Review Article

Pediatric bipolar disorder: validity, phenomenology, and recommendations for diagnosis

Objective: To find, review, and critically evaluate evidence pertaining to the phenomenology of pediatric bipolar disorder and its validity as a diagnosis.

Methods: The present qualitative review summarizes and synthesizes available evidence about the phenomenology of bipolar disorder (BD) in youths, including description of the diagnostic sensitivity and specificity of symptoms, clarification about rates of cycling and mixed states, and discussion about chronic versus episodic presentations of mood dysregulation. The validity of the diagnosis of BD in youths is also evaluated based on traditional criteria including associated demographic characteristics, family environmental features, genetic bases, longitudinal studies of youths at risk of developing BD as well as youths already manifesting symptoms on the bipolar spectrum, treatment studies and pharmacologic dissection, neurobiological findings (including morphological and functional data), and other related laboratory findings. Additional sections review impairment and quality of life, personality and temperamental correlates, the clinical utility of a bipolar diagnosis in youths, and the dimensional versus categorical distinction as it applies to mood disorder in youths.

Results: A schema for diagnosis of BD in youths is developed, including a review of different operational definitions of 'bipolar not otherwise specified.' Principal areas of disagreement appear to include the relative role of elated versus irritable mood in assessment, and also the limits of the extent of the bipolar spectrum – when do definitions become so broad that they are no longer describing 'bipolar' cases?

Conclusions: In spite of these areas of disagreement, considerable evidence has amassed supporting the validity of the bipolar diagnosis in children and adolescents.

Eric A Youngstrom[a], Boris Birmaher[b] and Robert L Findling[c]

[a]Department of Psychology, University of North Carolina at Chapel Hill, Chapel Hill, NC, [b]Child and Adolescent Mood Disorders, University of Pittsburgh Medical Center, Pittsburgh, PA, [c]Child and Adolescent Psychiatry, Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, OH, USA

Corresponding author: Eric A. Youngstrom, PhD, Department of Psychology, University of North Carolina at Chapel Hill, CB #3270 Davie Hall, Chapel Hill, NC 27599-3270, USA.
Fax: (216) 368 4891;
e-mail: eric.youngstrom@unc.edu

Bipolar disorder (BD) in children and adolescents has been a controversial topic that has received a great deal of recent scholarly and popular interest. There has been a tremendous increase in the number of trade books, articles in the popular media, and even television shows on the topic of BD (1), and there has been a similar rise in the rate at which it is being diagnosed and treated in youths. Although it was once considered primarily an adult-onset

disorder, more than 100,000 children were being medicated for BD in 2001 (2), with the percentage of children being clinically diagnosed more than doubling in the last 10 years (3, 4). Fortunately, the amount of research on the topic has also surged over the same time period, and there are significant areas of consensus in the findings (5–8).

The purpose of this paper was to review the available evidence about classic diagnostic validators as they apply to the diagnosis of BD in children and adolescents (9, 10). These include (i) phenomenology, (ii) demographic characteristics, (iii) family environmental characteristics, (iv) genetics, (v) longitudinal course, and (vi) neurobiology. This paper is not intended to be a comprehensive review of assessment or treatment strategies, but instead touches on these topics as they pertain to the validity of the bipolar diagnosis in youths. There have been fairly recent reviews on both assessment (11) and treatment guidelines (12, 13) that expand on clinical issues. It is worth noting that treatment response is considered one of the facets of validating a diagnostic entity (9), and so treatment reviews can be read with this in mind. After presenting the validity findings, the paper discusses what is known about sex and cultural differences, the implications of categorical versus dimensional approaches to diagnosis, what is known about temperament and personality correlates, and the burden associated with bipolar illness. In addition, working with youths typically requires involvement of parents, teachers, or other parties that raise issues of cross-informant agreement, impairment in single versus multiple settings, and boundary issues in terms of separating normative and pathologic behavior. The paper concludes with recommendations for refining diagnosis in youths, as well as identifying principal areas for future study.

Classical diagnostic validators of the construct of pediatric bipolar disorder

Phenomenology

Several different research groups have investigated the phenomenology of pediatric BD, using different approaches in terms of subject ascertainment, clinical interviewing (e.g., choice of diagnostic interview, level of training of the interviewer), choice of informant (e.g., parent only, parent and child, and adolescent only), method of reconciling discrepant information from multiple informants (e.g., algorithms such as consistently taking the higher score as the summary, versus using clinical judgment or joint interviews to reconcile differences), and different age groups. A recent meta-analysis synthesized seven published studies, and statistically tested whether there were differences in findings that were too large to attribute to random effects differing across studies (6). Meta-analytic methods indicate that there is considerable consistency in findings about the symptom presentation and diagnostic comorbidity associated with pediatric BD, especially after considering differences in methodology. In particular, there appears to be consensus that periods of increased energy will be evident in nearly 90% of cases with pediatric BD, and grandiosity will be clinically noteworthy in nearly four of five cases with pediatric BD (6). There was also general consensus that most other conventional symptoms of mania will manifest in 70–85% of cases with pediatric BD, with the exceptions of 'flight of ideas' (occurring in 56% of pediatric BD cases on average) and hypersexuality (occurring in a mean of 38% of pediatric BD cases). These patterns of symptom presentation also appear to be consistent with a recent analyses of a large group of children and adolescents with bipolar spectrum disorders (14) and what is being described as the phenomenology of cases with early onset BD in Europe (15) and America (14). Table 1 lists the symptoms of mania, along with associated features, and reviews presentations that would be more specific to mania as opposed to other diagnoses.

Elated mood. The two symptoms showing the most highly discrepant rates across studies are elated/euphoric mood and irritability. Some treat elated mood as a 'cardinal' symptom of mania, arguing that people not displaying periods of abnormally elevated mood (or perhaps grandiosity) should not be classified as having mania or a bipolar diagnosis (5). Other groups see high rates of irritable mood, including irritability in cases where pathologic elevations of mood do not appear evident (16, 17). Data across research groups indicate that elated mood is highly specific to BD. Episodes of elated mood that are developmentally abnormal in terms of context, frequency, intensity, or duration appear to rarely occur outside of the context of a manic episode (6–8, 14, 18). As a result, the presence of elated mood *helps* rule in the diagnosis of a bipolar illness (19). However, *requiring* the occurrence of elated mood could lead to the underdiagnosis of bipolar illness, as the sensitivity of the symptom is imperfect. Also, elated mood is not as impairing as other symptoms, and families will often describe episodes of frank exalted mood, and then say, 'I was not worried about it at the time, because at least he/she seemed happy, instead of violent.' Further, elated mood by itself is also not sufficient to warrant a diagnosis of mania or

Table 1. Sensitivity, specificity, and recommendations about the assessment of symptoms and associated features of bipolar disorder

Symptom	Sensitivity to pediatric BD (6)	Specificity to pediatric BD	Features suggestive of pediatric BD	Features suggestive of other diagnoses[a]	Recommendation
Elated, expansive, euphoric mood	70% (45–87%)	High	Extreme, causes impairment, situationally inappropriate, extreme duration	Transient, more responsive to redirection, more situationally driven. Substance abuse, use of medications (e.g., corticosteroids)	Emphasize as a highly specific feature – presence helps rule in diagnosis. Remember to assess even though it may not be considered part of presenting problem by family
Irritable mood	81% (55–94%)	Low	Irritability in context of other mood symptoms; high versus low energy irritability	Chronic oppositionality in absence of changes in mood or energy. It can be unipolar depression	Assess via collateral informant – self-report will underestimate. Collaterals denying irritability may effectively rule out pediatric BD because of high sensitivity. Embed in context of changes in mood and energy
Grandiosity	78% (67–85%)	Moderate – reduced by association with conduct disorder, developmental issues	Episodic quality, and should fluctuate with mood. Periods of grandiosity contrasted with low self-esteem, worthlessness	More chronic, arrogant, not associated with mood is suggestive of CD/APD or adolescent overconfidence. Substance induced	Worth emphasizing, but probably not specific enough to elevate to required feature. Fluctuations a key feature in discerning from CD/APD
Increased energy	89% (76–96%); highest sensitivity in meta-analysis (6)	Moderate for 'high energy' – which is also common in ADHD; episodic periods of high energy would be more specific to mood disorder	Higher if ask about fluctuation or change; low if ask about chronic (because common feature with ADHD)	Chronic high motor activity	Need to assess as change in functioning from youth's typical behavior. Episodic quality is more specific to bipolar. May be helpful to focus on *energy* versus motor activity for self-report (188); *change* in motor activity for collaterals
Distractibility	84% (71–92%)	Low – ADHD, unipolar, anxiety, PTSD, low cognitive functioning	Higher if ask about change from typical, embed in context of mood	Chronic problems much more suggestive of ADHD or neurologic impairment	Low specificity makes this symptom ambiguous. Probably important to assess via collateral instead of self-report. High sensitivity could make negative collateral helpful at ruling out
Pressured speech	82% (69–90%)	Unclear. Carlson raises issue of expressive language problems (171); these have not been evaluated in published samples to date	Episodic quality, change from typical for youth; set against slowed or impoverished speech during depression	Chronically 'chatty' or talkative more suggestive of ADHD	Emphasize changes from typical functioning embedded in shifts of mood or energy

Table 1. Continued

Symptom	Sensitivity to pediatric BD (6)	Specificity to pediatric BD	Features suggestive of pediatric BD	Features suggestive of other diagnoses[a]	Recommendation
Racing thoughts	74% (51–88%)	Good if embed in mood context	Ask about imagery as well as words (189)	Distinguish from expressive language disorder. Substance abuse, meds	
Decreased need for sleep	72% (53–86%)	High if framed as decreased need, not insomnia. Low if just focus on trouble falling asleep	High energy, actively engaged in activities, does not miss sleep the next day	Decreased sleep due to stimulant use (ADHD), use of substances, or medications (e.g., medications for asthma); difficulty falling asleep with unipolar depression (in depression there is no decreased need for sleep). In depression, the person wants to sleep, but she or he cannot	Emphasize decreased need for sleep, as distinct from difficulty falling asleep (particularly due to stress or rumination). High energy, little diminution of energy despite decreased sleep
Poor judgment	69% (38–89%)	Moderate	Episodic, embedded in mood/energy, not characteristic of youth	Impulsive or accident-prone, clumsy	Episodic, sensation-seeking may be most specific presentation
Flight of ideas	56% (46–66%)	Moderate		(Speech problems again), substance abuse, meds	
Hypersexuality	38% (31–45%)	High – typically either pediatric BD or sexual abuse	Hypersexuality not characteristic, embedded in episodes of energy/mood; has pleasure-seeking quality	Sexual abuse – linked to trauma, perhaps more seductive/re-enacting quality than sensation-seeking. Exposure to X-rated movies, actual sex	Not sensitive to pediatric BD, so absence of symptom not informative, but highly specific. Presence should trigger careful assessment of pediatric BD and abuse (recognize that they could co-occur)
Mood swings/lability	High	High – based on PGBI, CBCL, Conners items	Frequent, intense, with periods of long duration	May be induced by substance abuse, medications, medical/neurologic illnesses, borderline personality traits, disruptive disorders	Highly sensitive in parent report. If denied by parent, very unlikely to have pediatric BD. Specificity appears promising, based on multiple analyses of different questionnaires. Conceptualize as mixed state with volatile mood
Increased sense of well-being	Unknown (ICD-10, p. 113)	Unknown	Unknown, but theoretically likely to be low	Consistent with high positive affect model of mania	Needs investigation
Heightened physical and mental efficiency	Unknown (ICD-10, p. 113)	Unknown	Unknown, but theoretically likely to be low	Consistent with Kraepelin's observations about perceptions of fluctuating intellectual performance	Needs investigation

Table 1. Continued

Symptom	Sensitivity to pediatric BD (6)	Specificity to pediatric BD	Features suggestive of pediatric BD	Features suggestive of other diagnoses[a]	Recommendation
Hyperacuisis – experiencing sensations as being unusually vivid or intense		Unknown	Unknown		Needs investigation
Increased sociability/ people-seeking/overfamiliarity	ICD-10 (p. 113)	Added to WASH-U-KSADS; may be fairly sensitive	Unknown		Needs investigation
Intrusiveness; conceited or boorish behavior	Unknown. Criterion for 'severe mood dysregulation' in Leibenluft et al. (60); ICD-10 criterion for hypomania or mania (p. 113)	Unknown	Unknown	Appears conceptually similar to grandiosity and inflated self-esteem	Needs investigation

[a]The 'Features Suggestive of Other Diagnoses' are not exhaustive, but provide clinical examples often encountered. BD = bipolar disorder; CD/APD = Conduct disorder/Antisocial Personality Disorder; PTSD = post-traumatic stress disorder; ADHD = attention-deficit hyperactivity disorder; ICD-10 = International Classification of Diseases, 10th edition; CBCL = Child Behavior Checklist; PGBI = Parent General Behavior Inventory; WASH-U-KSADS = Washington University Kiddie Schedule for Affective Disorders and Schizophrenia.

hypomania, but instead needs to co-occur with other manic symptoms. Finally, there also appear to be cases for whom the predominant mood during mania or mixed episodes may be irritability.

Irritability. From a diagnostic point of view, irritability appears to be the complement of elated mood. The vast majority (80% +) of bipolar cases demonstrate periods of clinically marked irritability (i.e., high sensitivity) (6, 8, 14). However, irritable mood is not specific to BD. Instead, it appears analogous to 'fever' or 'pain' – it is a clear indication that something is wrong, but by itself it cannot provide clear guidance about exactly what the problem might be (20). Questions probing irritable mood occur in at least seven different modules in the semi-structured diagnostic interviews that are considered the research standard for assessment of pediatric BD (21): depression, mania, generalized anxiety disorder, post-traumatic stress disorder, oppositional defiant disorder, conduct disorder, and obsessive/compulsive disorder (22, 23). Irritable mood and aggressive behavior are also often associated with other disorders such as autism and Aspergers, attention-deficit hyperactivity disorder (ADHD), mental retardation, and adjustment disorders (20). Some argue that the severity of the aggressive behavior might distinguish BD from other conditions (24–26). Severity, however, is likely to be misleading in settings where the behavior of most patients is extremely impaired (such as inpatient units) or where aggression is likely to be common for other reasons besides mood disorder (such as forensic settings). On the other hand, aggression is one of the most distressing and impairing symptoms associated with pediatric BD as well as other conditions (27). Thus, aggression is likely to be a main 'presenting problem,' and treatments will need to reduce aggression to be seen as effective. Also, because irritable mood is so sensitive to pediatric BD, the absence of any episodes of irritability and aggressive behavior effectively 'rules out' a diagnosis of pediatric BD unless numerous other risk factors, or symptoms such as euphoria, are present; or unless BD is unusually common in a particular clinical setting (19). Aggression that is markedly episodic, and that co-occurs with other symptoms of mania, should definitely trigger careful assessment of mood pathology and family history of mood disorder.

Grandiosity. Some have suggested that grandiosity could also be considered a 'cardinal' symptom of pediatric BD (5). However, a fairly large percentage of youths with pediatric BD fail to show this symptom (6). At the same time, a large group of

youths without pediatric BD will show inflated self-esteem and arrogance. These traits are a core feature of antisocial behavior and contribute to several of the 20 items comprising the Psychopathy Checklist-Revised (28) and its adapted versions for youths (29). Early reports of the phenomenology of pediatric BD may have overestimated the specificity of this symptom to pediatric BD, because youths with diagnoses besides ADHD or pediatric BD were excluded from the sample (30) – thus eliminating youths with conduct disorder and other precursors to antisocial personality disorder. Moreover, there appear to be potential differences in cultural and research operational definitions of what constitutes pathologic grandiosity (31, 32). Adding to the complexity, clinical grandiosity can be a challenge to recognize in younger children, because they may fantasize that they are the 'best' dancer, football player, and so forth – all as part of developmentally appropriate imagination. Adolescents, particularly those with narcissistic personality traits, can also be quite grandiose, without a mood disorder necessarily being involved. Substance use can also trigger experiences of grandiosity. *Fluctuations* in self-esteem and grandiosity are theoretically more promising as a construct that would differentiate pediatric BD from other conditions such as conduct disorder, where inflated self-esteem would be more trait-like (33, 34).

Two other symptoms that appear to be fairly *specific* to BD are hypersexuality and decreased need for sleep. Hypersexuality in the absence of sexual abuse and exposure to sex (movies, or witnessing others having sex) appears to occur in less than half of cases with pediatric BD (6), but it is very rare to encounter in children outside of the context of abuse or mania. Similarly, decreased need for sleep is not evident in all cases of pediatric BD, but when a child or adolescent only sleeps 2 or 3 hours at night and the next day is not tired, then the behavior indicates need for careful evaluation of potential BD.

Finally, psychosis also appears to be associated with pediatric BD. Most research groups have found that approximately one-fifth of youths meeting diagnostic criteria for bipolar I will also have hallucinations or delusions during the course of a mood episode (6). When groups have identified substantially higher rates of psychosis, the discrepancy appears attributable to differences in the operational definitions of 'psychosis' (31, 32). The presence of hallucinations or delusions in a youth should trigger careful evaluation for mood disorder, for even though pediatric BD is uncommon, it appears much less rare than early-onset schizophrenia or other potential causes of psychotic features in children.

Symptoms that appear unhelpful in the assessment of pediatric BD

Data are consistently emerging to indicate that some symptoms are less helpful in the assessment of pediatric BD. Many of these are behaviors that, although strongly associated with pediatric BD, are not specific to the disorder, and thus often occur in the context of other conditions. Difficulty concentrating, high motor activity, and aggression are examples of symptoms that do not appear diagnostically specific (6). Although these symptoms may not be helpful in differential diagnosis, they can play a central role in treatment planning and outcome evaluation. When these symptoms are present, evaluators should be careful to gather information about whether the symptoms appear to ebb and flow with other mood symptoms and changes in energy, versus having a more chronic presentation suggestive of other disorders. Diagnostic assessment should also consider the possibility that the symptoms might be accounted for by substance abuse, medication interactions or side effects, or (more rarely) some other general medical condition (35).

There are other symptoms that appear less useful both diagnostically and in terms of evaluating treatment. These include 'lack of insight' and 'bizarre appearance', 2 of the 11 symptoms assessed on the industry-standard measure of severity of manic symptoms, the Young Mania Rating Scale (YMRS) (36). These two symptoms are compromised by developmental changes in the degree of insight that might be expected, as well as by cultural differences in appearance that might constitute 'adolescent experimentation.' Objectively, these two items do not load significantly on a general factor of manic behavior (37, 38), and they actually lower the reliability of the YMRS total score when included (37, 39). For all of these reasons, youths would be better served by de-emphasizing or eliminating these symptoms from evaluations of pediatric BD.

Ultradian cycling versus mixed states

One of the main points of seeming departure between descriptions of pediatric BD versus adult bipolar phenomenology pertains to rates of cycling. The 'rapid cycling' variant of BD in adults requires that a patient have four distinct mood episodes over the course of a year, regardless of polarity. The presence of four or more annual episodes is a clinically significant feature, auguring an earlier age of onset, a more chronic course, less response to lithium, and greater comorbid substance use (40, 41).

Descriptions of pediatric BD have involved careful characterization of mood phenomenology, including the rate of mood switches or cycles between polarity (5, 8). Detailed counts of the shifts in mood have led to estimates that some youths with pediatric BD experience thousands or tens of thousands of mood swings over the course of a year (5). These figures have been met with skepticism in some quarters, given that four episodes per year would portend bad outcomes in adult psychiatry. Apparent differences are probably due to discrepant operational definitions, and it is most likely that the clinical presentations are more similar than quantitative estimates might suggest. One recently clarified issue is the distinction between a 'cycle' (a pronounced shift in mood and energy from one extreme to another) versus an 'episode,' technically denoting an extended period of mood dysregulation often encompassing multiple cycles in polarity (42, 43). The pediatric BD data have often been reporting high rates of *cycling,* whereas the number of distinct *episodes* appears to be small, with long duration, some recovery or remission, but also a high risk of relapse (8, 43, 44).

The second, more subtle phenomenological issue involves different clinical presentations that could legitimately fit into the 'mixed' category. Broadly speaking, two major categories might be referred to as the 'chocolate milk' and 'fudge ripple' versions of mixed states. The 'chocolate milk' version takes symptoms of depression and symptoms of mania, and dissolves them together into a new, homogeneous state that is qualitatively different from either component, and it is not possible to isolate a sample from the new state that is a pure example of either depression or mania (45, 46).

However, it is also possible to satisfy DSM criteria for a mixed state by showing a 'fudge ripple' presentation, where there are 'chunks' of manic and 'chunks' of depressive symptoms manifest for much of each day, most days of the week (45). A week's worth of such presentation might show clear ripples of both mania and depression every day of the week, yet a more fine-grained analysis could distinguish distinct periods within each day that were associated with different mood polarities (47). This sort of volatile, shifting mood presentation appears to be a common expression of mixed states in BD in adults, and progressively more common in younger age groups (48). The similarity in clinical presentation has probably been obscured by confusion about the distinction between episodes versus cycles, and also by differences in the conceptualization of mixed states

versus 'ultradian' cycling, which are likely to be labels for the same underlying clinical phenomenon.

<u>Chronicity versus periodic episodes: are distinct episodes necessary for bipolar disorder?</u>

A point of contention has been whether youths with chronic mood dysregulation should be considered as being on the bipolar spectrum. Some groups argue that mood is often pervasively irritable, that the onset of a mood illness can be insidious versus involving an acute change in functioning, and that the mood remains irritable for spans of months or years at a time (17). Others argue that there should be clear fluctuations in mood and energy if the behaviors are due to a mood disorder (5), even if there is irritable mood both in the context of depression and mania (7).

Episodic presentation of mood disturbance is associated with differences in the course (49, 50) and treatment response of BD (51). For youths at familial risk of developing BD, subsyndromal episodic mood disturbance appears to be a precursor to full-blown mood episodes (52, 53). One speculative possibility is that mood disturbance falls along a continuum of episodicity, with longer and more discrete episodes characterizing 'classic' bipolar I, and briefer and more frequent mood episodes characterizing rapid cycling variants, which in turn might shade into the chronic mood dysregulation labeled as 'borderline personality disorder' in adults (54). An alternate possibility is that there are at least two gross, overarching subtypes of BD: an episodic version that may be more responsive to lithium and shows other characteristics of 'Cade's Disease' (55) and a more chronic version with poorer lithium response and higher rates of comorbidity (56).

Bipolar not otherwise specified or subsyndromal bipolar disorder

There have been a variety of different operational definitions used for BD 'not otherwise specified (NOS).' Table 2 presents recognized clinical definitions of bipolar spectrum disorders, as well as more provisional research definitions. These include having mood disturbance but an inadequate number of 'B Criteria' symptoms (8, 57, 58), versus having enough symptoms but inadequate duration of the index mood states (8, 59), as well as possibly requiring periods of elevated mood or grandiosity as a way of 'narrowing' the phenotype, versus more chronic severe mood dysregulation (60). There is some evidence that bipolar NOS is on a spectrum with bipolar I, showing levels of mood disturbance

Table 2. Different definitions of bipolar disorder not otherwise specified and the 'broad phenotype' of pediatric bipolar disorder

Definition (source)	Comment
Cyclothymia (DSM-IV-TR)	Technically not considered a type of 'bipolar NOS' in DSM
	Rarely diagnosed in children or adolescents in research or clinical settings (4)
	Many research groups lump cyclothymia together with bipolar NOS (8)
	Difficult to disentangle from normal development, temperament, and comorbid conditions due to the requirement that patient not meet criteria for full manic, mixed, or major depressive episode during initial year of illness
	Still possible to diagnose reliably, and associated with a significant amount of impairment (59)
Repeated hypomanias in the absence of lifetime mania or depression (DSM-IV-TR)	Unlikely to be impairing enough to lead to treatment seeking; thus not observed clinically
	Challenging to differentiate from behavior within developmental normal limits
Insufficient duration of mood episodes (DSM-IV-TR)	This appears to be a common presentation (59)
Leibenluft et al. (60) further distinguish between cases with elated mood and/or grandiosity versus those with only irritability as mood disturbance; following Geller and Luby (5)	It is associated with a high degree of impairment (14, 59)
	This definition may include cases with mood severity that would otherwise warrant a diagnosis of manic, mixed, or depressive state
	Also may include cases with mixed states that involve polarity shifts if the diagnostician expects a week's worth of duration for either polarity
	Important to note that adult data are calling durations into question (174)
Insufficient number of manic symptoms	This also appears to be more prevalent than cases meeting strict DSM criteria for bipolar I or II, both in adolescent data (190) and in re-analyses of adult epidemiologic data (191)
Leibenluft et al. (60) include 'irritable hypomania' and 'irritable mania' as another 'intermediate' phenotype, even if accompanied by four or more other manic symptoms	Captures a much more heterogeneous group, and it is possible to meet criteria for this category relying entirely on non-specific symptoms (e.g., irritable mood plus distractibility, high motor activity, and rapid speech)
	Research designs typically have not documented episodicity of symptoms (190, 191)
	In spite of these caveats, this definition of NOS is still associated with high rates of impairment and service utilization (190, 191)
Severe mood dysregulation (previously referred to as a 'broad phenotype') [Leibenluft et al., definition (60)]	Recommended criteria: abnormal mood (anger or sadness) present at least half the day most days; accompanied by 'hyperarousal' (insomnia[a], agitation, distractibility, racing thoughts/flight of ideas; pressured speech, or social intrusiveness[a]); also shows increased reactivity to negative emotional stimuli compared to peers[a]; onset before age 12; duration at least 12 months with no more than 2 months symptom free; symptoms severe in at least one setting
	Rule outs: elated mood, grandiosity, or episodically decreased need for sleep; distinct episodes of 4+ days duration; meeting criteria for schizophreniform, schizophrenia, pervasive developmental disorder, or post-traumatic stress disorder; or meeting criteria for a substance use disorder in the past 3 months; or IQ < 80; or symptoms are attributable to a medication or general medical condition
	Comments: not yet tested against data. The **exclusion** of episodicity and of several symptoms more specific to bipolar disorder both are likely to select against bipolar spectrum cases. The inclusion of chronic presentations and sensitive but non-specific symptoms are likely to include many cases with presentations that are not on the bipolar spectrum. This category appears likely to include a blend of different etiologies and mechanisms as a result

and family history of mood disorder that on average fall in between the rates in bipolar I versus other mood disorders (14). Roughly 20% of youths initially meeting criteria for bipolar NOS progress to meet full criteria for bipolar I or bipolar II within < 2 years (8). Although research groups have been using somewhat different definitions, a consistent picture is emerging that bipolar NOS is

Table 2. Continued

Definition (source)	Comment
Bipolar NOS – research criteria from 'Course and Outcomes of Bipolar Youth' Study (NIMH R01 MH059929; 8, 14)	Requires 'core positive' – presence of distinct period of abnormally elevated, expansive, or irritable mood Minimum of two other 'B Criteria' symptoms if mood is mostly elated; at least three 'B Criteria' if irritable Requires clear change from individual's typical functioning (consistent with DSM-IV and ICD guidelines for hypomania) Requires 4+ h of mood within a 24-h period to be counted as an index 'day' of disturbance Requires 4+ days at a minimum over the course of a lifetime to diagnose bipolar NOS; non-consecutive days are acceptable Beginning to garner empirical support (8, 14) Needs replication in other samples/research groups
Child Behavior Checklist proxy diagnosis [after Mick et al. (149), used in subsequent re-analyses (186, 187)]. Often operationally defined as parent-reported *T*-scores of 70+ on Aggressive Behavior, Attention Problems, and Anxious/Depressed scales	Convenient to use for large sample studies Avoid problems of rater training and anchoring effects Prone to factors that might bias parent report Does not capture diagnostically specific symptoms; instead concentrates on sensitive symptoms that might also have high false-positive rate Focuses on symptoms that are likely to be 'shared' with other disorders at a genetic level Concerns that agreement with clinical or research-interview-derived (KSADS) diagnoses of bipolar spectrum might be modest

NOS = not otherwise specified; KSADS = Kiddie Schedule for Affective Disorders and Schizophrenia.
[a]Symptom is not part of current DSM-IV nosology for mania.

a highly impairing condition in youths, deserving of clinical attention.

Comorbidity

Robins and Guze discussed clinical comorbidity as an example of clinically 'associated features' that might help validate a diagnostic construct if a consistent pattern emerged across investigations (9). Studies of pediatric BD have repeatedly found high rates of comorbid ADHD (averaging 62%) (6), followed by elevated rates of oppositional/defiant disorder or conduct disorder, substance abuse or dependence, and anxiety disorders (4, 5, 7, 14, 61). These patterns of comorbidity appear broadly consistent with the patterns of comorbidity reported in adult bipolar samples (62, 63). ADHD and separation anxiety appear as more common comorbidities with very early onset (prior to age 11) BD, whereas substance use and eating disorder comorbidities appear more commonly observed in adolescence. There is least clarity about the overlap with ADHD in adults. Until recently, ADHD was presumed to be a pediatric condition that most would outgrow by adulthood. More recent studies have found a substantial rate of ADHD to persist into adulthood (64), and also elevated rates of ADHD in adult bipolar samples (65). Interestingly, even these more recent studies have primarily relied on self-report in adult samples, which are prone to underestimate the occurrence of ADHD (66), versus

pediatric samples using parents and teachers, who are more sensitive to ADHD. Thus, the pattern of comorbidity appears similar between pediatric and adult BD, with ADHD deserving further inquiry using collateral informants in adult samples.

Extremely high rates of comorbidity raise concerns about whether ADHD and pediatric BD are actually distinct disorders (67–70). Possibly, the inattention, motor activity, and anxiety frequently seen in association with pediatric BD may actually be 'core features' of the condition and not indicators of psychiatry comorbidity involving multiple diagnoses (71). However, a growing number of studies indicate that pediatric BD appears to be distinct from ADHD in terms of familial aggregation patterns and clinical correlates (8, 59, 72, 73), strongly indicating that cases with pediatric BD should not be conceptualized as simply being an extreme variant of ADHD. When ADHD is superimposed on pediatric BD, this may reflect a distinct subtype of illness (73, 74).

Demographics

Non-clinical epidemiologic data do not yet afford investigation into potential demographic differences in the incidence of pediatric BD. Clinical data appear to indicate that bipolar I disorder shows no sex differences in incidence after adjusting for the fact that more young males present to clinics for externalizing problems in general (4, 75,

76), nor are differences in rates of cyclothymia or bipolar NOS evident. Some data show a possible higher rate of bipolar II in female than male adolescents (8, 14, 76), consistent with adult data (77), perhaps due to differences in referral pattern (with females being more willing to acknowledge depressive symptoms or to seek treatment for them) versus being a true sex difference in risk or incidence (78). However, females with BD often experience more depressive episodes, whereas adult males exhibit more manic episodes (79), and adult females may also show a higher rate of mixed states. Findings suggest that BD may occur at equal rates in males and females in youth, but males may present with more mania and more ADHD and females with more depression, consistent with adult findings (75, 76). Biological sex also has not proven predictive of length of illness or time until relapse (14, 44). Clinicians will need to be vigilant about the possibility of encountering BD in females whose presentation is less likely to show pure mania or unmixed hypomania.

Minority youths with a mood disorder are more likely to be misdiagnosed with conduct disorder or schizophrenia (80), and more likely to be treated with older and/or depot antipsychotic medications (81, 82), similar to adult findings (83–85). Clinicians should be careful to assess for mood disorder systematically with patients from ethnic minorities, particularly when the presenting problem involves aggressive behavior or psychosis. Clinicians should also be alert to the potential for racial bias in diagnosis when gathering family history, making it prudent to gather symptom level information when possible to ascertain familial risk.

Family environmental characteristics

Families with mood disorder show disrupted family functioning and greater conflict within the family (86–88). This is partially because biological parents often have a mood disorder, reflecting the heritable component of the illness. Families of youths with pediatric BD also tend to show high levels of expressed (negative) emotion, which is linked with earlier age of onset, more rapid relapse, and poorer response to treatment (44, 89, 90). At present, it is unclear whether these associations represent a specific risk factor connected to pediatric BD, versus being correlates of severe pathology in general (89, 91).

Genetics

At present there are no twin studies or adoption studies published that have specifically focused on pediatric BD. It is well established that BD is (i) highly heritable (79, 92, 93), (ii) not a single-gene disorder (94), (iii) a condition where partial genetic loading may actually confer adaptive advantages (95, 96), and (iv) a condition where genetic variations may moderate treatment response (51, 97). Greater familial loading for the condition may be associated with earlier ages of onset and more severe course (98–102). There is some evidence suggesting progressively earlier ages of onset and more virulent course in recent generations (64), potentially consistent with a 'genetic anticipation' model (103, 104). However, attempts to demonstrate the molecular genetic mechanism underlying anticipation, such as expansion via trinucleotide repetition, have not yet been successful (92).

Investigations focusing on specific genes have so far failed to demonstrate statistically significant associations with pediatric BD (105–107). This could be attributable to low power for small but significant effects found in adult samples, or perhaps due to the genes involved in pediatric onset being different from those in later onset (92), with the possible exception of the neurotrophic factor Val66Met polymorphism (108). Several authorities believe that pediatric-onset BD might actually represent one of the best choices of phenotype for genetic investigations, because it is likely to have a more homogeneous and penetrant genotype and greater familial loading (92, 109). There is also indication that there may be susceptibility loci specifically influencing the age of onset of mania (110). Pilot work is underway on multiple molecular genetic and familial aggregation and twin studies that promise to greatly enrich our understanding of the genetic underpinnings of pediatric BD.

Studies of youths at risk of developing BD

There have been multiple studies of offspring where at least one parent was affected by mood disorder, often BD (111–114). Evidence strongly suggests that youths who have a parent with BD have more than doubled risk of developing psychopathology in general, with an even greater risk of developing a mood disorder, and the greatest risk differential for developing a bipolar spectrum illness. The most recent meta-analysis found that 5% of the youths at risk met criteria for a lifetime bipolar spectrum diagnosis at the time of assessment, versus 0% of the youths in the comparison groups (114). Recent empirical studies have found lifetime rates of BD as high as 10% when youths were followed to ages 16–26 (115).

There are several caveats relevant to the high-risk studies. The wide ranges in the rates of bipolar

illness found across studies cannot be attributed to sampling error, but instead are partly due to differences in research instrumentation and in the definitions used for bipolar symptoms and diagnoses. A second, related limitation is that most studies concentrated on bipolar I, and to a lesser extent, bipolar II, presentations in the child, and did not gather systematic data about cyclothymia and bipolar NOS. A third limitation is that these studies typically did not follow the youths through the age of greatest risk for the development of bipolar illness, thus underestimating the lifetime risk for these offspring. A fourth limitation is that in most studies, raters were not blind to parent diagnoses, creating an opportunity for bias in child diagnoses.

More recent studies address some of these limitations via longer follow-ups and reliance on semi-structured interviews synthesizing information from both parent and child. These studies are identifying precursors and potential prodromes of BD, such as early-onset depression (115–117), or episodic problems with attention, anxiety, and aggression (52, 53, 115). These findings are also broadly consistent with follow-back studies investigating child and adolescent symptomatology in adults with BD (65, 118–121).

Longitudinal course

Prospective studies provide important information about the phenomenology and diagnostic evolution of pediatric BD, and they will be the most persuasive line of evidence about continuity between the pediatric and adult definitions of BD (32). Longitudinal studies of a cohort initially ascertained before puberty have found that youths with pediatric BD tend to show long episodes with frequent mixed states, and high rates of relapse following remission or recovery (8, 44, 122). Substantial mood symptoms also appear to persist even during periods between acute episodes, also consistent with recent findings in adults (123) and especially those with younger ages of onset (41). Mixed states are the predominant mood state for bipolar I and bipolar NOS, whereas depressed states are more common in bipolar II (8). Overall, the rates of depression (including mixed states) appear to be higher than sometimes described in initial assessments of young outpatient samples (7, 17) and broadly consistent with what has been found in the adult literature (124).

Longitudinal work focusing on bipolar NOS is more scarce. Available findings indicate that BD NOS may be associated with a more chronic course and continued impairment (8), even though only roughly one-third have progressed into more classically defined and severe mood disorder during follow-up periods ranging from 2 to 4 years (8; SY Kahana, EA Youngstrom, JR Calabrese and RL Findling, unpublished data). In general, longitudinal studies suggest that 'fuzzy' presentations continue to be complicated at follow-up, but with chronic course and continued impairment (8, 125; SY Kahana, EA Youngstrom, JR Calabrese and RL Findling, unpublished data). These findings strongly suggest that mood symptoms failing to meet strict DSM or ICD thresholds are not simply typical juvenile behavior, or in most cases do they appear to spontaneously remit. At the same time, it remains unclear whether the majority of youths so affected will develop more 'classic' bipolar presentations.

Neurobiology

When comparing pediatric BD versus healthy volunteers, findings include increased ventricular size (126, 127), decreased thalamic size (128), decreased intracranial volume (127), elevated glutamate/glutamine in both frontal lobes and basal ganglia (129), and possible increases in anterior cingulated myo-inositol/creatine that decrease in response to lithium therapy (130). However, none of these differences have demonstrated statistically significant separations between BD versus schizophrenia (127, 128), raising questions about whether these changes are indications of general pathology (131). This ambiguity heightens the need for studies including an ADHD comparison group when investigating pediatric BD, to identify when pathophysiology might be specific to pediatric BD.

Imaging studies have found decreased amygdalar volumes in youths with bipolar (132–137), in contrast to the finding of enlarged amygdalar volumes in adults with BD (138, 139). However, functional magnetic resonance imaging with emotion tasks in both age groups have consistently demonstrated differences in activation in circuitry implicated in the recognition and regulation of emotions (140), converging evidence from affective startle probes, and other neuroscience methods (141–143). These preliminary findings implicate emotion regulation systems in BD across the age ranges investigated (134, 144).

Special topics

Functional impairment and quality of life

Pediatric BD involves considerable functional impairment and reduces quality of life for both

the affected youths and their families (1). In terms of level of functioning, the average Global Assessment of Functioning or Child Global Assessment Scale score for youths with research diagnoses of bipolar I ranges between 43 and 50, and the average for youths with other bipolar spectrum diagnoses ranges from 49 to 55 (8, 17, 44, 145, 146). These are well below the accepted threshold of 60 that connotes clinical 'caseness' (147).

Pediatric BD is associated with aggressive behavior, attention problems, anxious and depressed symptoms, delinquent behavior, social problems, withdrawal, and thought problems (in descending order) (4, 148, 149). Youths with pediatric BD were showing mean levels of these problems that exceeded the problems reported in 94% of age- and sex-matched peers in a nationally representative standardization sample (150, 151). The level of aggressive behavior reported across the pediatric BD samples ($T = 77$), exceeds the level of behavior problems reported for 996 per 1,000 youths in the standardization samples. Self-report and teacher-reported data on the same behavioral domains show lower levels of impairment than indicated by parent-report (145, 148, 152, 153); however, youths with pediatric BD still show statistically significant elevations on externalizing behavior problems according to both youth and teacher report, and the level of impairment is significantly higher than would be expected based on the typical level of agreement between parents, youths, and teachers about functioning (45).

Direct interviews of the parent and youth about psychosocial functioning suggest that youths with pediatric BD experience significantly less maternal–child warmth, more tension between the child and the mother and father, and more impaired peer relationships than youths with ADHD or no diagnosis (154). Even in a non-clinical epidemiologic sample, pediatric BD was associated with high rates of treatment seeking (56%), social impairment (67%), family impairment (56%), and school impairment (83%) based on the Kiddie Schedule for Affective Disorders and Schizophrenia interviews with the adolescent (57). More strikingly, youths with 'subsyndromal' BD (defined as not meeting criteria for bipolar I, bipolar II, or cyclothymia, yet who reported a period of elated/irritable mood associated with at least one other DSM-III-R symptom of mania – called 'core positive' bipolar NOS) showed levels of impairment that were not statistically different than found with major depressive disorder, with more than 50% of cases reporting impairment in at least one setting, and 39% seeking treatment (57). Longitudinal follow-up indicates that through age 18 years, 44% of cases with bipolar diagnoses (excluding bipolar NOS) attempted suicide, versus 22% of cases with major depressive disorder, 18% of 'core-positive' bipolar NOS cases, and only 1% of cases with no diagnosis (155). Bipolar disorder was associated with the highest rates of suicidal ideation (72% of cases, versus 52% of major depressive disorder, 41% of core positive bipolar NOS, and 6% of participants with no diagnosis), as well as a younger age at first attempt (mean of 13.3 years), higher rates of multiple attempts (88% of cases), and significantly greater medical lethality of attempts (155).

Personality/temperament

From Kraepelin forward, there has been recognition that there are temperamental qualities associated with bipolar spectrum illness (48, 156). Investigations in youths at risk by dint of having parents affected with BD tend to show higher levels of trait negative affect, lower activity, and poorer sleep and rhythmicity (157). A comparison of temperament in youths diagnosed with prepubertal or early adolescent bipolar disorder (PEA-BD) (requiring elated mood and/or grandiosity) versus youths with ADHD and no comorbid mood, or normal controls, found that PEA-BD was associated with higher novelty seeking, and the PEA-BD group also differed from normal controls in terms of lower reward dependence, lower persistence, less self-direction, and lower cooperativeness (158).

Clinical utility

There are several important ways in which the diagnosis of pediatric BD has demonstrated clinical utility. One is its *predictive value*: pediatric BD has robust associations with measures of symptomatology, impairment, and caregiver burden. The pediatric BD diagnosis also shows *prognostic value*: youths with BD are at higher risk for suicidality, substance use, and juvenile offending and incarceration (44, 155). Although many youths experience periods of improvement, rates of relapse/recurrence are high and episodes tend to be long (8, 44), with youths typically spending most weeks of a given year experiencing impaired mood (8). Thus, identifying that a youth meets criteria for BD communicates important information about their long-term risk for critical outcomes.

The pediatric BD diagnosis is also accruing substantial *prescriptive value*. A correct diagnosis of pediatric BD indicates a set of treatment strategies, including pharmacologic mood stabilization using lithium, divalproex, or atypical antipsychot-

ics (13, 159), as well as psychosocial interventions concentrating on psychoeducation (160), family functioning (86), or modified versions of cognitive behavioral therapy designed to address the distinct issues involved in mania versus depression, as well as the triggers associated with mood dysregulation (161–163). These treatment recommendations were initially extrapolated from experience with treating adult BD, but increasingly they are being supported by clinical trials with pediatric samples. The consistency of treatment response in youths versus adults is circumstantial evidence suggestive of the validity of the diagnosis in youths (9).

The diagnosis of pediatric BD also has clinical utility by contraindicating treatments that are ineffective at stabilizing moods. Undiagnosed pediatric BD will rarely be mistaken for normal functioning, and instead will lead to well-intentioned treatments for other conditions. Although available evidence strongly suggests that stimulant medication is well tolerated in pediatric BD when mood stabilizers are already started, there is concern that the use of stimulants or antidepressants without concomitant mood stabilization could provoke new manic or mixed attacks (117, 164, 165). The evidence for pharmacotoxicity, or medications inducing new manic episodes, is currently ambiguous (166), but clearly there is clinical value in a diagnosis that focuses attention on efficacious interventions and proscribes treatments that are at best ineffective and at worst harmful.

Dimensional versus categorical diagnosis and the boundary problem

It is uncertain whether pediatric BD represents a distinct category of illness, versus involving the expression of extremes in mood and temperamental tendencies that are present to varying degrees throughout the population. On one hand, diagnoses of pediatric BD and its subtypes can be made reliably (22, 23). Pediatric BD diagnoses have also demonstrated compelling evidence of clinical validity, as well as neuropsychological features and familial aggregation with other mood disorders. On the other hand, the evidence could also be interpreted as a continuum of impairment and symptom severity, with bipolar I being the most extreme presentation along a continuum that includes bipolar II, cyclothymia, and bipolar NOS or 'core positive' cases (14), and perhaps shading into the 'broad phenotype' of severe mood dysregulation (60) as well as non-impairing variations in temperament. The current diagnostic categories have not been proven to reflect true qualitative differences in presentation or quantitative differences in course and outcome.

Another possibility is that there might be subtypes of illness that have not been accurately demarcated yet. For example, the high rate of comorbidity with ADHD in cases of pediatric BD is consistent with new data indicating that episodic problems with attention and energy may be prodromes of BD (53). There are similar issues attached to the high rates of comorbidity with conduct problems (167) and anxiety (8). Finally, there are data suggesting that clinically meaningful distinctions should be made between a 'Cade's Disease' presentation involving good premorbid functioning, distinct mood episodes, reasonable inter-episode functioning, and elated mood during at least some manic episodes (55), versus a clinical picture that involves more frequent mood episodes with more mixed states, and more gradual onset and offset or more chronic presentation (56, 168). However, none of these boundaries have yet been formally tested using statistical models specifically designed to evaluate the hypothesis that there are categories or subtypes versus a continuum of behavior (169). It is noteworthy that the available evidence is most consistent with a polygenic model for BD. Apparent comorbidities could be due to some 'bipolar' cases also having genes implicated in other disorder phenotypes, and also in some 'bipolar' genes occurring in youths with other non-bipolar diagnoses.

Conclusion and recommendations

Considerable progress has been made in validating the diagnosis of BD in children and adolescents. There exists a group of youths whose symptom presentation meets strict DSM-IV criteria for bipolar spectrum diagnoses, and there is a broader spectrum of cases that show symptoms of mania without meeting full criteria for a DSM diagnosis. Youths with bipolar spectrum diagnoses show considerable impairment, a strong familial association with mood disorder (and BD in particular), and morphological features and neuroaffective functioning that are consistent with findings in adults with BD, all of which are suggestive of continuity between the pediatric and adult diagnoses. The pattern of comorbid diagnoses and associated clinical features is generally consistent across research groups investigating pediatric samples, and appears broadly consistent between youth and adult findings insofar as investigations have measured comparable diagnoses.

The main points that are often considered to be differences between pediatric versus adult

presentation, upon close examination, do not appear to offer substantial challenges to the validity of the pediatric bipolar diagnosis. What has been characterized as 'ultra-rapid' or 'ultradian' cycling in youths appears to be a clinical presentation that would be described as a 'mixed state' in adult psychiatry. This sort of mixed presentation is both common in adults with BD, and it is associated with features making it plausible that it would be prevalent in youths (170). Many other critiques of pediatric BD have concentrated on how the modal presentation in youths differs from the 'classic' bipolar presentation (32, 70, 171). However, adult BD extends well beyond the boundaries of 'Cade's Disease' to encompass a broad spectrum of presentations, including predominantly rapid cycling and mixed states, or manias dominated by irritable instead of euphoric mood (172, 173). Adult studies are also beginning to document the existence of a 'soft spectrum' of bipolar illness, marked by shorter duration of mood states that appears highly prevalent and also associated with the potential for clinical impairment (174). The growing expectation is that there will be considerable developmental continuity between pediatric BD and adult presentations, where affected youths will continue to show more mixed states, frequent relapse, poorer response to lithium monotherapy, and the other features associated with non-classic presentation (54).

Schema for diagnosis

Clinicians and researchers should be open to the possibility of making a bipolar diagnosis in youths and adolescents, in light of the mounting prevalence data suggesting that affected cases are presenting to most types of clinical infrastructure. Cues that should trigger detailed assessment include a family history of mood disorder – and especially of BD – episodes of aggressive behavior (particularly in the context of other manic symptoms), early age of onset for depression, mood disorder with psychotic features, recurrent depressive episodes that are resistant to treatment (suggesting possible bipolar II), episodic presentation of symptoms otherwise appearing similar to ADHD, and mood destabilization secondary to trials of stimulant or antidepressant medications. It makes sense to screen for family history of BD and to have a familiar adult complete a lifetime screener for manic symptomatology in the youth prior to initiating pharmacologic treatment for depression or for complicated presentations of attention problems or anxiety.

The DSM and ICD set of symptoms appear to also apply to BD in youths, with some allowance made for developmental constraints on expression (175). However, 'bizarre appearance' and 'lack of insight' both show serious problems in terms of construct validity as associated features of mania (37). Diagnosis should routinely involve a collateral informant familiar with the child's behavior. Diagnostic interviews should also involve interview and observation of the youth, even though the youth's capacity to complete a formal interview might be limited. Direct interview of the youth offers opportunities to observe signs of pervasive developmental disorder that could contribute to poor frustration tolerance and symptoms that might be misattributed to mood disorder, as well as to ask youths about aspects of mood and cognitive functioning not readily observed by others (176, 177).

Confidence in a bipolar diagnosis increases when there is evidence of changes in mood that are associated with multiple other manic symptoms, particularly symptoms that are more specific to BD (although it must be kept in mind that some legitimate bipolar cases will not show these more specific symptoms). The manifestation of these symptoms in multiple settings also increases confidence in the diagnosis and provides a clinical marker for more severe impairment. However, given the low level of inter-rater agreement about youth behavior in general, often one informant will be much more concerned about mood symptoms than others. Family history and screening instruments will be helpful diagnostic aids, but they will not be decisive by themselves and cannot substitute for a careful diagnostic interview.

Diagnosticians need to attend to issues of comorbidity and symptom overlap. As outlined in Table 1, many symptoms could easily be due to other disorders either instead of or superimposed on top of a mood disorder. Some qualitative distinctions have been made between the characteristic phenomenology of symptoms in the context of a mood episode versus in the context of anxiety, ADHD, or conduct disorders (5, 171, 178, 179). One of the recurring themes in differentiating mood symptoms from other disorders is that anxiety, ADHD, and conduct disorder all tend to be associated with more *chronic* presentations of the behaviors, whereas mood symptoms may have more of a tendency to *fluctuate*. The DSM and ICD frameworks also require that the symptoms of anxiety, inattention, motor activity, psychosis, or rule-breaking behavior be present during periods of euthymia to warrant the addition of a separate 'comorbid' diagnosis. Diagnosis can be aided by assessing changes in

mood and energy both retrospectively and prospectively over the course of treatment, via techniques such as the life charting method, or clinical evaluation at subsequent treatment visits.

The current DSM criteria for a manic episode, mixed state, hypomanic episode, and depressive episode all appear reasonably validated for application to children and adolescents, with the possible exception of duration criteria. When describing mood presentation in children, it would be helpful to label unstable, oscillating shifts between manic and depressed poles within the course of the same week (or same day) as a form of 'mixed episode,' rather than multiple 'cycles' of episodes (42, 180). The validity of hypomania in children is less clear, both because it is challenging to distinguish from behavior 'within normal limits' for age, and also because of the frequency of oscillating mixed presentations. The four-day duration requirement for hypomania has not been supported by data in adults (174), and four days is likely to be longer than the typical duration of hypomania in youths as well. It would be useful to add 'mixed hypomania' as a mood state to capture episodes with hypomanic symptoms mingled with depressive symptoms. Such a category would better convey that the presentation appears to be on the bipolar spectrum than would labels such as 'depression' or 'agitated depression.'

Cyclothymia is rarely diagnosed either clinically (4) or in research (8, 17, 44), and much less is known about the validity of it as a diagnostic label in youths. Many are 'lumping' clinical presentations that could fit criteria for cyclothymia into the bipolar NOS category. The long duration (at least 1 year with no more than 2 months free of symptoms) and the exclusion of severe mood episodes (which would change the diagnosis if they reached sufficient acuity for a depressed, manic, or mixed state) make it challenging to differentiate cyclothymia both from temperament and also from common diagnoses with more chronic presentations. When bipolar NOS is diagnosed, it would be helpful to indicate the subtype of NOS involved (see Table 2), to help gain experience with the validity of the different types (60). Finally, one of the most clinically valuable distinctions may be between those cases with distinct mood episodes (especially with good premorbid or inter-episode functioning) versus those with more chronic mood dysregulation and insidious onset. Although not yet reflected in formal DSM or ICD guidelines, it is becoming evident that this distinction between 'Cade's Disease' or a 'narrow phenotype' versus a more 'broad phenotype' provides important information about prognosis and treatment selection (56).

Principal areas of disagreement

There are several remaining areas of controversy, including the relative role of elated versus irritable mood, the boundaries of the 'broad phenotype' of pediatric BD, and the question of whether DSM identifies the most clinically relevant categories or subtypes of BD. More work needs to employ theoretically driven models of aggression. Aggression in the context of a mood disorder may be more reactive and less proactive, more impulsive and less planful or instrumental – in short, more likely to be 'hot' rather than 'cold' aggression (181). Aggression might be linked to interpersonal status and social dominance in the family or peer group, consistent with older emotion models of depression (182) and also with the high rejection sensitivity often observed in BD (183).

How broad is the 'broad phenotype'?

Clinical presentations that involve mood dysregulation range from single episodes of depression or mania in otherwise well-functioning individuals, through rapid cycling [operationally defined as four distinct mood episodes in the course of a year, regardless of polarity (40, 47)], into more chronic presentations of rapidly fluctuating or oscillating moods. In adults, chronic yet oscillating or labile mood disturbance is a frequent clinical presentation that could be conceptualized variously as a long duration of a mixed episode, rapid cycling BD, cyclothymia, or borderline personality disorder (54). There is relatively little controversy about diagnosis of cases with distinct mood episodes and acute onset, even in youths – the 'Cade's Disease' presentation. However, this presentation appears to be rare in childhood. The more chronic and oscillating presentation appears to be much more prevalent. Different operational definitions of 'broad phenotypes' or bipolar NOS have been offered (60), all of which need rigorous testing with data collected in a methodologically stringent fashion.

Priority areas for future work

Continued longitudinal studies of both 'at risk' (53, 157, 184) as well as 'already identified' (8, 44, 185) samples are essential to understand developmental continuity between pediatric 'bipolar disorder' and adult BD. Studies where clinicians with experience in one age group have the opportunity to evaluate patients in a different age group also deserve emphasis. The balkanization of the field into 'child,' 'adult,' and 'late life' specializations hampers understanding of development and change.

Epidemiological studies that involve interviews with collateral informants, and that adapt probes and anchors to assess for mania in pediatric contexts, also should be a priority, along with re-analyses and add-on studies in samples ascertained for related disorders or behaviors. For example, longitudinal studies of ADHD should include a subset of youths likely to develop BD if prior estimates of comorbidity are accurate (186, 187). Investigations in samples ascertained for antisocial behavior and work in forensic settings will also be vital to clarify the boundaries between mania and other disorders affecting impulse control.

The most obvious, and from the consumer's perspective, the most important area for continued research is the arena of treatment. Until there are well-tolerated interventions that can produce remission and promote positive functioning in the majority of cases, or until there is effective and safe prophylaxis available, then the treatment of pediatric BD deserves to be one of the highest priorities in the mental health research agenda.

Acknowledgements

References

1. Lofthouse N, Fristad M. Psychosocial interventions for children with early-onset bipolar spectrum disorder. Clin Child Fam Psychol Rev 2004; 21: 71–89.
2. Hellander M. Lithium Testing in Children: A Public Health Necessity. Washington, DC: Testimony to the Food and Drug Administration, 2002.
3. Naylor MW, Anderson TR, Kruesi MJ, Stoewe M. Pharmacoepidemiology of Bipolar Disorder in Abused and Neglected State Wards. Poster presented at the National Meeting of the American Academy of Child and Adolescent Psychiatry, October 22–27, 2002, San Francisco, CA, USA.
4. Youngstrom EA, Youngstrom JK, Starr M. Bipolar diagnoses in community mental health: Achenbach CBCL profiles and patterns of comorbidity. Biol Psychiatry 2005; 58: 569–575.
5. Geller B, Luby J. Child and adolescent bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 1997; 36: 1168–1176.
6. Kowatch RA, Youngstrom EA, Danielyan A, Findling RL. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. Bipolar Disord 2005; 7: 483–496.
7. Findling RL, Gracious BL, McNamara NK et al. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. Bipolar Disord 2001; 3: 202–210.
8. Birmaher B, Axelson D, Strober M et al. Clinical course of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 2006; 63: 175–183.
9. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 1970; 126: 983–986.
10. Cantwell DP. Classification of child and adolescent psychopathology. J Child Psychol Psychiatry 1996; 37: 3–12.
11. Youngstrom EA, Findling RL, Youngstrom JK, Calabrese JR. Toward an evidence-based assessment of pediatric bipolar disorder. J Clin Child Adolesc Psychol 2005; 34: 433–448.
12. Carlson GA, Jensen PS, Findling RL et al. Methodological issues and controversies in clinical trials with child and adolescent patients with bipolar disorder: report of a consensus conference. J Child Adolesc Psychopharmacol 2003; 13: 1–15.
13. Kowatch RA, Fristad MA, Birmaher B, Wagner KD, Findling RL, Hellander M. Treatment guidelines for children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005; 44: 213–235.
14. Axelson DA, Birmaher B, Strober M et al. Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 2006; 63: 1139–1148.
15. Soutullo CA, Chang KD, Diez-Suarez A et al. Bipolar disorder in children and adolescents: international perspective on epidemiology and phenomenology. Bipolar Disord 2005; 7: 497–506.
16. Biederman J, Wozniak J, Kiely K et al. CBCL clinical scales discriminate prepubertal children with structured interview-derived diagnosis of mania from those with ADHD. J Am Acad Child Adolesc Psychiatry 1995; 34: 464–471.
17. Wozniak J, Biederman J, Kiely K et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry 1995; 34: 867–876.
18. Geller B, Williams M, Zimerman B, Frazier J, Beringer L, Warner KL. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. J Affect Disord 1998; 51: 81–91.
19. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-based Medicine: How to Practice and Teach EBM, 2nd edn. New York: Churchill Livingstone, 2000.
20. Jensen PS, Youngstrom EA, Steiner H et al. Consensus report on impulsive aggression as a symptom across diagnostic categories in child psychiatry – implications for medication studies. J Am Acad Child Adolesc Psychiatry 2007; 46: 309–322.
21. Nottelmann E, Biederman J, Birmaher B et al. National Institute of Mental Health research roundtable on prepubertal bipolar disorder. J Am Acad Child Adolesc Psychiatry 2001; 40: 871–878.
22. Kaufman J, Birmaher B, Brent D et al. Schedule for Affective Disorders and Schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997; 36: 980–988.
23. Geller B, Zimerman B, Williams M et al. Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. J Am Acad Child Adolesc Psychiatry 2001; 40: 450–455.
24. Mick E, Spencer T, Wozniak J, Biederman J. Heterogeneity of irritability in attention-deficit/hyperactivity disorder subjects with and without mood disorders. Biol Psychiatry 2005; 58: 576–582.
25. Papolos DF, Papolos J. The Bipolar Child: The Definitive and Reassuring Guide to Childhood's Most Misunder-

stood Disorder, 2nd edn. New York: Broadway Books, 2002.

26. Leibenluft E, Blair RJR, Charney DS, Pine DS. Irritability in pediatric mania and other childhood psychopathology. Ann N Y Acad Sci 2003; 1008: 201–218.

27. Arnold LE, Vitiello B, McDougle C et al. Parent-defined target symptoms respond to risperidone in RUPP autism study: customer approach to clinical trials. J Am Acad Child Adolesc Psychiatry 2003; 42: 1443–1450.

28. Hare RD. The Hare PCL-R: some issues concerning its use and misuse. Legal Criminol Psychol 1998; 3: 99–119.

29. Forth AE, Mailloux DL. Psychopathy in youth: what do we know? In: Gacono CB ed. The Clinical and Forensic Assessment of Psychopathy. Mahwah, NJ: Lawrence Erlbaum Associates, Inc., 2000: 25–54.

30. Geller B, Craney JL, Bolhofner K et al. Phenomenology and longitudinal course of children with a prepubertal and early adolescent bipolar disorder phenotype. In: Geller B, DelBello MP eds. Bipolar Disorder in Childhood and Early Adolescence. New York: Guilford, 2003: 25–50.

31. Geller B, Zimerman B, Williams M, Delbello MP, Frazier J, Beringer L. Phenomenology of prepubertal and early adolescent bipolar disorder: examples of elated mood, grandiose behaviors, decreased need for sleep, racing thoughts and hypersexuality. J Child Adolesc Psychopharmacol 2002; 12: 3–9.

32. Harrington R, Myatt T. Is preadolescent mania the same condition as adult mania? A British perspective Biol Psychiatry 2003; 53: 961–969.

33. Baumeister R, Bushman BJ, Campbell WK. Self-esteem, narcissism, and aggression: does violence result from low self-esteem or from threatened egotism? Curr Dir Psychol Sci 2000; 9: 26–29.

34. Frick PJ, Bodin SD, Barry CT. Psychopathic traits and conduct problems in community and clinic-referred samples of children: further development of the Psychopathy Screening Device. Psychol Assess 2000; 12: 382–393.

35. Soto O, Murphy TK. The immune system and bipolar affective disorder. In: Geller B, DelBello MP eds. Bipolar Disorder in Childhood and Early Adolescence. New York: Guilford, 2003: 193–214.

36. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity, and sensitivity. Br J Psychiatry 1978; 133: 429–435.

37. Youngstrom EA, Danielson CK, Findling RL, Gracious BL, Calabrese JR. Factor structure of the Young Mania Rating Scale for use with youths ages 5 to 17 years. J Clin Child Adolesc Psychol 2002; 31: 567–572.

38. Youngstrom EA, Findling RL, Sachs G et al. Manic Symptoms in Bipolar and Nonbipolar Youths Across Eleven Research Groups Using the Young Mania Rating Scale. Paper presented at the NIMH Pediatric Bipolar Disorder Conference, March 2003, Washington, DC, USA.

39. Gracious BL, Youngstrom EA, Findling RL, Calabrese JR. Discriminative validity of a parent version of the Young Mania Rating Scale. J Am Acad Child Adolesc Psychiatry 2002; 41: 1350–1359.

40. Dunner DL, Patrick V, Fieve RR. Rapid cycling manic depressive patients. Compr Psychiatry 1977; 18: 561–566.

41. Perlis R, Miyahara S, Marangell LB et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2004; 55: 875–881.

42. Kramlinger KG, Post RM. Ultra-rapid and ultradian cycling in bipolar affective illness. Br J Psychiatry 1996; 168: 314–323.

43. Tillman R, Geller B. Definitions of rapid, ultrarapid, and ultradian cycling and of episode duration in pediatric and adult bipolar disorders: a proposal to distinguish episodes from cycles. J Child Adolesc Psychopharmacol 2003; 13: 267–271.

44. Geller B, Tillman R, Craney JL, Bolhofner K. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch Gen Psychiatry 2004; 61: 459–467.

45. Youngstrom EA, Meyers OI, Youngstrom JK, Calabrese JR, Findling RL. Diagnostic and measurement issues in the assessment of pediatric bipolar disorder: implications for understanding mood disorder across the life cycle. Dev Psychopathol 2006; 18: 989–1021.

46. Jamison KR. An Unquiet Mind: A Memoir of Moods and Madness. New York: Vintage Books, 1995.

47. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th – Text Revision ed. Washington, DC: 2001.

48. Kraepelin E. Manic-depressive Insanity and Paranoia. Edinburgh: Livingstone, 1921.

49. Bhangoo RK, Dell ML, Towbin K et al. Clinical correlates of episodicity in juvenile mania. J Child Adolesc Psychopharmacol 2003; 13: 507–514.

50. Duffy A, Alda M, Kutcher S, Fusee C, Grof P. Psychiatric symptoms and syndromes among adolescent children of parents with lithium-responsive or lithium-nonresponsive bipolar disorder. Am J Psychiatry 1998; 155: 431–433.

51. Duffy A, Alda M, Kutcher S et al. A prospective study of the offspring of bipolar parents responsive and nonresponsive to lithium treatment. J Clin Psychiatry 2002; 63: 1171–1178.

52. Egeland JA, Shaw JA, Endicott J et al. Prospective study of prodromal features for bipolarity in well Amish children. J Am Acad Child Adolesc Psychiatry 2003; 42: 786–796.

53. Shaw JA, Egeland JA, Endicott J, Allen CR, Hostetter AM. A 10-year prospective study of prodromal patterns for bipolar disorder among Amish youth. J Am Acad Child Adolesc Psychiatry 2005; 44: 1104–1111.

54. MacKinnon DF, Pies R. Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders. Bipolar Disord 2006; 8: 1–14.

55. Ghaemi SN, Ko JY, Goodwin FK. 'Cade's disease' and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. Can J Psychiatry 2002; 47: 125–134.

56. Masi G, Perugi G, Toni C et al. The clinical phenotypes of juvenile bipolar disorder: toward a validation of the episodic-chronic-distinction. Biol Psychiatry 2006; 59: 603–610.

57. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. J Am Acad Child Adolesc Psychiatry 1995; 34: 454–463.

58. Chang K, Saxena K, Howe M. An open-label study of lamotrigine adjunct or monotherapy for the treatment of adolescents with bipolar depression. J Am Acad Child Adolesc Psychiatry 2006; 45: 298–304.

59. Findling RL, Youngstrom EA, McNamara NK et al. Early symptoms of mania and the role of parental risk. Bipolar Disord 2005; 7: 623–634.

60. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. Am J Psychiatry 2003; 160: 430–437.

61. Biederman J, Mick E, Faraone SV, Spencer T, Wilens TE, Wozniak J. Pediatric mania: a developmental subtype of bipolar disorder? Biol Psychiatry 2000; 48: 458–466.

62. Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 1997; 27: 1079–1089.

63. Kogan JN, Otto MW, Bauer MS et al. Demographic and diagnostic characteristics of the first 1000 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Bipolar Disord 2004; 6: 460–469.

64. Kessler RC, Berglund P, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry 2005; 62: 593–602.

65. Nierenberg AA, Miyahara S, Spencer T et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. Biol Psychiatry 2005; 57: 1467–1473.

66. Pelham JWE, Fabiano GA, Massetti GM. Evidence-based assessment of attention deficit hyperactivity disorder in children and adolescents. J Clin Child Adolesc Psychiatry 2005; 34: 449–476.

67. McClellan J. Mania in young children. J Am Acad Child Adolesc Psychiatry 1998; 37: 346–347.

68. Kihlstrom JF. To honor Kraepelin: from symptoms to pathology in the diagnosis of mental illness. In: Beutler LE, Malik M eds. Rethinking the DSM: Psychological Perspectives. Washington, DC: American Psychological Association, 2001: 279–303.

69. Carlson GA. Mania and ADHD: comorbidity or confusion. J Affect Disord 1998; 51: 177–187.

70. Klein RG, Pine DS, Klein DF. Resolved: mania is mistaken for ADHD in prepubertal children. J Am Acad Child Adolesc Psychiatry 1998; 37: 1093–1096.

71. Papolos DF. Bipolar disorder and comorbid disorders: the case for a dimensional nosology. In: Geller B, DelBello MP eds. Bipolar Disorder in Childhood and Early Adolescence. New York: Guilford, 2003: 76–106.

72. Wozniak J, Biederman J, Mundy E, Mennin D, Faraone SV. A pilot family study of childhood-onset mania. J Am Acad Child Adolesc Psychiatry 1995; 34: 1577–1583.

73. Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? J Am Acad Child Adolesc Psychiatry 1997; 36: 1378–1387.

74. Faraone SV, Biederman J, Monuteaux MC. Attention deficit hyperactivity disorder with bipolar disorder in girls: further evidence for a familial subtype? J Affect Disord 2001; 64: 19–26.

75. Duax J, Scovil K, Youngstrom EA et al. Effects of sex on rates of bipolar spectrum disorder and presenting mood state in youth ages 5–17. Bipolar Disord 2005; 7 (Suppl. 2): 49.

76. Biederman J, Kwon A, Wozniak J et al. Absence of gender differences in pediatric bipolar disorder: findings from a large sample of referred youth. J Affect Disord 2004; 83: 207–214.

77. Berk M, Dodd S. Bipolar II disorder: a review. Bipolar Disord 2005; 7: 11–21.

78. Cyranowski JM, Frank E, Young E, Shear K. Adolescent onset of the gender difference in lifetime rates of major depression. Arch Gen Psychiatry 2000; 57: 21–27.

79. Goodwin FK, Jamison KR. Manic-depressive Illness. New York: Oxford University Press, 1990.

80. DelBello MP, Lopez-Larson MP, Soutullo CA, Strakowski SM. Effects of race on psychiatric diagnosis of hospitalized adolescents: a retrospective chart review. J Child Adolesc Psychopharmacol 2001; 11: 95–103.

81. DelBello MP, Soutullo CA, Strakowski SM. Racial differences in treatment of adolescents with bipolar disorder. Am J Psychiatry 2000; 157: 837–838.

82. Arnold LM, Strakowski SM, Schwiers ML et al. Sex, ethnicity, and antipsychotic medication use in patients with psychosis. Schizophr Res 2004; 66: 169–175.

83. Arnold LM, Keck PE Jr, Collins J et al. Ethnicity and first-rank symptoms in patients with psychosis. Schizophr Res 2004; 67: 207–212.

84. Strakowski SM, Hawkins JM, Keck PE Jr et al. The effects of race and information variance on disagreement between psychiatric emergency service and research diagnoses in first-episode psychosis. J Clin Psychiatry 1997; 58: 457–463.

85. Neighbors HW, Trierweiler SJ, Ford BC, Muroff JR. Racial differences in DSM diagnosis using a semi-structured instrument: the importance of clinical judgment in the diagnosis of African Americans. J Health Soc Behav 2003; 44: 237–256.

86. Miklowitz DJ, George EL, Axelson DA et al. Family-focused treatment for adolescents with bipolar disorder. J Affect Disord 2004; 82 (Suppl. 1): S113–S128.

87. Chang KD, Blasey C, Ketter TA, Steiner H. Family environment of children and adolescents with bipolar parents. Bipolar Disord 2001; 3: 73–78.

88. DuRocher Schudlich T, Youngstrom EA, Calabrese JR, Findling RL. The Role of Family Functioning in Bipolar Disorder in Families. J Abnormal Child Psychol 2007; in press.

89. Miklowitz DJ. The role of family systems in severe and recurrent psychiatric disorders: a developmental psychopathology view. Dev Psychopathol 2004; 16: 667–688.

90. Fristad MA, Goldberg-Arnold JS, Gavazzi SM. Multi-family psychoeducation groups (MFPG) for families of children with bipolar disorder. Bipolar Disord 2002; 4: 254–262.

91. Hooley JM, Hiller JB. Family relationships and major mental disorder: risk factors and preventive strategies. In: Sarason BR, Duck S eds. Personal Relationships, Implications for Clinical and Community Psychology. Wiley: New York, 2001: 61–87.

92. Faraone SV, Glatt SJ, Tsuang MT. The genetics of pediatric-onset bipolar disorder. Biol Psychiatry 2003; 53: 970–977.

93. McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch Gen Psychiatry 2003; 60: 497–502.

94. Grigoroiu-Serbanescu M, Martinez M, Nothen MM et al. Different familial transmission patterns in bipolar I disorder with onset before and after age 25. Am J Med Genet 2001; 105: 765–773.

95. Jamison KR. Touched with Fire: Manic-depressive Illness and the Artistic Temperament. New York: Free Press, 1993.

96. Simeonova DI, Chang KD, Strong C, Ketter TA. Creativity in familial bipolar disorder. J Psychiatr Res 2005; 39: 623–631.

97. Alda M, Grof P, Rouleau GA, Turecki G, Young LT. Investigating responders to lithium prophylaxis as a strategy for mapping susceptibility genes for bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2005; 29: 1038–1045.

98. Bellivier F, Golmard J-L, Rietschel M et al. Age at onset in bipolar I affective disorder: further evidence for three subgroups. Am J Psychiatry 2003; 160: 999–1001.

99. Pauls DL, Morton LA, Egeland JA. Risks of affective illness among first-degree relatives of bipolar I old-order Amish probands. Arch Gen Psychiatry 1992; 49: 703–708.

100. Strober M, Morrell W, Burroughs J et al. A family study of bipolar I disorder in adolescence: early onset of symptoms linked to increased familial loading and lithium resistance. J Affect Disord 1988; 15: 255–268.

101. Rice J, Reich T, Andreasen NC et al. The familial transmission of bipolar illness. Arch Gen Psychiatry 1987; 44: 441–447.

102. Neuman RJ, Geller B, Rice JP, Todd RD. Increased prevalence and earlier onset of mood disorders among relatives of prepubertal versus adult probands. J Am Acad Child Adolesc Psychiatry 1997; 36: 466–473.

103. McInnis MG, McMahon FJ, Chase GA, Simpson SG, Ross CA, DePaulo JR Jr. Anticipation in bipolar affective disorder. Am J Hum Genet 1993; 53: 385–390.

104. Post RM, Weiss SRB, Leverich GS. Recurrent affective disorder: Roots in developmental neurobiology and illness progression based on changes in gene expression. Special Issue: Neural plasticity, sensitive periods, and psychopathology. Dev Psychopathol 1994; 6: 781–813.

105. Geller B, Cook EH Jr. Serotonin transporter gene (HTTLPR) is not in linkage disequilibrium with prepubertal and early adolescent bipolarity. Biol Psychiatry 1999; 45: 1230–1233.

106. Geller B, Cook EH Jr. Ultradian rapid cycling in prepubertal and early adolescent bipolarity is not in transmission disequilibrium with val/met COMT alleles. Biol Psychiatry 2000; 47: 605–609.

107. Ospina-Duque J, Duque C, Carvajal-Carmona L et al. An association study of bipolar mood disorder (type I) with the 5-HTTLPR serotonin transporter polymorphism in a human population isolate from Colombia. Neurosci Lett 2000; 292: 199–202.

108. Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K, Cook EH Jr. Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. Am J Psychiatry 2004; 161: 1698–1700.

109. Todd RD, Neuman R, Geller B, Fox LW, Hickok J. Genetic studies of affective disorders: should we be starting with childhood onset probands? J Am Acad Child Adolesc Psychiatry 1993; 32: 1164–1171.

110. Faraone SV, Glatt SJ, Su J, Tsuang MT. Three potential susceptibility loci shown by a genome-wide scan for regions influencing the age at onset of mania. Am J Psychiatry 2004; 161: 625–630.

111. DelBello MP, Geller B. Review of studies of child and adolescent offspring of bipolar parents. Bipolar Disord 2001; 3: 325–334.

112. Chang KD, Steiner H, Dienes K, Adleman N, Ketter T. Bipolar offspring: a window into bipolar disorder evolution. Biol Psychiatry 2003; 53: 945–951.

113. Lapalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. Can J Psychiatry 1997; 42: 623–631.

114. Hodgins S, Faucher B, Zarac A, Ellenbogen M. Children of parents with bipolar disorder. A population at high risk for major affective disorders. Child Adolesc Psychiatr Clin N Am 2002; 11: 533–553.

115. Hillegers MHJ, Reichart CG, Wals M, Verhulst FC, Ormel J, Nolen WA. Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. Bipolar Disord 2005; 7: 344–350.

116. Chang KD, Steiner H, Ketter TA. Psychiatric phenomenology of child and adolescent bipolar offspring. J Am Acad Child Adolesc Psychiatry 2000; 39: 453–460.

117. Geller B, Fox LW, Clark KA. Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children. J Am Acad Child Adolesc Psychiatry 1994; 33: 461–468.

118. Egeland JA, Hostetter AM, Pauls DL, Sussex JN. Prodromal symptoms before onset of manic-depressive disorder suggested by first hospital admission histories. J Am Acad Child Adolesc Psychiatry 2000; 39: 1245–1252.

119. Sachs GS, Baldassano CF, Truman CJ, Guille C. Comorbidity of attention deficit hyperactivity disorder with early- and late-onset bipolar disorder. Am J Psychiatry 2000; 157: 466–468.

120. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. J Affect Disord 1994; 31: 281–294.

121. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder J Clin Psychiatry 2003; 64: 161–174.

122. Geller B, Craney JL, Bolhofner K, Nickelsburg MJ, Williams M, Zimerman B. Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype. Am J Psychiatry 2002; 159: 927–933.

123. Benazzi F. Bipolar II. Disorder family history using the family history screen: findings and clinical implications. Compr Psychiatry 2004; 45: 77–82.

124. Judd LL, Akiskal HS, Schettler PJ et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002; 59: 530–537.

125. Lewinsohn PM, Rohde P, Seeley JR, Klein DN, Gotlib IH. Natural course of adolescent major depressive disorder in a community sample: predictors of recurrence in young adults. Am J Psychiatry 2000; 157: 1584–1591.

126. Botteron KN, Vannier MW, Geller B, Todd RD, Lee BC. Preliminary study of magnetic resonance imaging characteristics in 8- to 16-year-olds with mania. J Am Acad Child Adolesc Psychiatry 1995; 34: 742–749.

127. Friedman L, Findling RL, Kenny JT et al. An MRI study of adolescent patients with either schizophrenia or bipolar disorder as compared to healthy control subjects. Biol Psychiatry 1999; 46: 78–88.

128. Dasari M, Friedman L, Jesberger J et al. A magnetic resonance imaging study of thalamic area in adolescent patients with either schizophrenia or bipolar disorder as compared to healthy controls. Psychiatry Res 1999; 91: 155–162.

129. Castillo M, Kwock L, Courvoisie H, Hooper SR. Proton MR spectroscopy in children with bipolar affective disorder: preliminary observations. AJNR Am J Neuroradiol 2000; 21: 832–838.

130. Davanzo P, Thomas MA, Yue K et al. Decreased anterior cingulate myo-inositol/creatine spectroscopy resonance with lithium treatment in children with bipolar disorder. Neuropsychopharmacology 2001; 24: 359–369.

131. McDonald C, Bullmore ET, Sham PC et al. Association of genetic risks for schizophrenia and bipolar disorder

with specific and generic brain structural endopheno-types. Arch Gen Psychiatry 2004; 61: 974–984.

132. Blumberg HP, Fredericks C, Wang F et al. Preliminary evidence for persistent abnormalities in amygdala volumes in adolescents and young adults with bipolar disorder. Bipolar Disord 2005; 7: 570–576.

133. Chen BK, Sassi R, Axelson D et al. Cross-sectional study of abnormal amygdala development in adolescents and young adults with bipolar disorder. Biol Psychiatry 2004; 56: 399–405.

134. Chang K, Karchemskiy A, Barnea-Goraly N, Garrett A, Simeonova DI, Reiss A. Reduced amygdalar gray matter volume in familial pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005; 44: 565–573.

135. Frazier JA, Chiu S, Breeze JL et al. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am J Psychiatry 2005; 162: 1256–1265.

136. Adler CM, Levine AD, DelBello MP, Strakowski SM. Changes in gray matter volume in patients with bipolar disorder. Biol Psychiatry 2005; 58: 151–157.

137. DelBello MP, Zimmerman ME, Mills NP, Getz GE, Strakowski SM. Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. Bipolar Disord 2004; 6: 43–52.

138. Strakowski SM, DelBello MP, Sax KW et al. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Arch Gen Psychiatry 1999; 56: 254–260.

139. Altshuler LL, Bartzokis G, Grieder T, Curran J, Mintz J. Amygdala enlargement in bipolar disorder and hippocampal reduction in schizophrenia: an MRI study demonstrating neuroanatomic specificity. Arch Gen Psychiatry 1998; 55: 663–664.

140. Chang K, Adleman NE, Dienes K, Simeonova DI, Menon V, Reiss A. Anomalous prefrontal-subcortical activation in familial pediatric bipolar disorder: a functional magnetic resonance imaging investigation. Arch Gen Psychiatry 2004; 61: 781–792.

141. Dickstein DP, Treland J, Snow J et al. Neuropsychological performance in pediatric bipolar disorder. Biol Psychiatry 2004; 55: 32–39.

142. Rich BA, Bhangoo RK, Vinton DT et al. Using affect-modulated startle to study phenotypes of pediatric bipolar disorder. Bipolar Disord 2005; 7: 536–545.

143. McClure EB, Treland JE, Snow J et al. Deficits in social cognition and response flexibility in pediatric bipolar disorder. Am J Psychiatry 2005; 162: 1644–1651.

144. Chang K, Adleman N, Dienes K, Barnea-Goraly N, Reiss A, Ketter T. Decreased N-acetylaspartate in children with familial bipolar disorder. Biol Psychiatry 2003; 53: 1059–1065.

145. Youngstrom EA, Findling RL, Calabrese JR et al. Comparing the diagnostic accuracy of six potential screening instruments for bipolar disorder in youths aged 5 to 17 years. J Am Acad Child Adolesc Psychiatry 2004; 43: 847–858.

146. Youngstrom E, Meyers O, Demeter C et al. Comparing diagnostic checklists for pediatric bipolar disorder in academic and community mental health settings. Bipolar Disord 2005; 7: 507–517.

147. Bird HR, Yager TJ, Staghezza B, Gould MS, Canino G, Rubio-Stipec M. Impairment in the epidemiological measurement of childhood psychopathology in the community. J Am Acad Child Adolesc Psychiatry 1990; 29: 796–803.

148. Kahana SY, Youngstrom EA, Findling RL, Calabrese JR. Employing parent, teacher, and youth self-report checklists in identifying pediatric bipolar spectrum disorders: an examination of diagnostic accuracy and clinical utility. J Child Adolesc Psychopharmacol 2003; 13: 471–488.

149. Mick E, Biederman J, Pandina G, Faraone SV. A preliminary meta-analysis of the child behavior checklist in pediatric bipolar disorder. Biol Psychiatry 2003; 53: 1021–1027.

150. Achenbach TM. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Burlington: Department of Psychiatry, University of Vermont, 1991.

151. Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, 2001.

152. Hazell PL, Lewin TJ, Carr VJ. Confirmation that Child Behavior Checklist clinical scales discriminate juvenile mania from attention deficit hyperactivity disorder. J Paediatr Child Health 1999; 35: 199–203.

153. Geller B, Warner K, Williams M, Zimerman B. Prepubertal and young adolescent bipolarity versus ADHD: assessment and validity using the WASH-U-KSADS, CBCL and TRF. J Affect Disord 1998; 51: 93–100.

154. Geller B, Bolhofner K, Craney JL, Williams M, DelBello MP, Gundersen K. Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. J Am Acad Child Adolesc Psychiatry 2000; 39: 1543–1548.

155. Lewinsohn PM, Seeley JR, Klein DN. Bipolar disorder in adolescents: epidemiology and suicidal behavior. In: Geller B, DelBello MP eds. Bipolar Disorder in Childhood and Early Adolescence. New York: Guilford, 2003: 7–24.

156. Akiskal KK, Akiskal HS. The theoretical underpinnings of affective temperaments: implications for evolutionary foundations of bipolar disorder and human nature. J Affect Disord 2005; 85: 231–239.

157. Chang KD, Blasey CM, Ketter TA, Steiner H. Temperament characteristics of child and adolescent bipolar offspring. J Affect Disord 2003; 77: 11–19.

158. Tillman R, Geller B, Craney JL et al. Temperament and character factors in a prepubertal and early adolescent bipolar disorder phenotype compared to attention deficit hyperactive and normal controls. J Child Adolesc Psychopharmacol 2003; 13: 531–543.

159. McClellan J, Werry J. Practice parameters for the assessment and treatment of children and adolescents with bipolar disorder. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry 1997; 36: 157S–176S.

160. Fristad MA, Gavazzi SM, Mackinaw-Koons B. Family psychoeducation: an adjunctive intervention for children with bipolar disorder. Biol Psychiatry 2003; 53: 1000–1008.

161. Danielson CK, Feeny NC, Findling RL, Youngstrom EA. Psychosocial treatment of bipolar disorders in adolescents: a proposed cognitive-behavioral intervention. Cogn Behav Pract 2004; 11: 283–297.

162. Feeny NC, Danielson CK, Schwartz L, Youngstrom EA, Findling RL. Cognitive-behavioral therapy for bipolar disorders in adolescents: a pilot study. Bipolar Disord 2006; 8: 508–515.

163. Pavuluri MN, Graczyk PA, Henry DB, Carbray JA, Heidenreich J, Miklowitz DJ. Child- and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: development and preliminary results. J Am Acad Child Adolesc Psychiatry 2004; 43: 528–537.

164. DelBello MP, Soutullo CA, Hendricks W, Niemeier RT, McElroy SL, Strakowski SM. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. Bipolar Disord 2001; 3: 53–57.

165. Reichart CG, Nolen WA. Earlier onset of bipolar disorder in children by antidepressants or stimulants? An hypothesis J Affect Disord 2004; 78: 81–84.

166. Carlson GA. The bottom line. J Child Adolesc Psychopharmacol 2003; 13: 115–118.

167. Wozniak J, Biederman J, Faraone SV, Blier H, Monuteaux MC. Heterogeneity of childhood conduct disorder: further evidence of a subtype of conduct disorder linked to bipolar disorder. J Affect Disord 2001; 64: 121–131.

168. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. J Clin Psychopharmacol 1996; 16: 4S–14S.

169. Schmidt NB, Kotov R, Joiner T. Taxometrics: Toward a New Diagnostic Scheme for Psychopathology. Washington, DC: American Psychological Association, 2004.

170. McElroy SL, Strakowski SM, Keck PEJ, Tugrul KL, West SA, Lonczak HS. Differences and similarities in mixed and pure mania. Compr Psychiatry 1995; 36: 187–194.

171. Carlson GA. Bipolar disorder in children and adolescents: a critical review. In: Shaffer D, Waslick B eds. The Many Faces of Depression in Children and Adolescents, Vol. 21. Washington, DC: American Psychiatric Association, 2002: 105–128.

172. Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. Psychiatr Clin North Am 1999; 22: 517–534. vii.

173. Benazzi F. Inter-episode mood lability in mood disorders: residual symptom or natural course of illness? Psychiatry Clin Neurosci 2004; 58: 480–486.

174. Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rossler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003; 73: 133–146.

175. Geller B, Zimerman B, Williams M et al. DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. J Child Adolesc Psychopharmacol 2002; 12: 11–25.

176. Tillman R, Geller B, Craney JL, Bolhofner K, Williams M, Zimerman B. Relationship of parent and child informants to prevalence of mania symptoms in children with a prepubertal and early adolescent bipolar disorder phenotype. Am J Psychiatry 2004; 161: 1278–1284.

177. Quinn CA, Fristad MA. Defining and identifying early onset bipolar spectrum disorder. Curr Psychiatry Rep 2004; 6: 101–107.

178. Weckerly J. Pediatric bipolar mood disorder. J Dev Behav Pediatr 2002; 23: 42–56.

179. Biederman J, Klein RG, Pine DS, Klein DF. Resolved: mania is mistaken for ADHD in prepubertal children. J Am Acad Child Adolesc Psychiatry 1998; 37: 1091–1093.

180. Geller B, Sun K, Zimerman B, Luby J, Frazier J, Williams M. Complex and rapid-cycling in bipolar children and adolescents: a preliminary study. J Affect Disord 1995; 34: 259–268.

181. Ruths S, Steiner H. Psychopharmacologic treatment of aggression in children and adolescents. Pediatr Ann 2004; 33: 318–327.

182. Plutchik R. Emotion: A Psychoevolutionary Synthesis. New York: Harper and Row, 1980.

183. Benazzi F, Rihmer Z. Sensitivity and specificity of DSM-IV atypical features for bipolar II disorder diagnosis. Psychiatry Res 2000; 93: 257–262.

184. Henin A, Biederman J, Mick E et al. Psychopathology in the offspring of parents with bipolar disorder: a controlled study. Biol Psychiatry 2005; 58: 554–561.

185. Lewinsohn PM, Seeley JR, Buckley ME, Klein DN. Bipolar disorder in adolescence and young adulthood. Child Adolesc Psychiatr Clin N Am 2002; 11: 461–476.

186. Hazell PL, Carr V, Lewin TJ, Sly K. Manic symptoms in young males with ADHD predict functioning but not diagnosis after 6 years. J Am Acad Child Adolesc Psychiatry 2003; 42: 552–560.

187. Galanter C, Carlson G, Jensen P et al. Response to methylphenidate in children with attention deficit hyperactivity disorder and manic symptoms in the multimodal treatment study of children with attention deficit hyperactivity disorder titration trial. J Child Adolesc Psychopharmacol 2003; 13: 123–136.

188. Thayer RE. The Origin of Everyday Moods: Managing Energy, Tension, and Stress. New York: Oxford, 1996.

189. Fristad MA, Goldberg Arnold JS. Raising a Moody Child: How to Cope with Depression and Bipolar Disorder. New York: Guilford Press, 2004.

190. Lewinsohn PM, Klein DN, Seeley J. Bipolar disorder during adolescence and young adulthood in a community sample. Bipolar Disord 2000; 2: 281–293.

191. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. J Affect Disord 2003; 73: 123–131.