic disorder, and other specified and related bipolar disorder. The clinical features and diagnosis of these subtypes are described separately. (See "Pediatric bipolar disorder: Clinical manifestations and course of illness", section on 'Terminology' and "Pediatric bipolar disorder: Assessment and diagnosis", section on 'Bipolar disorders'.)

EPIDEMIOLOGY

The prevalence of pediatric bipolar disorder is not well established due to multiple issues, one of which is that diagnosing bipolar disorder in youth is complex [2,4,12]. Patients frequently have a variable course with rapid fluctuation in mood symptoms during acute episodes, and developmental issues influence the clinical picture [2,11,13]. In addition, youth can have difficulties verbalizing their emotions and symptoms, the symptoms of bipolar disorder overlap with symptoms of other psychiatric disorders, and pediatric bipolar disorder is characterized by high rates of comorbidity [4,5].

Another issue that interferes with determining the prevalence of pediatric bipolar disorder is that studies differ in their definitions of bipolar disorder and timeframe. Some studies assess lifetime prevalence, whereas others estimate prevalence over limited time periods (eg, one year) [14]. Surveys also differ in whether they present a single prevalence rate or separate rates based upon parent and youth report. Another difference among surveys is whether diagnostic interviews are completed by clinicians or trained lay interviewers.

Prevalence estimates of pediatric bipolar disorder in the community are based upon surveys of school-age children as well as adolescents; the youngest age of participants in these studies is typically 11 years [14]. Nevertheless, bipolar disorder may occur at earlier ages, and is rarely found in preschool-age children as young as four or five years [15,16]. Although the prevalence of bipolar disorder in preschoolers is not known, it is our opinion that bipolar disorder occurs much less often in preschool children than school-age children and adolescents.

Prevalence — A meta-analysis of community surveys in different countries suggested that the lifetime prevalence of bipolar disorder (bipolar I disorder, bipolar II disorder, cyclothymic disorder, or other specified and related bipolar disorder) in the general population of children and adolescents is approximately 3.9 percent [14]. However, heterogeneity across studies was large. Studies in clinical settings have found relatively low rates of 1 percent or less, which may indicate underrecognition [17].

General population — Multiple studies have examined the prevalence of pediatric bipolar disorder in the general population of Western countries. In one review, 19 studies were identified: 7 from the United States, 8 from Europe, 2 from Brazil, and 1 each from Canada and Mexico [14]. The total sample of children and adolescents exceeded 56,000, ranging in age from 5 to 21 years, and included nearly 1400 youth diagnosed with bipolar disorder. Meta-analyses showed that:

- The prevalence of bipolar disorder was 3.9 percent. However, heterogeneity across studies was statistically significant.
- The prevalence of bipolar I disorder was 0.6 percent; again, heterogeneity was significant.

- The prevalence of bipolar disorder remained stable over time.
- The prevalence rate of bipolar disorder, pooled separately for the United States and for other countries, was comparable.

  Significant heterogeneity of the results across studies appears to be due to differences in the criteria that were used to diagnose bipolar disorder, the relatively small number of studies that assessed prepubertal children, and differences in the timeframe that was assessed. The meta-analyses indicated that higher prevalence rates of bipolar disorder occurred in surveys that used broad diagnostic criteria (ie, more loosely interpreted standardized criteria rather than applying the criteria as written) [14]. In addition, the meta-analyses found that the prevalence was higher in surveys with an older minimum age (>12 versus ≤12 years), and in surveys that assessed lifetime prevalence rather than shorter time periods.

Clinical settings — Across studies in clinical settings, the prevalence of pediatric bipolar disorder is 1 percent or less:

- **United States**
  - Outpatients – A nationally representative survey of outpatient visits found that among youths age 0 to 19 years, the prevalence of bipolar disorder was 1 percent [18].
  - Inpatients – Studies utilizing nationally representative surveys of hospital discharges found the following prevalence rates [19,20]:
    - Youth age 1 to 19 years – 0.10 percent
    - Children age 5 to 13 years – 0.07 percent
    - Adolescents age 14 to 18 years – 0.20 percent
- **Denmark** – A national registry study examined all hospital contacts for inpatient, outpatient, and emergency department visits [17]. The cumulative incidence of bipolar disorder through age 17 years in females and males was comparable:
  - Females – 0.10 percent
  - Males – 0.06 percent
- **England** – A study of an administrative dataset that included hospital discharges found that among children and adolescents age 1 to 19 years, the prevalence of bipolar disorder

was 0.001 percent [19].

Clinicians in the United States appear to diagnose pediatric bipolar disorder, particularly the subtype other specified bipolar disorder, more often than clinicians in some other countries. In a study of children and adolescents who were hospitalized for psychiatric disorders in the United States and England between 2000 and 2010, discharge rates for pediatric bipolar disorder in both countries were stable over the 11-year study period [19]. However, bipolar disorder was diagnosed 12.5 times more often in the United States than in England. Given that epidemiologic studies suggest the “true prevalence” of pediatric bipolar disorder in the United States and in other countries is comparable (see 'General population' above), the disparity in discharge rates for pediatric bipolar disorder seems to be the result of differences in diagnostic practices and how the clinical picture is interpreted [2,12,14,21]. Possible explanations for why diagnostic practices differ is that clinicians in the United States are more confident that bipolar disorder exists in youths, and conceptualize the disorder more broadly [22].

Risk factors — One risk factor for pediatric bipolar disorder is a positive family history. Youth are at high risk of developing bipolar disorder if at least one parent has the disorder, especially if onset of bipolar disorder in the parent is early (eg, less than 21 years old) [12,15,23-26]. (See "Bipolar disorder in adults: Epidemiology and pathogenesis", section on 'Genetics'.)

Among youth with at least one parent who has bipolar disorder, other risk factors for developing pediatric bipolar disorder include depressive/anxious symptoms, mood lability, and subsyndromal manic/hypomanic symptoms [24,25]. Offspring of parents with bipolar disorder who present with all three factors have a nearly 50 percent risk of developing pediatric bipolar disorder. (See "Pediatric bipolar disorder: Clinical manifestations and course of illness", section on 'Offspring of bipolar parents'.)

It is not clear if sex is a risk factor for pediatric bipolar disorder due to mixed results across studies. A nationally representative survey of outpatient visits found that the prevalence of bipolar disorder was greater in males than females [18]. However, a national registry study, which examined all hospital contacts for inpatient, outpatient, and emergency department visits, found that the cumulative incidence of bipolar disorder was comparable in male and female youths [17].

The factors discussed in this section can be used to judge the risk of bipolar disorder in a group of youth, but do not inform clinicians about the specific risk for a single individual. To meet this need, a calculator has been developed to predict the five-year risk of new-onset bipolar disorder in a particular youth whose parent has bipolar disorder [27]. However, external validation is required before the risk calculator can be incorporated into routine clinical practice.

PATHOGENESIS

The pathogenesis of bipolar disorder in youth is not known, but research findings suggest that biologic and psychosocial factors are involved. One hypothesis proposes that genes associated with bipolar disorder give rise to aberrant prefrontal-subcortical neural networks, which lead to abnormal mood regulation that is reinforced or exacerbated by environmental stress and maladaptive reactions to stress [12,28].

A separate topic discusses the pathogenesis of bipolar disorder in adults. (See "Bipolar disorder in adults: Epidemiology and pathogenesis", section on 'Pathogenesis'.)

Genetics — The genetics of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Epidemiology and pathogenesis", section on 'Genetics'.)

Obstetric complications and bipolar disorder in offspring — Obstetrical complications do not appear to play a role in the pathogenesis of bipolar disorder. (See "Bipolar disorder in women: Contraception and preconception assessment and counseling", section on 'Obstetric complications and bipolar disorder in offspring'.)

Psychosocial factors — Psychosocial (environmental) factors may precipitate bipolar mood episodes in children and adolescents [29]. In studies that evaluated the effects of psychosocial factors upon the onset and maintenance of pediatric bipolar disorder, low socioeconomic status, exposure to negative events, and high “expressed-emotion” were associated with poor prognosis [2,3,11,30,31]. Expressed emotion refers to family environments marked by emotional overinvolvement, critical comments, and hostility [32].

One of the negative events that may be associated with onset of bipolar disorder is childhood abuse. In retrospective studies of youth with bipolar disorder (n = 466 and n = 151), physical and/or sexual abuse had occurred in 20 to 30 percent, and was associated with an earlier age of onset and more prolonged course [33,34].

Additional information about the association between psychosocial factors and the pathogenesis of bipolar disorder is discussed separately in the context of adults. (See "Bipolar disorder in adults: Epidemiology and pathogenesis", section on 'Psychosocial factors'.)

NEUROBIOLOGY

Multiple lines of evidence demonstrate that brain structure, function, and chemistry are altered in pediatric bipolar disorder. However, it is not clear whether the observed abnormalities

represent etiologic causes, sequelae, neither, or both.

Neuroimaging — Structural and functional brain magnetic resonance imaging (MRI) studies have shown that several brain networks involved in cognition (eg, the dorsolateral prefrontal cortex) and emotional functioning (eg, amygdala) are altered in youth with bipolar disorder, as well as individuals at risk to develop bipolar disorder [12,35,36]. However, it remains unclear whether the changes are trait or state characteristics, and the findings lack sufficient specificity and predictive validity for diagnosing the disorder. Potential confounding factors in neuroimaging studies include age at onset of bipolar disorder, mood state at time of assessment, length of illness, presence of comorbidities, and exposure to stressors and medications [12,28].

Although neuroimaging is not part of standard care for diagnosing pediatric bipolar disorder, preliminary studies suggest that neuroanatomical findings may perhaps serve as a diagnostic marker. As an example, a structural magnetic resonance imaging study found that abnormalities in the amygdala could be used to categorize youth with bipolar disorder (n = 16) and healthy controls (n = 16), with good sensitivity (81 percent), specificity (75 percent), and positive predictive value (76 percent) [37].

Additional information about the association between bipolar disorder and neuroimaging abnormalities is discussed in the context of adults. (See "Bipolar disorder in adults: Epidemiology and pathogenesis", section on 'Neuroimaging'.)

Brain structure — Structural brain alterations observed in youth with bipolar disorder include anomalies in the frontal-limbic networks, which are involved in processing and regulating emotions [12,36,38]. Multiple studies suggest that these abnormalities may be a trait marker of pediatric bipolar disorder [39,40].

- **Amygdala** – Structural MRI studies suggest that the volume of the amygdala is smaller in children and adolescents with bipolar disorder than controls [12]:
  - A meta-analysis of five studies (n = 112 bipolar youth and 89 controls) found that the amygdala was reduced in bipolar youth and the clinical difference was moderate to large [41].
  - A meta-analysis of eight studies (sample size not reported) found that the amygdala was smaller in bipolar youth than controls and the effect was large [42].
- **Other gray matter structures** – Gray matter structures in the frontal and temporal lobes are smaller in children and adolescents with bipolar disorder, compared with controls [38].

Among youth at risk for bipolar disorder, parietal cortical thickness may be reduced [43].

- **White matter microstructure** – Diffusion tensor imaging studies in youth with bipolar disorder, youth at risk for bipolar disorder, and controls suggest that pediatric bipolar disorder is associated with white matter microstructure abnormalities [12,36,44]. Observed reductions in white matter integrity in frontal areas are consistent with hypothesized connectivity deficits between prefrontal areas and the limbic system. One study found that these deficits improved in patients who responded to treatment [45].

Multiple studies suggest that in pediatric bipolar disorder, with or without psychotic features, structural brain alterations are generally comparable [38,46].

Brain functioning — A review examined functional neuroimaging studies in youth with bipolar disorder [12], including two meta-analyses, each of which identified more than 20 task-based functional MRI studies in children and adolescents with bipolar disorder (n = 452 and 534) and healthy controls [47,48]. The review found that prefrontal areas are hypoactive and do not efficiently modulate hyperactive limbic structures [12]. In addition, results across multiple studies suggested that prefrontal-limbic functional connectivity, which is involved in the processing of attention, emotion, and reward, is abnormal. Subsequent studies also indicate that prefrontal activity and prefrontal-subcortical connectivity are altered [49,50].

Functional imaging in youths and adults with bipolar disorder suggests that both groups exhibit similar deficits in activation of some brain structures, and dissimilar deficits in other brain areas [51]. As an example, a motor inhibition task elicited hypoactivation of the nucleus accumbens in both youths (n = 16) and adults (n = 23); by contrast, hypoactivation of the anterior cingulate cortex was observed in youths and hyperactivation in adults [52]. In addition, activation in the amygdala in response to emotional face recognition may be greater in youths with bipolar disorder than in adults with bipolar disorder [47].

Functional brain abnormalities have also been identified in youth who do not have bipolar disorder, but are at increased risk for developing it by virtue of having a parent with bipolar disorder [53,54]. (See "Bipolar disorder in adults: Epidemiology and pathogenesis", section on 'Genetics'.)

Brain chemistry — Proton magnetic resonance spectroscopy studies have reported abnormalities in glutamate in prefrontal brain areas of youths with bipolar disorder, compared with controls [12]. In addition, patients with pediatric bipolar disorder had abnormal levels of metabolites (eg, increased myo-inositol and decreased N-acetyl-aspartate levels) that are viewed as markers of mitochondrial or cell energy metabolism dysfunction. However, the results have been inconsistent.

Inflammation — Compared with neuroimaging studies, there are relatively few studies of inflammation biomarkers in pediatric bipolar disorder [12]. Nevertheless, multiple studies report that peripheral markers of inflammation may be increased in pediatric bipolar disorder, suggesting that the disorder is possibly associated with immune system dysregulation [28,55]. A literature review found that serum concentrations of C-reactive protein, nuclear factor kappa-beta, interleukin 1 beta, interleukin 6, and tumor necrosis factor-alpha were greater in youths with bipolar disorder, compared to youths with unipolar depression and healthy controls [12].

Additional information about the association between bipolar disorder and serum inflammatory proteins is discussed separately in the context of adults. (See "Bipolar disorder in adults: Epidemiology and pathogenesis", section on 'Inflammation'.)

SUMMARY

- **Terminology** – Bipolar disorder is characterized by episodes of mania (table 1) and/or hypomania (table 2). These episodes consist of concurrent symptoms (eg, decreased need for sleep and pressured speech) that always include elevated mood or irritability and persistently increased activity or energy. In addition, youth with bipolar disorder usually have recurrent episodes of major depression (table 3); however, depressive episodes are not necessary for making the diagnosis. The subtypes of bipolar disorder include bipolar I disorder, bipolar II disorder, cyclothymic disorder, and other specified and related bipolar disorder. (See "Pediatric bipolar disorder: Clinical manifestations and course of illness", section on 'Terminology' and "Pediatric bipolar disorder: Assessment and diagnosis", section on 'Bipolar disorders'.)

- **Prevalence** – The estimated lifetime prevalence of bipolar disorder in the general population of children and adolescents across Western countries is 3.9 percent, and the prevalence of bipolar I disorder is 0.6 percent. The prevalence of pediatric bipolar disorder in the community has remained relatively stable, and the prevalence in the United States and other countries is comparable. (See 'Prevalence' above.)

- **Pathogenesis** – The pathogenesis of bipolar disorder in youth is not known, but genetic factors are heavily involved. In addition, psychosocial factors that may be involved in the onset and course of pediatric bipolar disorder include low socioeconomic status, exposure to negative events (eg, childhood abuse), and high expressed-emotion. (See "Bipolar disorder in adults: Epidemiology and pathogenesis", section on 'Genetics' and 'Psychosocial factors' above.)

- **Neurobiology** – Structural and functional neuroimaging studies have found that several brain regions and networks involved in cognition (eg, the prefrontal cortex) and emotional functioning (eg, amygdala) are associated with bipolar disorder. However, these findings have not been consistent replicated and are not applicable to clinical practice. (See 'Neuroimaging' above.)

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