Progress in diagnosis and treatment of bipolar disorder among children and adolescents: an international perspective

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ABSTRACT

Bipolar disorder (BPD) is a potentially lifelong condition characterised by extreme changes in mood that may begin in childhood and cause substantial impairment. Over the past decades, BPD has been the focus of increased attention mainly due to controversies surrounding its prevalence, diagnosis and treatment in children and adolescents. This report addresses these controversies by reviewing the extant evidence base, providing clinicians with a summary of the literature on diagnosis, phenomenology and treatment of paediatric BPD. The debate regarding diagnosing children with BPD based on severe irritability and aggression is mostly resolved. The current data support utilising the diagnostic criteria based on episodic changes of mood polarity. Therefore, longitudinal course of illness should be explored in detail when diagnosing BPD. Given high rates of genetic predisposition for BPD, assessment of youth should focus on obtaining accurate family history of this condition. Additionally, there has been a substantial increase in randomised placebo-controlled clinical trials evaluating pharmacological agents for mood stabilisation in children and adolescents, which we summarise in this review. Despite significant progress being made in the field of paediatric BPD, more research is needed in the areas of phenomenology, pathophysiology, course and treatment of this condition in youth.

There is now substantial research validating the diagnosis of and identifying interventions for bipolar disorder (BPD) in children and adolescents, often a lifelong, highly impairing mood disorder. In fact, there were nearly three times the number of published articles focused on BPD in 2016 compared with 2000 (w1; see online supplementary file 1 for numbered references that start with 'w'). However, BPD has continued to be controversial, particularly as growing rates of clinical diagnosis in the USA have led to questions of whether this reflects a corrective change in practice, a true change in prevalence or overdiagnosis of BPD. Adding to this controversy is the lingering debate about the most appropriate definition of BPD in youth and a concern that the estimated prevalence in the USA has been higher than that of European countries.[1]

Given that BPD is associated with significant social, academic and cognitive impairments and increased risk of suicide and psychosis,[2 3] the aforementioned concerns warrant further research and clarification. This report presents a brief summary of the controversies surrounding BPD and the recent data that has contributed to the evidence-based nosology, phenomenology, treatment and neurobiology of paediatric BPD.

NOSOLOGY

BPD encompasses a spectrum of conditions of various severity, the prototype being bipolar disorder I (BP-I), which is characterised by manic and often depressive episodes. Manic episodes typically present as abnormally elevated or irritable mood with other associated symptoms, such as decreased need for sleep, racing thoughts, distractibility, increased goal-directed activity and others, as well as impairment in social and occupational functioning (w2). Mixed episodes include additional depressive symptoms during a manic episode, such as dysphoria, anhedonia, fatigue and worthlessness, and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) mixed specifier notes that manic symptoms also can occur during depressive episodes. The specific criteria for the diagnosis of BPD differ between the DSM-5, commonly used in the USA, and the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (w3), which is accepted in Europe. While both classifications recognise BPD, there are a number of differences between the two which could potentially result in significant variability in identification of affected individuals.[4] The criteria for a manic episode in both classifications are fairly similar; however, the ICD-10 requires the presence of a depressed episode in addition to a manic episode in order to meet criteria for BPD, while a single manic episode alone is sufficient to satisfy DSM-5 criteria. Therefore, an individual presenting with the first manic episode may meet DSM-5 but not ICD-10 criteria for BPD. Furthermore, DSM-5 offers more specifiers than ICD-10 to allow for more detailed characterisation of BPD.

In addition to BP-I, the spectrum of BPD also includes other subtypes, such as BP-II (described in the DSM but not in the ICD-10), characterised by hypomanic episodes that have shorter duration and less functional impairment than manic episodes, as well as cyclothymia and unspecified BPD (referred to as BPD not otherwise specified (BP-NOS), in the prior edition of the DSM (w4)), which usually includes individuals with spontaneous mood episodes not meeting duration criteria for the manic episode.[5] It should be noted that the recently released ICD-11 does include BPD subtypes.

Controversies in diagnosis

The field of child and adolescent BPD has undergone significant transformation over the past 20 years. Youth with BPD often present with irritability, which was historically postulated as a hallmark of the 'broad phenotype' of BPD.[6] In contrast, the 'narrow phenotype' required classic euphoric/elated mood and discrete mood episodes to satisfy criteria for the diagnosis of BPD.[6] However, more recent empirical evidence suggests that youth primarily presenting with chronic irritability are unlikely to have BPD.[7] The current consensus is that accurate diagnosis of paediatric BPD can be achieved with implementation of DSM criteria.[2]

The course of and impairment associated with BPD may depend on its subtype (BP-I, BP-II or BP-NOS). Youth diagnosed with BP-I are more symptomatic and have higher level of functional impairment and are more likely to attempt suicide, have psychotic symptoms and history of psychiatric hospitalisations than those with BP-NOS.[5] In addition, younger patients more commonly experience subsyndromal symptoms and multiple mood cycles.[8]

BP-II, cyclothymia and BP-NOS are diagnosed using the DSM criteria; however, these subtypes may be less stable across the lifespan. In a longitudinal study, 25% of participants with BP-II converted into BP-I, and 38% of participants with BP-NOS/cyclothymia converted into BP-I/II over a 4-year period.[8] Poor outcomes were associated with early onset, low socioeconomic status and family history of mood disorders, among other factors.[8]

BPD is a highly heritable condition; having relatives with BPD confers increased risk for developing BPD, as well as other psychopathology[9] (w5, w6). First-degree relatives of individuals diagnosed with BPD have higher rates of mood disorders, including BPD.[10] Therefore, it is important for clinicians to screen and carefully monitor children of parents with BPD for the emergence of mood symptoms, especially if they exhibit sleep and anxiety disorders, which often predate BPD in high-risk groups (w7).

PREVALENCE

Overall prevalence of paediatric BP-I is estimated at 1 in 200 across the globe.[1] However, the rate of subthreshold symptoms of BPD is much higher (4.3%).[11] There does not seem to be a difference in the prevalence of BPD between the USA and other countries. Results of a study comparing Dutch and US offspring of parents with BPD found similar prevalence of BP-I and BP-II between the samples, but higher rates of non-mood diagnoses in the US (80%) versus Dutch (34%) samples.[12]

A meta-analysis of 12 epidemiological studies of BPD included 16 222 youths aged 7–21 from the USA, the Netherlands, UK, Mexico, Spain, Ireland and New Zealand.[1] The methodology of this meta-analysis did not require concordance between parent and adolescent reports. The decision to include studies where parent and youth reports might diverge is based on the observation that individuals experiencing mood problems often have poorer insight, and this appears even more pronounced in youths than adults.[13 14] For example, Freeman *et al* demonstrated that parents and youths reported the same symptoms at different levels of severity, and for many of the more diagnostically specific symptoms, the youth had to be much sicker before they had a 50% chance of endorsing the same symptom that caregivers noted at lower, hypomanic levels.[15] In short, this meta-analysis demonstrated similar rates in US and non-US studies. There was significant heterogeneity between studies, which was largely attributable to whether studies included subthreshold cases or used a narrower definition of BPD.[1] Additionally, the reported prevalence and the year of data collection were not correlated, suggesting that the true prevalence of the disorder is not increasing.

Further, a recent meta-analysis of adult epidemiological studies found significantly lower rates in Africa and Asia than other parts of the world.[16] This study suggests that there could be some regional variability, though neither adult nor child epidemiological studies indicate a higher rate of BPD in the USA than the rest of the world. However, in contrast to epidemiological studies, the rates of outpatient and inpatient diagnoses of paediatric BPD have increased significantly in the USA in clinical settings since 1990s, which could suggest overdiagnosis or increasing sensitivity to BPD in clinical practice[17] (w8). There has been some concern that clinicians in the USA diagnose BPD in youth more commonly than clinicians in Europe. One study presented case vignettes to UK and US clinicians and found that US clinicians were more likely to diagnose mania in complex cases though there was agreement regarding classical mania.[18] In a study evaluating the agreement between the research and the clinical diagnoses in a paediatric mental health clinic, BPD was underdiagnosed in the clinical setting when compared with the research standard.[19] Training in cognitive debiasing and evidence-based decision tools (ie, nomograms) help to improve assessment of BPD (w9, w10).

PHENOMENOLOGY

Paediatric BPD is associated with significant morbidity and comorbidity.[3] Results of a recent meta-analysis of 20 studies examining the phenomenology and clinical characteristics of paediatric BPD found that rates of manic symptoms were similar across studies after differences in methodology were accounted for: the most common symptom was increased energy (79%) followed by irritability (77%), mood lability (76%), distractibility (74%), goal-directed activity (72%), euphoria/elated mood (64%), pressured speech (63%), hyperactivity (62%), racing thoughts (61%), poor judgement (61%), grandiosity (57%), inappropriate laughter (57%), decreased need for sleep (56%) and flight of ideas (54%).[3 20] Periods of depression are also common among youth with BPD.[5] Similar symptoms were found to be common in a European sample (w11). There is substantial heterogeneity in symptom prevalence across samples[20]; possible explanations include ascribing to the broad (periods of chronic irritability and mood lability without distinct episodes) versus narrow (requiring distinct periods of euphoria/elated mood) phenotype of BPD (description of these phenotypes is included above in the Nosology section) and differing assessment methods. Evidence synthesised in this meta-analysis[20] comes from cross-sectional and longitudinal studies and retrospective reviews of medical records, which may have also contributed to heterogeneity.

Many of the aforementioned symptoms (irritability, distractibility, poor judgement, among others) are highly prevalent but not specific to BPD—they also occur in other disorders. However, elated mood and decreased need for sleep (but not insomnia) are highly specific for paediatric BPD and can help rule in the diagnosis when present.[2]

Results from the Longitudinal Assessment of Manic Symptoms (LAMS) study found that, among a sample of youth selected for elevated symptoms of mania, manic symptoms decreased over a 24-month period for most youth.[21] The Course and Outcome of Bipolar Youth Study (COBY) found that, among youth diagnosed with BPD, 82% recovered from their index mood episode after 2.5 years; however, 1.5 years after recovery, 63% experienced recurrence. Further, many youth experienced mood symptoms between episodes.[8] Further analysis of COBY data suggests that there is variability in the course of BPD in youth: 35% had a moderately euthymic course, 24% a predominantly euthymic course, 22% a predominantly ill course, and 19% an ill with improvement course over a period of 4 years or longer. Earlier age of onset of mood symptoms was associated with a poorer longitudinal course.[22] Importantly, all of the youth in COBY were receiving treatment, which likely affected their symptom trajectories. Additionally, analysis of two large epidemiological studies suggested that there may be a 'developmentally limited' trajectory for a subset of cases; while prevalence of BPD was around 6% among youths aged 18–24 years, it was approximately 3% among those aged 25–29 years.[23]

While research indicates that BPD is a substantially impairing condition whether it begins in childhood, adolescence or adulthood, there are some differences in functional and clinical outcomes by age of onset. One study pooled data from seven sites associated with an International Consortium for Bipolar Research (located in Boston, Massachusetts, USA; New York, New York, USA; Cagliari, Italy; Buenos Aires, Argentina; Barcelona, Spain; Lugano, Switzerland and Izmir, Turkey) in order to examine differences in clinical outcome by age of onset (age <12, 12–18 or 19–55) among 1665 individuals with BP-I. They found that, overall, earlier onset appeared to be associated with worse functional outcomes (employment, living independently, marriage and children, education) and positive family history.[24] Other studies have found childhood-onset of BPD to be associated with other pernicious outcomes including increased irritability, mood lability, worse severity and course of illness, psychotic symptoms, worse response to lithium and increased risk for comorbid diagnoses and suicidality[25] (w12–14). Studies comparing the USA to European countries demonstrate an earlier age of onset among US samples than European samples[12] (w15). Reasons for differing ages of onset are yet unclear.

Comorbidity among youth with BPD is likely, with the most prevalent comorbid diagnoses being attention deficit/hyperactivity disorder (ADHD), oppositional defiant disorder/conduct disorder, substance use disorders and anxiety disorders (see table 1).[2 20 26 27] Rates of comorbid diagnoses vary with age such that ADHD is more common among children with paediatric BPD, while substance use disorders are more common among adolescents.[26] As previously noted, paediatric BPD is associated with significant impairment, but comorbid ADHD or anxiety is associated with more severe mood symptoms and worse clinical course, neurocognitive functioning and global functioning among youth with BPD.[27]

Table 1 Rates of common comorbidities among youth with bipolar disorder (estimates from Van Meter *et al*'s updated meta-analysis[20])

Comorbid diagnosis	Weighted average (%)
Attention deficit hyperactivity disorder	53
Oppositional defiant disorder	42
Anxiety	23
Conduct disorder	27
Substance use disorder	9

ASSESSMENT

Given the poor outcomes associated with delayed diagnosis and treatment (w16), careful and accurate assessment is of great importance (see box 1).

Diagnostic interviews should assess symptoms specific to BPD (eg, elevated mood, grandiosity, decreased need for sleep and racing thoughts) and spontaneous episodicity (changes in mood and functioning that are unusual for the child). Euphoria/elated mood is a common and highly specific feature of BPD, and extreme, impairing, situationally inappropriate euphoria/elated mood may help to rule in a BPD diagnosis when other manic symptoms are present.[2] Further, to aid in assessing episodicity, diagnosis should also consider the longitudinal course of any bipolar symptoms.[28] Understanding of past mood, behaviour and prior comorbidities is essential to assessing a youth's baseline functioning.[28] It is also important to rule out mood changes dependent on environmental factors, prescribed medications, active substance use and/or medical problems. Given the high heritability of BPD, particularly among those with child-onset BPD, gathering data on paternal and maternal family psychiatric history can provide helpful information.[28] It is often necessary to not only inquire about the diagnosis of BPD in the family but also to ask more details about specific symptoms of elated mood, decreased need for sleep and engagement in risky activities. While some family members may not have been appropriately diagnosed with BPD, others will report inaccurate diagnoses of BPD (w17). Careful assessment of past or present manic symptoms in family members may provide a more accurate family history.

Though it should be noted that most offspring of parents with BPD will not meet criteria for BPD, these youngsters are at increased risk for other psychiatric problems. Assessment of symptoms of possible comorbid disorders should focus on symptoms present independent of mood. For instance, prior to diagnosing comorbid ADHD, clinicians should assess whether hyperactivity and distractibility are present exclusively during a mood episode or whether they also occur outside of the context of a mood episode. Assessment should include both observation of the youth and an interview of a collateral informant (eg, parent/guardian). A recent meta-analysis of parent, youth and teacher report in diagnosing BPD indicated that reports from all three aid in discriminating BPD, but parent report demonstrates the strongest validity.[14]

Box 1 Assessment

Key factors to consider when assessing bipolar disorder in children and adolescentsKey factors to consider when assessing bipolar disorder in children and adolescents

- Longitudinal course of symptoms.
- Family history of bipolar disorder.
- Presence of spontaneous episodicity.
- Perspectives of multiple informants.

Table 2 Medications that have shown evidence in the treatment of mixed/manic, depressive and maintenance phases of bipolar disorder among children and adolescents

Phase of bipolar disorder	Medications
Mixed/manic	Lithium Divalproex Risperidone Olanzapine Quetiapine Aripiprazole Ziprasidone Asenapine
Maintenance	Aripiprazole Lamotrigine (in adolescents only) Lithium Divalproex
Depressive	Olanzapine+fluoxetine Lurasidone

TREATMENT

The current recommendations for the treatment of paediatric BPD is primarily for psychopharmacological management combined with psychosocial interventions.[29] However, significant concerns have emerged in the field of child and adolescent psychiatry regarding overmedicating youth with psychotropic medications[30] (w18). While none of the reports are focused on paediatric BPD per se, the rates of antipsychotic prescriptions in the USA for children and adolescents have increased sixfold from 1988–1994 to 2007–2010.[31] To address this concern, Merikangas *et al* evaluated the use of psychotropic medications in more than 10 000 adolescents and found no evidence of misuse of psychiatric medications in patients with a variety of psychiatric disorders, including BPD.[32] Kowatch *et al* assessed medication use in a cohort of youth with elevated symptoms of mania,[33] concluding that patients with greater severity and more comorbidity were most likely to be prescribed two or more medications. In the same cohort, youth receiving antipsychotics were more likely to have a diagnosis of psychotic disorder or BP-I and have lower overall psychosocial functioning.[34] It is noteworthy that 38% of youths with research-grade diagnoses of ADHD were not receiving any medication, despite practice parameters clearly indicating that medication is a front-line treatment option.[29 33]

Medication management of BPD in youth is guided by the phase of illness. Table 2 shows empirically supported options for manic/mixed, depressive or maintenance of euthymic mood.

Both lithium[35] and atypical antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, asenapine (w21–26)) are generally safe and effective for the short-term management of acute manic/mixed state. The depressive phase of BPD in youth is more difficult to treat pharmacologically due to increased risk of mania with antidepressant treatment (w27) and limited data available on the management of bipolar depression. The combination of olanzapine and fluoxetine was shown to be effective in the treatment of bipolar depression in youth (w28). In a recent clinical trial, monotherapy with lurasidone decreased depressive symptoms in youth with BPD (w29). Quetiapine was found to be effective for the management of bipolar depression in adults (w30), but it did not separate from placebo in depressed children with BPD[36] (w31). A study of youth with depressive symptoms at risk for development of BPD showed poor tolerability of paroxetine/divalproex combination, with increased manic symptoms and thoughts of suicide.[37] Maintenance of euthymia can be achieved with aripiprazole[38] (w32). Although in a discontinuation study, lamotrigine did not separate from placebo in youth 10–17 years of age, it was effective in maintaining euthymic mood in adolescents 13–17 years of age, when compared with younger children.[39]

Meta-analyses examined the risks and benefits of pharmacotherapy of children and adolescents with BD and revealed greater efficacy of second-generation antipsychotics (SGAs) when compared with anticonvulsants and lithium.[40] Liu *et al* found that among 2666 participants in 46 open-label trials, there was a significant effect of SGAs, a non-significant effect of divalproex and a more modest but significant effect of other anticonvulsants.[41] However, the benefits of SGAs come at a cost of side effects (increased weight, cholesterol and triglyceride levels, hyperprolactinaemia and extrapyramidal symptoms). Additionally, most clinical trials focus on the acute management of BPD and do not address long-term risks and benefits. In a head-to-head comparison of risperidone, lithium and divalproex, risperidone was more effective than traditional mood stabilisers over 8 weeks. Increased weight and prolactin levels were associated with risperidone treatment.[42]

Although monotherapy is generally recommended for the management of paediatric BPD,[43] combination therapy is often implemented due to partial response to treatment with a single agent. Combination of quetiapine and divalproex provided greater control of manic symptoms compared with divalproex or placebo (w33). Similarly, combination of risperidone and either lithium or divalproex was effective in decreasing manic symptoms in youth (w34). Earlier identification, including attention to prodromal and spectrum presentations, offers opportunity for earlier and titrated intervention. This includes psychosocial interventions, stimulant trials for attention problems and lower dosing of other medications. Intriguingly, with treatment, positive trajectories have been observed.[22] Given the high rates of suicide risk and impairment associated with BP-II, cyclothymia, and NOS,[8 20] having a range of titrated interventions and deploying lower risk, broad-spectrum approaches appear to be a sensible course of management, consistent with evidence-based medicine principles.[44]

Psychosocial interventions are recommended as adjunctive treatment for BPD in youth.[29] Such interventions can support overall psychosocial development, treat symptoms of comorbid psychopathology, decrease relapse rates and improve adherence (see table 3).[29 45 46] There is substantial empirical support for psychotherapies that are family focused, psychoeducational and based in cognitive behavioural skills.[45 46]

NEUROBIOLOGY

The bulk of structural and functional imaging results appear consistent between youth and adult samples with BPD. Diffusion tensor imaging studies have shown decreased fractional anisotropy in superior and right orbital frontal regions[47] (w35), as well as anterior regions of the corpus callosum and anterior commissure in patients with BPD, when compared with healthy controls (w36). Functional MRI (fMRI) studies determined hyperactivation of amygdala, prefrontal and visual system and hypoactivation of the anterior cingulate cortex in BPD,[48] suggesting reduced control of the limbic regions by the prefrontal areas.[49] One exception is that MRI studies have associated smaller amygdala volumes in youth with BPD when compared with controls, but not in adults with BPD.[50]

Table 3 Psychotherapy for bipolar disorder in children and adolescents

Features common to efficacious psychotherapies[45]	Benefits of psychotherapy
► Family focused ► Psychoeducational ► Based on cognitive behavioural therapy skills ► Efficacious psychotherapies include: psychoeducational psychotherapy, family-focused treatment, child and family focused cognitive behavioural therapy	► Supports overall psychosocial development ► Addresses symptoms of comorbid psychopathology ► Improves treatment adherence ► Decreases relapse rates ► Improves global functioning

CONCLUSIONS

The field of child mental health has made significant progress in characterising the phenomenology, course of illness, treatment and outcomes for BPD. BPD in children and adolescents has been the focus of controversy due to concerns about overdiagnosis, appropriate assessment methods and overuse of prescription medications. Much of this controversy appears now resolved on the basis of empirical study. There appears to be international consensus (although not unanimity) regarding the presence of BPD in paediatric samples. While there continues to be some disparate views on how to best define childhood BPD, there is substantial evidence for the validity of using DSM criteria to diagnose BPD in children and adolescents. Recent research suggests that the prevalence of BP-I and BP-II in youth is similar across the USA and Europe. However, global consensus regarding diagnosis of cyclothymia and BP-NOS is still needed. Additionally, while the overall prevalence is similar, there appears to be an earlier age of onset for BPD (which is associated with worse functional and clinical outcomes) in US samples compared with the European ones. Continued international research collaboration will help to elucidate potential reasons for differences between the continents.

Some of the prior controversies continue to be addressed with methodologically stringent empiric research. In order to constructively address existing concerns about this condition going forward, we believe it is far better to apply efforts towards advancing the field with empiric evidence. That means continuing to conduct methodologically rigorous research rather than taking tendentious positions that do not help advance the field.

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