Pediatric Bipolar Disorders and ADHD

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Background and Significance

Introduction

Bipolar disorder (BD) is a familial illness characterized by episodes of abnormally elevated mood that are above and beyond the child's developmental stage [1, 2]. It is now widely accepted that Bipolar Disorder (BD) occurs in children and adolescents and the controversy has shifted from a debate about *whether* it can be diagnosed in youth, now to *how* it can be diagnosed, differentiated from more common psychiatric disorders in childhood such as attention deficit hyperactivity disorder (ADHD), and *how* it can be treated and prevented [3].

BD in youth is increasingly recognized as a significant public health problem that is often associated with impaired family and peer relationships, poor academic performance, high rates of chronic mood symptoms and mixed presentations, psychosis, disruptive behavior disorders, anxiety disorders, substance use disorders, medical problems (e.g., obesity, thyroid problems, diabetes), hospitalizations, and suicide attempts and completions [3]. Early identification of BD in youth is essential for not only stabilizing their mood but also for enabling them to follow a normative developmental path and prevent an unrecoverable loss in their psychosocial development and education [4]. Moreover, youth with BD can have greater utilization of medical services and higher behavioral health costs relative to youth with unipolar depression or non-mood disorders. Youth with *undiagnosed* BD may have even more behavioral health costs than those with *diagnosed* BD [3]. This chapter reviews the epidemiology, clinical aspects, differential diagnosis, natural course, and treatment of pediatric BD with ADHD.

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Epidemiology

Recent studies have shown dramatic increases in recognition and rates of BD in youth over the past 20 years and some authors have questioned the possibility of overdiagnosing children with BD in the US, whereas many others have brought up the possibility of long neglecting the presence of this condition in childhood [5]. The prevalence BD spectrum in adults is around 5% (BD I is around 1%), and the majority had the onset of their mood symptoms before age 20 years [6]. Those with ADHD usually have an early onset BD.

In clinical populations of youth in the US, the prevalence of BD has been reported between 0.6 and 15% depending on the setting, the referral source, and the methodology to ascertain BD [7]. Based on findings from two separate samples of juveniles with ADHD, Wozniak, Biederman, and colleagues have reported 20–21% had comorbid bipolar disorders [8, 9]. Other investigators have been skeptical about so many patients with ADHD meeting true diagnostic criteria for bipolar disorders. The skeptics have argued that: (1) the chronic irritability of these children was inconsistent with the episodic nature of mania described in DSM criteria; (2) the investigators did not consider the overlap of ADHD and manic symptoms (e.g., talkativeness, distractibility and hyperactivity); and (3) there was also an unusually high rate of bipolar disorders among subjects in the control groups of these samples. Instead, Klein and colleagues have argued that the children with ADHD described by the MGH group as having bipolar disorders most likely had severe conduct disorders or intermittent explosive disorders instead [10].

A recent meta-analysis about epidemiology of BD in youth around the world reported that the overall rate of BD was 1.8% (95% CI, 1.1–3.0%), enrolling 16,222 youth between the ages of 7 and 21 years during a period from 1985 to 2007 [11]. This meta-analysis suggested that there was no significant difference in the mean rates of BD-I in youth between the US and the non-US studies, but the US studies had a wider range of rates, especially when a broader definition of BD was used. In addition, the prevalence of BD-I in youth is similar to the current prevalence estimates of BD in adults, and while BD it is being diagnosed more commonly in clinical settings, the prevalence of BD in youth in the community is not increasing [11]. The same meta-analysis concluded that BD can begin in childhood, but the prevalence is much higher during the adolescence [11]. A large epidemiological study in the US reported slightly higher rates of BD-I and BD-II in female than in male adolescents (3.3% vs. 2.6%, respectively) with increasing rates of BD with older ages [12]. Studies in clinical populations have reported that the rates of bipolar spectrum disorders in youth are equally common in males and females [1, 13]. The rates of BD-II and adolescent-onset BD are more common in females [2].

Etiological Factors

Twin and adoption studies have demonstrated that the heritability of BD is quite high at 80%, indicating that 80% of the condition is determined by genetic rather than environmental factors [14–16]. However, several genes and epigenetic factors

seem relevant to the manifestation of this illness, and identification of the genes associated with BD has not been conclusive. Other factors such as variation in ascertainment, phenotype definition, control selection, and limited power have led to inconsistent results.

Studies evaluating the risk for BD in offspring of parents with BD and in first-degree relatives of youth with BD have provided further evidence that BD runs in families [2, 16, 17]. It is suggested that offspring of parents with BD have up to 25-fold greater rates of BD when compared to offspring of control parents [2, 18, 19]. Importantly, a large prospective, high-risk BD study has suggested that offspring with mood lability, depression/anxiety, and in particular having subsyndromal manic symptoms and parents who had early-onset BD were at 50% risk to develop BD [20]. However, children of parents with BD are also at risk to develop depression, anxiety, ADHD, and behavioral problems [2, 21]. It is suggested that ADHD was associated with a significantly higher risk for switches from unipolar to bipolar disorder (28% vs. 6%, over 7 years) [22]; however, a review of high-risk studies suggested that the clinical diagnosis of childhood ADHD is not a reliable predictor of the development of BD in offspring studies [23]. Similarly, in Pittsburgh Bipolar Offspring Study, the rates of ADHD were not statistically different (38.9% vs. 19.8%) between bipolar offspring who did or did not develop BD during follow-up [2]. However, symptoms of inattention (in addition to depression and anxiety) may be part of a mixed clinical presentation during the early stages of evolving BD in high-risk offspring [23]. The same analysis reported preliminary evidence that childhood ADHD may form part of a neurodevelopmental phenotype in offspring at risk for developing a subtype of bipolar disorder unresponsive to lithium stabilization [23].

Research and clinical experience also suggest that trauma or stressful life events can trigger an episode of BD, though many BD episodes occur without an obvious or identifiable cause. In brief, the etiology is multifactorial, with complex interactions of biological vulnerabilities and environmental influences. The few studies that have evaluated the effects of psychosocial factors on the onset and maintenance of pediatric BD have found that low socioeconomic status (SES), exposure to negative events, and high "expressed-emotion" (EE) in the family are associated with poor prognosis [2, 24–27].

Assessment and Differential Diagnosis

Bipolar Symptoms and Subtypes

It is very important to have a common language and to use similar terms appropriately between professionals (and with patients and families) when describing, reporting, and monitoring mood changes in youth. According to the DSM-IV, there were four subtypes of BD: Bipolar I, Bipolar II, Cyclothymia and Other Specified/Unspecified Bipolar and Related Disorders (BD-Not Otherwise Specified; NOS) and their diagnostic criteria were the same between adults and children, with the exception of cyclothymia [28]. Of note, subtypes of BD in youth may not be stable over time. In a 4-year follow-up study, 25% of youth with BD-II converted to

bipolar I and 45% of those with BD-NOS converted to BD-I or II [29]. Similar to the offspring studies [2, 23], it is important to note that the rates of ADHD in converters vs. non-converters were not significantly different (61.9% vs. 63.6%, respectively), nor were rates of stimulant use (33.33% vs. 28.6%) or family history of ADHD (42.9% vs. 40.3%), respectively [29].

To date, almost all studies in pediatric BD have employed the Diagnostic and Statistical Manual (DSM)-IV criteria [30]. However, there are important differences to keep in mind regarding the diagnostic criteria of BD in DSM-5 [31]. Key changes regarding criteria for bipolar and related disorders in DSM-5 relative to DSM-IV include: (1) requiring "increased energy or goal-directed activity" as a main symptom criteria for a manic episode (in addition to "elated mood or irritability"); (2) replacing mixed episodes with the new specifier of "mixed features (presence of three or more depressive symptoms during the course of a manic episode); and (3) introducing the new specifier of "anxiety features (presence of anxiety symptoms specifically during the course of an manic episode)" [31].

There are also now several important differences in the diagnostic criteria of DSM-5 relative to the latest International Classification System (ICD-10) [32]. In order to make the bipolar affective disorder diagnosis, in DSM-5 only a single manic episode is required [31], while in ICD-10, at least two mood episodes are required, one of which is manic or mixed (e.g., a mixture or rapid alteration of manic and depressive symptoms), while the other could be a depressive, hypomanic, manic, or mixed [32]. In both DSM-5 and ICD-10, duration criteria for hypomanic and a manic episodes are 4 and 7 days, respectively. Having a history of a hypomanic episode plus at least one major depressive episode is classified as a "bipolar II disorder" in DSM-5, and as an "other bipolar affective disorder" in ICD 10. Finally, the DSM-5 criteria require the presence of functional impairment with these altered moods, while ICD-10 criteria require that mood and activity levels must be "significantly disturbed."

Figure 8.1 shows various presentations of either BD-I or BD-2 based on their combination of manic, hypomanic, and major depressive episodes. BD-I requires presence or history of a manic episode with or without major depressive episode. For BD-I diagnosis, both symptom criteria (three or four symptoms in addition to elation or irritability, respectively) and duration criteria should be met, in addition to the "significant functional impairment or psychosis" during mania. For the duration criteria, a manic episode should last at least seven consecutive days or lead to an inpatient admission anytime during the episode. Mixed presentations of mania in DSM-5 require three or more depressive symptoms during a manic episode, while mixed episodes in DSM-IV required meeting symptom criteria of both mania and major depression during the same mood episode (simultaneously or in rapid sequence).

BD-II is characterized by at least one major depressive episode (for at least 2 weeks with functional impairment) and at least one hypomanic episode (lasting at least four consecutive days). Hypomania is described as the milder form of a manic episode during which the patient has a "distinct change" from the baseline functioning (sometimes patients may appreciate these changes in functioning, for example being able to work on more projects), but should "not have marked functional impairment" during the course of the hypomanic episode.

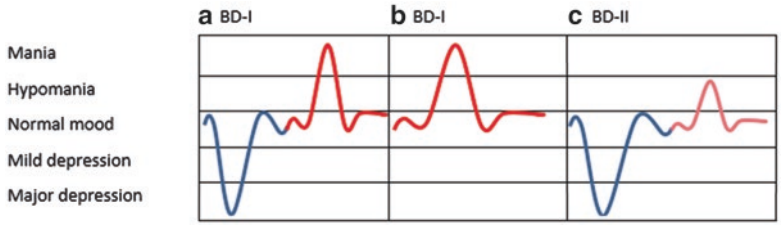


Fig. 8.1 This figure illustrates the minimum combinations of mood episodes required over time for patients with the two main types of bipolar disorders. Figure (**a**) depicts one potential presentation of a patient with bipolar I (BD-I), who has had an early major depressive episode followed by a manic episode. Figure (**b**) depicts another potential presentation of BD-I, in a patient who has had a single episode of mania but no other mood episodes. Figure (**c**) depicts a potential presentation of a bipolar II disorder (BD-II), with at least one major depressive episode, followed by an episode of hypomania with insufficient duration and symptom severity to meet criteria for full manic episode, which would make it convert to a BD-I diagnosis

Cyclothymia is characterized by numerous periods of hypomania alternating with numerous periods of depressive mood or loss of interest or pleasure, which do not meet full criteria for a BD or a major depressive episode. The abnormal mood swings must be present for at least 1 year in youth or for 2 years in adults for the diagnosis.

Other specified BD (a.k.a. BD-NOS) is used when there are features of hypomanic or mixed episodes that do not meet the diagnostic criteria for any of the more specific BD subtypes. Because BD-NOS criteria is vague in DSM, researchers have developed clearer definitions to identify a BD-NOS diagnosis, such as having had at least one episode of hypomanic symptoms for 2 days, or at least four episodes of hypomania lasting 4 h each but being one symptom shy of meeting full symptom criteria [13, 15].

Clinical Presentations and Assessment of Bipolar Disorder

There is consensus in the field that children and adolescents may fulfill the strict DSM criteria for BD-I and II. The American Academy of Child and Adolescent Psychiatry (AACAP) has released the practice parameters for BD and recommended that clinicians should adhere to the DSM, including the duration criteria (requirement of an episodic change in mood lasting at least 4 days for hypomania and 7 days for mania) [33]. Typically, youth are given a BD NOS diagnosis, when they do not meet the duration criteria for a diagnosis of BD-I or BD-II [29].

The assessment of symptoms of mania, hypomania, and depression requires careful probing and in most cases, longitudinal assessment. In addition to the specific manic/hypomanic and depressive symptoms, it is important to ascertain the frequency, intensity, number, and duration (FIND) of the depressive and manic/hypomanic episodes [1, 3]. *Most experts agree that these mood symptoms should exist as a collection of concurrent symptoms and behaviors* (i.e., *"cluster together"), occur episodically, and reflect a change in the child's baseline characteristics. For example, preexisting hyperactivity and inattentiveness should not be counted towards mood symptoms unless there is significant worsening of these symptoms during the mood episode.*

It is also imperative to obtain information from caregivers, teachers, and other providers in order to accurately assess symptoms and potential change in functioning. Children's chronological age, intellectual capabilities, and environmental factors are important when assessing their levels of functional impairment or improvement.

The most widely used interviews in BD studies are the Kiddie Schedule for Affective Disorders and Schizophrenia for school-age children-Present and Lifetime version (K-SADS-PL) (available for free at http://www.wpic.pitt.edu/research under tools and assessments) and the Washington University KSADS (WASH-U-KSADS) [1, 2]. However, these are mainly used for research purposes, require training of the interviewer, and are lengthy and time-consuming. Thus, symptom checklists for BD are also useful, such as Parent General Behavior Inventory (GBI-10; [34]) and the parent Child Mania Rating Scale (CMRS-10; [35]). Dimensional scales such as Child Behavior Checklist (CBCL) [36] and some of its subscales such as dysregulation profile (attention, aggression, and anxiety/depression) and externalizing problems can help identify significant psychopathology in those with ADHD and/or at risk for BD [37], but they are not specific for BD [38].

As expected, because of varying methodologies and conceptualizations of pediatric BD, there is also significant variability in the prevalence of individual manic symptoms among the studies. Similar to the meta-analysis published in 2005 [39], a recent meta-analysis (average age: 11.5 years old, 64% male, mainly Caucasian, 2226 youth in 20 published studies) reported that the most common symptoms across BD subtypes include increased energy, irritability and mood lability, distractibility, and goal directed activity (all approximately 75%) [40]. Grandiosity and hypersexuality were the most specific symptoms, but they were less common (57% and 32%, respectively). There are key issues about making an accurate BD diagnosis in youth, such as the requirement of clearly identified mood episodes (e.g., episodicity), the importance of cardinal symptoms and irritability, subthreshold presentations, bipolar depression, and preschool presentations.

Episodicity

Despite suggestions by some investigators that episodicity is not needed to diagnose pediatric BD, most other investigators and clinicians, as well as the AACAP guidelines [33], recommend that episodicity be required to diagnose BD diagnosis in youth. In fact, it is suggested to first focus on determining the presence of mood episodes based on the DSM manic/hypomanic symptoms, and then to determine how much these DSM manic/hypomanic symptoms occur during an identifiable time frame.

Cardinal Symptoms

Few investigators, aiming to be more specific and avoid misdiagnosing BD in youth, have suggested that elated mood and grandiosity must be present together to diagnose pediatric BD [41]. However, this is not required in DSM and some youth may

have BD without elation and grandiosity. There is considerable heterogeneity among studies in the rates of these symptoms reflecting differences in samples (e.g., origin and age) and methodologies. It is important to consider difficulties in identifying elation and grandiosity, especially in younger children.

Irritability

Irritability is a very common symptom present in BD youth [39] and the absence of any episodes with irritability decreases the likelihood of a BD diagnosis. *On the other hand*, *irritability rarely occurs in manic youth without elation*. Irritability is also part of the other disorders such as Oppositional Defiant, Major Depressive, Generalized Anxiety, and Post-Traumatic Stress Disorders, and is also frequently present in youth with other psychiatric diagnoses such as ADHD and Autism Spectrum Disorders. Thus, *irritability has low specificity for BD, and is analogous to how having fever/pain suggests only suggests that "something is wrong"* [39]. DSM criteria for a manic episode explicitly allows for the presence of irritable mood alone to satisfy the main criterion. However, they require an additional manic symptom to meet the manic episode criteria (e.g., four or more manic symptoms should accompany irritability during the same time frame (clustering) for the mood episode). It is suggested that the severity and duration of irritability (the "super-angry/grouchy/cranky-type" of irritability, but not the "mad/cranky" or oppositional defiant disorder-type irritability) [42] are important clinical factors when assessing BD subjects. Furthermore, in order to be counted as a symptom of manic episode, irritability needs to be episodic even if the child has preexisting irritability (e.g., worsening of irritability during the manic episode when other comorbid disorders exist such as anxiety disorders, ADHD, or ODD) [43].

In contrast to episodic irritability, chronic irritability has recently been conceptualized as the core feature of a new diagnosis category that is included in the DSM-5 (a.k.a. disruptive mood dysregulation disorder (DMDD)). DMDD has previously been referred to as temper dysregulation disorder with dysphoria (TDDD) and severe mood dysregulation (SMD). Chronic irritability has also been associated with attention deficit hyperactivity disorder, oppositional defiant disorder, and major depressive disorder rather than with BD, whereas episodic irritability has been associated with BD and anxiety [44].

Depression

Most youth seen in psychiatric clinics experience their first episode of BD as depression (Birmaher et al. 2007) [2]. Similar to adults, depressive episodes are reported to be the most common manifestation of BD in children and adolescents based on both frequency and duration [15]. The presence of psychosis, family history of BD, and pharmacologically induced mania/hypomania may indicate susceptibility to develop

BD [45–47]. Early identification and treatment of BD depression is of vital importance, because it is associated with increased risk for psychosocial impairment and suicide as compared to unipolar depression [48].

Preschool Presentations

Validity of manic symptoms such as grandiosity and elation have been questioned in preschool children (aged from 3 to 7 year old) given the emotional and cognitive developmental stage of the younger children. Few available studies have suggested that preschool children may have BD diagnosis [49]. Irritability is more common, and grandiosity and elation are also suggested as helpful in preschool children when differentiating BD from other disorders such as major depressive disorder and disruptive behavior disorder (DBD) [49].

Bipolarity and Comorbidities

The presence of the comorbid disorders affects the child's and adolescent's response to treatment and prognosis, indicating the need to identify and treat them effectively. Comorbid disorders, particularly disruptive behavior disorders (DBD; 30–70%), ADHD, (50–80%), and anxiety disorders (30–70%) are very common [1, 3]. Beginning in adolescence, the rate of comorbid substance abuse steadily increases [50, 51]. The prevalence of these disorders will depend on the methods used to diagnose them, the source of the sample studied (e.g., more common in clinical versus community), and the age range of its members, with more ADHD and Oppositional Defiant Disorder (ODD) in children, and more conduct and substance use disorders in adolescents.

Bipolar Disorders and ADHD

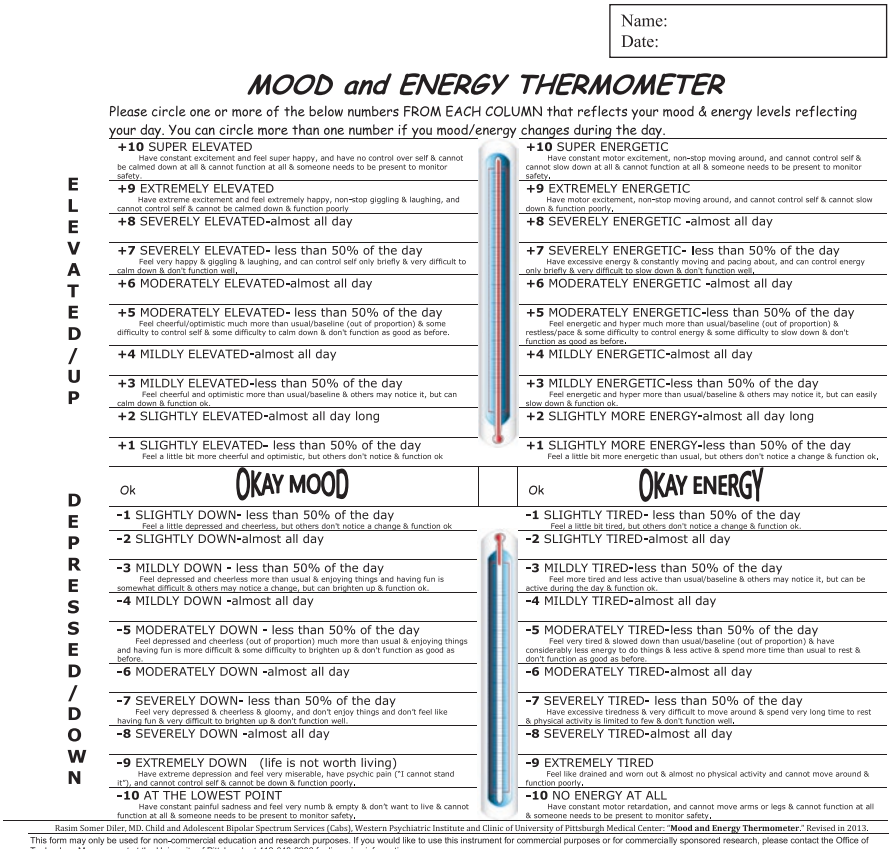
Clinicians must be cautious about attributing symptoms to mania or hypomania unless they show a clear temporal association with the abnormally elevated, expansive and/or irritable mood (plus increased activity/energy levels). *Clinicians should also carefully observe in a child with possible BD whether the symptoms of the comorbid disorder disappear or persist while the suspected child with BD is euthymic, and whether the symptoms associated with BD worsen during the mood episode.* Biederman and colleagues have argued that comorbidity between ADHD and BD cannot be dismissed due to the shared features of the two disorders (e.g., distractibility, motor hyperactivity, and talkativeness) [52]. These investigators have shown that even after removing overlapping diagnostic criteria, children with each condition can still be distinguished. Geller and colleagues have reported that several manic symptoms such as elated mood, grandiosity, hypersexuality, decreased need for sleep, racing thoughts (but not hyperenergetic and distractibility) are substantially and significantly more frequent

among youth with BD relative to youth with ADHD [53]. The following features, when present, were *suggested* to help distinguish the diagnosis of BD in a child with ADHD: (a) the ADHD symptoms appear later in life (e.g., after age 12 years old), (b) the symptoms of ADHD appear abruptly in an otherwise healthy child, (c) the ADHD symptoms previously responded to stimulants but now do not, (d) the ADHD symptoms come and go and tend to occur with mood changes, (e) periods of exaggerated elation, grandiosity, depression, no need for sleep, or inappropriate sexual behaviors, (f) recurrent, severe mood swings, temper outbursts, or rages, (g) hallucinations and/or delusions, (h) a strong family history of BD, particularly if the child is not responding to appropriate ADHD treatments [54].

Longitudinal Course and Differential Diagnosis

The differential diagnosis may require longitudinal rather than a cross-sectional assessment. Mood time-lines or diaries and using school years, birthdays, and holidays as anchors are very helpful in the assessment and monitoring mood symptoms and episodes. The mood time lines (mood monitoring) instruments should be user/child-friendly and can be modified (regarding the child's age, culture, and interests) to increase compliance. In addition to mood, energy levels can be monitored simultaneously for diagnostic clarification. *From this perspective, Dr. Diler has developed a novel self-report mood rating (the "Mood and Energy Thermometer, MET©") for daily assessment and monitoring of mood state in bipolar track adolescents (as shown in* Fig. 8.2*)* [55]. This scale aims to provide a practical way of monitoring complex mood cycles and daily schedule. Given the confusion about several 1 to 10 scales (e.g., a 10 could mean extreme depression or extreme mania or no depression), a common language between the youth, care givers, and providers is necessary. Moreover, many children report their energy levels more accurately than their mood and therefore, energy levels are incorporated in the mood rating. The Mood and Energy Thermometer (MET©) rates mania and increased energy on a 1 to 10 scale and rates depression and tiredness on −1 to −10 scale, and aims to form a common language between patients, families, and clinicians (please see MET© at the end of the chapter). The inclusion of energy level measurements is consistent with the DSM-5, because energy level is now considered as a main symptom criterion for mania. Bipolar or depressed patients are encouraged to rate their mood and energy levels every day on this scale to make them better able to identify and record their mood symptoms, which has significant clinical value for not only treatment but also to detect and prevent a future episode early.

It is important to be aware of various potential trajectories of mood and ADHD symptoms over time. For example, though youth with ADHD may show different trajectories, their hyperactivity and impulsivity may lessen as they age into adolescence and adulthood [56]. Recent studies have shown that BD is mainly characterized by recovery and recurrences, and that ongoing fluctuations in mood symptoms, especially subsyndromal depressive and mixed symptoms, are common [15, 26]. In a sample of youth with BD followed over a 9-year period, a recent study used


Name:
Date:

MOOD and ENERGY THERMOMETER

Please circle one or more of the below numbers FROM EACH COLUMN that reflects your mood & energy levels reflecting your day. You can circle more than one number if you mood/energy changes during the day.

ELEVATED/UP

+10 SUPER ELEVATED
Have constant excitement and feel super happy, and have no control over self & cannot be calmed down at all & cannot function at all & someone needs to be present to monitor safety.

+9 EXTREMELY ELEVATED
Have extreme excitement and feel extremely happy, non-stop giggling & laughing, and cannot control self & cannot be calmed down & function poorly

+8 SEVERELY ELEVATED-almost all day

+7 SEVERELY ELEVATED- less than 50% of the day
Feel very happy & giggling & laughing, and can control self only briefly & very difficult to calm down & don't function well.

+6 MODERATELY ELEVATED-almost all day

+5 MODERATELY ELEVATED- less than 50% of the day
Feel cheerful/optimistic much more than usual/baseline (out of proportion) & some difficulty to control self & some difficulty to calm down & don't function as good as before.

+4 MILDLY ELEVATED-almost all day

+3 MILDLY ELEVATED-less than 50% of the day
Feel cheerful and optimistic more than usual/baseline & others may notice it, but can calm down & function ok.

+2 SLIGHTLY ELEVATED-almost all day long

+1 SLIGHTLY ELEVATED- less than 50% of the day
Feel a little bit more cheerful and optimistic, but others don't notice & function ok

+10 SUPER ENERGETIC
Have constant motor excitement, non-stop moving around, and cannot control self & cannot slow down at all & cannot function at all & someone needs to be present to monitor safety.

+9 EXTREMELY ENERGETIC
Have motor excitement, non-stop moving around, and cannot control self & cannot slow down & function poorly.

+8 SEVERELY ENERGETIC -almost all day

+7 SEVERELY ENERGETIC- less than 50% of the day
Have excessive energy & constantly moving and pacing about, and can control energy only briefly & very difficult to slow down & don't function well.

+6 MODERATELY ENERGETIC -almost all day

+5 MODERATELY ENERGETIC-less than 50% of the day
Feel energetic and hyper much more than usual/baseline (out of proportion) & restless/pace & some difficulty to control energy & some difficulty to slow down & don't function as good as before.

+4 MILDLY ENERGETIC-almost all day

+3 MILDLY ENERGETIC-less than 50% of the day
Feel energetic and hyper more than usual/baseline & others may notice it, but can easily slow down & function ok.

+2 SLIGHTLY MORE ENERGY-almost all day long

+1 SLIGHTLY MORE ENERGY-less than 50% of the day
Feel a little bit more energetic than usual, but others don't notice a change & function ok.

Ok OKAY MOOD

Ok OKAY ENERGY

DEPRESSED/DOWN

-1 SLIGHTLY DOWN- less than 50% of the day
Feel a little depressed and cheerless, but others don't notice a change & function ok

-2 SLIGHTLY DOWN-almost all day

-3 MILDLY DOWN - less than 50% of the day
Feel depressed and cheerless more than usual & enjoying things and having fun is somewhat difficult & others may notice a change, but can brighten up & function ok.

-4 MILDLY DOWN -almost all day

-5 MODERATELY DOWN - less than 50% of the day
Feel depressed and cheerless (out of proportion) much more than usual & enjoying things and having fun is more difficult & some difficulty to brighten up & don't function as good as before.

-6 MODERATELY DOWN -almost all day

-7 SEVERELY DOWN- less than 50% of the day
Feel very depressed & cheerless & gloomy, and don't enjoy things and don't feel like having fun & very difficult to brighten up & don't function well.

-8 SEVERELY DOWN -almost all day

-9 EXTREMELY DOWN (life is not worth living)
Have extreme depression and feel very miserable, have psychic pain ("I cannot stand it"), and cannot control self & cannot be down & function poorly.

-10 AT THE LOWEST POINT
Have constant painful sadness and feel very numb & empty & don't want to live & cannot function at all & someone needs to be present to monitor safety.

-1 SLIGHTLY TIRED- less than 50% of the day
Feel a little bit tired, but others don't notice a change & function ok.

-2 SLIGHTLY TIRED-almost all day

-3 MILDLY TIRED-less than 50% of the day
Feel more tired and less active than usual/baseline & others may notice it, but can be active during the day & function ok.

-4 MILDLY TIRED-almost all day

-5 MODERATELY TIRED-less than 50% of the day
Feel very tired & slowed down than usual/baseline (out of proportion) & have considerably less energy to do things & less active & spend more time than usual to rest & don't function as good as before.

-6 MODERATELY TIRED-almost all day

-7 SEVERELY TIRED- less than 50% of the day
Have excessive tiredness & very difficult to move around & spend very long time to rest & physical activity is limited to few & don't function well.

-8 SEVERELY TIRED-almost all day

-9 EXTREMELY TIRED
Feel like drained and worn out & almost no physical activity and cannot move around & function poorly.

-10 NO ENERGY AT ALL
Have constant motor retardation, and cannot move arms or legs & cannot function at all & someone needs to be present to monitor safety.

Rasim Somer Diler, MD. Child and Adolescent Bipolar Spectrum Services (Cabs), Western Psychiatric Institute and Clinic of University of Pittsburgh Medical Center: "**Mood and Energy Thermometer.**" Revised in 2013.

Fig. 8.2 This figure shows the Mood and Energy Thermometer, which allows patients with potential bipolar disorders to quantify how their levels of mood and energy vary over time

latent growth class analyses to identify the proportions of the overall sample falling into one of four different mood trajectories: (1) 24.0% had a "predominantly euthymic" course; (2) 34.6% had a "moderately euthymic" course, (3) 19.1% had an "ill with improving" course, and (4) 22.3% had a "predominantly ill" course [57]. While a majority of all youth with BD in this study (59%) had at least a somewhat favorable course (groups 1 and 2), each less favorable trajectory group had a higher rate of ADHD (42.1% in "predominantly euthymic" group, 59.1% in "moderately euthymic" group, 64.3% in "ill with improving" group, and 72% in "predominantly ill" group) [57]. However, whether subjects managed to achieve a euthymic mood of ≥18 months during the study, was *not* associated with having ADHD. While many children and adolescents with BD may also have ADHD, most longitudinal studies have not reported an association between ADHD or

stimulant treatment with conversions to mania [23, 29]. In another study, which involved the longitudinal assessment 707 children for manic symptoms, 421 had ADHD alone, 45 had manic-symptoms alone, 117 had both ADHD and manic symptoms, and 124 had neither [58]. Comorbidity (16.5%) was slightly *less* than expected by chance (17.5%), suggesting ADHD was not a risk factor for manic symptoms [58]. The investigators speculated that the increased rates of bipolarity noted in other studies of ADHD samples are likely due to excessive rates of these disorders in child outpatient settings, not because ADHD is a true risk factor for BD [58]. Once again, the co-occurrence of ADHD and BD was associated with significantly worse global functioning, symptom severity, and comorbidities relative than in either condition alone [58]. However, the rates of ADHD were not significantly different between the four different trajectories of manic symptoms during the 24-month follow-up [59].

Treatment

Psychoeducation and support start with the assessment phase and are always indicated at any phases of treatment. Family members and the patient should be educated about the causes, symptoms, course, and different treatments of BD and the risks associated with treatment options [1]. Sleep hygiene and routine are also very important, especially because sleep deprivation leading to worsening of mood symptoms. Ensuring a stable circadian rhythm has a positive effect on physiology and daily functioning. In addition to supportive psychotherapy, specific psychosocial treatment packages for youth with BD target acute affective symptoms and prevention, or delay of recurrences, improvement of adherence to treatment, and management of comorbid conditions. A central feature of all psychosocial treatment models [such as Child and Family Focused Cognitive Behavior Therapy (CFF-CBT) [61], Multi-family Psychoeducation Groups (MFPG) and Individual Family Psychoeducation (IFP) [61], Family Focused Therapy (FFT) specifically for adolescents with BD (FFT-A) [62], Interpersonal and Social Rhythm Therapy (IPSRT) [63], and Dialectical Behavior Therapy (DBT) [64] for pediatric BD] is that they include psychoeducation, problem-solving, and coping skills. Parents are closely engaged in their child's therapy and are referred for treatment themselves if they too have clinically significant symptoms.

Current studies suggest that the most efficacious and fastest way to yield response for acute manic/mixed episodes is with the atypical antipsychotics such as aripiprazole [65], asenapine [66], olanzapine [67], risperidone [68], quetiapine [69], and ziprasidone [70]. Response rates to the atypical antipsychotics in studies of acute manic and mixed episodes among children and adolescents are comparable to those among adults, but youth are more sensitive to these medications' metabolic side effects [71, 72]. The antiepileptic mood stabilizers and lithium can also be helpful, but seem less efficacious in younger patients than in adults. However, most of the studies in children or adolescents have lasted only 8 weeks, possibly an inadequate time to observe a full response to these medications [1].

BD comorbid with ADHD presents unique treatment considerations. The AACAP treatment guidelines advise that symptoms of BD should be stabilized first, and if impairing symptoms of ADHD persist, they may be judiciously treated, with stimulants as first-line [73]. Several studies have suggested that comorbid ADHD may reduce the responsivity of acute mania to pharmacotherapy [74–77], especially in patients who are adolescents or have BD-I [76]. Although longitudinal, naturalistic studies did not find an association between stimulant treatment and emergence of BD [2, 29], there have been concerns about the risk of treatment-emergent mania or mood destabilization with stimulant treatment [78]. For example, 2.5–10% of BD youth treated with stimulants or atomoxetine (adjunctive to mood-stabilizing medication) experience psychiatric adverse events (i.e., hypo/mania and/or suicidality), and discontinuation of stimulants is often associated with an improvement in such events [79–82].

Tricyclic antidepressants have been reported to help improve comorbid ADHD symptoms, but also significantly increase the risk for manic symptoms [83]. In an open-label trial of valproate in 40 youth with BD and ADHD, only 7.5% had a positive response for their ADHD, while 80% had a positive response for their bipolar disorder. In the same study, using a 2-week crossover design with mixed amphetamine salts (MAS; 5 mg twice daily) or placebo, ADHD symptom reduction was significantly greater for MAS compared to placebo [81]. Similarly, a subsequent 4-week, randomized control trial of adjunctive methylphenidate vs. placebo reported significant improvement with methylphenidate [80]. In a randomized trial of adjunctive methylphenidate or placebo added to aripiprazole, ADHD symptoms showed no significant between-group differences, but self-reported depressive symptoms improved more with methylphenidate [79]. An open-treatment study of atomoxetine suggested that it may be effective for comorbid BD and ADHD [82].

Conclusions and Future Directions

Much evidence now shows that youth may manifest classical symptoms of BD; however, many youth do not fulfill the current DSM BD-I or II criteria for such diagnoses, primarily because they lack the required duration of symptoms. Moreover, many youth referred for evaluation for BD have severe mood lability, irritability, inattentiveness, hyperactivity, verbal and/or physical aggression that need careful baseline assessment, and longitudinal follow-up to ascertain whether these symptoms are indeed manifestations of BD (e.g., clustering of manic symptoms, change from baseline and functional impairment). Early recognition and acute and maintenance treatment of BD in children and adolescents is of vital importance to ameliorate ongoing syndromal and subsyndromal symptomatology and to reduce or prevent the serious psychosocial morbidity and risk for suicide. There are growing numbers of imaging [84–86] and neurocognitive [87–90] studies attempting to identify core features of BD that can distinguish it from other disorders including ADHD; however, larger longitudinal studies are needed in BD and ADHD youth for this expanding knowledge about neurobiology/cognition to be implemented into clinical practice for each patient.

The extant pharmacological studies suggest that the atypical antipsychotics are helpful for the acute treatment of manic/mixed symptoms, and stimulants can be added for ADHD *after* mood stabilization. However, studies of longer duration, including maintenance trials to reduce the risk of relapses and recurrences, as well as to examine the effects of development, family environment and psychopathology, and side effects are urgently needed in BD and ADHD youth. Future studies evaluating possible preventative strategies for ADHD and depressed youth at high risk for BD are indicated. In addition, studies to evaluate protective factors (e.g., cognitive development, social and coping skills, environmental factors) are warranted. Genetic and other biological studies, including pharmacogenetic studies that correlate the effects of treatment and biochemical changes on the brain, are also needed to improve precision in matching potentially helpful treatments with the most suitable patients.

References

1. Diler RS, Birmaher B. Bipolar disorder in children and adolescents. In: IACAPAP e-Textbook of Child and Adolescent Mental Health [Internet]. Geneva: International Child and Adolescent Psychiatry and Allied Professionals; 2012. p. 1–30. http://iacapap.org/wp-content/uploads/E.2-BIPOLAR-072012.pdf.
2. Birmaher B, Axelson D, Monk K, Kalas C, Goldstein B, Hickey MB, et al. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. Arch Gen Psychiatry. 2009;66(3):287–96.
3. Diler RS. Pediatric bipolar disorder: a global perspective. In: Diler RS, editor. New York: Nova Science Publishers, Inc.; 2007.
4. Birmaher B, Axelson D. Pediatric Psychopharmacology. In: Sadock BJ, Sadock VA, editors. Kaplan and Sadock's comprehensive textbook of psychiatry. II. 8th ed. Philadelphia: Lippincott, Williams, and Wilkins; 2005. p. 3363–75.
5. Soutullo CA, Chang KD, Diez-Suarez A, Figueroa-Quintana A, Escamilla-Canales I, Rapado-Castro M, et al. Bipolar disorder in children and adolescents: international perspective on epidemiology and phenomenology. Bipolar Disord. 2005;7(6):497–506.
6. Perlis RH, Dennehy EB, Miklowitz DJ, Delbello MP, Ostacher M, Calabrese JR, et al. Retrospective age at onset of bipolar disorder and outcome during two-year follow-up: results from the STEP-BD study. Bipolar Disord. 2009;11(4):391–400.
7. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry. 2005;44(9):846–71.
8. Wozniak J, Biederman J, Kiely K, Ablon JS, Faraone SV, Mundy E, et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry. 1995;34(7):867–76.
9. Biederman J, Faraone S, Mick E, Wozniak J, Chen L, Ouellette C, et al. Attention-deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? J Am Acad Child Adolesc Psychiatry. 1996;35(8):997–1008.
10. Klein RG, Pine DS, Klein DF. Resolved: mania is mistaken for ADHD in prepubertal children, negative. J Am Acad Child Adolesc Psychiatry. 1998;37(10):1093–6.
11. Van Meter AR, Moreira AL, Youngstrom EA. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. J Clin Psychiatry. 2011;72(9):1250–6.
12. Merikangas KR, He JP, Burstein M, Swanson SA, Avenevoli S, Cui L, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010;49(10):980–9.

13. Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry. 2006;63(10):1139–48.
14. Axelson D, Goldstein B, Goldstein T, Monk K, Yu H, Hickey MB, et al. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. Am J Psychiatry. 2015. https://doi.org/10.1176/appi.ajp.2014.14010035.
15. Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. Am J Psychiatry. 2009;166(7):795–804.
16. Goodwin FK, Jamison KR. Manic-depressive illness: bipolar disorders and recurrent depression. 2nd ed. New York: Oxford University Press; 2007.
17. Duffy A, Alda M, Crawford L, Milin R, Grof P. The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. Bipolar Disord. 2007;9(8):828–38.
18. Mesman E, Nolen WA, Reichart CG, Wals M, Hillegers MH. The Dutch bipolar offspring study: 12-year follow-up. Am J Psychiatry. 2013;170(5):542–9.
19. DelBello MP, Geller B. Review of studies of child and adolescent offspring of bipolar parents. Bipolar Disord. 2001;3(6):325–34.
20. Hafeman DM, Merranko J, Axelson D, Goldstein BI, Goldstein T, Monk K, et al. Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. Am J Psychiatry. 2016;173(7):695–704. https://doi.org/10.1176/appi.ajp.2015.15040414.
21. Birmaher B, Axelson D, Goldstein B, Monk K, Kalas C, Obreja M, et al. Psychiatric disorders in preschool offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring Study (BIOS). Am J Psychiatry. 2010;167(3):321–30.
22. Biederman J, Petty CR, Byrne D, Wong P, Wozniak J, Faraone SV. Risk for switch from unipolar to bipolar disorder in youth with ADHD: a long term prospective controlled study. J Affect Disord. 2009;119(1–3):16–21.
23. Duffy A. The nature of the association between childhood ADHD and the development of bipolar disorder: a review of prospective high-risk studies. Am J Psychiatry. 2012;169(12):1247–55.
24. Bella T, Goldstein T, Axelson D, Obreja M, Monk K, Hickey MB, et al. Psychosocial functioning in offspring of parents with bipolar disorder. J Affect Disord. 2011;133(1–2):204–11.
25. Geller B, Tillman R, Bolhofner K, Zimerman B. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. Arch Gen Psychiatry. 2008;65(10):1125–33.
26. DelBello MP, Hanseman D, Adler CM, Fleck DE, Strakowski SM. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. Am J Psychiatr. 2007;164(4):582–90.
27. Miklowitz DJ, Hooley JM. Developing family psychoeducational treatments for patients with bipolar and other severe psychiatric disorders. A pathway from basic research to clinical trials. J Marital Fam Ther. 1998;24(4):419–35.
28. APA. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.
29. Axelson DA, Birmaher B, Strober MA, Goldstein BI, Ha W, Gill MK, et al. Course of subthreshold bipolar disorder in youth: diagnostic progression from bipolar disorder not otherwise specified. J Am Acad Child Adolesc Psychiatry. 2011;50(10):1001–16.e3.
30. APA. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 2004.
31. APA. Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition, DSM 5). Washington, DC: American Psychiatric Association; 2013.
32. WHO. The ICD-10 Classification of Mental and Behaviour Disorders-Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization; 1992.
33. McClellan J, Kowatch R, Findling RL, Work GoQI. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder.[erratum appears in J Am

Acad Child Adolesc Psychiatry. 2007 Jun;46(6):786]. J Am Acad Child Adolesc Psychiatry. 2007;46(1):107–25.
34. Youngstrom EA, Frazier TW, Demeter C, Calabrese JR, Findling RL. Developing a 10-item mania scale from the Parent General Behavior Inventory for children and adolescents. J Clin Psychiatry. 2008;69(5):831–9.
35. Henry DB, Pavuluri MN, Youngstrom E, Birmaher B. Accuracy of brief and full forms of the Child Mania Rating Scale. J Clin Psychol. 2008;64(4):368–81.
36. Achenbach TM. Child Behavior Checklist and related instruments, vol. 637. Hillsdale: Lawrence Erlbaum Associates, Inc; 1994. p. 517–49.
37. Diler RS, Birmaher B, Axelson D, Obreja M, Monk K, Hickey MB, et al. Dimensional psychopathology in offspring of parents with bipolar disorder. Bipolar Disord. 2011;13(7-8):670–8.
38. Diler RS, Birmaher B, Axelson D, Goldstein B, Gill M, Strober M, et al. The Child Behavior Checklist (CBCL) and the CBCL-bipolar phenotype are not useful in diagnosing pediatric bipolar disorder. J Child Adolesc Psychopharmacol. 2009;19(1):23–30.
39. Kowatch RA, Youngstrom EA, Danielyan A, Findling RL. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. Bipolar Disord. 2005;7(6):483–96.
40. Van Meter AR, Burke C, Kowatch RA, Findling RL, Youngstrom EA. Ten-year updated meta-analysis of the clinical characteristics of pediatric mania and hypomania. Bipolar Disord. 2016;18(1):19–32.
41. Geller B, Zimerman B, Williams M, Delbello MP, Bolhofner K, Craney JL, 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. 2002;12(1):11–25.
42. Mick E, Spencer T, Wozniak J, Biederman J. Heterogeneity of irritability in attention-deficit/hyperactivity disorder subjects with and without mood disorders. Biol Psychiatry. 2005;58(7):576–82.
43. Leibenluft E, Rich BA. Pediatric bipolar disorder. Annu Rev Clin Psychol. 2008;4:163–87.
44. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Chronic versus episodic irritability in youth: a community-based, longitudinal study of clinical and diagnostic associations. J Child Adolesc Psychopharmacol. 2006;16:456–66.
45. Geller B, Tillman R, Craney JL, Bolhofner K. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch Gen Psychiatry. 2004;61(5):459–67.
46. Uchida M, Serra G, Zayas L, Kenworthy T, Hughes B, Koster A, et al. Can manic switches be predicted in pediatric major depression? A systematic literature review. J Affect Disord. 2014;172C:300–6.
47. Strober M, Carlson G. Bipolar illness in adolescents with major depression: clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. Arch Gen Psychiatry. 1982;39:549–55.
48. Wozniak J, Spencer T, Biederman J, Kwon A, Monuteaux M, Rettew J, et al. The clinical characteristics of unipolar vs. bipolar major depression in ADHD youth. J Affect Disord. 2004;82(Suppl 1):S59–69.
49. Luby JL, Tandon M, Nicol G. Three clinical cases of DSM-IV mania symptoms in preschoolers. In: Luby JL, Riddle MA, editors. Advances in preschool pharmacology. New Rochelle: Mary Ann Liebert; 2009. p. 79–85.
50. Wilens TE, Biederman J, Adamson JJ, Henin A, Sgambati S, Gignac M, et al. Further evidence of an association between adolescent bipolar disorder with smoking and substance use disorders: a controlled study. Drug Alcohol Depend. 2008;95(3):188–98.
51. Goldstein BI, Strober M, Axelson D, Goldstein TR, Gill MK, Hower H, et al. Predictors of first-onset substance use disorders during the prospective course of bipolar spectrum disorders in adolescents. J Am Acad Child Adolesc Psychiatry. 2013;52(10):1026–37.
52. Biederman J, Faraone SV, Wozniak J, Monuteaux MC. Parsing the association between bipolar, conduct, and substance use disorders: a familial risk analysis. Biol Psychiatry. 2000;48(11):1037–44.

53. Geller B, Williams M, Zimerman B, Frazier J, Beringer L, Warner KL. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. J Affect Disord. 1998;51(2):81–91.
54. Birmaher B. New hope for children and adolescents with BD disorder. New York: Three Rivers Press, a division of Random House, Inc.; 2004.
55. Diler RS. Child and adolescent bipolar spectrum disorders research and clinic instruments: the mood & energy thermometer. Pittsburgh: University of Pittsburgh; 2016. http://www.pediatricbipolar.pitt.edu/content.asp?id=2333#3604.
56. Kim JW, Yu H, Ryan ND, Axelson DA, Goldstein BI, Goldstein TR, et al. Longitudinal trajectories of ADHD symptomatology in offspring of parents with bipolar disorder and community controls. J Clin Psychiatry. 2015;76(5):599–606.
57. Birmaher B, Gill MK, Axelson DA, Goldstein BI, Goldstein TR, Yu H, et al. Longitudinal trajectories and associated baseline predictors in youths with bipolar spectrum disorders. Am J Psychiatry. 2014;171(9):990–9.
58. Arnold LE, Demeter C, Mount K, Frazier TW, Youngstrom EA, Fristad M, et al. Pediatric bipolar spectrum disorder and ADHD: comparison and comorbidity in the LAMS clinical sample. Bipolar Disord. 2011;13(5-6):509–21.
59. Findling RL, Jo B, Frazier TW, Youngstrom EA, Demeter CA, Fristad MA, et al. The 24-month course of manic symptoms in children. Bipolar Disord. 2013;15(6):669–79.
60. West AE, Henry DB, Pavuluri MN. Maintenance model of integrated psychosocial treatment in pediatric bipolar disorder: a pilot feasibility study. J Am Acad Child Adolesc Psychiatry. 2007;46(2):205–12.
61. Fristad MA. Psychoeducational treatment for school-aged children with bipolar disorder. Dev Psychopathol. 2006;18(4):1289–306.
62. Miklowitz DJ, Chang KD, Taylor DO, George EL, Singh MK, Schneck CD, et al. Early psychosocial intervention for youth at risk for bipolar I or II disorder: a one-year treatment development trial. Bipolar Disord. 2011;13(1):67–75.
63. Hlastala SA, Kotler JS, McClellan JM, McCauley EA. Interpersonal and social rhythm therapy for adolescents with bipolar disorder: treatment development and results from an open trial. Depress Anxiety. 2010;27(5):457–64.
64. Goldstein TR, Axelson DA, Birmaher B, Brent DA. Dialectical behavior therapy for adolescents with bipolar disorder: a 1-year open trial. J Am Acad Child Adolesc Psychiatry. 2007;46(7):820–30.
65. Findling RL, Correll CU, Nyilas M, Forbes RA, McQuade RD, Jin N, et al. Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomized, placebo-controlled study. Bipolar Disord. 2013;15(2):138–49.
66. Findling RL, Landbloom RL, Szegedi A, Koppenhaver J, Braat S, Zhu Q, et al. Asenapine for the acute treatment of pediatric manic or mixed episode of Bipolar I Disorder. J Am Acad Child Adolesc Psychiatry. 2015;54(12):1032–41.
67. Tohen M, Kryzhanovskaya L, Carlson G, Delbello M, Wozniak J, Kowatch R, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. Am J Psychiatr. 2007;164(10):1547–56.
68. Haas M, Delbello MP, Pandina G, Kushner S, Van Hove I, Augustyns I, et al. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. Bipolar Disord. 2009;11(7):687–700.
69. Pathak S, Findling RL, Earley WR, Acevedo LD, Stankowski J, Delbello MP. Efficacy and safety of quetiapine in children and adolescents with mania associated with bipolar I disorder: a 3-week, double-blind, placebo-controlled trial. J Clin Psychiatry. 2013;74(1):e100–9.
70. Findling RL, Cavus I, Pappadopulos E, Vanderburg DG, Schwartz JH, Gundapaneni BK, et al. Efficacy, long-term safety, and tolerability of ziprasidone in children and adolescents with bipolar disorder. J Child Adolesc Psychopharmacol. 2013;23(8):545–57.
71. Geller B, Luby JL, Joshi P, Wagner KD, Emslie G, Walkup JT, et al. A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar i disorder, manic or mixed phase, in children and adolescents. Arch Gen Psychiatry. 2012;69:515.

72. Goldstein BI, Sassi R, Diler RS. Pharmacologic treatment of bipolar disorder in children and adolescents. Child Adolesc Psychiatr Clin N Am. 2012;21(4):911–39.
73. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M, et al. Treatment guidelines for children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2005;44(3):213–35.
74. State RC, Frye MA, Altshuler LL, Strober M, DeAntonio M, Hwang S, et al. Chart review of the impact of attention-deficit/hyperactivity disorder comorbidity on response to lithium or divalproex sodium in adolescent mania. J Clin Psychiatry. 2004;65(8):1057–63.
75. Strober M, DeAntonio M, Schmidt-Lackner S, Freeman R, Lampert C, Diamond J. Early childhood attention deficit hyperactivity disorder predicts poorer response to acute lithium therapy in adolescent mania. J Affect Disord. 1998;51(2):145–51.
76. Consoli A, Bouzamondo A, Guile J-M, Lechat P, Cohen D. Comorbidity with ADHD decreases response to pharmacotherapy in children and adolescents with acute mania: evidence from a metaanalysis. Can J Psychiatr Rev Can Psychiatr. 2007;52(5):323–8.
77. Masi G, Perugi G, Millepiedi S, Mucci M, Pfanner C, Berloffa S, et al. Pharmacological response in juvenile bipolar disorder subtypes: a naturalistic retrospective examination. Psychiatry Res. 2010;177(1-2):192–8.
78. Goldsmith M, Singh M, Chang K. Antidepressants and Psychostimulants in pediatric populations: is there an association with mania? Paediatr Drugs. 2011;13(4):225–43.
79. Zeni CP, Tramontina S, Ketzer CR, Pheula GF, Rohde LA. Methylphenidate combined with aripiprazole in children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder: a randomized crossover trial. J Child Adolesc Psychopharmacol. 2009;19(5):553–61.
80. Findling RL, Short EJ, McNamara NK, Demeter CA, Stansbrey RJ, Gracious BL, et al. Methylphenidate in the treatment of children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46(11):1445–53.
81. Scheffer RE, Kowatch RA, Carmody T, Rush AJ. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. Am J Psychiatry. 2005;162(1):58–64.
82. Chang K, Nayar D, Howe M, Rana M. Atomoxetine as an adjunct therapy in the treatment of co-morbid attention-deficit/hyperactivity disorder in children and adolescents with bipolar I or II disorder. J Child Adolesc Psychopharmacol. 2009;19(5):547–51.
83. Biederman J, Mick E, Prince J, Bostic JQ, Wilens TE, Spencer T, et al. Systematic chart review of the pharmacologic treatment of comorbid attention deficit hyperactivity disorder in youth with bipolar disorder. J Child Adolesc Psychopharmacol. 1999;9(4):247–56.
84. Diler R. Neuroimaging can help identify biomarkers of early onset bipolar disorder. Bull Clin Psychopharmacol. 2011;22(1):1–4.
85. Diler RS, de Almeida JR, Ladouceur C, Birmaher B, Axelson D, Phillips M. Neural activity to intense positive versus negative stimuli can help differentiate bipolar disorder from unipolar major depressive disorder in depressed adolescents: a pilot fMRI study. Psychiatry Res. 2013;214(3):277–84.
86. Diler RS, Pan LA, Segreti A, Ladouceur CD, Forbes E, Cela SR, et al. Differential anterior cingulate activity during response inhibition in depressed adolescents with bipolar and unipolar major depressive disorder. J Can Acad Child Adolesc Psychiatry. 2014;23(1):10–9.
87. Altshuler LL, Ventura J, van GWG, Green MF, Theberge DC, Mintz J. Neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia and normal control subjects. Biol Psychiatry. 2004;56(8):560–9.
88. Doyle AE, Wilens TE, Kwon A, Seidman LJ, Faraone SV, Fried R, et al. Neuropsychological functioning in youth with bipolar disorder. Biol Psychiatry. 2005;58(7):540–8.
89. Doyle AE, Wozniak J, Wilens TE, Henin A, Seidman LJ, Petty C, et al. Neurocognitive impairment in unaffected siblings of youth with bipolar disorder. Psychol Med. 2009;39(08):1253–63.
90. Pavuluri MN, O'Connor MM, Harral EM, Moss M, Sweeney JA. Impact of neurocognitive function on academic difficulties in pediatric bipolar disorder: a clinical translation. Biol Psychiatry. 2006;60(9):951–6.