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Frontiers Between Attention Deficit Hyperactivity Disorder and Bipolar Disorder

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The co-occurrence of attention deficit hyperactivity disorder (ADHD) and bipolar disorder (BD) has received much recent attention in the literature. First, there is symptom overlap between the two illnesses (Table 1) [1], including disordered attention, activity, and speech. Second, children who have BD are often irritable during and between episodes of mania and depression [2]. Irritability can be associated with ADHD and other childhood psychopathologies that are often comorbid with ADHD, however, including oppositional defiant disorder (ODD), major depressive disorder (MDD), and generalized anxiety disorder [1]. Questions have arisen as to how to differentiate irritable children who have ADHD from children who have BD.

ADHD is a non-episodic illness, whereas BD is an episodic illness. A closely related scientific question concerns whether severe and chronic (ie, persistent, non-episodic) irritability is a developmental presentation of mania [3,4]. Clinicians and researchers are usually able to recognize children who have episodic BD with euphoric mood, and they are usually able to recognize children who have ADHD and no mood disturbance. Diagnosing children who have ADHD and severe irritability can be difficult, however.

We review the literature examining associations between ADHD and BD in children and data concerning severe irritability in youth who have

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Table 1
Attention deficit hyperactivity disorder and bipolar disorder criteria from the DSM-IV-TR with overlapping symptoms highlighted

ADHD	Bipolar disorder
Inattention ($\geq$ 6 symptoms for $\geq$ 6 mo)	A Criteria (lasting $\geq$ 1 wk; less if hospitalization is required)
Fails to give attention to detail or makes careless mistakes	Distinct period of abnormally and persistently elevated, expansive, or [a]irritable mood
Difficulty with sustained attention	B Criteria ($\geq$ 3 are present during period of mood disturbance; $\geq$ 4 if mood disturbance is irritability)
Often does not seem to listen when spoken to	[a]Increased self-esteem or grandiosity
Often does not follow through on instructions or fails to finish activities	Decreased need for sleep
Often has difficulty organizing tasks	***More talkative or pressured speech***
Often avoids, dislikes tasks that require sustained attention	Flight of ideas or racing thoughts
Often loses things	***Distractibility***
Is often easily distractible by extraneous stimuli	***Increased goal-directed activity, psychomotor* agitation**
Is often forgetful	[a]Excessive involvement in risky, pleasurable activities
Fails to give attention to detail or makes careless mistakes	
Difficulty with sustained attention	
Hyperactivity/impulsivity ($\geq$ 6 symptoms for $\geq$ 6 mo)	
Often fidgets	
Often leaves seat when staying in seat is expected	
Often runs about or climbs in inappropriate situations	
Often has difficulty playing quietly	
Is often "on the go" or "driven by a motor"	
Often talks excessively	
Often blurts out answers	
Often has difficulty awaiting turn	
Often interrupts, intrudes	
Selected diagnostic and associated features	
[a]Engaging in risky activities secondary to impulsivity	Episodic antisocial behavior
[a]Low frustration tolerance	Rapid mood shifts
[a]Bossiness	
Temper outbursts	
Mood lability	

Bold face italicized text indicates overlapping symptoms.

[a] Bipolar symptoms that overlap with associated features of ADHD.

Modified from American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Text revision. Washington, DC: American Psychiatric Association; 2000.

ADHD. We focus on (1) population-based studies that examined ADHD and BD or ADHD and co-occurring irritability, (2) the co-occurrence and prospective relationships of ADHD and BD in clinical samples, (3) phenomenology and assessment of BD and ADHD, including recommendations for differentiating DSM-IV-TR BD from ADHD, (4) treatment of comorbid ADHD and BD, (5) family and genetic studies of ADHD and BD, and (6) pathophysiologic comparisons between children who have ADHD and irritability and BD.

Attention deficit hyperactivity disorder and bipolar disorder in population-based samples

Cross-sectional studies

Six studies reported population-based rates of ADHD and BD in youth, three of which showed elevated rates of BD in participants who have ADHD (Table 2). The negative studies included the Great Smoky Mountains Study [6], which found low rates of mania (0 cases of mania; 0.1% had hypomania) and ADHD (1.9%). Second, in a nonreferred sample of twins enriched for ADHD and a random control twin sample, 0.2% of youth from the control twin sample had possible BD and 0.84% of those diagnosed with ADHD had possible BD [7]. Among youth who had BD or subthreshold BD, 33% had ADHD. This finding suggests that youth who have ADHD are not at elevated risk for BD, but youth who have BD are at elevated risk for ADHD. Third, in a Finnish birth cohort of 457 16- to 18-year-old patients, also enriched for ADHD, only 2 adolescents had BD, neither of whom also had ADHD [9]. These studies have low rates of BD, and the lack of correlation with BD and ADHD should be interpreted cautiously.

Three studies indicated that people who have ADHD are more likely than people without to have comorbid BD and that people who have BD are more likely than people without to have comorbid ADHD. In a sample of 1709 high school seniors, 1% had a lifetime diagnosis of BD (primarily BD II and cyclothymia) and 3% had a lifetime diagnosis of ADHD [5]. Of those who had ADHD, 3.8% had BD. Of those who had BD, 11.1% had ADHD. The Children in the Community study, a prospective epidemiologic sample of 776 youth, had similar findings [11]. Specifically, 12% of early adolescents had ADHD and 6.2% had BD; however, 18.3% of the youth who had ADHD had BD, and 35.4% of the youth who had BD had ADHD. Finally, in an adult sample ($N = 3199$), participants who had ADHD had elevated rates of BD, and participants who had BD had elevated rates of ADHD [8]. Specifically, 19.4% of adults who had ADHD had BD and 21% of adults who had BD had ADHD.

Taken together, the data suggest preliminarily that children, adolescents, and adults who have ADHD, compared with individuals who do not have

Table 2
Epidemiologic studies citing rates of comorbidity between attention deficit hyperactivity disorder and bipolar disorder or mood disorders

Reference	Sample (n)	Sample Age (y)	Assessment	Informant(s)	Rate of ADHD (%)	Rate of BD (%)	Comorbidity and predictive findings
Cross-sectional studies							
Lewinsohn, et al, 1995 [5]	1709	14–18	K-SADS	youth	3.1	1 (2 BD-I, 11 BD-II, 5 cyclothymia)	3.8% of persons with ADHD had BD 11.1% of persons with BD had ADHD
Costello, et al, 1996 [6]	1015	9–13	CAPA	parent, youth	1.9	0 (mania) 0.1 (hypomania)	17.8% of persons with behavioral disorders had emotional disorders; 55.2% of persons with depressive disorders had behavioral disorders
Reich, et al, 2005 [7]	1610 (MZ and DZ twins; enriched for ADHD)	7–18	MAGIC	parent	22.3	0.2 (1 BD-I, 1 BD-II, 1 hypomania)	0.84% of persons with ADHD had BD 33% of persons with BD had ADHD
Kessler, et al, 2006 [8]	3199	18–44	DIS	adult	4.4	2.6	19.4% of persons with ADHD had BD 21% of persons with BD had ADHD

Hurtig, et al, 2007 [9]	457 (from a birth cohort of 6622; enriched for ADHD)	16–18	K-SADS-PL	parent, youth	23	0.4	Neither of the two individuals with BD had ADHD
Prospective studies							
Kim-Cohen, et al, 2003 [10]	925 at age 11	11–15, 26 at follow-up	DISC (ages 11–15) DIS (ages 18–26)	parent, youth (ages 11–15) adult (ages 18–26)	approximately 6 (aged 11–15)	Not assessed in childhood 2.2 at age 26	approximately 4% of adults with mania had childhood ADHD Childhood ADHD did not predict BD at age 26
Galanter, et al, 2003 [11]	776 at mean age 13.7	Mean ages: T1: 13.7 ± 2.8 T2: 16.2 ± 2.8 T3: 22.1 ± 2.7 T4: 33.1 ± 2.9	DISC (T1, T2) SCID-IV-NP and ADHD symptom checklist (T3, T4)	Parent, youth (T1, T2) adult (T3, T4)	12.0 (T1) 7.6 (T2) 1.1 (T3) 2.4 (T4)	6.2 (T1) 5.8 (T2) 4.6 (T3) 1.5 (T4)	Individuals with ADHD compared with those without ADHD had greater rates off BD at all four assessments; ADHD at T1 predicted BD at mean age T2, and T3, but only at T2 when controlling for baseline ADHD

Abbreviations: CAPA, Children and Adolescent Psychiatric Assessment; DIS, Diagnostic Interview Schedule for DSM-IV; DISC, Diagnostic Interview Schedule for Children; DZ, dizygotic; K-SADS(-PL), Schedule for the Affective Disorders and Schizophrenia for School-Age Children (Present and Lifetime Version); MAGIC, Missouri Assessment of Genetics Interview of Children; MZ, monozygotic; SCID-IV-NP, Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient Version; T1, time of first diagnostic assessment; T2, time of second diagnostic assessment; T3, time of third diagnostic assessment; T4, time of fourth diagnostic assessment.

ADHD, may have elevated rates of BD. Individuals of all ages who have BD also seem to have high rates of ADHD.

Longitudinal studies

Two prospective epidemiologic studies examined whether ADHD in youth predicts BD in adolescence or adulthood. In the Dunedin Multidisciplinary Health and Development Study, ADHD at age 11 to 15 did not predict BD at age 26 years, but depression and conduct/ODD did [10]. In the Children in the Community sample, when the data were controlled for baseline BD, ADHD at mean age 13.7 (SD = 2.8) predicted BD at mean age 16.3 (SD = 2.8) but not at mean age 22.1 (SD = 2.7) or 33.1 (SD = 2.9) [11]. These data do not indicate that having ADHD in youth is a risk factor for adult BD.

Because investigators have suggested that children and adolescents who have ADHD and non-episodic severe irritability are exhibiting a developmental phenotype of BD, it is also important to study the diagnostic outcome of such youth. Leibenluft and colleagues [12] examined data from the Children in the Community sample and found that episodic irritability at mean age 13.7 (SD = 2.8) was associated with mania and anxiety disorders at mean age 16.3 (SD = 2.8), whereas chronic irritability at mean age 13.7 (SD = 2.8) was associated with ADHD at mean age 16.3 (SD = 2.8) and MDD at mean age 22.1 (SD = 2.7). These investigators also analyzed data from the Great Smoky Mountains Study to determine the diagnostic correlates of childhood severe mood dysregulation (SMD), a construct that includes irritable mood, emotional reactivity, and hyperarousal [13]. Lifetime prevalence of SMD was 3.3%, and 26.9% of youth who had SMD had ADHD. Youth who had SMD at wave one (mean age 10.6, SD = 1.4) were more likely than youth who never met criteria for SMD to meet criteria for depressive disorder at the last wave (mean age 18.3, SD = 2.1) (OR = 7.21, CI, 1.34–38.85). The low association between wave one SMD and last wave BD may be partly caused by the study's overall low rates of BD, and some participants with depressive disorder eventually may develop BD. These studies indicated that youth with severe irritability may not have BD as adults but are at elevated risk for depressive disorders. They are post hoc analyses, however, and prospective studies are needed.

Clinical samples

In assessing ADHD in clinical samples of youth who have BD or rates of BD in youth who have ADHD, it is important to note that assessment techniques of BD vary across research groups, leading to variations in the characteristics of the diagnosed sample. One approach is to use DSM-IV-TR (adult) criteria and adhere to mood and episode requirements (the "A" criterion; see

Table 1) [14,15]. Other investigators waive the "A" episodicity criterion for mania if a child presents with particularly severe irritability [16,17]. A third approach requires elevated mood or grandiosity for the diagnosis of mania and redefines an episode as a mood state that is at least 2 weeks long or has the onset to offset of a period of cycling and a cycle as mood switches during an episode [18]. These and other variations in assessment are likely to affect the characteristics of the recruited patients and the rates of BD.

Bipolar disorder in patients who have attention deficit hyperactivity disorder

Cross-sectional studies

Several clinical studies have found rates of BD ranging from 11% to 23% in youth who have ADHD [16,17,19]. Of note, most of these studies were at one site—a tertiary care medical center that specializes in studies of ADHD and BD; studies in different settings are needed.

Longitudinal studies

Longitudinal studies that examine the development of BD in clinical samples of youth who have ADHD have yielded conflicting results. Several studies that examined the adult outcome of children who have ADHD have not found increased rates of BD [20–22]. In contrast, Biederman and colleagues [16] found that compared with controls, youth who had ADHD had higher baseline rates of BD (11% versus 0%) and higher conversion rates to BD by year 4 (13/128 versus 2/109). Similarly, Tillman and Geller [23] found that 28.5% of 81 children who had ADHD, who were first assessed at mean age 9.7 (SD = 2.0), developed BD over 6-year follow-up. These variations from the earlier negative studies may result from differences in the techniques used to diagnose BD. Several investigators have examined children who have ADHD prospectively and found that the presence of some manic symptoms is not associated with increased risk for later BD (Galanter and colleagues, unpublished data) [24–26].

Attention deficit hyperactivity disorder in patients who have bipolar disorder

Clinical studies generally demonstrate high rates of ADHD in patients who have BD. Rates vary widely across samples, from 4% to 98% [14,27,28]. Setting, participant age, age of onset of BD, referral source, and ascertainment bias affect these rates. Bipolar type also may affect rates of comorbidity. For example, in a large study that examined the course and phenomenology of children and adolescents who have BD, youth who had BD II were less likely to have ADHD than youth who had BD I or BD not otherwise specified (BD-NOS) (31.6% versus 61.2% and 59.8%) [14]. Some of these studies did not specifically assess ADHD symptoms during euthymic periods, which might artificially inflate the rates of ADHD.

Few studies described the ages of onset of ADHD and BD. Two studies demonstrated that ADHD preceded prepubertal BD by approximately 2 years [17,29]. In one study, mean age of onset was 4.8 years (SD = 1.5) for ADHD and 6.8 years (SD = 3.4) for the first manic episode [29], whereas in another study, mean age of onset was 2.5 years (SD = 1.9) for ADHD and 4.4 years (SD = 3.1) for mania [17]. These studies are remarkable for the early age of onset of BD, and several studies indicated that earlier onset of BD is associated with higher rates of ADHD. In patients who have BD, Faraone and colleagues [30] found that rates of ADHD were 93% in children, 88% in adolescents who had childhood-onset mania, and 59% in adolescents who had adolescent-onset BD. In 1000 adults who had BD, Perlis and colleagues [31] found that ADHD was more common in the prepubertal-onset group (< 13 years old; 53/272, 20.4%) than in the adolescent-onset (13–18 years old; 27/370, 7.6%) or adult-onset (> 18 years old; 19/341, 5.7%) groups [31].

Finally, data indicate that comorbid ADHD in patients who have BD is associated with greater psychosocial impairment [32], fewer periods of wellness, more frequent episodes of depression, and higher rates of comorbidity with other psychiatric disorders, including anxiety and substance use disorders [33].

Summary

Data are mixed as to whether having ADHD increases one's risk for developing BD, but overall, community and clinical data show an increased risk of BD in people who have ADHD. Having ADHD with some manic symptoms seems not to increase one's risk for future BD, although some studies may be too small to detect increased risk of moderate or small magnitude. It is clear that youth who have BD are more likely to have ADHD than youth who do not have BD, although the precise degree of risk is unclear. For participants who have BD, rates of comorbid ADHD seem to be greater with younger age of onset, and comorbid ADHD is associated with greater morbidity.

Assessment

In this section, we review the literature relevant to the assessment and differentiation of ADHD and BD and focus on the identification of episodes, symptoms that differentiate ADHD from BD, the differential diagnosis of irritability in a child who has ADHD, and the use of screening tools. Although we focus on the diagnosis of BD I and II, clinicians often give children the diagnosis of BD-NOS. The DSM-IV-TR does not operationalize BD-NOS but notes that the category includes disorders with bipolar features that do not meet criteria for any specific BD [1]. For clinicians who wish to diagnose a child with BD-NOS, it is important to specify which criteria for BD the child meets and why the child does not meet full criteria

for BD I or II. In practice, there are two common usages for the BD-NOS diagnosis on youth. First, it is assigned often when children have distinct episodes that meet criteria for hypomania or mania but the episodes are too short to meet DSM-IV criteria. In the Course of Bipolar Youth study, specific criteria were defined to capture this group, and data indicated that approximately one third of these youth meet full criteria for BD within 2 years [14]. The second major use of BD-NOS is for youth who do not have distinct episodes of mania but instead have non-episodic, impairing irritability. In the case of these youth, data indicate that they may have a particularly high risk for major depression in early adulthood rather than BD [12,13]. Clinicians who assign the diagnosis of BD-NOS should be aware that the term is used frequently for several populations of patients who may have different outcomes, and they should document clearly the reasoning behind their assignment of this diagnosis.

Episodes

By definition, BD is episodic. That is, to fulfill DSM-IV-TR criteria for bipolar I disorder, a child must have a distinct period (ie, an episode) of elevated, expansive, or irritable mood that lasts at least 7 days and three of the "B" symptoms of mania (four if the mood is irritable), with the "B" criteria occurring at the same time as the change in mood [1]. (See Table 1 for a description of diagnostic criteria of BD and ADHD.) For BD II, the episode must last for at least 4 days and be noticeable to others rather than be severely impairing, as in mania. Consistent with the practice parameters of the American Academy of Child and Adolescent Psychiatry, we recommend that clinicians adhere to DSM-IV-TR criteria when diagnosing mania in youth. That is, only diagnose BD when episodes are present and, in the absence of elevated or expansive mood, only diagnose BD if the irritability is episodic and worsens in concert with the onset of the associated "B" symptoms [34].

One effective way to ascertain whether episodes have occurred is for the clinician to meet with the child and guardian together and ask them to identify a period of time when the child had a distinct period of abnormally and persistently elevated, expansive, or irritable mood that lasted the requisite duration. During the episode, the child's behavior should differ from baseline to an extent that is noticeable to others (hypomania) or is impairing (mania). It is often helpful to inquire about the most recent episode and the most severe and to anchor episodes to events that the child is likely to remember (eg, start of school, Halloween).

Once a period of mood change has been identified, the clinician can determine whether the child has the other symptoms of BD ("B" criteria) at the same time. For example, the clinician might say, "During the period when your son was extremely irritable, did he sleep less but still wake up feeling rested?" If clinician and family cannot discern a period when the child's mood was different from his or her baseline (ie, if the child's mood

is chronically irritable without discernable periods of several days or weeks when the irritability worsened), it is unlikely that the child has BD. Instead, the child's irritability is probably caused by another condition, such as ODD, which is a chronic non-episodic condition.

Differentiating attention deficit hyperactivity disorder and bipolar disorder symptoms

Several investigators have tried to discern which symptoms are the most helpful in distinguishing ADHD from BD. Geller and colleagues [35], who required elation or grandiosity for the diagnosis of BD, found that five symptoms (elation, grandiosity, flight of ideas/racing thoughts, decreased need for sleep, and hypersexuality) best discriminated children who had BD from children who had ADHD or from a community control group. For example, 83 of 93 (89.3%) children who had BD had elated mood compared with 11 of 81 (13.6%) children who had ADHD and 0 ($N = 94$) controls. Irritability, hyperactivity, accelerated speech, and distractibility were frequent in both patient groups [35].

Children who have comorbid ADHD and BD may report that their ADHD-like symptoms are worse during a manic episode. A child who has ADHD and always has been active may be even more so during a manic phase. For example, when a patient who has comorbid ADHD and BD presents to a clinician's office in a euthymic phase, he or she may shift around in his or her seat or start playing with things in the office that do not belong to him or her, whereas in a manic phase the patient may be unable to stay in his or her chair and do push-ups. Children who have ADHD are often distractible and sometimes may be hard to follow as they jump from one topic to another, but children who have BD have even more severely discordant thoughts. For example, they may describe racing thoughts in terms such as "my brain feels like it is on fast forward." Children who have ADHD often have difficulty getting ready for bed and falling asleep [36]. In contrast, children who have BD may have decreased need for sleep, staying up late playing and being well rested after little sleep.

The differential diagnosis of attention deficit hyperactivity disorder and irritability

ODD, conduct disorder (CD), MDD, and anxiety disorders are frequently comorbid with ADHD and are associated with irritability. In a child who has ADHD, anxiety disorders and MDD can be difficult to differentiate from BD because of overlapping symptoms (eg, irritability, psychomotor agitation, and sleep disturbances). To differentiate BD from other mood and anxiety disorders, it is important to elicit the predominant mood and specific examples of precipitants for irritability or outbursts. For example, children who have severe irritability in response to separations or other anxiety-provoking situations may have an anxiety disorder. To differentiate

MDD from BD, in addition to eliciting mood symptoms, it is helpful to examine other criteria for each illness, such as decreased need for sleep (mania) versus difficulty sleeping and feeling tired (MDD) or inflated (mania) versus decreased (MDD) self-esteem. Mood lability (''mood swings'') manifested by changes from euthymia to depression in the absence of other manic symptoms is more likely to be evidence of depression than BD.

ODD and CD also can be difficult to discern from BD because of shared symptoms, such as irritability, defiance (a symptom of ODD that may be difficult to discern from grandiosity of BD), and reckless behavior. Differentiating between episodic and non-episodic irritability and between episodic and non-episodic grandiosity/oppositionality can be especially helpful in distinguishing BD from ODD and CD. Children who have symptoms of ADHD and of a pervasive developmental disorder can become irritable because of rigidity and difficulties with transitions. Children who have ADHD and a learning disorder may be more irritable or disruptive because they have the wrong classroom placement.

In sum, children who have ADHD and irritability may have one of several comorbid diagnoses. Distinguishing between chronic and episodic symptoms, assessing carefully the associated BD criteria, eliciting details around precipitants for irritability, and ruling in or out commonly associated comorbid conditions through interviews and with screening tools are helpful techniques in clarifying a child's diagnosis.

Screening tools

Several rating scales, including the Young Mania Rating Scale [37], the Child Mania Rating Scale [38], the General Behavior Inventory [39], the Mood Disorders Questionnaire [40,41], and the Child Behavior Checklist (CBCL) [42], can be effective screening tools for BD and may assist clinicians in differentiating BD from ADHD and other behavioral disorders. Youngstrom and colleagues [43] compared several rating tools and determined that the parent–General Behavior Inventory and the parent–Mood Disorders Questionnaire were the most efficient in predicting BD in a community mental health center setting. Several studies also showed that screening instruments completed by caregivers are more effective than instruments completed by teachers or children and that combining screening instrument data from multiple informants does not provide additional information [44]. The CBCL is not specific for identifying BD in community samples [42], and the CBCL-juvenile BD (CBCL-JBD) profile (elevated scores on the attention, aggression, and anxious/depressed subscales) often identifies youth with other disorders [45]. In addition to a thorough clinical assessment that includes parent and child interviews, clinicians should use a parent-report rating scale, such as the Mood Disorders Questionnaire, General Behavior Inventory, or Child Mania Rating Scale, to support decision making, especially in patients with complicated presentations.

Treatment

Treating attention deficit hyperactivity disorder in children and adolescents who have bipolar disorder

Two studies addressed treating ADHD in youth who have BD. In one study ($N = 40$), mixed amphetamine salts, added to divalproex sodium, were more effective than placebo in treating the symptoms of ADHD, and no significant worsening of manic symptoms emerged [46]. The second study was a chart review ($N = 38$) that concluded that mood stabilization was a prerequisite for ADHD treatment [47].

Treating attention deficit hyperactivity disorder with irritability and subthreshold bipolar disorder

Post hoc analyses indicate that children who have ADHD and some manic symptoms (but who do not meet full criteria for BD) can be treated effectively with stimulants. In the Multimodal Treatment Study of Children with ADHD ($N = 289$), children who had some manic symptoms (who did not meet full criteria for BD) responded well to treatment with stimulants [24,48]. Similarly, Carlson and colleagues [25] demonstrated that of 75 6- to 12-year-old boys treated for hyperkinetic reaction of childhood, the 23% who had symptoms that suggested childhood mania (eg, irritability) did not differ in their response to methylphenidate and were no more likely than youth without manic symptoms to develop BD at ages 21 to 23. Stimulants generally decrease irritability and aggression in children who have ADHD [49]. Of note, children who have ADHD may exhibit affective symptoms as their stimulant wears off, and this "rebound" may be misdiagnosed as BD [50].

Treating bipolar disorder with comorbid attention deficit hyperactivity disorder

Two studies demonstrated that adolescents who have BD and comorbid ADHD are less likely than youth without comorbid ADHD to respond well to antimanic medication. In one chart review of adolescents hospitalized for mania, a history of ADHD was associated with a diminished response to divalproex sodium or lithium [51]. In a naturalistic treatment study of 40 adolescents who had BD, ADHD, and CD, baseline severity correlated with nonresponse [52]. In another treatment study of 48 adolescents who had BD, however, a history of ADHD was not associated with a poor lithium response [53].

Stimulants precipitating mania or bipolar disorder

Case studies describe stimulants precipitating manic symptoms in children [54]. In reviewing several pharmaceutical company–sponsored trials, the US Food and Drug Administration found that stimulant-associated

psychotic-like and manic-like symptoms occurred rarely—in approximately 0.25% of children treated with stimulants [55]. In 55 of 60 reported cases of psychotic-like or manic-like symptoms in response to stimulants, the symptoms resolved when the stimulant was discontinued [55]. In the five cases that did not, the patients were rediagnosed with schizophrenia or BD. In some cases, children may tolerate a carefully monitored rechallenge of stimulant at a lower dose [55].

Investigators have hypothesized that stimulants may hasten the onset of mania. Reichart and Nolen [56] estimated that the rate of BD in the Netherlands was much lower than that in the United States and proposed that medication exposure may hasten the onset of BD, especially in youth with a family history of BD [56]. In a retrospective analysis of 80 hospitalized manic adolescents, stimulant exposure was associated with more severe hospital course, younger age, ADHD, and ODD [57]. In another study from the same institution, prior stimulant treatment was associated with earlier onset of BD; however, ADHD was not associated with age of onset of BD [58]. These studies were retrospective and uncontrolled (ie, more severe ADHD may be associated independently with stimulant treatment and earlier BD onset). In contrast, in one prospective study of 81 children who had ADHD, 28.5% switched to BD, and less stimulant use was associated with developing BD [23]. Future studies should examine treated and untreated children who have ADHD and investigate irritability, comorbidity, and onset of new psychopathology.

Family and genetic studies

Top-down studies

A number of "top-down" studies have examined offspring of bipolar parents for ADHD. Several have not found increased risk for ADHD [59] or ADHD symptoms [60], whereas others have. For example, Carlson and Weintraub [61] found that children of parents who had BD and children of psychiatric controls had greater rates of attention and behavior problems than the children of normal controls [61]. Childhood attention problems were related to young adult mood disorder only in the BD offspring group. Another group found that children of parents who had BD had higher rates of ADHD than children of parents who had panic disorder or MDD [62]. In a study of 60 children of parents who had BD, Chang and colleagues [63] also found high rates of ADHD (28%).

Bottom-up studies

Several investigators examined rates of BD and ADHD in first-degree relatives of youth who have these illnesses ("bottom-up" studies). Faraone and colleagues [30] found that first-degree relatives of youth who have BD

and ADHD were more likely to have comorbid ADHD and BD than were the relatives of probands with ADHD alone or controls, which suggests cofamiliality of BD and ADHD. Other research from this group indicated that antisocial and bipolar ADHD subtypes may be different manifestations of the same condition [64].

Several investigators examined the first-degree relatives of youth who have BD for psychopathology [65,66]. Geller and colleagues [65] found that probands with BD have first-degree relatives with greater morbidity risk of BD than relatives of ADHD or healthy controls and that the risk of BD was similar in the relatives of probands with ADHD and the relatives of healthy controls. In a pilot study, Wozniak and colleagues [66] found that first-degree relatives of children who have BD (most with comorbid ADHD) had higher rates of ADHD than the normal control group and higher rates of BD than the nonbipolar ADHD group and that ADHD cosegregated in these relatives. In another study, investigators found that the most common diagnosis in the first-degree relatives of youth who have BD was MDD, but there were also high rates of BD, anxiety, ADHD, CD, substance use, and suicidal ideation, especially in the relatives of youth who have childhood-onset BD [67]. These studies indicated that rates of ADHD are elevated in family members of children who have BD (many of whom had comorbid ADHD). They did not demonstrate elevated rates of BD in children who have ADHD, although this negative finding may be because the studies were not powered to detect this elevation.

Twin studies

In a large sample of Dutch twin pairs examined prospectively [67], investigators found that the CBCL-JBD phenotype identified by high scores on attention, anxious-depressed, and aggression subscales, was present in approximately 1% of the population overall and in 20% of individuals with high scores on the CBCL attention problems scale. They also found that ADHD was more genetically influenced, whereas the CBCL-JBD phenotype had a stronger environmental contribution.

Molecular studies

One study found no common genes between ADHD and BD when scanning an estrogen receptor and thyroid hormone receptor gene [68]. Several studies proposed that dopamine transporter genes are implicated in ADHD [69,70] and BD [71–73]. Several studies have shown that the brain-derived neurotrophic factor (BDNF) gene is involved in the pathogenesis of ADHD [74] and BD [75]. However, there are also studies which show a lack of association between the Val66Met polymorphism of BDNF, including a meta-analysis [76], so the data are not currently conclusive. One study also identified ADHD subjects with the A559V variant of the dopamine

transporter gene [77], which was previously identified in a subject who had BD [78].

Pathophysiology

Pathophysiologic studies are needed to compare patients who have ADHD or BD (with and without comorbid ADHD) and controls. One important question concerns whether ADHD that occurs in the setting of BD is similar pathophysiologically to ADHD that occurs alone or, alternatively, represents a phenocopy. It is important to determine whether neuropsychological tests and imaging can assist in making clinical diagnoses and whether pathophysiology might ultimately help guide our interventions.

The literature is mixed as to whether youth who have ADHD, BD with ADHD, and BD without ADHD can be differentiated neuropsychologically. One study found that patients who had ADHD with and without BD showed more deficits than patients who had BD alone or controls on processing speed, automatized naming speed, memory, and executive functioning [79]. A second study of neurologic examination abnormalities found that children who had ADHD alone were impaired on repetitive task reaction time, whereas children who had BD—with and without comorbid ADHD—were impaired on sequential task reaction time [80]. Two studies examined executive function in youth with BD with and without ADHD and in healthy controls [81,82]. These studies demonstrated that youth with BD, with and without comorbid ADHD, had impaired executive function and that those youth with both disorders had poorer function. Other studies did not find differences between the BD groups with and without ADHD when examining factors such as biologic risk factors [83], prepulse inhibition [84], limbic hyperactivation while processing neutral faces [85], and cognitive flexibility [86].

With regard to neuroimaging, one study of 368 youth hospitalized with various DISC-defined diagnoses found that individuals who had BD ($N = 56$) or ADHD/CD ($N = 94$) had significantly more white matter hyperintensities than controls, but the two groups did not differ significantly from each other [87]. Moore and colleagues [88] examined brain chemistry in children and adolescents who had ADHD with and without comorbid BD. They found that children who had ADHD alone had significantly higher ratios of glutamate plus glutamine to myo-inositol than did children who had ADHD and BD, which suggested a means for differentiating the two illnesses. Two studies that compared youth with BD with and without comorbid ADHD found possible differences in neural activation during attentional or motor inhibitory tasks [89,90], although a different study found no differences between ADHD and BD groups [85].

Overall, these studies indicate that some neuropsychological, neurologic, and neuroimaging measures may differentiate BD from ADHD. Many of the "negative studies" were post hoc analyses in BD samples either controlling

for ADHD or comparing participants with and without ADHD, and they may not have been adequately powered to detect differences. Further research is needed before using these pathophysiologic measures to guide diagnosis.

Summary

Often when a child has ADHD and mood dysregulation, it can be difficult to make an accurate diagnosis and decide on an evidence-based treatment plan. Research in epidemiology, assessment, treatment, family studies, genetics, and pathophysiology can help guide our diagnostic and treatment decisions. We draw from this research to make clinical recommendations while highlighting important directions for future research.

Clinical recommendations

1. Keep base rates in mind when considering a diagnosis. ADHD is a common childhood disorder. BD is much less common, although it may occur more frequently than we once thought. Statistically speaking, a child is much less likely to have BD than ADHD. These likelihoods differ according to setting. For example, a child in a pediatric office who has ADHD is much less likely to have BD than one in a tertiary care clinic that specializes in BD or in an inpatient psychiatric unit. Similarly, if a child has ADHD and irritability, consider not only BD but also ODD, CD, generalized anxiety disorder, and MDD, which are much more common than BD.
2. Conduct a thorough diagnostic interview with both child and guardian when assessing for possible BD in children who have ADHD or possible ADHD in children who have BD. To diagnose BD, look for an episode of extremely elevated or expansive mood. If none exists, look for an episode of irritability that is more severe than the child's baseline. Then determine if the child had the associated "B" symptoms of mania at the same time as the mood symptoms. Those B symptoms that are not shared by ADHD (grandiosity, flight of ideas/racing thoughts, decreased need for sleep, and hypersexuality) are especially helpful in discriminating between the two disorders. When looking for ADHD in a child who has BD, look for decreased attention and increased activity which are non-episodic and occur at times other than during a mood episode.
3. Use rating scales to support clinical decision making. If you suspect BD, parent-report rating scales with symptoms specific to BD are the best predictors.
4. The data are limited as to how to best treat a child or adolescent with both BD and ADHD. A good diagnostic assessment is essential, because the treatment of ADHD and BD may be different than the treatment of ADHD and irritability secondary to another condition. Children who have ADHD and irritability who do not meet criteria for BD may benefit

from medications that we are wary of prescribing to patients who have BD. For example, children who have ADHD and irritability may respond to stimulants with decreased irritability [91]. Children who have ADHD and anxiety or irritable depression may benefit with treatment for their anxiety or depression, such as a selective serotonin reuptake inhibitor or psychotherapy. If a child has ADHD and BD, the limited data indicate that first you should stabilize the BD and, if residual ADHD symptoms remain, then treat the ADHD. Take into account the risk of adverse effects or destabilization from medication and discuss this with families, but do not overweigh the possibility of risk when making a recommendation.

Directions for future research

1. Although there is some indication of elevated rates of BD in ADHD samples and strong data to support elevated rates of ADHD in BD samples, further research is needed to investigate the rates of comorbidity in younger population-based samples. Few data are available for school-aged children or toddlers and in clinical samples in varied settings. Similarly, more data are needed on the longitudinal relationship between ADHD and BD in youth, specifically examining onset and offset of the two illnesses, symptoms or risk factors that predispose a child with ADHD to developing BD, and the question of whether ADHD with severe irritability is continuous with ADHD or BD.
2. The assessment of ADHD and BD and the use of diagnostic instruments may vary from site to site in research settings. The field would benefit from greater standardization of instruments, symptom description, and symptom interpretation, which would lead to improved capacity to compare results across settings.
3. Similarly, clinicians would benefit from screening tools and diagnostic instruments that are designed to differentiate between BD and ADHD in clinical settings.
4. Further treatment trials of BD with comorbid ADHD are needed. In particular, are some medications particularly effective in treating both disorders? Are some ADHD treatments more or less likely to destabilize children with BD? If a child has ADHD but is at risk for BD because of family history or symptom profile, should the prescribing clinician avoid stimulants or only prescribe stimulants after a child has been stabilized on other medications? If a child has an adverse ''manic-like'' reaction to an ADHD medication, does this have diagnostic implications?
5. Further family studies and genetic studies are needed. Specific questions include quantifying the risk of developing BD in a child who has ADHD and a first-degree relative who has BD. High-risk studies may permit us to see the antecedents of BD in a child who has ADHD and may lead to opportunities for intervention. Studies also should investigate the possibility of shared risk-related genes.

6. Further pathophysiologic and neuroimaging studies are needed to compare youth who have BD (with and without comorbid ADHD), youth who have ADHD alone (with and without irritability), and controls. Studying the underlying mechanisms of behavior and contrasting these different groups may allow us to determine whether ADHD in children who have BD is a phenotypic copy of ADHD in non-BD patients, create better treatment interventions, and ultimately develop laboratory tests to assist in differentiating between the two disorders in clinical practice.

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