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Prevalence, Clinical Presentation, and Differential Diagnosis of Pediatric Bipolar Disorder

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Abstract

Background—Over the past 20 years, the evidence regarding pediatric bipolar disorder (BP) has increased substantially. As a result, recent concerns have focused primarily on prevalence and differential diagnosis.

Method—Selective review of the literature.

Results—BP as defined by rigorously applying diagnostic criteria has been observed among children and especially adolescents in numerous countries. In contrast to increasing diagnoses in clinical settings, prevalence in epidemiologic studies has not recently changed. BP-spectrum conditions among youth are highly impairing and confer high risk for conversion to BP-I and BP-II. Compared to adults, youth with BP have more mixed symptoms, more changes in mood polarity, are more often symptomatic and seem to have worse prognosis. The course, clinical characteristics, and comorbidities of BP among children and adolescents are in many ways otherwise similar to those of adults with BP. Nonetheless, many youth with BP receive no treatment and most do not receive BP-specific treatment.

Conclusion—Despite increased evidence supporting the validity of pediatric BP, discrepancies between clinical and epidemiologic findings suggest that diagnostic misapplication may be common. Simultaneously, low rates of treatment of youth with BP suggest that withholding of BP diagnoses may also be common. Clinicians should apply diagnostic criteria rigorously in order to optimize diagnostic accuracy and ensure appropriate treatment.

BACKGROUND

Pediatric bipolar disorder: unicorn or ubiquitous?

The concept of children and adolescents suffering from bipolar disorder (BP) is not a new one. However, whereas case descriptions of pediatric mania have been available for nearly a century,^(1, 2) it is only within approximately the last two decades that rigorous research on this topic has been conducted.¹ Questions have been raised as to reasons for increased

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¹For the purpose of this review, unless otherwise indicated, the term BP encompasses all subtypes (I, II, cyclothymia, not-otherwise-specified [NOS]), and the term pediatric refers to children and/or adolescents < 19 years of age.

attention to pediatric BP, and simplistic conspiracy theories abound: an American invention, a fabrication born of Big Pharma influence, self-serving researchers seeking to create a niche.(3) Nonetheless, arguments against the existence of pediatric BP have waned in recent years, and one hopes that the quality of the research cited in this and other articles in this edition of the Journal had a salutary effect.

More recently, prevalence and diagnostic accuracy have become the primary controversies. Prior to the last twenty years, childhood mania was considered exceedingly rare, and there are still settings in which this is the case.(4) This stood in contrast to findings that up to two-thirds of adults with BP report child- or adolescent-onset of impairing mood symptoms(5–7), and approximately 10% report childhood (<13 years of age) onset of mania or significant manic symptoms.(5, 7) An influential 1995 paper by Wozniak and colleagues 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 BP was being overlooked.(8) By many accounts, concerns regarding missed diagnoses of BP and under-estimates of prevalence have been replaced with concerns regarding misdiagnoses of BP and over-estimates of prevalence. These concerns are in part owing related to the possible over-use of mood-stabilizing medications. Although prescriptions for mood-stabilizing medications for children have indeed increased dramatically(9), unfortunately the majority of adolescents with BP do not access treatment for their illness.(10) Similarly, although concerns have been raised regarding increased use of the BP diagnosis among youth(11), the number of youth who receive diagnoses of BP in clinical settings falls far short of what would be expected based on the population prevalence of BP.(12)

Pediatric BP diagnosis presents a challenging dialectic. Withholding of diagnoses and treatment of BP from patients who truly have BP presents substantial morbid risks, including suicidality and marked functional impairment.(13, 14) However, unnecessary diagnoses and unnecessary exposure to mood-stabilizing medications risk unduly invoking concerns about a life-long illness, pre-empting psychosocial treatments, delayed and/or suboptimal pharmacological treatment of other psychiatric conditions such as major depressive disorder (MDD) or attention-deficit hyperactivity disorder (ADHD), and significant physical risks. (15) As such, one focus of this review is on summarizing recent literature that can inform considerations regarding accurate diagnoses of individual children and adolescents with and without BP. Another focus of this review is on highlighting various demographic, clinical, and familial characteristics that are salient to the diagnosis, monitoring, and treatment of youth with BP.

PREVALENCE

The prevalence of BP among youth varies depending on how and where the sample is ascertained and the methods used to diagnose BP. Moreno and colleagues reported a 40-fold increase in visits for BP among youth in managed care between 1994–1995 and 2002–2003. (11) 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. That is, clinicians may diagnose pediatric BP because treatment for this diagnosis is often subject to fewer

constraints within managed care organizations, whereas diagnoses such as conduct disorder often have comparatively less allocation of resources or have low expenditure limits relative to BP. Moreover, the estimated change was likely inflated by counting multiple visits by the same patients, and frequent use of health services is common in BD.(16) In addition, the baseline proportion of psychiatric visits for pediatric BD in 1994–5 was 0.42%, meaning that fewer than 1 in 200 children and adolescents receiving psychiatric care carried a diagnosis of BP. Over a similar time period, rates of hospital discharges of children with a primary diagnosis of BD increased from 1.3 per 10,000 in 1996 to 7.3 per 10,000 in 2004. (17) Therefore, these large relative increases may be accentuated by what some would describe as an exceedingly low initial base rate, particularly in light of the fact that child- or adolescent-onset is common among adults with BP.(5–7)

The recent National Comorbidity Survey Replication-Adolescent Supplement (NCS-A) found that approximately 1% of adolescents have strictly defined BP-I and if subsyndromal symptoms of BP are included, the rates increase to approximately 6%.(18) The prevalence of BP-I or -II in the NCS-A doubled between ages 13–14 and 17–18 years of age.(12) Previous epidemiologic data from the Oregon Adolescent Depression Project (OADP) nearly 20 years prior indicated a combined prevalence of 5.7% for full- and sub-threshold BP (0.1% BP-I) among adolescents.(19) The 2002 Canadian Community Health Survey included a proxy for BP comprising episodes with sufficient symptoms and severity to be characterized as mania, but with the exception that duration of symptoms did not have to reach a full week.(20) Similar to the NCS-A finding of increasing prevalence with age, that study found a nearly two-fold increased prevalence between adolescence (15–18 years, 2.1%) and young adulthood (19–24 years, 3.8%). A recent meta-analysis of epidemiological studies of pediatric BP included 16,222 youths (7–21 years) from 12 studies (6 from U.S., 6 international) conducted between 1985 and 2007.(21) The mean prevalence of BP spectrum disorders was 1.8% (95% confidence interval [CI] 1.1%–3.0%), and the mean prevalence of BP-I was 1.2% (95% CI 0.7%–1.9%). Rates of BP spectrum disorders in studies of adolescents only (12 years and older) averaged 2.7% (95% CI 1.6–4.6%), higher than the overall prevalence in studies combining children and adolescents (1.8%, 95% CI 1.1–3.0%). Methodological differences may explain in part the variability in prevalence. For example, the OADP found only 0.1% prevalence of BP-I, contrasting other epidemiologic samples with rates of up to 2–3% of BP-I among adolescents.(22, 23) The OADP enrolled students from the high-school setting (vs. households) and did not interview parents, either of which may have contributed to the low BP-I prevalence, although other factors may also contribute. Perhaps surprisingly, the mean rate of BP in the 6 studies from the U.S.A. (1.7%) did not differ from the mean rate in the 6 studies from outside the U.S.A. (1.9%), this despite the fact that two U.S.A studies included BP-spectrum conditions other than BP-I and BP-II and therefore had the highest prevalence.(18, 19) Importantly, and in contrast to temporal trends in clinical diagnoses, there was no evidence of increasing prevalence of BP spectrum disorders over time. In summary, there has been stable prevalence over time of youth BP spectrum (particularly adolescent BP) as ascertained by rigorous semi-structured interviews in unselected epidemiologic sample, where there has been increased prevalence of youth BP in clinical settings. Explanations for this phenomenon include higher rates of treatment-seeking for pediatric BP over time, or insufficiently stringent application of diagnostic

criteria in clinical settings. At least in Canada and the United States the former explanation does not appear likely, as rates of treatment-seeking are concerningly low (discussed below). (10, 18, 20) Therefore, strategies for addressing false positive diagnoses of BP among youth likely need to be informed by a better understanding of what is driving the excess of clinical diagnoses. Similarly, strategies for addressing untreated BP in the community need to be informed by a better understanding of barriers to accurate diagnoses and appropriate treatment. Thus far, rigorous epidemiologic studies have focused on adolescents, such that little is known regarding the epidemiology pre-adolescent BP. Pharmaco-epidemiologic studies that have examined pre-adolescent BP have not employed standardized assessments. Although these studies can address billing diagnoses, they cannot address questions about the epidemiologic prevalence of rigorously defined BP. Given that the prevalence of BP was substantially higher among older adolescents vs. younger adolescents in the NCS-A, it is possible that the prevalence of BP among pre-adolescent children is even lower. However, definitive conclusions are deferred pending large epidemiologic studies of children.

CLINICAL PRESENTATION

Manic/hypomanic Symptoms

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) symptom criteria for BP are the same for children, adolescents, and adults. However, as discussed below there are developmental differences in the presentation of mania/hypomania in youth. Symptoms of mania are the hallmark of BP. Either elation/euphoria or irritability are required. Other symptoms include grandiosity, distractibility, decreased need for sleep, increased amount and/or rate of speech, increased rate of thoughts or rapid flow of expressed ideas, increased involvement in risky pleasurable activities, increased motoric activity or restlessness, and increased productivity or goal-directed activity. Because silly, rambunctious, and/or impulsive behavior often characterizes childhood and adolescence, it is important particularly for 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. Beyond these general considerations, it is central to accurate diagnoses to determine whether a given symptom is pathological for an individual child in a particular situation or setting. Take for example a child who has clear-cut 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 is consistently agreeable and well-behaved, and who is generally subdued with regard to expression of affect. If *this* child suddenly presents as hyperactive, silly, distractible, and defiant for several days, then it becomes important to determine whether these are symptoms of hypomania or are better explained by other factors (e.g., stress, substance use). In terms of sleep specifically, it is critical to parse insomnia from reduced need for sleep. The former is associated with difficulty rousing whereas the latter may in fact be characterized by early waking and intact alertness despite substantially fewer hours of sleep. Case-based descriptions of how children with mania differ from healthy children and from adults with

mania are available.(24) Because irritability is a symptom common to multiple psychiatric disorders (e.g. MDD, generalized anxiety disorder, oppositional defiant disorder), one approach that has been taken in order to optimize diagnostic specificity is to require elation or grandiosity.(25) However DSM-IV-TR does not necessitate this, and indeed studies from different research groups have questioned the necessity of elation/euphoria.(26, 27) Findings from the 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 BP youth and, with few exceptions, the course, comorbidity and family psychiatric history of youth with solely irritable mania/hypomania does not substantially differ from that of youth with solely elation or those with both elation and irritability.(27)

Manic/hypomanic Episodes

The diagnosis of bipolar I disorder (BP-I) is given when a patient has had at least one clear manic or mixed manic (mania concurrent with depression) episode in his/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 comorbid condition such as anxiety or attention-deficit hyperactivity disorder (ADHD). If the requirement for episodes were to be waived, this raises concerns about misdiagnosis, particularly among youth with ADHD which has multiple over-lapping symptoms. To count as a manic episode, symptoms must cause marked functional impairment and must last at least one week or necessitate hospitalization. A diagnosis of bipolar II disorder (BP-II) is given when a patient has had at least one hypomanic episode (similar symptoms, but absent major functional impairment, psychosis, or the need for hospitalization) and one major depressive episode in his/her lifetime. Other BP-spectrum diagnoses are less clearly defined, and include cyclothymia (numerous brief depressive and hypomanic intervals without prolonged recovery for 1 year) and BP not otherwise specified (BP-NOS; described below). There is substantial consensus that episodes are one of the hallmarks of BP and that phenotypes characterized by chronic irritability and ADHD, absent episodicity, often are not consistent with a diagnosis of BP.(28, 29)

Bipolar Disorder Not Otherwise Specified and Subthreshold Bipolar Disorder

Although BP is classically thought of in terms of the acute manic episodes of BP-I, there is convergent evidence from adolescent and adult epidemiologic studies that subthreshold BP or BP-NOS (henceforth BP-NOS) is a more common presentation.(18, 30) In addition, there is also convergent evidence from clinical and epidemiologic studies that BP-NOS is clinically impairing, and clinical studies suggest further that BP-NOS is familial and predictive of conversion to BP-I and BP-II.(18, 19, 30–33) However, in comparison with BP-I or –II, DSM-IV criteria for BP-NOS are less clearly defined. American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters advise as a clinical guideline that BP-NOS should be used to describe youth with brief hypo/manic episodes lasting hours to less than 4 days, or describe youths with chronic manic-like symptoms that comprise their baseline level of functioning.(34) Because of an important need for a clearer definition of what comprises BP-NOS, the COBY study offered an operationalized definition 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 BP-NOS.(35) These

children have very similar symptoms, comorbidities, and family histories to children with BP-I.(31, 35) Moreover, 45% of these children will go on to meet strict criteria for BP-I or BP-II within 5 years, and nearly two-thirds of BP-NOS youth with family history of BP “convert” to BP-I or BP-II.(36) Even in epidemiologic samples, sub-threshold episodic BP is associated with substantial functional impairment and comorbidity, and rates of treatment use that approach that of BD.(19, 33) However, the Longitudinal Assessment of Manic Symptoms (LAMS) study suggests that despite the fact that *symptoms* of mania are evident in approximately 40% of children (6–12 years of age) attending outpatient psychiatric clinics, most youth presenting with these symptoms (75%) do not meet the criteria for BP-I, -II, or -NOS, highlighting the importance of ensuring minimal symptom number and duration criteria are met before assigning a BP-spectrum diagnosis.(37)

AACAP vs. NICE

The DSM-IV-TR criteria for manic and hypomanic episodes do not differ for children and adolescents, although clinical judgment is required to allow for developmentally-sensitive approaches to inquiring about and classifying symptoms. The AACAP practice parameters advise that these unaltered criteria should be employed with children and adolescents, and allow for use of BP-I, BP-II, or BP-NOS among children and adolescents.(34) In contrast, the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) clinical guideline for BP suggests diagnostic modifications for children and adolescents.(38) The guideline acknowledges that BP-I can be diagnosed in pre-pubertal children, but requires that euphoria is present and does not allow irritability as a core diagnostic criterion. For adolescents, the NICE guideline indicates that “irritability can be helpful in making a diagnosis if it is episodic, severe, results in impaired function and is out of keeping or not in character”(p.56), but should nonetheless not be used as a core diagnostic criterion. According to NICE, use of the BP-II diagnosis is not advised among children or adolescents, with the exception of “older or developmentally advanced” adolescents, in which case adult criteria should be used. Further elaboration of international differences in rates of BP and in diagnostic criteria can be found in the article by Dr. Carlson in this journal.

Course and Outcome

Information regarding the clinical course of adolescent BP was until recently limited to relatively small studies. However, larger studies have yielded crucial longitudinal data.(31, 39, 40) The course of adolescent BP following first hospitalization for mania is characterized by both recovery and recurrence.(40) Geller and colleagues recently published 8-year follow-up data regarding a cohort of pre-pubertal children and early adolescents with BP-I, and found that subjects spent 60% of the time symptomatic (either in full-threshold mood episodes or with clinically significant sub-threshold symptoms), and continue experiencing mood episodes in young-adulthood.(39) The COBY study, the largest of its kind (N=413), suggests that in many ways the longitudinal course of youth BP-I mirrors that of adults: most experience episodic recovery and recurrences; depression is the prevailing polarity; and subsyndromal symptoms, particularly of the mixed and depressive type, predominate.(31) However, compared to adults with BP-I, youth with BP-I spend more time with syndromal and clinically significant subsyndromal symptoms (59% vs. 47%), spend more time in mixed episodes, and have far more changes in polarity and in symptomatic

status.(41) Across subtypes of BP in COBY (including types I, II, and NOS), this illness is characterized by recovery (8 contiguous weeks of remission) and recurrences.(31) During 4 years of prospective follow-up, participants spent 16.6% (2 months/year) of the time in full-threshold mood episodes and 41.8% (5 months/year) of the time suffering from sub-threshold but clinically significant mood symptoms. Changes in mood polarity were common, and 51% had 5 annual polarity changes (note: polarity changes are not always part of full-threshold mood episodes, so that this is not synonymous with DSM-IV rapid-cycling). Finally, COBY provides validation for the operationalized definition of BP-NOS described above. Nearly 40% of children and adolescents with BP-NOS “convert” to BP-I or BP-II during prospective follow-up, thus demonstrating that in addition to significant episodicity and symptomatic impairment, the COBY-operationalized diagnosis of BP-NOS frequently forebodes more classical BP-I and BP-II.(31, 35) Whereas to date studies demonstrate diagnostic continuity of pediatric BP(31, 39, 40), there is evidence from adults of diagnostic conversion over time, most commonly to primary psychotic disorders.(42) Longer follow-up of extant pediatric BP cohorts will be needed to determine the rate of conversion to primary psychotic disorders.

Bipolar Disorder in School-age Children vs. Adolescents

Relatively few studies have directly compared the symptoms and clinical presentations of children with BP to those of adolescents. One study compared children with BP to adolescents with childhood-onset BP and adolescents with adolescent-onset BP, finding that euphoria was more common among adolescents with childhood-onset BP, whereas irritability was least common among adolescents with adolescent-onset BP.(43) Childhood-onset BP was associated with greater severity of increased energy, and this was observed among children with BP as well as among adolescents with childhood-onset BP. Findings from some of the larger cohorts of BP youth suggest no significant differences in symptoms between children and adolescents with BP.(25, 44) Several studies have found that the prevalence of ADHD and/or ODD may be higher among children versus adolescents with BP.(45, 46) Recent findings based on the National Hospital Discharge Survey suggest that children with BP are most likely to have been in a mixed episode (32%), followed by adolescents (25%) and adults (13%).(17)

This topic was also examined comprehensively in the COBY study. Familial loading of psychopathology may be greater in childhood-onset versus adolescent-onset BP.(47) Adolescents were more likely to have had a lifetime major depressive episode, and were more likely to have had depression as the initial polarity of illness, whereas children were more likely to have first presented with manic/hypomanic symptoms. Manic and depressive symptom severity was greater among adolescents vs. children, and this was true also for the severity of most individual symptoms.(48) Comorbid conduct disorder and comorbid SUD were more common among adolescents than among children, comorbid ADHD was more common among subjects with childhood-onset ADHD, and panic disorder was most common among adolescents with adolescent-onset BP.

Bipolar Disorder in Preschool-age Children

In comparison to the topic of BP among school-age youth, BP among preschoolers is perhaps more controversial and has been the subject of comparatively little research to date. One of the few “minimal standard” recommendations in the AACAP practice parameter for BP is that caution is advised before diagnosing pre-schoolers with BP, due to uncertain validity.(34) That said, several groups have reported on small samples of preschoolers who present with symptoms of hypo/mania.(49–54) In one cases series, preschool mania was consistently characterized by strong family history of mood disorders and by antecedent ADHD.(54) Perhaps surprisingly, descriptions of preschoolers with BP have often included classical features. For example, specific symptoms of mania such as elation and grandiosity have been prominent in several reports, and the course of illness in a series of 26 patients was significant for high recovery and relapse rates (i.e. episodicity).(49, 51, 55) One study included 26 preschoolers with BP as well as comparison groups of preschoolers with depression, disruptive behavior disorders, and no psychiatric disorders.(50) Even after controlling for comorbid ADHD, preschoolers with BP demonstrated significantly greater functional impairment than did preschoolers with disruptive behavior disorders or healthy preschoolers.

Clearly, the diagnosis of BP in preschoolers should be used judiciously, and prevalence estimates in this age range are not presently available. Extant challenges in the accurate diagnosis of BP in school-age children, particularly those related to developmentally sensitive symptom ascertainment, are further accentuated in the preschool age group. However, compelling descriptions of directly observed manic symptoms have been published. Kraepelin referred to the case of a 5-year old boy with mania(2)(p.167). Poznanski and colleagues described the case of a 4-year-old child with maternal history of BP who presented with recurrent brief hypomanias against a background of consistent ADHD symptoms. In that case report, the inclusion of parent and teacher reports, the nuanced behavioral descriptions including developmental context, and the care taken to demonstrate differences from the usual ADHD symptoms together make a compelling argument for preschool BP. In our view, BP is likely less common among preschoolers than among school-age children and adolescents, however recognition of how symptoms of BP manifest in a preschooler can provide a framework for when to include BP on the differential diagnosis in such young children.

Suicidality

Similar to adults, BP among youth is a potent risk factor for completed suicide.(56–58) Whether in community or clinical samples, approximately 3 in 4 youth with BP endorse lifetime suicidal ideation.(19, 35) The lifetime prevalence of suicide attempts among youth with BP varies across studies, but appears to be at least 20% and sometimes nearly 50%.(13, 59, 60) Epidemiologic findings from the United States indicate that the lifetime prevalence of suicide attempts among adolescents with BP spectrum disorders (44%) was double that of adolescents with MDD (22%) which was in turn far greater than that of healthy adolescents (1%).(19) Moreover, adolescents with BP in this sample make more attempts, make more lethal attempts, and are younger at the time of their first attempt.

The question arises as to which youth among those with BP are at greatest risk for attempting suicide. The prevalence of suicide attempts appears to be greater among older youth.(13, 61) With the exception of older age, findings from the COBY study do not suggest any demographic predictors of suicide attempts.(13) Interestingly, rates of suicide attempts did not significantly differ across BP subtypes. Clinical predictors of lifetime suicide attempt include mixed episodes, psychosis, psychiatric hospitalization, comorbid panic disorder, comorbid SUD, poor family functioning, family history of suicide attempt, history of physical or sexual abuse, suicidal ideation, and non-suicidal self-injury.(13, 61)

Impairment in Functioning and Quality of Life

The NCS-A characterized impairment as “some”, “a lot”, or “extreme”.(12) Fully 90% of adolescents with BP endorsed severe impairment, whereas this was true for 74% of adolescents with MDD, 49% of adolescents with disruptive behavior disorders, and 26% of adolescents with anxiety disorders. A recent study found lower quality of life among youth BP than among youth with other medical and psychiatric disorders.(14) Quality of life in important domains such as family, friends, and school was especially reduced compared to other youth, and was even poorer than among youth with MDD. Comorbid anxiety disorders and disruptive behavior disorders, especially in the context of maternal mood disorders, appear to be associated with worse family functioning among youth with BP.(62)

Medical and Mental Health Service Utilization

Epidemiologic findings from studies in the United States and Canada suggest that under-treatment of BP among adolescents is problematic, as only 45–55% of adolescents with BP report accessing any mental health services in their lifetime.(19, 20) Treatment rates are especially poor for adolescents with BP when disorder-specific services are examined, rather than any overall mental health services. Only 22.2% of adolescents with BP-I or -II in the NCS-A report accessing treatment in their lifetimes specifically targeting BP.(10) By comparison, 59.8% of adolescents with ADHD and 39.4% of adolescents with MDD or dysthymia reported lifetime use of services targeting those disorders. However, findings based on health insurance claims indicate that those adolescents with BP who do access treatment incur markedly increased behavioral health costs than adolescents with other mood disorders or non-mood disorders.(16) Youth diagnosed with BP do often access treatment for ADHD, depression, and disruptive behavior.(63) It is possible that some treatments for these problems may benefit youth with BP (e.g. cognitive-behavioral therapy, family therapy). However, failure to integrate the BP diagnosis could lead to suboptimal psychosocial treatment, which relies on appropriate psycho-education (e.g. misinterpreting manic symptoms as “behaving badly”), or to potentially mood-destabilizing pharmacologic interventions (e.g. stimulants, anti-depressants), in addition to prolonging the delay to appropriate treatment. Unfortunately, it is precisely the adults with youth-onset BP who report both the most prolonged delays in treatment for BP and most severe courses of illness (historically and prospectively).(6, 7, 64, 65)

Psychiatric Comorbidity

Comorbidity is the norm in BP, and the majority of adults with BP have 2 other psychiatric conditions, most commonly anxiety disorders and substance use disorders (SUD).(30) A

meta-analysis of children and adolescents with BP found that ADHD (62%) was the most common comorbidity, followed by oppositional defiant disorder (ODD; 53%), anxiety disorders (27%), conduct disorder (CD; 19%), and SUD (12%).(66) Comorbidities such as eating disorders and pervasive developmental disorders occur less commonly. ADHD appears to be more common among children with BP, whereas panic disorder, conduct disorder, and SUD appear to be more common among adolescents with BP.(48) Studies suggest that comorbidities may exacerbate the course and outcome of BP. 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 BP-I.(67) Comorbid anxiety disorders have been associated with greater depression severity, and with reduced efficacy of antimanic treatment.(68, 69) Finally, comorbid SUD are associated with concerning outcomes such as medication non-adherence, suicide attempts, legal problems, and teenage pregnancy and abortion.(40, 70) The impact of comorbidity, particularly ADHD(71), on treatment decisions is elaborated elsewhere in this journal.

Medical Comorbidity

Medical comorbidity is a major concern in BP. Cardiovascular disease is both exceedingly prevalent and premature among adults with BP, leading to excessive cardiovascular mortality.(72) Although psychiatric medications are associated with metabolic disturbances, the association between BP 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 BP, and are associated with a more pernicious course of illness, including increased functional impairment, suicide attempts, and manic and depressive episodes.(73) Recent findings suggest that despite their young age, children and adolescents with BP may also incur increased risk of medical comorbidities. Between 28–36% of youth with BP suffer from multiple medical conditions, whereas this is true for only 8% of youth with other psychiatric disorders combined.(74, 75) Obesity, hypertension, and diabetes are highly prevalent and often precede BP, and use of specialty cardiology services is doubled. Correlates of overweight/obesity among youth with BP include history of physical abuse, comorbid SUD, psychiatric hospitalizations, and exposure to multiple classes of mood-stabilizing medication.(76) Migraine, asthma, and neurological conditions such as epilepsy may also co-occur disproportionately with BP.(74, 75)

Differential Diagnosis

The primary differential diagnosis of pre-adolescent BP is ADHD. The overall rate of comorbid ADHD among studies of pediatric BP (62%)(66) is problematic because the extent of overlapping symptoms of ADHD presents unique diagnostic challenges. Methods for distinguishing BP from the more prevalent ADHD have been described previously. The two primary distinguishing features of BP are the discrete episodes of BP and the distinguishing symptoms of mania.(77) Different approaches have been taken to delineate BP (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 two symptoms would be counted toward a diagnosis of ADHD as well as toward a manic episode (i.e. BP).

Proponents of this strategy argue that it is impossible to reliably attribute the “cause” of one symptom to one disorder over another. An advantage of this strategy is that it requires less clinical discretion and judgment, which may enhance reliability if at the expense of validity. The primary disadvantage of this approach is that it may sacrifice specificity, leading to numerous diagnoses of BP among youth with ADHD. An alternative 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. The same strategy can be applied to diagnoses of generalized anxiety disorder or oppositional defiant disorder, other comorbidities that include more chronic symptoms that overlap with manic symptoms. For example, a child with generalized anxiety disorder consistently experiences irritability, impaired concentration, and restlessness. Therefore, in order to meet criteria for mania or hypomania, there would need to be a distinct exacerbation in these symptoms, as well as at least two additional symptoms of mania.

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 other 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 among youth, generalized anxiety disorder, and oppositional defiant disorder. Irritability also frequently accompanies pervasive developmental disorders, conduct disorder, ADHD, substance use disorders, and obsessive compulsive disorder. As such, it is important to determine 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 including several of those described above. 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 subjects whose hypo/manic episodes include elation.(27) In summary, the keys to interpreting irritability with respect to a possible BP diagnosis are the determination of episodicity and of temporal contiguity with sufficient other symptoms of mania.

The concept of chronic, non-episodic irritability is central to differential diagnosis, and has led to the consideration of a new proposed diagnosis for the upcoming DSM-V, Temper Dysregulation Disorder with Dysphoria (TDD) or more recently Disruptive Mood Dysregulation Disorder (DMDD), based on research regarding severe mood dysregulation (SMD; severe, nonepisodic irritability with hyperarousal symptoms), which was earlier described as “broad phenotype” BP.(29, 78) However, children with SMD (of whom 86% have ADHD, 85% have ODD and 75% have both)(29), have different symptoms, comorbidities, family histories, neuropsychology, and neurobiology from children with BD-I.(29) (79, 80) (81, 82) By definition, these children do not have distinct hypomanic/manic

episodes. Use of a BP diagnosis in these cases is of questionable value because of the cross-sectional differences noted above, and because SMD-like phenotypes do not appear to be particularly predictive of future BP.(29)

Familial High-Risk for Bipolar Disorder

BP is among the most highly familial of psychiatric illnesses. Twin studies suggest that heritability of BP is approximately 0.7–0.8, whereas heritability for MDD is approximately 0.3.(83) Evidence from bottom-up (children as probands) studies suggests that the prevalence of BP is increased among relatives of children and adolescents with BP when compared to healthy children or those with other psychiatric illnesses such as ADHD or anxiety disorders.(84, 85) In addition, multiple studies have examined for the presence of psychiatric disorders among the offspring of parents with BP, and these studies consistently demonstrate increased risk of mood disorders among offspring.(86, 87) Recent findings from the large-scale Pittsburgh Bipolar Offspring Study (BIOS) indicate that offspring of parents with BP (N=388; mean age 11.9 years) have approximately a 13-fold increased risk (10.6% vs. 0.8%) compared to control offspring (N=251) of having bipolar spectrum disorders (BP-I, -II, or -NOS).(32) Although most cases were BP-NOS, the rate of BP-I among high-risk offspring (2.1%) was significantly higher than among control offspring (0%). Of note, 75.6% of BP offspring who had any bipolar spectrum disorder had onset prior to age 12. Preliminary analysis showed that after 10 years of follow-up rates of BP in the offspring of the parents with BP were 20-fold greater compared to offspring of controls.(88) Recent findings in a large sample of adolescent offspring (mean age 16.7 years) of parents with BP found that 8.5% had a bipolar spectrum disorder, and 4.3% had BP-I specifically.(89) Some studies have found lower rates of bipolar spectrum disorders than those described above(91, 92), and possible reasons for this discrepancy include nationality, age of subjects at intake, sample size, and interpretation of symptoms among children. Nonetheless, approximately 90% of school-aged offspring of parents with BP do *not* suffer from BP, raising the question of who among these offspring is at especially increased risk. Risk factors for BP among school-aged offspring may include antecedent anxiety disorders and disruptive behavior disorders, and the risk of BP may be increased if both parents have BP.(90) Although odds ratios are greatest for bipolar spectrum disorders, offspring of parents with BP also incur increased risk for anxiety disorders, depressive disorders, and disruptive behavior disorders.

Clinical High-Risk for Bipolar Disorder

Several studies suggest that pre-natal and peri-natal risk factors, as well as stressful life events, may contribute to risk for BP, albeit that the data are more tenuous than those relating to schizophrenia and major depression, respectively.(93, 94) Several psychiatric disorders may commonly precede the onset of BP. The incidence of BP among clinically-ascertained children and adolescents with MDD appears to be approximately 15–20% within 3–6 years, with higher rates generally observed among inpatient samples and in studies with longer follow-up. Risk factors for BP among adolescents with depression include rapid-onset of depression, familial loading of mood disorders, the presence of psychotic features, and the presence of treatment-emergent mania.(95) Epidemiologic data suggest that anxiety disorders and oppositional defiant/conduct disorders may also be strongly predictive of subsequent BP, although in these cases clinical risk factors for conversion to BP have yet to

be identified.(23) Perhaps surprisingly, it is not as clear that ADHD is a risk factor for BP, particularly in the absence of other comorbidities.(96)

Summary

Taken together, the literature to date suggests several conclusions. BP as defined by rigorously applying diagnostic criteria has been observed among children and more commonly in adolescents in numerous countries. The prevalence of clinically meaningful BP-spectrum conditions is greater than that of BP-I, and, importantly, BP-NOS among youth is often a “gateway” to BP-I or BP-II. Substantially increased use of the BP diagnosis has been observed in clinical but not epidemiologic studies, potentially implicating non-adherence with diagnostic criteria. The course, clinical characteristics, and comorbidities of BP among children and adolescents are in many ways similar to those of adults with BP, and continuity of pediatric BP into adulthood has recently been demonstrated. Together with family studies, treatment studies and neurobiological studies, these data provide increased support for the validity of pediatric BP. The challenge of how to reduce the disparity between clinical and epidemiologic findings remains, and this may be in part due to the difficulties ascertaining symptoms such as elation and grandiosity in children.

The complexity of BP, particularly the high rate of comorbidity with diagnoses that include overlapping symptoms, is also likely contributory. Up to 55% of youth with BP receive no treatment whatsoever, and rates of diagnosis-specific treatment lag well behind those among youth with ADHD and MDD. Redoubled effort is warranted to ensure that clinicians screen for and treat BP among youth when indicated, and that diagnoses of and treatment for BP are only given after systematically ascertaining the necessary symptoms and episodes of mania and hypomania. In addition, clinically applicable biomarkers and psychometrically sound screening strategies summarized elsewhere in this edition of the Journal offer hope that diagnostic accuracy will improve further in coming years.

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Key Points

- Billing diagnoses of pediatric bipolar disorder have increased dramatically, whereas epidemiologic studies employing standardized interviews suggest relatively stable prevalence.
- There is increasing consensus that pediatric mania or hypomania can be euphoric, irritable, or both, provided that sufficient other symptoms are present, and that symptoms track together episodically.
- Similar to bipolar I disorder, sub-threshold bipolar disorder (e.g. bipolar disorder not otherwise specified) is associated with suicidality, significant functional impairment, and substantial comorbidity. If defined by an episodic course, nearly half of cases sub-threshold bipolar disorder “convert” to bipolar I or II disorder over 5 years.
- The course of pediatric bipolar disorder is characterized by recovery, recurrence, and persistence into young adulthood.
- Compared to the course of adult bipolar disorder, the course of pediatric bipolar disorder is characterized by a greater proportion of time symptomatic, a greater proportion of time in mixed states, and more frequent polarity switches.
- Approximately 50% of youth with bipolar disorder receive no treatment. Among those who do receive treatment, approximately 50% do not receive bipolar-specific treatment, raising concerns about exposure to antidepressants and/or stimulants in the absence of mood-stabilizing medication.
- Psychiatric and medical comorbidities are common, present diagnostic and treatment challenges, and vary depending on age and gender.
- Adherence with established diagnostic criteria, including the requirements regarding sufficient number of symptoms and the presence of episodes, may serve to optimize diagnostic accuracy; automatic “double-counting” of overlapping symptoms is not advised.
- Children of parents with bipolar disorder are at increased risk for several psychiatric diagnoses, but especially bipolar disorder. Clinical risk factors for pediatric bipolar disorder include major depressive disorder, anxiety disorders, and disruptive behavior disorders