REVIEW ARTICLE

ONLINE FIRST

Recent Progress in Understanding Pediatric Bipolar Disorder

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Bipolar disorder is one of the most severe psychiatric illnesses, particularly when onset occurs during childhood or adolescence. With recent empirical evidence, questions regarding the existence of bipolar disorder among children and adolescents have given way to questions regarding prevalence. There are substantial risks inherent in misapplying diagnoses and treatments of bipolar disorder when not warranted and in withholding these diagnoses and treatments when they are warranted. As with adults, the course of bipolar disorder among children and adolescents diagnosed using unmodified diagnostic criteria is characterized by recovery and recurrence, functional impairment, suicidality, and high rates of comorbid psychiatric and medical problems. Discrepancies between increasing billing diagnoses and a stable epidemiologic prevalence of bipolar disorder suggest the possibility that diagnostic criteria are not being systematically applied in some clinical settings. Introducing new diagnoses may exacerbate rather than mitigate concerns regarding misdiagnosis and excessive use of mood-stabilizing medications. Several medications, particularly second-generation antipsychotics, are efficacious for treating acute manic episodes of bipolar I disorder. However, less is known regarding the treatment of other mood states and subtypes of bipolar disorder. Psychosocial treatments provide a forum in which to educate children and families regarding bipolar disorder and its treatment, and may be especially beneficial for reducing depressive symptoms. Offspring of parents with bipolar disorder are at increased risk of developing the illness, as are youth with major depressive disorder and certain psychiatric comorbidities. Preliminary findings regarding biomarkers offer hope that, in the future, these biomarkers may inform diagnostic and treatment decisions.

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Reports of mania among adolescents and even among prepubertal children have sporadically showed up in the literature for nearly a century.[1,2] As arguments against the existence of pediatric bipolar disorder (BD) have waned in recent years, prevalence has become the leading extant controversy. Until recently, childhood mania was considered a rare entity. This stood in contrast to findings that up to two-thirds of adults with BD report onset occurring during childhood or adolescence and that, in such cases, the course and outcome of BD is substantially more pernicious.[3-6] An influential 1995 study by Wozniak and colleagues[7] indicated that 16% of children presenting for treatment at a tertiary academic child psychiatric clinic evidenced symptoms consistent with mania, and raised the question of whether pediatric BD was being overlooked. By many accounts, concerns regarding missed diagnoses of BD and underestimates of prevalence have been replaced with concerns regarding misdiagnoses of BD and overestimates of prevalence.

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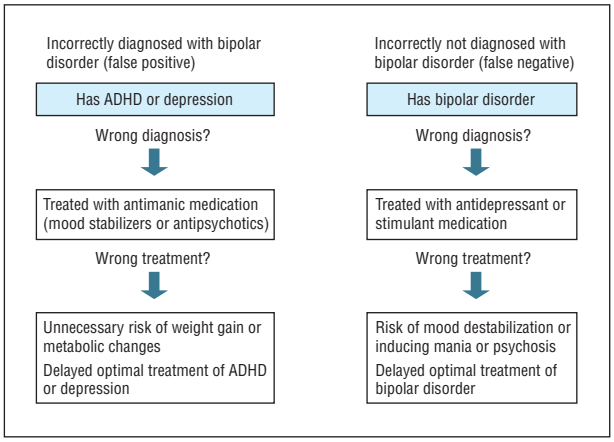

Figure. Risks of false-positive and false-negative diagnoses of bipolar disorder. ADHD indicates attention-deficit/hyperactivity disorder.

As the pendulum struggles to regain its neutral position, parents, clinicians, teachers, and children themselves are seeking guidance with regard to the reliability and validity of diagnosing pediatric BD and with regard to how this diagnosis effects treatment decisions. Although prescriptions for mood-stabilizing medications for children have increased dramatically,[8] unfortunately the majority of adolescents with BD do not access treatment for their illness, despite the fact that, even in unselected epidemiologic samples, BD is a severely impairing illness.[9] Similarly, although concerns have been raised regarding the increased use of the BD diagnosis among youth,[10] the number of youth who receive diagnoses of BD in clinical settings falls far short of what would be expected based on the prevalence of BD in the population.[11]

The decision of whether or not to diagnose pediatric BD presents a challenging dialectic. Withholding of the diagnosis and treatment of BD from patients who truly have BD could exacerbate the substantial risks associated with this illness, including suicidality, legal problems, development of substance abuse, and marked functional impairment.[12-15] However, an unnecessary diagnosis or unnecessary exposure to psychotropic medications arguably presents equally unpalatable risks (**Figure**).[16] As such, the focus of this review is not on what the prevalence of BD ought to be (or whether BD is "overdiagnosed" or "underdiagnosed" or treated at the population level) but rather on summarizing recent literature that can inform considerations of the risks and benefits of diagnosing and treating (or not diagnosing or treating) individual children and adolescents with BD.

DIAGNOSIS

Symptoms

The *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) (*DSM-IV-TR*) symptom criteria for BD are the same for children, adolescents, and adults. However, as will be discussed, there are developmental differences in how symptoms are manifested among youth. Symptoms of mania are the hallmark of BD. Either elation/euphoria or irritability are required, and other symptoms are listed in **Table 1**. Because silly, rambunctious, and/or impulsive behavior often characterizes childhood and adolescence, it is important, particularly for diagnosing hypomania, to be able to distinguish normal childhood behavior from psychiatric symptoms. In order to be considered a pathological symptom, elation must be inappropriate to context and associated with a change in functioning, and the same applies for grandiosity.[17] Other symptoms also require nuanced inquiry. For example, it is important to distinguish insomnia from reduced need for sleep. The former is associated with frustrated attempts to fall asleep and difficulty rousing, whereas the latter is often characterized by early waking and lack of increased fatigue or somnolence despite substantially fewer hours of sleep. Detailed case-based descriptions of how children with mania differ from healthy children and from adults with mania are available.[17] Because irritability is a symptom common to multiple psychiatric disorders (eg, major depressive disorder, generalized anxiety disorder, and oppositional defiant disorder [ODD]), one approach that has been taken to optimize diagnostic specificity is to require the criterion of either elation or grandiosity.[18] However *DSM-IV-TR* does not necessitate this, and several studies have

Table 1. Diagnostic Criteria for Mania and Hypomania From the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision)[a]

Symptoms and Disorders
Elation or euphoria (with or without irritability) in addition to 3 of the 7 following symptoms; or irritability in addition to 4 of the 7 following symptoms[b]
1. Inflated self-esteem or grandiosity
2. Decreased need for sleep (eg, feels rested after only 3 h of sleep)
3. More talkative than usual or pressure to keep talking
4. Flight of ideas or subjective experience that thoughts are racing
5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
6. Increase in goal-directed activity (socially, at work or school, or sexually) or psychomotor agitation
7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
Mania
A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 wk (or any duration if hospitalization is necessary).
The mood disturbance must be sufficiently severe to cause marked functional impairment (eg, social or academic) or to necessitate hospitalization to prevent harm to self or others, or there must be associated psychotic features (eg, grossly disorganized thinking or hallucinations and/or delusions).
Hypomania
A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 d, that is clearly different from the usual nondepressed mood.
The mood disturbance must be associated with an unequivocal and uncharacteristic change in functioning, and the mood symptoms and change in functioning must be observable by others.
Marked impairment, need for hospitalization, and psychotic features preclude a diagnosis of hypomania.

[a] Mania or hypomania deemed to be caused by the direct physiological effects of a substance (eg, illicit drugs or medications), a medical condition (eg, hyperthyroidism), or somatic treatments (such as electroconvulsive therapy or light therapy) precludes a diagnosis of bipolar disorder.
[b] The other symptoms must co-occur with euphoria and/or irritability.

questioned the necessity of elation/euphoria.[19,20] Findings from the Course and Outcome of Bipolar Illness among Youth (COBY) study, for example, suggest that, in about 80% of the cases, both elation and irritability are present during the most severe symptomatic episodes among youth with BD and that, with few exceptions, the course, comorbidity, and family psychiatric history of youth with solely irritable mania/hypomania do not substantially differ from that of youth with solely elation or youth with both elation and irritability.[20]

Episodes

The diagnosis of bipolar I disorder (BD-I) is given when a patient has had at least 1 clear manic or mixed manic (mania concurrent with depression) episode in his or her lifetime. An episode is a period of time during which symptoms comprise a noticeable change from that person's baseline, whether that baseline is one of health or one that is affected by symptoms of a co-occurring illness such as anxiety or attention-deficit/hyperactivity disorder (ADHD). A diagnosis of bipolar II disorder (BD-II) is given when a patient has had at least 1 hypomanic episode (Table 1) and 1 major depressive episode in his or her lifetime. Other BD-spectrum diagnoses are less clearly defined and include cyclothymia (numerous, brief depressive and hypomanic intervals without prolonged recovery for ≥1 year) and BD not otherwise specified (BD-NOS). The American Academy of Child and Adolescent Psychiatry (AACAP) practice parameter advises that unaltered *DSM-IV-TR* criteria should be used with children and adolescents, and this parameter allows for the use of BD-I, BD-II, or BD-NOS among children and adolescents.[21] The COBY study offered (and prospectively validated) an operationalized definition of BD-NOS as requiring that symptoms must be evident for a minimum of 4 hours in a day on a minimum of 4 separate lifetime days in order to be classified as BD-NOS.[22]

Assessment Strategies

Previous publications entirely dedicated to describing the assessment of BD in children and adolescents are available,[23] and the following section focuses on several key elements. Recent approaches to assessment have highlighted ways to incorporate such factors as family history of BD, expected prevalence within a given setting, multiple sources of information (eg, child, parent, and teacher), and information gleaned from questionnaires, checklists, and diagnostic interviews.[24] Comprehensive diagnostic interviews offer several advantages. These interviews allow detailed probing of symptoms to ensure that they reach a clinical significance threshold, take into consideration other sources of psychopathology when evaluating symptoms, and generally incorporate some degree of clinical judgment. However, such interviews are relatively time-consuming and may not be feasible in many settings. Briefer checklists or screening instruments that do not require an interviewer offer their own advantages and disadvantages. For example, the Child Behavior Checklist offers norms and is a time-efficient way of determining overall psychiatric burden. However, despite some initial promising findings, it does not appear that this instrument offers good psychometric properties in terms of accurately classifying presence vs absence of BD.[25]

Symptoms that are relatively specific to BD include pathological elation, decreased need for sleep, and hypersexuality.[24] Increased energy and distractibility have the greatest sensitivity to BD; however, these symptoms may yield many false positives if efforts are not made to ensure that the symptoms co-occur with mood changes and comprise a distinct change from baseline (whether baseline is healthy or includes ADHD). The AACAP practice parameter provides 4 recommendations as part of the minimal standard of assessment: (1) include screening questions for BD during psychiatric assessments of children and adolescents; (2) use unmodified *DSM-IV-TR* criteria, including duration, when diagnosing mania or hypomania in youth; (3) if BD is suspected, evaluate for suicidality, comorbidities (including substance abuse and medical problems), and evaluate for psychosocial stressors; and (4) be cautious when diagnosing preschoolers with BD, owing to uncertain validity.

DIFFERENTIAL DIAGNOSIS: BD vs OTHER PSYCHIATRIC CONDITIONS

Table 2 highlights several symptoms of mania that may also be associated with ADHD and/or ODD. These disorders have some overlapping symptoms and, therefore, may be confused with BD, but they also frequently co-occur with BD.

BD vs ADHD

Methods for distinguishing BD from the more prevalent ADHD have been described previously. The 2 primary distinguishing features of BD are (1) the discrete episodes of BD and (2) the distinguishing symptoms of mania.[24] Different approaches have been taken to delineate BD (with or without ADHD) from ADHD. One approach is to "double count" symptoms. That is, if a child is highly distractible and hyperactive, then these 2 symptoms would be automatically counted toward a diagnosis of ADHD as well as toward a manic episode (ie, BD). Proponents of this strategy argue that it is impossible to reliably attribute the "cause" of 1 symptom to 1 disorder over another. A more parsimonious approach is to endeavor to determine whether any overlapping symptoms are clearly exacerbated in the context of mood disturbance. That is, if ADHD is present, overlapping symptoms such as distractibility or hyperactivity are only counted toward a diagnosis of mania or hypomania if they intensify concurrently with episodes of elation or irritability.

Whether a given symptom should count toward a diagnosis of mania depends on the individual child. Take, for example, a child who has clear-cut symptoms of ADHD, who usually has significant insomnia, and who is consistently silly and somewhat defiant. If this child on a given day is hyperactive, silly, distractible, and defiant with his teacher, that would not comprise a distinct mood-related change from baseline behavior. But take, for example, a child who does not have ADHD, who

Table 2. Differential Diagnosis of Manic Symptoms

Symptom	Bipolar Mania/Hypomania	ADHD	ODD
Elation	Episodic, prolonged, pathological (inappropriate to context or uncharacteristic), associated with change in functioning, "travels" with ≥3 other manic symptoms	If present, not clearly episodic or pathological	If present, not clearly episodic or pathological
Irritability	Episodic, prolonged, pathological, associated with change in functioning, "travels" with ≥4 other manic symptoms	Can be an associated feature, related to stimulant rebound, or due to a comorbid illness (eg, ODD)	Diagnostic criterion, lacks distinct prolonged episodes, does not "travel" with other manic symptoms
Sleep	Reduced need for sleep (ie, significantly less sleep than usual without increased daytime fatigue or somnolence); change must be mood-related	Insomnia, (ie, difficulty falling asleep), can be an associated feature or associated with stimulants, but need for sleep is unchanged	Not a symptom or common characteristic, may defy bedtime rules or routine
Grandiosity	Distinct uncharacteristic increase in confidence or self-importance; change must be mood-related	Not a symptom or common characteristic	Defiance toward authority figures is common but not necessarily mood-related
Hyperactivity and distractibility	Episodic; if comorbid ADHD is diagnosed, then distinctly "worse than usual"; change must be mood-related	Diagnostic criteria, nonepisodic	Not prominent or episodic

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder.

is consistently agreeable and well-behaved, and who is generally subdued with regard to emotional expression. If this child suddenly presents as uncharacteristically giddy and elated, hyperactive, distractible, and defiant for several days, then it becomes important to consider carefully whether these may be symptoms of hypomania or mania.

BD vs Other Diagnoses

The same strategy can be applied to diagnoses of generalized anxiety disorder or ODD, other comorbidities that include more chronic symptoms that overlap with manic symptoms. For example, a child with generalized anxiety disorder may experience chronic irritability, impaired concentration, and restlessness. Therefore, to count toward a diagnosis of BD, there would need to be a distinct exacerbation in these symptoms, as well as 2 or more additional symptoms of mania. To differentiate mania from substance intoxication or withdrawal (ie, substance-induced), one would have to rely on a thorough evaluation of the temporal course of both problem areas, and obtaining urine drug screening can improve the reliability of clinical interviews or questionnaires about substance use.[26] It is important to note that the association may be bidirectional: substance use can increase because of the risk-taking behaviors associated with manic symptoms, but substance use can also precipitate manic symptoms. Moreover, epidemiologic data suggest that most adults with substance-induced mania also have manic episodes that are not precipitated by substances, therefore qualifying for a diagnosis of BD.[27]

BD vs Major Depressive Disorder

Major depressive disorder poses specific challenges in terms of differential diagnosis because, unlike the other conditions already described, and similar to BD, it is generally an episodic disorder. Moreover, despite the fact that manic symptoms are the distinguishing diagnostic feature of BD, depressive symptoms comprise the main source of illness burden for most youth with BD.[28] The key to the differential diagnosis of BD vs major depressive disorder is to screen for episodes of mania or hypomania in addition to depression, as already described. Some symptoms of hypomania may be desirable to patients and parents, such as increased productivity, energy, and confidence. Therefore, it is important to determine whether these symptoms indeed comprise a "back to normal" state or whether they are actually a "better than normal" state for youth with recent depression. Mixed episodes are common in pediatric BD, so clinicians should be alert to the possibility that patients may experience mania or hypomania concurrently with a depressive episode. For example, on the same day, such patients may experience depressive symptoms in the morning and manic symptoms in the evening, but they may also experience concurrent symptoms of depression and mania. Mixed episodes are especially concerning because of their strong association with suicidality.[12]

Irritability and Differential Diagnosis

One symptom that generates substantial diagnostic uncertainty is irritability. The *DSM-IV-TR* indicates that irritability is a core symptom of mania and hypomania. Provided that 4 or more other contiguous symptoms of mania are present, an episode of increased irritability, even in the absence of elation, is sufficient to warrant a diagnosis of mania or hypomania. Irritability can pose diagnostic challenges among youth because it is also a diagnostic criterion for major depressive episodes, generalized anxiety disorder, and ODD. Irritability also frequently accompanies pervasive developmental disorders, conduct disorder, ADHD, substance use disorders, and obsessive-compulsive disorder. As such, it is important to deter-

mine whether mania or hypomania is a likely factor in explaining irritability or whether irritability is better explained in a given patient by other forms of psychopathology. It is crucial for the purpose of differential diagnosis to clarify whether there are episodes of irritability, or episodic unequivocal exacerbations in baseline irritability, that are associated temporally with other manic symptoms. Irritable mania/hypomania in the absence of elation was a relatively uncommon scenario in the COBY study; however, it is important to note that the 10% of patients with this presentation had demographic, clinical, and familial characteristics that were highly comparable to those of subjects whose manic or hypomanic episodes included elation.[20] In summary, the keys to interpreting irritability with respect to a possible BD diagnosis are the determination of episodicity and of temporal contiguity with a sufficient number of other symptoms of mania.

The concept of chronic, severe, nonepisodic irritability is central to a differential diagnosis and has led to the consideration of a new proposed diagnosis for the upcoming *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*): temper dysregulation disorder with dysphoria, more recently described as disruptive mood dysregulation disorder, based on research regarding severe mood dysregulation (SMD; severe, nonepisodic irritability with hyperarousal symptoms).[29] However, children with SMD (of whom 86% have ADHD, 85% have ODD, and 75% have both)[29] have different symptoms, comorbidities, family histories, and neuropsychological and neurobiological findings from children with BD.[29-33] By definition, these children do not have distinct hypomanic/manic episodes. Use of a BD diagnosis in these cases is often of questionable value because of the cross-sectional differences already noted and because SMD-like phenotypes do not appear to be particularly predictive of future BD.[29] The question of whether or not disruptive mood dysregulation disorder with dysphoria is a phenotype that merits inclusion in the *DSM-5* is a divisive one, and concerns have been raised about the risks of adding this new diagnosis with the limited current information on the course and treatment of SMD. These risks include conflating a symptom (irritability) with a syndrome, lack of vigilance for other causes of irritability that could inform individualized treatment, and potentially excessive use of mood-stabilizing medication.[34]

WHEN TO REFER

By definition, mania is not a subtle condition. Any child or adolescent presenting with a distinct change in mood, thought, and behavior consistent with a manic episode (ie, high severity and substantial impairment) should be referred for psychiatric evaluation. However, hypomania can be more subtle, especially if functioning improves during hypomania or if the child presents with symptoms that are desirable to parents or teachers (eg, increased productivity or increased sociability in an otherwise anxious child). In such cases, a specialist's opinion may clarify whether symptoms are normative or pathological. Questions about whether BD is present are especially clinically relevant when the decision to prescribe or not prescribe medications is taken (Figure), and this decision point is often an appropriate one for referral if there are concerns about the presence of BD spectrum conditions.

Safety concerns should also inform referral decisions. Depending on the experience and comfort level of the pediatrician, youth who present with clinically significant suicidal ideation, self-injury, or suicide attempts should also be referred. Although not unique to BD, concerns about psychosis (delusions, hallucinations, and/or incoherent thought process) or severe aggression often indicate the need for referral.

As will be indicated, offspring of parents with BD are at increased risk for having the disorder themselves. Pharmacological treatment for this population invokes unique risk-benefit considerations because these youth may (or may not) be especially susceptible to treatment-emergent mania when exposed to antidepressant or stimulant medication. Whether for the purpose of guidance regarding treatment or to clarify diagnoses, pediatricians may wish to keep a lower threshold for referral of youth with a family history of BD.

PREVALENCE

The prevalence of BD among youth is highly dependent on how diagnoses are determined. Moreno and colleagues[10] reported a 40-fold increase in visits for BD among youth between 1994-1995 and 2002-2003. However, diagnoses were determined via billing codes, which are of uncertain reliability and which may be influenced by external factors such as "up-coding" in order to ensure that children receive sufficient mental health services. In contrast, contemporaneous epidemiologic studies based on representative, unselected population-based samples have not demonstrated such marked variability. The recent National Comorbidity Survey Replication–Adolescent Supplement found that approximately 1% of adolescents have strictly defined BD-I, that 6.2% have impairing symptoms of bipolar spectrum disorders, and that the prevalence of BD-I or BD-II doubles between ages 13 to 14 years and 17 to 18 years.[11] Previous epidemiologic data from nearly 20 years prior indicated a combined prevalence of 5.7% for full-threshold and subthreshold BD among adolescents.[35] A recent meta-analysis[36] of epidemiological studies of pediatric BD included 16 222 youth (7-21 years of age) from 12 studies (6 studies from the United States and 6 international studies) conducted between 1985 and 2007. The mean prevalence of bipolar spectrum disorders was 1.8% (95% CI, 1.1%-3.0%), and the mean prevalence of BD-I was 1.2% (95% CI, 0.7%-1.9%). There was neither evidence of higher rates of BD in studies conducted in the United States nor evidence of increasing prevalence over time.

COURSE AND OUTCOME

Information regarding the clinical course of adolescent BD was until recently limited to relatively small studies. However, larger studies have yielded crucial longitudinal data.[28,37,38] The course of adolescent BD following first hospitalization for mania is characterized by both recovery and recurrence.[38] Geller and colleagues[37] recently pub-

lished 8-year follow-up data regarding a cohort of prepubertal children and early adolescents with BD-I, and they found that subjects spent 60% of the time symptomatic (either in full-threshold mood episodes or with clinically significant subthreshold symptoms) and continue experiencing mood episodes in young adulthood. The COBY study, the largest of its kind (with 413 youth 7-17 years of age), suggests that, in many ways, the longitudinal course of adolescent BD-I mirrors that of adults: 90% experience pathological elation, most experience recovery and recurrences, depression is more often problematic than is mania, and subsyndromal symptoms predominate.[28] However, compared with adults with BD, youth with BD spend more time with syndromal and clinically significant subsyndromal symptoms (59% vs 47%), are more likely to simultaneously experience mixed symptoms of depression and mania, and have far more changes in symptomatic status.[39] Across subtypes of BD in the COBY study (including types I, II, and NOS), this illness is characterized by recovery (8 contiguous weeks of remission) and recurrences.[28] During 4 years of prospective follow-up, participants spent 16.6% (2 mo/y) of the time in full-threshold mood episodes and 41.8% (5 mo/y) of the time experiencing subthreshold but clinically significant mood symptoms. Changes in mood polarity were common, and 51% had 5 or more annual polarity changes. Finally, the COBY study provides validation for the operationalized definition of BD-NOS. Nearly 40% of children and adolescents with BD-NOS "convert" to BD-I or BD-II during prospective follow-up, thus demonstrating that, in addition to significant episodicity and symptomatic impairment, the COBY-operationalized diagnosis of BD-NOS frequently forebodes more classical BD-I and BD-II.[22,28]

SUICIDALITY

Similar to BD among adults, BD among youth is a potent risk factor for completed suicide.[40-42] Whether in community or clinical samples, approximately 3 in 4 youth with BD endorse lifetime suicidal ideation.[22,35] The lifetime prevalence of suicide attempts among youth with BD varies across studies but appears to be between 20% and 50%.[12,43,44] Epidemiologic findings from the United States indicate that the lifetime prevalence of suicide attempts among adolescents with BD spectrum disorders (44%) was double that of adolescents with major depressive disorder (22%), which was, in turn, far greater than that of healthy adolescents (1%).[35] Moreover, adolescents with BD in this sample make more attempts, make more lethal attempts, and are younger at the time of their first attempt. Interestingly, rates of suicide attempts do not appear to differ significantly across BD subtypes.[12]

COMORBIDITY

Psychiatric Comorbidity

Comorbidity is the norm in BD, and the majority of adults with BD have 2 or more other psychiatric conditions, most commonly anxiety disorders and substance use disorders. A meta-analysis of children and adolescents with BD found that ADHD was the most common comorbidity (62% of children and adolescents), followed by ODD (53%), anxiety disorders (27%), conduct disorder (19%), and substance use disorders (12%).[45] Comorbidities such as eating disorders and pervasive developmental disorders occur less commonly. Attention-deficit/hyperactivity disorder appears to be more common among prepubertal children with BD, whereas panic disorder, conduct disorder, and substance use disorders appear to be more common among adolescents with BD.[46]

Studies suggest that comorbidities may exacerbate the course and outcome of BD. For example, comorbid ADHD has consistently been associated with decreased response to mood-stabilizing medications, and this effect is especially pronounced among adolescents (vs children) and among those with BD-I.[47] Comorbid anxiety disorders have been associated with greater depression severity and with reduced efficacy of antimanic treatment.[48,49] Finally, comorbid substance use disorders are associated with concerning outcomes such as suicide attempts, legal problems, and teenage pregnancy and abortion.[50]

Medical Comorbidity

Medical comorbidity is a major concern in BD. Cardiovascular disease is both exceedingly prevalent and premature among adults with BD, leading to excessive cardiovascular mortality.[51] Although psychiatric medications are associated with metabolic disturbances, the association between BD and cardiovascular disease was observed prior to the advent of modern medications.[2] Metabolic syndrome components (dyslipidemia, hyperglycemia, hypertension, and obesity) are also exceedingly prevalent among adults with BD and are associated with a more pernicious course of illness, including increased functional impairment, suicide attempts, and manic and depressive episodes.[52] Recent findings suggest that, despite their young age, children and adolescents with BD may also incur increased risk of medical comorbidities. Between 28% and 36% of youth with BD have multiple medical conditions, whereas this is true for only 8% of youth with other psychiatric disorders combined.[53,54] Obesity, hypertension, and diabetes are exceedingly prevalent and often precede BD, and the use of specialty cardiology services is doubled. Correlates of overweight/obesity among youth with BD include history of physical abuse, presence of comorbid substance use disorders, psychiatric hospitalizations, and exposure to multiple classes of mood-stabilizing medication.[55] Migraine, asthma, and neurological conditions such as epilepsy may also co-occur disproportionately with BD.[53,54]

HIGH-RISK POPULATIONS

Familial High Risk

Bipolar disorder is among the most highly familial of psychiatric illnesses. Multiple studies have compared the prevalence of psychiatric disorders among the offspring of parents with vs without BD, and these studies consistently demonstrate an increased risk of mood disorders among high-risk offspring.[56,57] Recent findings from the large-scale Pittsburgh Bipolar Offspring Study[58] indicate that offspring of parents with BD (N=388) have approximately a

13-fold increased risk compared with control offspring (N = 251) of having bipolar spectrum disorders (BD-I, BD-II, or BD-NOS) (10.6% vs 0.8%). Although these offspring also incur approximately double the risk for anxiety disorders, depressive disorders, and disruptive behavior disorders, the magnitude of the association is greatest for BD. Nonetheless, approximately 90% of school-aged offspring of parents with BD do not have BD, raising the question of who among these offspring is at an especially increased risk. Risk factors for BD among school-aged offspring may include antecedent anxiety disorders and disruptive behavior disorders, and the risk of BD may be increased if both parents have BD.[59]

Clinical High Risk

Several studies suggest that prenatal and perinatal risk factors, as well as stressful life events, may contribute to the risk for BD, albeit the data are more tenuous than the data relating to schizophrenia and major depression, respectively.[60,61] Several psychiatric disorders may commonly precede the onset of BD. The incidence of BD among clinically ascertained children and adolescents with major depressive disorder appears to be approximately 15% to 20% within 3 to 6 years, with higher rates generally observed among inpatient samples and in studies with longer follow-up. Risk factors for BD among adolescents with depression include the rapid onset of depression, familial loading of mood disorders, the presence of psychotic features, and the presence of treatment-emergent mania.[62] Epidemiologic data suggest that anxiety disorders and oppositional defiant/conduct disorders may also be strongly predictive of subsequent BD, although, in these cases, clinical risk factors for conversion to BD have yet to be identified.[63] Perhaps surprisingly, it is not clear that ADHD is a risk factor for BD in the absence of other comorbidities.[63,64]

NEUROBIOLOGY

Neuroimaging and Neuropsychology

Structural and functional neuroimaging studies of pediatric BD generally converge with adult studies in implicating frontolimbic structures.[65] However, the most replicated finding among youth vs healthy controls (and not consistently observed among adults) is that of smaller amygdala size.[66] Preliminary spectroscopy studies suggest that prefrontal cortical concentrations of *N*-acetylaspartate may be reduced.[67,68] Preliminary findings also suggest white matter pathology and impaired task-independent frontotemporal functional connectivity.[69,70] There is increasing evidence of neuropsychological and functional neuroanatomical differences among children with BD vs controls, subjects with ADHD, and subjects with SMD, including neural activation in response to images of faces of various emotional valences and during various tasks (including those invoking motor inhibition).[71] A recent meta-analysis[72] of neurocognitive performance in pediatric BD indicated multiple putative problematic domains, including verbal, visual, and working memory, attention, and executive functioning.

Peripheral Biomarkers

Findings from adults with BD suggest that peripheral (eg, serum and plasma) biomarkers, particularly brain-derived neurotrophic factor (BDNF) and markers of inflammation and oxidative stress, may be informative in BD.[73] However, few studies have examined peripheral biomarkers as they relate to pediatric BD. One study[74] found significantly decreased messenger RNA levels of lymphocyte-derived BDNF, which normalized with treatment, and decreased protein BDNF levels in platelets among unmedicated children and adolescents who had manic or mixed episodes compared with controls. Another study[75] found that a proinflammatory gene expression signature was observed among 88% of offspring (adolescents and young adults whose parents had BD) with mood disorders, 45% of offspring without mood disorder, and 19% of control adolescents. Preliminary findings from 30 adolescents in the COBY study suggest that levels of high-sensitivity C-reactive protein may be elevated, that high-sensitivity C-reactive protein levels are associated with severity of manic symptoms, and that levels of BDNF may be inversely associated with those of inflammatory markers.[76]

Genetics

In contrast to the robust evidence that BD, including pediatric BD, is highly familial, relatively few molecular genetic studies have been conducted on pediatric BD.[77] Although linkage disequilibrium of the BDNF val66met, glutamate decarboxylase 1, and dopamine transporter polymorphisms have been reported, replicated findings are still lacking.[77,78]

TREATMENT

Pharmacological Treatment

The majority of rigorous randomized double-blind placebo-controlled trials for pediatric BD have focused on acute mania. Relatively little is known regarding the pharmacological treatment of the depressive phase of BD,[79] regarding the maintenance and/or continuation of treatment,[80] or regarding other BD subtypes. Differences between adolescents and adults have been highlighted in a recent meta-analysis[81] of acute mania trials, which included 5 trials (with 1140 participants) evaluating second-generation antipsychotics (SGAs; aripiprazole, olanzapine, quetiapine fumarate, risperidone, and ziprasidone hydrochloride) and 4 trials (with 469 participants) evaluating non-SGA mood stabilizers among youth. The SGAs appear to be more efficacious than the non-SGA mood stabilizers (divalproex sodium, lithium carbonate, and oxcarbazepine) among youth (effect size, 0.65 vs 0.20), whereas these agents are equally effective among adults (effect size, 0.48 vs 0.46). The SGAs are associated with greater weight gain, greater somnolence, and less akathisia among youth than among adults. Recent large-scale randomized controlled trials of oxcarbazepine and divalproex for pediatric mania have been negative,[82] and a trial of topiramate was discontinued prematurely be-

cause of lack of efficacy for adult mania. Recent pharmacotherapy reviews since the AACAP treatment guidelines were published emphasize the role of SGAs as first-line treatments for mania, in part because of their rapid onset of action.[83] Augmentation and combination treatment may involve various multimedication strategies, such as SGAs combined with lithium or divalproex.[84] Nonadherence is common and appears to be associated with poorer outcomes.[38] Significant concerns regarding the adverse metabolic consequences of these medications exist, and preliminary preventive strategies have been articulated.[85,86] Metabolic monitoring guidelines for SGAs provide a strategy for early identification of adverse metabolic consequences, but, unfortunately, adherence with these guidelines is especially poor among youth. In addition to metabolic tolerability of mood-stabilizing medications, there are concerns about the potential for treatment-emergent mania or suicide-related behaviors among youth with BD who are treated with antidepressants or stimulants.[87] For children with comorbid ADHD and BD, AACAP treatment guidelines recommend treating first with mood-stabilizing medication and only subsequently pharmacologically treating ADHD judiciously if there are residual clinically impairing symptoms of ADHD. Indeed, controlled studies suggest that this is an effective and well-tolerated approach.[88] Similarly, it is advisable to first stabilize mood prior to initiating treatment with a selective serotonin reuptake inhibitor for the depressive phase of BD or for comorbid anxiety.[84] Previous publications[21,83,84] provide detailed approaches to selecting, evaluating, and monitoring psychotropic medications among youth with BD.

Psychosocial Treatment

Several psychosocial treatments, adjunctive to pharmacotherapy, have been examined for pediatric BD. Approaches shared by these treatments include psychoeducation to increase acceptance of the diagnosis and adherence to medications, improving the ability to manage stress, bolstering the protective effects of the family, and enhancing functioning. Family-focused therapy has been most rigorously examined for the treatment of adolescents with BD. It focuses on reducing "expressed emotion," comprising a triad of familial criticism, hostility, and emotional overinvolvement, and is associated primarily with reduced burden of depression symptoms.[89] In an open trial of dialectical behavior therapy, which primarily targets emotion regulation and communication skills, participants demonstrated significant improvements in depressive symptoms, emotion dysregulation, suicidality, and nonsuicidal self-injury.[90] Several other approaches, including interpersonal and social rhythm therapy (focusing on social and circadian rhythms), cognitive behavioral therapy, and multifamily group psychoeducation appear promising as well.[91-93]

SUMMARY

The past 15 years have seen substantial and rapid progress regarding the diagnosis, course, and treatment of pediatric BD. Adhering to *DSM-IV-TR* diagnostic criteria, taking comorbid illnesses into account when evaluating symptoms, and requiring episodes can serve to optimize diagnostic accuracy. When defined with similar criteria, pediatric BD bears much resemblance to adult BD, particularly youth-onset adult BD. The differences that do exist (ie, more mixed episodes, more symptomatic status changes, greater percentage of time with impairing symptoms, and lesser response to non-SGA mood stabilizers) may contribute to the complexity of diagnosing pediatric BD. Diagnosing BD does invoke mood-stabilizing medications as the foundation of treatment, which underscores the importance of differentiating BD from ADHD, major depressive disorder, and cases in which chronic irritability in the absence of hypomanic or manic episodes is salient. Adjunctive psychosocial interventions are also important and are increasingly supported by empirical data. Biomarker validation is urgently needed. At present, differential diagnosis is challenging and requires rigorous and often time-consuming interviews that remain at least to some degree constrained by the subjective nature of current assessment strategies. Prevention, of BD or of accumulation of psychiatric and medical comorbidities, is a lofty but worthwhile challenge. Given the deleterious effect of BD on psychological and emotional development, even delaying onset or progression of BD and its comorbidities would be a great success.

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