Pediatric bipolar disorder: Comorbidity

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Literature review current through: **Oct 2023.**
This topic last updated: **Jan 05, 2023.**

INTRODUCTION

Bipolar disorder in children and adolescents is characterized by recurrent episodes of elevated mood (mania or hypomania), which exceed what is expected for the child's developmental stage and are not better explained by other psychiatric and general medical conditions [1-3]. In addition, youth with bipolar disorder usually have recurrent episodes of major depression; however, depressive episodes are not necessary for diagnosing bipolar disorder. Pediatric bipolar 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 [1,4].

The large majority of patients with pediatric bipolar disorder have comorbid psychiatric and general medical conditions, and many bipolar patients have multiple comorbid illnesses [5-7]. The presence of comorbidities can hinder clinicians from recognizing bipolar disorder, particularly in youth with bipolar II disorder (periods of hypomania and/or major depression). Clinicians should identify and treat comorbidities because they may adversely affect response to treatment of bipolar disorder and the course of illness [5,8,9].

This topic describes the comorbid psychiatric and general medical illnesses that commonly occur in pediatric bipolar disorder. The epidemiology, pathogenesis, clinical features, assessment, diagnosis, and treatment of bipolar disorder in children and adolescents are discussed separately.

- (See "Pediatric bipolar disorder: Epidemiology and pathogenesis".)

- (See "Pediatric bipolar disorder: Clinical manifestations and course of illness".)
- (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".)

DEFINITION OF BIPOLAR DISORDER

Bipolar disorder is characterized by episodes of mania (table 1) and/or hypomania (table 2); in addition, episodes of major depression (table 3) usually occur [3]. According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), the subtypes of bipolar disorder include bipolar I disorder, bipolar II disorder, cyclothymic disorder, and other specified 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'.)

PSYCHIATRIC COMORBIDITY

The large majority of patients with pediatric bipolar disorder have a co-occurring psychiatric condition, such as an anxiety disorder, attention deficit hyperactivity disorder (ADHD), or oppositional defiant disorder, and many patients have multiple comorbid illnesses [5-7]. Clinicians should identify and treat comorbidities because they may adversely affect response to treatment of bipolar disorder and the course of illness; treatment of these comorbidities differs from that of bipolar disorder [5,8-10].

Some comorbidities, such as ADHD or oppositional defiant disorder, may be difficult to distinguish from mania/hypomania because the symptoms of ADHD or oppositional defiant disorder can overlap with those of mania/hypomania (table 4) [7]. (See "Pediatric bipolar disorder: Assessment and diagnosis", section on 'ADHD, conduct disorder, oppositional defiant disorder, and DMDD'.)

Comorbid psychiatric disorders in adults with bipolar disorder are discussed separately. (See "Bipolar disorder in adults: Clinical features", section on 'Psychiatric disorders'.)

Anxiety disorders — In youth with bipolar disorder, the prevalence of comorbid anxiety disorders ranges from approximately 40 to 66 percent, as indicated by nationally representative community surveys, as well as studies in clinical settings and studies of administrative claims databases [6,9,11-13]. As an example, a meta-analysis of 37 studies found that among children and adolescents with bipolar disorder (n >2200), the lifetime prevalence of comorbid anxiety disorders was as follows [14]:

- Any anxiety disorder – 45 percent
- Generalized anxiety disorder – 27 percent
- Separation anxiety disorder – 26 percent
- Social anxiety disorder (social phobia) – 20 percent
- Panic disorder – 13 percent

Some youth had more than one comorbid anxiety disorder [14]. In addition, the lifetime prevalence of any anxiety disorder was greater in youth with childhood-onset bipolar disorder than adolescent-onset bipolar disorder.

The temporal sequence of bipolar disorder and co-occurring anxiety disorders is such that anxiety disorders typically arise prior to onset of the first manic episode [14-17].

Pediatric bipolar disorder mood episodes are more likely to persist longer in patients with comorbid anxiety disorders than patients without comorbidity; following recovery from mood episodes, recurrences are more likely in patients with comorbid anxiety disorders [13,14]. In addition, co-occurring anxiety disorders are often protracted; a five-year prospective study of children and adolescents with bipolar disorder found that among those with anxiety disorders during follow-up (n = 137), the average duration of the anxiety disorder was approximately one year [18].

The clinical features and diagnosis of pediatric anxiety disorders are discussed separately. (See "Anxiety disorders in children and adolescents: Epidemiology, pathogenesis, clinical manifestations, and course", section on 'Clinical manifestations' and "Anxiety disorders in children and adolescents: Assessment and diagnosis", section on 'Diagnosis'.)

Attention deficit hyperactivity disorder — Among youth with bipolar disorder who present to clinical settings, approximately 50 percent have comorbid ADHD [9,19]. This estimate is based upon a meta-analysis of 20 observational studies that included youth with bipolar I disorder and other specified bipolar disorder (total n >2000, average age 11 years) [19], as well as a pooled analyses of 14 observational studies (number of patients not reported) [9]. ADHD typically begins before onset of the first manic episode [15,16,20]. Although shared genetic factors for

ADHD and bipolar disorder may perhaps be involved in the high rate of co-occurrence of the two disorders [21], some studies suggest otherwise [22].

Among youth who are treated for bipolar disorder, comorbid ADHD is associated with poorer outcomes. As an example, a meta-analysis of five observational studies of children and adolescents with bipolar disorder (n = 273) found that treatment response was less likely to occur in youth with comorbid ADHD than youth without ADHD (relative risk 0.82, 95% CI 0.69-0.97) [23].

The clinical features and diagnosis of pediatric ADHD are discussed separately. (See "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and diagnosis".)

Oppositional defiant disorder — In youth with bipolar disorder, the prevalence of comorbid oppositional defiant disorder is approximately 40 percent [19].

Oppositional defiant disorder is characterized by a persistent pattern of angry or irritable mood, argumentativeness, defiant behavior, and vindictive behavior [3]. The diagnosis requires at least four of the following symptoms during the past six months, which occur frequently and during interactions with at least one person who is not a sibling:

- Loses temper
- Easily annoyed
- Angry or resentful
- Argues with authority figures or adults
- Refuses to comply with rules or requests from authority figures
- Intentionally annoys others
- Blames others for their mistakes or misbehavior
- Spiteful or vindictive behavior two or more times in the past six months

In addition, the disturbed behavior and problematic interactions with others causes distress in the patient or close social contacts, or impairs functioning in social, school, work, or other settings [3]. The symptoms do not occur solely during acute episodes of bipolar disorder, depressive disorders, psychotic disorders, or substance-related and addictive disorders.

Conduct disorder — In children and adolescents with bipolar disorder, the prevalence of comorbid conduct disorder is approximately 30 percent [19]. Conduct disorder may begin before or at the same time as onset of bipolar disorder [7].

Conduct disorder is characterized by a persistent pattern of aggression toward people or animals, destruction of property, deceitfulness or theft, and serious violation of rules [3]. The

diagnosis requires at least three of the following symptoms during the past 12 months and at least one symptom in the past six months:

- Frequently bullies or menaces others
- Frequently starts physical fights
- Has used a weapon that can cause serious injury to others (eg, bat, knife, or gun)
- Physically cruel to people
- Physically cruel to animals
- Sexual assault
- Stealing while confronting the victim (eg, mugging, purse snatching, and armed robbery)
- Intentionally setting fires to damage property
- Destroying property by means other than setting fires
- Stealing without confronting others (eg, shoplifting or forgery)
- Forced entry into a car, house, or building
- Frequently lies to obtain favors, merchandise, or possessions, or to avoid responsibilities
- Prior to age 13 years:
  - Frequently truant from school
  - Frequently disobeys parents/caregivers and stays out late at night
- While living with parents or caregivers, ran away from home overnight at least two times, or once without returning for an extended period (eg, two days)

In addition, the disturbed behavior impairs functioning in social, school, or work settings [3]. Conduct disorder is not diagnosed in patients aged 18 years or older who are diagnosed with antisocial personality disorder.

Substance use disorder — Studies in clinical settings and in the general population indicate that among pediatric patients with bipolar disorder, the prevalence of comorbid substance use disorder is as follows [9,11,24,25]:

- Adolescents (age ≥13 years) – Approximately 20 to 30 percent

- Children (age <13 years) – 0 percent

Bipolar disorder tends to emerge in youth prior to the onset of substance use disorders [25,26]. Beginning in adolescence, the rate of comorbid substance abuse progressively increases with age [27], such that substance use disorders occur more often in youth with bipolar disorder than either healthy controls or youth with other psychiatric disorders [25]. Comorbid substance use disorders commonly include cannabis and alcohol [24,26,28,29]. Suicide attempts, legal problems, and functional impairment are more common in youth with bipolar disorder plus substance use disorders, compared to youth with bipolar disorder alone [29,30]. In addition, time to recovery from depressive episodes increases as the severity of substance use worsens [31].

Multiple risk factors for comorbid substance use disorders in pediatric bipolar disorder have been identified. A prospective observational study found that among adolescents with bipolar disorder who do not have a comorbid substance use disorder when they first present (n = 167), experimentation with alcohol at the start of the study was the single strongest predictor of later substance abuse, although experimentation with cannabis also predicted later substance abuse [24]. Other risk factors for developing a substance use disorder included greater severity of hypomanic/manic symptoms; poor family functioning; lifetime history of alcohol use (experimentation), panic disorder, or oppositional defiant disorder; and family history of substance use disorder. Onset of substance use disorders was more likely in teens with three or more risk factors than teens with zero to two risk factors (55 versus 14 percent). This study suggests that there may be a window of two to three years during which clinicians can attempt to prevent substance abuse in these youth by targeting the risk factors that are amenable to intervention.

- Cannabis – Cannabis use disorder is common in pediatric bipolar disorder. An administrative claims database of youths with mood disorders (n >200,000, mean age 17 years) found that after adjusting for potential confounding demographic, clinical, and treatment factors, the risk of comorbid cannabis use disorder was greater in patients with bipolar disorder than depressive disorders (relative risk 1.24, 95% CI 1.21-1.29) [32]. In addition, the entire sample was followed for up to one year, during which the risk of nonfatal self-harm was greater in youths with mood disorders plus cannabis use disorder, compared to those without cannabis use disorder (hazard ratio 3.3, 95% CI 2.6-4.2). Comorbid cannabis use disorder was also associated with an increased risk of all-cause mortality (1.6, 95% CI 1.1-2.2).

- Tobacco – Smoking is also common in pediatric bipolar disorder. In a prospective observational study of 441 youth with bipolar spectrum disorder, current daily smoking

was present in 11 percent, and a history of smoking in the past but not currently was present in another 14 percent [33]. However, it is not clear that the prevalence of smoking differs between youth with bipolar disorder and the general population of youth.

Youth with bipolar disorder and a current or past history of smoking were more likely to have a history of other substance use disorders and suicide attempts, compared to bipolar youth with no history of smoking. These findings suggest that bipolar patients who smoke should be evaluated for abuse of other substances and risk of suicide, as well as the physical effects of smoking.

The clinical features and diagnosis of substance use disorder in adolescents is discussed separately. (See "Substance use disorder in adolescents: Epidemiology, clinical features, assessment, and diagnosis".)

Autism spectrum disorder — Among patients with pediatric bipolar disorder, comorbid high-functioning autism spectrum disorder has been reported in at least 20 percent [7,34]. However, this is controversial because patients with autism spectrum disorder usually have mood lability that may be confused with the mood changes that occur in bipolar disorder. The clinical features and diagnosis of pediatric autism spectrum disorder are discussed separately. (See "Autism spectrum disorder in children and adolescents: Clinical features" and "Autism spectrum disorder in children and adolescents: Evaluation and diagnosis".)

Other — Other less common comorbid disorders observed in pediatric bipolar disorder include binge eating, obsessive-compulsive disorder, and posttraumatic stress disorder [7,9,13,35-37]. In addition, some adolescents with bipolar disorder have comorbid symptoms of borderline personality disorder (eg, identity confusion, interpersonal problems, impulsivity, and emotional dysregulation) [38].

GENERAL MEDICAL COMORBIDITY

Youth with bipolar disorder appear to be at increased risk of comorbid general medical disorders, including cardiovascular disease, neurologic disorders, and respiratory disorders. One study of medical claims data found that in youth with bipolar disorder (n >800), treatment for comorbid chronic medical conditions occurred in approximately 75 percent [39]. Across multiple studies of claims data, approximately 25 to 33 percent of bipolar patients had multiple medical comorbidities [20,39]. In many instances, co-occurring general medical disorders predate onset of bipolar disorder [20].

The increased risk of comorbid general medial illnesses in youth with bipolar disorder may be due to biologic vulnerability, increased weight, increased smoking, poor eating habits, insufficient physical activity, and use of medications that can increase weight and induce the metabolic syndrome as well other medical conditions (eg, fatty liver and extra pyramidal symptoms) [33,37,39-41]. In addition, patients treated for bipolar disorder may receive greater monitoring of overall health, leading to detection of general medical problems that might not otherwise be observed. Conversely, youths with bipolar disorder may have poor access to medical care, which may lead to onset of medical illnesses.

Comorbid general medical disorders in adults with bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Clinical features", section on 'General medical illnesses'.)

Cardiovascular — We suggest that adolescents with bipolar disorder be monitored for cardiovascular disease. Adolescent bipolar disorder appears to be associated with premature atherosclerosis and cardiovascular disease [40,42]. The association may involve multiple systemic processes, including inflammation, oxidative stress, and autonomic dysfunction [43,44]. Several traditional cardiovascular risk factors (eg, diabetes mellitus, sedentary lifestyle, and tobacco smoking) are more prevalent among adolescents with bipolar disorder compared with the general pediatric population. Although psychotropic medication may contribute to the elevated risk of cardiovascular disease, it appears that a substantial portion of the association between bipolar disorder and cardiovascular disease is independent of medication effects. In 2015, the American Heart Association proposed that bipolar disorder be positioned alongside other pediatric diseases (chronic inflammatory disease, infection with the human immunodeficiency virus, Kawasaki disease, and nephrotic syndrome) that are considered moderate risk factors for early cardiovascular disease [42]. Additional information about diseases that are associated with pediatric atherosclerosis is discussed separately, as is the management of youth at risk for atherosclerosis (algorithm 1). (See "Overview of risk factors for development of atherosclerosis and early cardiovascular disease in childhood" and "Overview of the management of the child or adolescent at risk for atherosclerosis".)

Studies of medical claims data have found that the prevalence of cardiovascular disease was 40 to 100 percent greater in children and adolescents with bipolar disorder, compared with control groups:

- In one study of an administrative claims database that identified youth with bipolar disorder (n >800) and youth with other psychiatric disorders (n >21,000), youth with bipolar disorder were twice as likely to have comorbid cardiovascular disease (odds ratio 2.0, 95% CI 1.6-2.4) [39].

- A second study of medical claims identified youth with bipolar disorder (n >1800) and youth with no psychiatric disorders (n = 4500), and found that youth with bipolar disorder were 40 percent more likely to have comorbid cardiovascular disease (odds ratio 1.4, 95% CI 1.1-1.8), such as arrhythmias and congestive heart failure [20].

Adolescents with bipolar disorder and a family history of bipolar disorder appear to have elevated rates of cardiovascular-related conditions (eg, diabetes, hypertension, obesity, dyslipidemia, stroke, angina, and myocardial infarction) in first- and second-degree relatives, compared to adolescents without bipolar disorder [45]. This suggests the possibility that there is genetic overlap between bipolar and cardiovascular illness, shared environmental factors that contribute to both conditions, or a combination of these factors.

Excess weight and obesity — Many children and adolescents with bipolar disorder are overweight or obese, at rates comparable to those in the general population. Studies in both community and clinical samples of youth with bipolar disorder suggest that excess weight (body mass index [BMI] 85th to <95th percentile) is observed in 20 to 25 percent, and that obesity (BMI ≥95th percentile) occurs in approximately 17 percent:

- A nationally representative survey of adolescents in the United States (n >10,000) showed that among those with bipolar disorder (n = 295), 21 percent were overweight and 17 percent were obese, which was comparable to the weight status of controls [46]. After controlling for potential demographic and clinical confounders, the analyses found that adolescents with bipolar who were overweight or obese were more likely to have a history of suicide attempt, binge eating and bulimia, and conduct disorder, compared to adolescents with bipolar disorder who were normal weight.

- An observational study of patients with pediatric bipolar disorder (n = 348) found that at study intake, 25 percent were overweight and 17 percent obese [47]. These rates were approximately comparable to published rates for the United States general population.

- A cross-sectional study of adolescents and young adults with bipolar spectrum disorder (n = 162, mean age 21 years) found that the metabolic syndrome was present in 20 percent [40].

A history of physical abuse in patients with pediatric bipolar disorder appears to be associated with excess weight or obesity [46,47].

Juvenile bipolar disorder is often treated with second-generation antipsychotics, which can cause weight gain and may also be associated with insulin resistance and diabetes. (See

"Pediatric mania and second-generation antipsychotics: Efficacy, administration, and side effects", section on 'Weight gain'.)

Other disorders — Studies of medical claims data have found that the prevalence of neurologic, respiratory, and other chronic general medical disorders was greater in children and adolescents with bipolar disorder, compared with control groups. In addition, approximately 25 to 33 percent of patients had multiple medical comorbidities:

- In one study of an administrative claims database that identified youth with bipolar disorder (n >800) and youth with other psychiatric disorders (n >21,000), youth with bipolar disorder were more likely to have comorbid neurologic disorders, respiratory disorders, gastrointestinal and hepatic disorders, and female reproductive disorders [39]. Many youths with bipolar disorder had more than one comorbidity, and multiple medical comorbidities were observed in more youth with bipolar disorder than controls (36 versus 8 percent).

- A second study of medical claims identified youth with bipolar disorder (n >1800) and youth with no psychiatric disorders (n = 4500), and found that the prevalence of epilepsy, migraine headaches, neurodevelopmental disorders (eg, intellectual disability), asthma, and endocrine disorders was greater in youth with bipolar disorder than controls [20]. Among children and adolescents with bipolar disorder, 28 percent had two or more comorbid illnesses.

Bipolar disorder may also be associated with cerebrovascular dysfunction. A study examined cerebrovascular reactivity (a marker of cerebrovascular health measured by the vasodilatory capacity of cerebral blood vessels in response to vasoactive substances) in 25 adolescents with bipolar disorder and 25 healthy controls [48]. The results indicated that in the temporal poles, supramarginal gyrus, lingual gyrus, and periventricular white matter, cerebrovascular reactivity was worse in adolescents with bipolar disorder.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bipolar disorder".)

SUMMARY

- Bipolar disorder is characterized by episodes of mania (table 1) or hypomania (table 2), and often periods of major depression (table 3). The subtypes of bipolar disorder include bipolar I disorder, bipolar II disorder, cyclothymic disorder, and other specified 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'.)

- The large majority of patients with pediatric bipolar disorder have a comorbid psychiatric condition, and many patients have multiple comorbid illnesses. Clinicians should identify and treat comorbidities because they can adversely affect response to treatment of bipolar disorder and the course of illness. The estimated prevalence of common comorbidities is as follows:

  - Any anxiety disorder – 45 percent
  - Attention deficit hyperactivity disorder – 50 percent
  - Oppositional defiant disorder – 40 percent
  - Conduct disorder – 30 percent
  - Substance use disorder, such as alcohol, cannabis, or tobacco – 20 to 30 percent
  - Autism spectrum disorder – At least 20 percent

(See 'Psychiatric comorbidity' above.)

- Youth with bipolar disorder appear to be at increased risk of comorbid general medical disorders, particularly cardiometabolic, neurologic, and respiratory conditions. In many cases, multiple comorbidities are present. (See 'General medical comorbidity' above.)

Topic 111828 Version 8.0

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