

Pediatric Bipolar Disorder: A Review of the Past 10 Years

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ABSTRACT

Objective: To review the literature of the past decade covering the epidemiology, clinical characteristics, assessment, longitudinal course, biological and psychosocial correlates, and treatment and prevention of pediatric bipolar disorder (BD). **Method:** A computerized search for articles published during the past 10 years was made and selected studies are presented. **Results:** Pediatric BD is increasingly recognized, and there are several prevailing views on core features of this disorder. The incidence and prevalence of the disorder and the associated comorbidities vary according to study setting and criteria used. This disorder is highly recurrent and accompanied by substantial psychiatric and psychosocial morbidity. Familial studies, including “top down” (offspring of parents with BD) and “bottom up” (relatives of youths with BD) studies indicate that pediatric BD is aggregated in families with adult or later-onset BD and suggest the existence of genetic predisposition. Greater understanding of the risk factors for early onset BD and recognition of the phenomenology of prodromal symptoms offers hope for early identification and prevention. Neuroimaging studies indicate frontotemporal and frontostriatal pathology, but none of these findings seems to be disorder specific. Combination pharmacotherapies appear promising, and the field awaits further short- and long-term randomized, placebo-controlled trials. Preliminary studies of various psychotherapies, including psychoeducation strategies tailored specifically for BD in youths, look encouraging. **Conclusions:** Considerable advances have been made in our knowledge of pediatric BD; however, differing viewpoints on the clinical presentation of BD in children are the rule. Phenomenological and longitudinal studies and biological validation using genetic, neurochemical, neurophysiological, and neuroimaging methods may strengthen our understanding of the phenocopy. Randomized, controlled treatment studies for the acute and maintenance treatment of BD disorder are warranted. *J. Am. Acad. Child Adolesc. Psychiatry*, 2005;44(9):846–871. **Key Words:** bipolar disorder, biology, psychopharmacology, treatment.

There has been increasing recognition of pediatric bipolar disorder (BD) in the psychiatric literature during the past 10 years. Despite the dramatic increase in our knowledge of pediatric BD, there is considerable controversy about the clinical presentation, particularly its core symptoms, and hence the prevalence. This article reviews the literature of the past 10 years as it relates to the epidemiology, phenomenology, longitudinal course,

pathophysiology, and pharmacological and psychosocial treatments.

CLINICAL CHARACTERISTICS

The clinical presentation of this disorder in the pre-adolescent and early adolescent age groups is greatly debated, although mid- to late-adolescent-onset BD is considered similar to that of adult BD. The National Institute of Mental Health Research Roundtable on pre-pubertal BD (2001) reached an agreement that pediatric BD can present as “narrow” or “broad” phenotypes. Children and adolescents with the “narrow” phenotype have recurrent periods of major depression and mania or hypomania fitting the classic definitions of BD type I or II described in *DSM-IV* (American Psychiatric Association, 1994). Most of these children experience multiple episodes with rapid cycling (Findling et al., 2001; Geller et al., 2002), and their symptomatology is colored

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by their developmental stage. Despite having the classic symptoms of mania or hypomania, a great proportion of children fail to meet the duration criteria of 4–7 days required to fulfill the *DSM-IV* criteria for hypomania or mania criteria, respectively, and are usually diagnosed as BD not otherwise specified (NOS). This appears to be an adaptation to accommodate children with severe affective instability into the diagnostic criteria for bipolar disorders. In contrast with the “narrow” phenotype, children with the “broad” phenotype constitute the majority of the referrals to clinicians and present with severe irritability, “affective storms,” mood lability, severe temper outbursts, symptoms of depression, anxiety, hyperactivity, poor concentration, and impulsivity with or without clear episodicity (Biederman et al., 1996). Chronic unipolar mania with irritability can potentially be classified or adapted to fit BD-NOS; however, if youths never experienced major depression in this population, the validity of this diagnosis is called into question. Additional studies are needed to determine whether these children actually have BD, prodromal symptoms of BD, or other psychiatric disorders accompanied by mood dysregulation or instability.

Building on this discussion, a framework for classification of pediatric BD spectrum into subtypes was introduced by Leibenluft et al. (2003). They suggested defining pediatric BD into “narrow,” “intermediate,” and “broad” phenotypes. The narrow phenotype is attributed to those that meet the full *DSM-IV* diagnostic criteria for mania or hypomania, including the duration criterion of 7 and 4 days, respectively, and have the hallmark symptoms of elevated mood or grandiosity. The intermediate phenotypes include two subcategories: those with hallmark symptoms of short duration, i.e., 1–3 days, and those with episodic irritable mania or hypomania meeting the duration criteria without elation. The broad phenotype consists of nonepisodic symptoms of severe irritability and hyperarousal with the narrow phenotypes without the hallmark symptoms of elated mood or grandiosity. The BD-NOS category in *DSM-IV* corresponds to the intermediate and broad phenotypes (National Institute of Mental Health Research Roundtable, 2002). Efforts such as these will aid in the development of uniform terminology for phenotypic description. This phenotyping is critical in determining biological variables related to psychopharmacology, genetics, neurophysiology, treatment response, and prognosis.

Although there is general agreement that broad and narrow phenotypes exist (National Institute of Mental Health Research Roundtable, 2001), several prevailing lines of research are central to the debate on the key symptoms for diagnosing BD. For example, Geller et al. (1998b, 2000) compared the clinical characteristics of a sample of children 7–16 years old with BD and attention-deficit/hyperactivity disorder (ADHD) and healthy controls referred from community practitioners. They found that grandiosity, elated mood, hypersexuality, flight of ideas, and decreased need for sleep differentiated children with BD from the other two groups. Irritability was a common symptom in subjects in both BD (96.7%) and ADHD (71.7%) groups. These results need to be interpreted on the premise that children with BD were included in the study if they had grandiosity and/or elation, and it was hypothesized that these two core symptoms are central to differentiating youths with BD from those with ADHD and healthy controls. In contrast, Biederman et al. (1995, 1998, 2000) examined the phenomenology of pediatric BD in a sample of children 12 years old and younger referred to a psychopharmacology program. Children characterized as manic had markedly and chronically elevated levels of irritability (seen in as many as 77%), with a lower percentage (14%) currently with elevated mood (Wozniak et al., 1995). The authors emphasized the centrality of irritability in establishing the diagnosis and recommend diagnosing BD if the child meets *DSM-IV* criteria with irritability as a core symptom, even in the absence of elation, grandiosity, and episodicity. Others (Birmaher et al., 2004; Carlson and Kelly, 1998; Findling et al., 2001; Pavuluri et al., 2004a,b) use unmodified *DSM-IV* symptom criteria (American Psychiatric Association, 1994) to establish the diagnosis. Some researchers consider irritability as a core symptom only if it co-occurs with elated mood or grandiosity (Birmaher et al., 2004; Leibenluft et al., 2003; Pavuluri et al., 2004 a,b) in defining the BD types I and II. Grandiosity as a core symptom without mood symptoms (elated or irritable mood) is also not considered adequate.

Broader phenotypes were carefully discriminated from these narrow phenotypes. For example, Carlson and Kelly (1998) examined an inpatient sample of youths between 6 and 10 years old with BD in whom mania was endorsed by extreme mood changes, difficulty concentrating, feeling too “up” to sit still, and racing thoughts. They do not consider this group as unequivocal

BD in the absence of the full range of *DSM-IV* criteria and in the absence of an episodic pattern. These subjects resemble the large percentage of youths referred for treatment because of mood dysregulation, irritability, and/or aggression, many of whom may meet the BD-NOS diagnosis. They may or may not eventually meet full criteria for BD types I and II based on *DSM-IV* or *ICD-10* criteria (World Health Organization, 1992). Additional longitudinal studies are needed to clarify whether it is required to consider core symptoms of elation, grandiosity, and symptom periodicity or whether severe irritability without elation and/or grandiosity is sufficient to diagnose BD.

In addition to the debate on requisite core symptoms and the presence or absence of episodes in defining pediatric BD, there are various definitions of cycling. Geller et al. (1995) coined the term *complex cycling* to describe the presence of short cycles embedded within a more prolonged cycle or episode. The terms ultrarapid cycling (5–364 cycles per year) and ultradian cycling (>365 cycles per year) have been used to document rapid mood fluctuation (Geller et al., 1998a). In ultradian cycling, mania needed to occur for ≥ 4 hours per day (Geller et al., 2001). The ultradian cycles or “mini-cycles” are variably considered to be mood swings, mood lability, and affect dysregulation by some researchers (National Institute of Mental Health Research Roundtable, 2002). According to *DSM-IV* criteria, an ultradian cycle cannot be considered an episode or a cycle of mania, hypomania, or depression. Furthermore, labile, unstable, and changeable mood is prominent in children younger than 10 years of age (Carlson, 1983). Although affect dysregulation is common in pediatric BD, the extent to which this is specific to the disorder is unknown. The symptoms of the BD superimposed on a developing child who has yet to achieve emotional, neurocognitive, and physical maturity and often has other comorbid disorders can present a complicated and variegated clinical picture (Bowring and Kovacs, 1992).

Further complicating the diagnosis of BD is the fact that symptoms of mania are not yet in the behavioral repertoire of young children (Bowring and Kovacs, 1992). For example, symptoms such as disinhibition as manifested by immodest attire or excessive spending may be present as parents exert control over their child’s manner of dress and money management. Symptom expressions concerning inflated self-esteem and increased

goal-directed activity are best judged in the context of the child’s history because behaviors in isolation may be misleading and may be accounted for by the child’s cognitive, biological, or social development. Variability in the reported rates of psychosis may be caused by differences in interpretation as well as methodology (Pavuluri et al., 2004c). Psychosis has been reported in 16%–60% of youths with BD (Findling et al., 2001; Geller et al., 1998a; Wozniak et al., 1995), with auditory hallucinations being the most common (Pavuluri et al., 2004c). The prevalence of psychotic features is lower in adolescent mania as compared with adult mania, with lower ratings on thought disorder and delusions (McElroy et al., 1997). It is critical to pay attention to age-specific manifestation of the symptoms.

Apart from ongoing discussions on what constitutes pediatric BD, there are several unique features that are uniformly agreed on and are typical for pediatric BD (Birmaher et al., 2002; Findling et al., 2001; Geller et al., 1998a; McClellan et al., 1999; Wozniak et al., 1995): (1) chronicity with long episodes, (2) predominantly mixed episodes (20%–84%) and/or rapid cycling (46%–87%), (3) prominent irritability (77%–98%), and (4) high rate of comorbid ADHD (75%–98%) and anxiety disorders (5%–50%).

EPIDEMIOLOGY

Definition of caseness is central to estimating the prevalence, and given the continuing debate in characterizing pediatric BD it should not be surprising that there are no data on the prevalence of preadolescent BD. There is only one community study evaluating the rates of bipolar spectrum disorders in adolescents in high school (Lewinsohn et al., 1995). This study showed a lifetime prevalence of approximately 1% in youths 14–18 years old using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) (Orvaschel and Puig-Antich, 1987), with the majority having BP type II and cyclothymia. An additional 5.7% of the youths had subsyndromal symptoms of BD defined as a “distinct period of abnormally and persistently elevated, expansive or irritable mood.” This study did not include parent interviews, however, and was based purely on interviews with adolescents. A 6-month study in a national sample of 13- to 18-year-old Dutch adolescents with the Child Behavior Checklist (Achenbach and Edelbrock, 1983) and the parent

TABLE 1

Assessment Measures Developed for or Tested in Pediatric Bipolar Disorder

Ref. ^a	Instrument	Type of Measure/Rater	Developed for BD/for Children and Adolescents	Sample No./Age/Setting	Reliability	Validity
Fristad et al., 1992	YMRS	Clinician rating scale	Yes/no	BD = 11/ADHD = 11/6–12 yr/outpatient	IC = 0.7–0.86 for 8 items, 0.45 for 1 item (appearance), 0.13–0.34 for 2 items (sexual interest and insight)	Good DV from ADHD
Biederman et al., 1995 ^b	CBCL	Parent report	No/yes	N = 228/mean age range of 8–9 yr; psychopharmacology clinic and community controls	Not reported	Good DV with ADHD and normal controls, with a pattern of significantly high scores on 5 subscales of CBCL: delinquent, aggressive, somatic, anxious, social and thought problems
Hazell et al., 1999	CBCL	Parent report	No/yes	N = 151/9–13-yr-old boys/psychiatry and pediatric clinics and community	Not reported	Children with BD and ADHD scored significantly high on thought problems, withdrawn, delinquent, and aggressive behavior scales
Youngstrom et al., 2001	GBI	Parent report	Yes/no	N = 152/5–17 yr/mood disorders clinic	IC = depression scale –0.97; hypomanic-biphasic scale = 0.95	DV = classification rates >80% from disruptive behavior disorder and normals; AUC >0.84 with differentiating from disruptive disorders; 0.97 from no diagnosis
Findling et al., 2002	GBI	Modified for parent rating and youth self-report	Yes/no	N = 196/5–17 yr/mood and disruptive disorders clinic	Parent–child agreement was ≥0.41 on both scales	On hypomanic-biphasic scale, maximum efficiency for parent report was at cutoff score of 17 with sensitivity of 0.91 and specificity of 0.68; cutoff score had to be higher at 32 for youth report to achieve maximum efficiency with sensitivity of 0.63 and specificity of 0.92. Combining information from multiple informants did not improve accuracy in diagnostic assignment; AUC was 0.82 for youth report and 0.88 for parent report
Youngstrom et al., 2002	YMRS	Clinician rating scale	Yes/no	N = 612/5–17 years/specialty clinic of mood and disruptive disorders	IC = 0.91	Single factor solution on factor analysis

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TABLE 1 (Continued)

Ref. ^a	Instrument	Type of Measure/Rater	Developed for BD/for Children and Adolescents	Sample No./Age/Setting	Reliability	Validity
Gracious et al., 2002	Parent-YMRS (P-YMRS)	Parent rating scale	Yes/no	N = 117/5–17 years/specialty clinic of mood and disruptive disorders	IC = 0.75	Unidimensional measure, good DV from unipolar and disruptive behavior disorder, AUC >0.82
Axelson et al., 2003	K-SADS, MRS	Clinician rating scale	Yes/yes	BD = 81, others = 1,905/8–18.8 yr/mood and anxiety disorders clinic	IC = 0.90 IR = 0.97	Convergent validity with CGI-BP severity = 0.89
Danielson et al., 2003	GBI	Self-report	Yes/no	N = 197/10–17 yr/mood disorders clinic	IR = >0.85 IC = depression scale = 0.97; hypomanic-biphasic scale = 0.94	Good DV from unipolar and disruptive behavior disorders including ADHD; AUC >0.76–0.77 in differentiating from ADHD
Pavuluri et al., 2004d	CMRS	Parent rating scale	Yes/yes	N = 150/5–17 years/specialty clinic and community	IC = 0.96 TR = 0.96	Single-factor solution on factor analysis, correlated 0.84 with WASH-U K-SADS mania module and 0.79 with K-YMRS total score. Sensitivity for differentiating between mania and ADHD = 0.82 and specificity = 0.94 with cutoff score of 20. Sensitivity for differentiating between mania and HC = 0.84 and specificity = 0.98 with cutoff score of 20

Note: ADHD = attention-deficit/hyperactivity disorder; AUC = area under the curve; BD = bipolar disorder; CBCL = Child Behavior Checklist; CGI-BP = Clinical global impression for bipolar disorder-severity scale; CMRS = Child Mania Rating Scale; DV = discriminant validity; GBI = General Behavior Inventory; HC = healthy control; IC = internal consistency; IR = interrater reliability; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; MRS = Mania Rating Scale; TR = test-retest reliability; WASH-U = Washington University; YMRS = Young Mania Rating Scale.

^a Listed in order of publication.

^b Mick et al. (2003) have completed a meta-analysis of all of the studies that used the Child Behavior Checklist and came up with a consistent pattern similar to that reported by Biederman et al. (1995).

and child versions of the Diagnostic Interview Schedule for Children (National Institute of Mental Health, 1992) reported a prevalence of 1.9% for mania and 3.6% for major depression (Verhulst et al., 1997). These results need to be interpreted with caution. The Child Behavior Checklist is not a diagnostic instrument and does not identify specific manic symptoms, and items on the Diagnostic Interview Schedule for Children are not robust enough to identify bipolar diathesis. Data from the Great Smoky Mountains Study showed no BD type I cases using the Child and Adolescent Psychiatric Assessment (Costello et al., 1996). Brotman et al. (2005) pooled items from several diagnostic sections of the Child and Adolescent Psychiatric Assessment (depression, hypomania/mania, hyperactivity/attention deficit, sleep disorders, oppositional defiant disorder [ODD]/conduct disorder [CD]) to construct a severe mood and behavioral dysregulation approximating the proposed broad phenotype of Leibenluft et al. (2003). Based on the data from the Great Smoky Mountains Study, they reported a 4% prevalence of severe mood and behavioral dysregulation. The major difficulty with this secondary analysis, however, is a lack of validity studies of the severe mood and behavioral dysregulation construct, especially its link with bipolar diathesis. Retrospective studies in adults with BD have reported that as many as 60% experienced the onset of their BD before 20 years of age, and 10%–20% reported the onset before 10 years of age (Egeland et al., 2000; Joyce, 1984; Lish et al., 1994; Loranger and Levine, 1978). Because BD may initially present with an episode of major depression and BD with childhood onset was recognized only recently, the prevalence of BD may have been underestimated. Interestingly, prodromal symptoms in patients ultimately diagnosed with BD in adults typically begin 10 years before the formal diagnosis of BD (Egeland et al., 2000). Although unrelated to the population prevalence, BD is noted in 0.6%–15% of a clinic population depending on the instrument used to ascertain diagnoses, the referral source, and the clinic's specialization (Biederman et al., 1995; Geller et al., 2001; Lewinsohn et al., 1995; Strober et al., 1995).

More population-based studies using valid diagnostic instruments and multiple informants are needed. Until the issues related to accurate characterization of the pediatric BD are resolved, however, results regarding the incidence and prevalence of pediatric BD will remain unresolved.

ASSESSMENT MEASURES

There are several research interviews that can be used to characterize BD such as K-SADS (Ambrosini, 2000; Orvaschel and Puig-Antich, 1987) and the Washington University K-SADS (Geller et al., 1998a, 2001). The K-SADS epidemiological version (KSADS-E) completed by trained raters shows good concurrent validity, with 97% agreement with an expert clinical interview (Wozniak et al., 2003). In addition to semistructured diagnostic interviews, several broad- and narrow-band rating scales were tested in children and adolescents with BD. They are summarized in Table 1. These instruments appear to have good psychometric properties and some discriminate BD from other psychiatric disorders (Danielson et al., 2003; Findling et al., 2002; Fristad et al., 1992; Pavuluri et al., 2004d; Youngstrom et al., 2001). In a study comparing the screening potential of various rating scales, parents outperformed teachers and youths in identifying cases of BD, underscoring the critical importance of obtaining parents' report (Youngstrom et al., 2004). This finding has implications in interpreting the prevalence rate of epidemiological studies based on adolescent interview alone (Lewinsohn et al., 1995). Additional studies are needed to evaluate the sensitivity and specificity of these promising scales, particularly in youths with broader phenotypes. This will enable researchers to conduct larger-scale epidemiological studies.

DIFFERENTIAL DIAGNOSIS

Because of the overlapping symptoms of BD and other psychiatric disorders, it is difficult to differentiate BD from other disorders, particularly ADHD. BD can be differentiated from ADHD by the presence of grandiosity, elated mood, flight of ideas, hypersexuality, and decreased need for sleep (Geller et al., 2002). In older adolescents, the presence of mood-incongruent delusions and hallucinations and thought disorder can lead to the misdiagnosis of BD as schizophrenia in as many as 50% of cases (Carlson, 1990; Werry et al., 1991). The irritability, mood lability, and aggression sometimes seen in pervasive developmental disorder can potentially be mistaken for mania (Wozniak et al., 1997), and substance abuse may cause activation and disinhibition that may resemble mania (Wilens et al., 1999).

COMORBIDITY

More often than not, children and adolescents with BD will present with other psychiatric disorders, particularly ADHD, ODD, CD, and anxiety disorders. The rates of comorbid disorders vary according to the age of the child, sample selection (clinical versus community), and the methods used to ascertain the psychiatric symptomatology (e.g., clinical interviews versus structured diagnostic interviews, type of instruments, interview with informant [the parent and/or child alone], and clinical experience of the person interviewing the child). Another factor that adds to the complexity in determining comorbidity is the current diagnostic classification system. For example, using strict *DSM-IV* criteria, the diagnosis of ODD cannot be considered if present exclusively in the presence of a mood disorder such as BD. This will potentially lead to lower rates of comorbidity, especially if BD is chronic. There is no consensus among researchers on the rates of diagnostic comorbidity. Rates for comorbid disorders range between 11% and 75% for ADHD, 46.4% and 75% for ODD, 5.6% and 37% for CD, 12.5% and 56% for anxiety disorders, and 0% and 40% for substance abuse disorders (Biederman et al., 1997; Findling et al., 2001; Geller et al., 1998b, 2002; Lewinsohn et al., 1995; McClellan et al., 1999; Wozniak et al., 1995). Comorbidity also varies with age. Children with pediatric BD tend to have higher rates of ADHD than do adolescents with BD, whereas the latter have higher rates of substance abuse (Findling et al., 2001; Lewinsohn et al., 1995; McClellan et al., 1999). Wilens et al. (2004) found that the risk of substance abuse was 8.8 times higher in adolescent-onset BD than childhood-onset adolescent BD. As in adult BD, pediatric BD is specifically associated with panic disorder (Biederman et al., 1997; Birmaher et al., 2002). Pediatric BD is comorbid with pervasive developmental disorder, particularly Asperger's disorder, in 11% (Wozniak et al., 1997).

LONGITUDINAL STUDIES

There is a consensus for definitions used to characterize the longitudinal course of BD. Recovery is defined as eight consecutive weeks without meeting *DSM-IV* criteria for mania, hypomania, depression, or mixed affective state. Remission is defined as 2–7 weeks without meeting *DSM-IV* criteria for affective episodes. Relapse is defined as two consecutive weeks of *DSM-IV* criteria

for affective episodes with clinically significant impairment (Children's Global Assessment Scale score of ≤ 60). Chronicity is defined as failure to recover from an affective episode for a period of at least 2 years. Retrospective studies (e.g., Werry et al., 1991) and naturalistic longitudinal studies of children and adolescents with BD (Birmaher et al., 2004; Carlson et al., 2000a, 2002; Geller et al., 2004a; Jairam et al., 2004; Lewinsohn et al., 1995; Strober et al., 1995) have reported that 40%–100% will recover in a period of 1–2 years. Of those patients who recovered, however, approximately 60%–70% showed recurrences in an average of 10–12 months.

Recent evidence has suggested that the traditional survival analyses involving the conceptualization of BD as having sustained symptom-free periods of euthymia punctuated by full syndromal major depressive episodes or episodes of mania/hypomania are inadequate (Judd et al., 2002). Therefore, to provide a more complete picture of the longitudinal course of BD, two recent studies analyzed the proportion of follow-up weeks that youths with BD experienced in the different mood states (e.g., mania, hypomania, major depression, mixed, and subsyndromal symptoms). These studies showed that nearly 70% of the follow-up time, subjects experienced syndromal or subsyndromal BD symptoms (Birmaher et al., 2004; Geller et al., 2004a). During a 4-year follow-up, Geller et al. (2004a) described polarity switches at 1.1 ± 0.7 times per year. Low maternal warmth predicted faster recurrence after recovery from mania, and psychosis predicted more weeks ill with mania or hypomania. Pubertal status and sex were not predictive of outcome. Furthermore, some studies, but not all, have reported that subjects of low socioeconomic status, rapid cycling, mixed episodes, comorbid disorders, and family conflicts have a worse prognosis (Birmaher et al., 2004; Carlson et al., 2002; Geller et al., 2004a; Lewinsohn et al., 1995; Strober et al., 1995). Additional studies evaluating the risk and protective factors with larger samples of children and adolescents with bipolar spectrum disorders are needed.

A recent study found that youths with BD-NOS, operationalized as (1) elated mood plus two *DSM-IV* BD symptoms or irritability plus three *DSM-IV* BD symptoms, (2) at least 4 hours of symptoms in a 24-hour period, and (3) lifetime of 4 days total of symptoms, showed levels of severity, comorbidity, and family history that were comparable with those of youths with

BD types I and II (Birmaher et al., 2004). At follow-up, youths with BD-NOS showed longer time to recovery and a shorter time to recurrence than youths with other types of BD, perhaps because they had more chronic subsyndromal presentations that may prove to be more resistant to treatment. Moreover, approximately 25% of youths with BD-NOS converted to BD type I or II. These results are important because a great proportion of children and adolescents are being classified as BD-NOS because they do not fulfill the *DSM-IV* requirements for BD types I and II (Leibenluft et al., 2003). Other investigators have diagnosed these youths as having BD with very rapid cycling (Craney and Geller, 2003) or chronic BD (Biederman et al., 2000) and reported that these children have poor prognosis (e.g., Biederman et al., 2000; Craney and Geller, 2003).

In another longitudinal study of an adolescent community sample, 5.7% of patients with abnormal and persistently elevated, expansive, or irritable mood who did not meet *DSM-IV* criteria did not go on to meet diagnostic criteria for BD by their early 20s but had an increased rate of depression and other psychiatric disorders (Lewinsohn et al., 1998). At this time, evidence is not sufficient to indicate that pediatric BD is continuous with adult BD (Harrington and Myatt, 2003), although psychotic adolescent-onset mania appears to be similar to adult BD (McClellan et al., 1999). A retrospective interview of a large sample of adult BD indicated that approximately 30% experienced very early onset (age younger than 13 years) and approximately 40% experienced early onset (ages 13–18 years; Perlis et al., 2004). Earlier onset was associated with greater rates of anxiety and substance abuse disorders, more recurrences, shorter periods of euthymia, and higher incidence of suicide attempts and violence. Also, approximately 20%–30% of depressed children, particularly those with psychosis, a family history of BD, and/or pharmacologically induced mania eventually develop BD (Geller et al., 1994; Strober and Carlson, 1982; Yung and McGorry, 1996).

BIOLOGICAL FACTORS

Given the continuing debate on the clinical picture of pediatric BD, it is even more critical now to determine the genetic contribution and the affective and cognitive neuroscience systems that underlie the mood and affect dysregulation in various subtypes of BD (type I

or II or NOS). It is distinctly possible that the differing clinical presentations of pediatric BD are not unitary entities but diverse in etiology and pathophysiology.

GENETICS

There are several lines of evidence to suggest heritability in pediatric BD. Although twin, adoption, and molecular genetic studies have established heritability in adult BD, such studies are lacking in the pediatric population. Genetic studies pertaining to pediatric BD can be discussed within two categories: familial studies (top-down studies examining the offspring of parents with BD and bottom-up studies estimating the prevalence of BD among relatives of children with BD) and molecular genetics studies.

FAMILY STUDIES

High-Risk or Top-Down Studies

Offspring of bipolar probands provide a rich source for identifying prodromal forms of the disorder. Studying populations at high risk of BD raises the possibility of discovery of biological and phenomenological markers. One phenomenological marker of pediatric BD appears to be the combination of mood disorder and behavioral problems (Chang et al., 2003b). A meta-analysis of studies conducted before 1997 found offspring of parents with BD to be at 2.7 times higher risk of developing any psychiatric disorder and at four times higher risk of developing a mood disorder than are children of parents without psychiatric illness (Lapalme et al., 1997). One of the largest studies among them ($N = 72$ offspring) reported significantly more psychopathology (60% versus 25%), in particular, disruptive disorders and depression, in the offspring of parents with BD as compared with the offspring of normal controls (Grigoriu-Serbanescu et al., 1989). Furthermore, among more recent studies, offspring studies of bipolar parents in the United States reported a 14%–50% incidence of bipolar spectrum disorders (Chang et al., 2000; Duffy et al., 1998). In contrast, a Dutch study reported only a 2.8% incidence of bipolar spectrum disorders in offspring of adult BD (Wals et al., 2004). This discrepancy with higher incidence in the United States was explained as possibly caused by methodological differences such as the use of standardized diagnostic

instruments that captured affective psychopathology more efficiently, different methods to recruit the sample, and the increased use of antidepressants and psychostimulants in the United States (DelBello et al., 2001). Unfortunately, the majority of studies of children at high risk are limited by small sample sizes, lack of longitudinal follow-up, inclusion of a group of parents with heterogeneous diagnoses (bipolar and unipolar), failure to control for parental comorbid disorders, lack of normal controls, retrospective assessments, offspring assessments not conducted blind to parental diagnosis, no direct assessment of offspring, lack of analysis of developmental and parental psychiatric disorder influences on the child's psychopathology, lack of standardized assessments of psychopathology and family psychiatric history, no measurement of the effects of environmental stresses, and no evaluation of the presence of subsyndromal symptoms.

Familial Risk or Bottom Up Studies

Most of the genetic evidence of early-onset bipolar illness comes from familial studies. Several studies have shown a strong link between early age at onset and risk of BD among first-degree relatives of youths with BD as compared with relatives of youths with schizophrenia and unipolar major depressive disorder and normal controls (Kutcher and Marton, 1991; Lewinsohn et al., 2000; Neuman et al., 1997; Pauls et al., 1992; Rice et al., 1987; Spitzer, 1987; Strober et al., 1988). Furthermore, earlier onset of BD is associated with greater familial loading of BD (Neuman et al., 1997; Rice et al., 1987; Strober et al., 1988). Relatives of adolescents with subsyndromal symptoms of BD also have increased family history of BD, comparable with those with the full syndrome (Lewinsohn et al., 2000).

Relatives of children with comorbid ADHD and BD have a five times greater rate of BD than do relatives of probands with ADHD alone (Faraone et al., 1997a, b). Furthermore, youths with psychotic depression have increased familial aggregation of mania with a substantially increased risk (20%–40%) of developing BD (Kovacs et al., 1984; Loranger and Levine, 1978; Puig-Antich et al., 1989; Rao et al., 1995; Strober and Carlson, 1982).

Molecular Genetics Studies

The focus of molecular genetics in pediatric BD has focused on allelic associations with the disorder. Geller

et al. (2004b) examined the commonly studied Val/Met amino acid variant and showed preferential transmission of the brain-derived neurotrophic factor val66 alleles in children with prepubertal and early adolescent BD. Geller and Cook (1999) have also studied genetic transmission of the serotonin transporter–linked promoter region short and long alleles using the transmission disequilibrium test. They found no evidence of such an association. These results concurred with the meta-analysis of adult studies (Craddock et al., 2001) but differed from another pediatric BD sample that showed significantly more short serotonin transporter alleles (Ospina-Duque et al., 2000). The catechol-*O*-methyltransferase, a dopamine-metabolizing enzyme, lacked linkage disequilibrium with ultradian rapid cycling pediatric BD (Geller and Cook, 2000). This is in opposition to findings documented in adult studies (Craddock et al., 2001). This could be the result of phenotypic differences, inadequate sample sizes, or developmental influences on gene expression. Given that the genes of interest, such as *HTT*, are abundantly expressed in limbic regions (critical for affect regulation), they are considered a priori good candidates for further study (Faraone et al., 2003). Several researchers have suggested that BD is associated with genetic anticipation defined as an apparent tendency of certain diseases to appear at earlier age at onset and with increasing severity in successive generations. This was indicated by trinucleotide repeats (CAG/CTG) coding for polyglutamine tracts (Schurhoff et al., 2000; Verheyen et al., 1999; Vincent et al., 2000). Evidence is emerging that polyglutamine is in fact linked to neurotoxicity (Poirier et al., 2005), although the specific mechanisms that underlie this association remain to be established. Scrambler et al. (1992) found that pediatric BD was significantly associated with microdeletion of chromosome 22, possibly representing a susceptibility gene for pediatric BD. Although results are pointing to strong familial transmission in the early-onset variant of BD, there are no reliable indicators of genetic risk and efforts toward further exploration have just begun. For a more comprehensive review on genetics in pediatric BD, refer to Faraone et al. (2003).

IMAGING STUDIES

Given the development of new imaging techniques, research to characterize the pathophysiology and

treatment effects in BD is progressing rapidly. Most of the studies are preliminary, however, and include small samples with confounding factors such as comorbid disorders, various phases of illness (depressed, manic, hypomanic, euthymic), and receipt of multiple medications.

Structural Magnetic Resonance Imaging (MRI) Studies

There is accumulating evidence to suggest white matter hyperintensities (WMHs) in both cortical and subcortical regions of the brain and smaller amygdalar size in pediatric BD as compared with adults (Blumberg et al., 2003; Botteron et al., 1992; DelBello et al., 2004; Pillai et al., 2002). Botteron et al. (1992) reported deep WMH in 4 of 10 subjects with BD compared with one control subject. Deep WMH are nonspecific findings and have been associated with several disease processes such as ischemia, inflammation, and demyelination (Coffey and Figiel, 1991). These findings need to be replicated in a larger sample. Building on these findings, Pillai et al. (2002) reported WMHs in 67% of adolescents with BD compared with 37% of schizophrenic and 31% of healthy controls. Most of the WMHs in subjects with BD were located in the frontal cortex. No significant differences in volumetric measures were observed between subjects with BD and schizophrenia. The frontal and temporal sulcal size was increased, intracranial volume was decreased (Friedman et al., 1999), and bilateral thalamic size was reduced (Dasari et al., 1999) in both groups compared with healthy controls. Furthermore, smaller parietal and temporal lobe cortical gray matter was noted in pediatric BD (Frazier et al., in press b). Voxel-based morphometric studies indicated reduced gray matter volume in the dorsolateral prefrontal cortex (DLPFC) (Dickstein et al., in press), but findings on such a decrease in the orbitofrontal cortex were divided with no difference (Dickstein et al., in press) to decreased orbitofrontal cortex volume (Wilke et al., 2004). Bilaterally larger basal ganglia (Wilke et al., 2004), specifically larger putamen (DelBello et al., 2004), were reported in adolescent BD, suggesting the striatal involvement in BD. Recent findings indicate a bilateral (Blumberg et al., 2003; DelBello et al., 2004) and left-sided (Dickstein et al., in press) reduction in the size of the amygdala and a bilateral decrease in the hippocampal volume (Frazier et al., in press a) in pediatric BD. In contrast, adult studies have reported enlarged amygdala (Altshuler et al., 1998; Strakowski et al.,

1999). This could be a reflection of a lack of pruning in adult BD or early degenerative changes in pediatric BD.

Functional MRI Studies

Functional MRI allows examination of the patterns of brain activation as subjects perform cognitive tasks while undergoing a scan. These tasks are selected as probes in hypothesized areas of dysfunction in BD. For example, with the Stroop task as a probe, activation in the frontostriatal system correlated positively with increasing age among healthy controls but not in adolescents with BD. Left thalamus and putamen activation was significantly greater in BD (Blumberg et al., 2003). These findings suggest cortical as well as subcortical dysfunction. Children and adolescents with familial BD showed greater left DLPFC, bilateral anterior cingulate, left thalamus, and right inferior frontal gyrus during a visuospatial working memory task, whereas controls showed greater activation in cerebellar vermis (Chang et al., 2004). In the same sample, negatively valenced stimuli activated the bilateral DLPFC, inferior frontal gyrus, and right insula in BD as compared with the posterior cingulate gyrus in controls. In contrast, positive stimuli elicited greater activation in the bilateral caudate and putamen and thalamus, left frontal gyrus, and left anterior cingulate areas in BD, with no greater areas of activation in controls. Increased activation in frontal areas and the anterior cingulate gyrus may be related to abnormal neuronal densities (particularly in DLPFC) or compensatory recruitment of frontal areas (DLPFC and orbitofrontal cortex) in youths with BD to modulate overactive subcortical structures. Also, it is possible that healthy controls are recruiting cognitive areas in modulating emotion such as the posterior cingulate. It is important to note that most of the functional MRI studies to date have been limited to relatively older children and adolescents because this technique is particularly sensitive to motion.

Proton Magnetic Resonance Spectroscopy (¹H-MRS) Studies

¹H-MRS is a noninvasive procedure that provides details on neuronal substrates such as *N*-acetyl-aspartate (NAA), choline, myoinositol, and creatine/phosphocreatine (Cr; Chang et al., 2003c). NAA is found in high concentrations in neurons as opposed to glial cells and may serve as a marker for neuronal integrity.

Cr is present in both white and gray matter and is used as a reference point for the amount of brain tissue in the voxels placed in the region of interest. Myoinositol is crucial for the resynthesis of phosphoinositides and plays a role in neuronal homeostasis. Castillo et al. (2000) examined 6- to 12-year-old subjects with BD and showed an elevated glutamate/glutamine ratio in frontostriatal areas. The levels of NAA and choline were not increased in the frontotemporal areas. In contrast, bipolar offspring carrying a bipolar diagnosis who are euthymic on multiple medications showed decreased NAA/Cr ratios in the right DLPFC (Chang et al., 2004). There was a tendency of NAA/Cr ratios to decrease with duration of illness. It may be that the decreased DLPFC NAA/Cr ratio is specific to familial BD. In a separate study, a trend toward lower NAA/Cr ratio was noted in cerebellar vermis in 8- to 12-year-old subjects with BD (Cecil et al., 2003). In another study, myoinositol/Cr ratio and myoinositol levels (mmol/L) were found to be higher in the anterior cingulate cortex in acutely manic BD as compared with subjects with intermittent explosive disorder and healthy controls (Davanzo et al., 2003). Cecil et al. (2003) found that myoinositol concentration was elevated in frontal areas in subjects with BD as compared with healthy controls. Findings such as these could potentially aid in early detection and differential diagnosis. Furthermore, MRS studies can also be applied to examine mechanisms of treatment efficacy. In pediatric BD, lithium treatment was shown to reduce a high baseline myoinositol/Cr ratio in acute mania (Davanzo et al., 2001). Much more work is needed on the application of MRS to BD in children. MRS studies conducted to date are often based on different a priori hypotheses of specific regions of interest, consist of small sample sizes, and are not always controlled for medications that by design affect brain chemistry. These factors, together with variable results from various studies, require that studies on larger samples control for potential confounds to solidify our understanding of brain chemistry in BD.

NEUROCOGNITIVE FUNCTION

Children and adolescents with BD often present with significant cognitive deficits that may adversely affect school functioning. A study using the Cambridge Neuropsychological Test Automated Battery reported difficulties in attentional set shifting and visuospatial

memory in pediatric BD as compared with healthy controls (Dickstein et al., 2004). The generalizability of these findings is limited by the naturalistic design of the study. Subjects were taking various psychotropic medications, had heterogeneous BD diagnoses, and were in various states of their illness (BD type I or II or NOS; euthymic, depressed, or hypomanic). A small cohort of subjects with CD plus BD showed almost identical deficits as those with only CD in set shifting/inhibition, planning, and verbal memory (Olvera et al., 2005). This raises the question of whether these cognitive deficits are specific for BD. Beyond these cognitive tasks, assessments of social cognition are also crucial in BD. A study compared children with BD and anxiety disorders and healthy controls in their ability to accurately interpret facial expressions and nonverbal cues of adult and child faces (McClure et al., 2003). Children with BD misinterpreted sad, happy, and fearful child faces, but not adult faces, as angry, as compared with anxious and healthy groups. These results suggest that youths with BD possibly overperceive anger among peers, which may relate to social difficulties. Introduction of contingencies and frustration with negative feedback was associated with disrupted attention allocation with no decrease in reaction time or modulated response in pediatric BD as compared with healthy individuals (Rich et al., in press). This has direct implications for designing interventions in both classroom settings and behavior therapy, in lieu of unmodified contingency-based treatments.

PSYCHOSOCIAL RISK FACTORS

Although their exact mechanism is unknown, psychosocial factors play a critical role when planning therapeutic interventions. Geller et al. (2002) reported that more than half of youths diagnosed with BD had poor social skills, had no friends, and were teased by other children. They had poor relationships with siblings and conflictual relationships with their parents. Specifically, there was a high degree of hostility and low warmth in maternal-child relationships, poor agreement between parents on child-rearing practices, and minimal problem-solving skills. Parent and child reported elevated novelty-seeking traits in pediatric BD compared with those with ADHD and healthy controls (Tillman and Geller, 2003). Adolescents with BD demonstrated significant social impairment compared

with healthy controls, although they functioned better than did teens with schizophrenia (Cannon et al., 1999). Additional studies are required to clarify whether social skill deficits are related to BD, comorbid disorders, family psychopathology, or demographic factors, and the interactions among these variables.

EARLY CLINICAL INDICATORS AND OPPORTUNITY FOR PREVENTION

Phenomenological research on youths at risk of developing BD has identified symptoms that presage the later development of BD. Youths with cyclothymia or BD type II (Klein et al., 1985) and prepubertal major depressive disorder (Geller et al., 1994, 2001) seem to be at high risk of BD type I. Although more controversial, the presence of severe disruptive disorders (e.g., symptoms that suggest ADHD accompanied by uncontrollable temper outbursts or rage) in the context of family history of BD may be associated with increased risk of BD (Strober et al., 1988; Biederman, 1998; Faraone et al., 1997a,b). Offspring with bilineal pedigrees of mood disorders demonstrated high scores on irritability, depression, rejection sensitivity, and lack of mood reactivity as compared with unilineal pedigrees (Chang et al., 2000). A 7-year follow-up study of Amish offspring of parents with BD type I reported clusters of episodic prodromal symptoms including mood lability, low energy, anxiety, excitability, sensitivity, attention problems/distractibility, hyperalertness, and stubborn behavior rather than a chronic pattern of disruptive behavior (Egeland et al., 2003). What appears to be prodromal symptoms of BD may not always lead to BD, as previously noted (Lewinsohn et al., 1998). In addition, prodromal symptoms may not precede the abrupt onset of classic BD often seen in adolescents (Kutcher et al., 1998; Strober et al., 1988).

With the exception of possible prodromal symptoms and positive family history for BD, there are few other correlates that contribute to the cumulative risk of BD. Low birth weight among bipolar offspring, although not specific for BD, was associated with increased risk of psychopathology (Wals et al., 2003). With regard to early psychosocial indicators of stress, high-risk youths who live with a parent(s) with BD are also more likely to be exposed to negative life events than children and adolescents of normal parents. Few studies have evaluated the effects of psychosocial stresses on the onset and

maintenance of pediatric BD (Gershon et al., 1985; Hammen et al., 1990; Kashani et al., 1985; LaRoche et al., 1985). These studies reported that conflict and low socioeconomic status in families of parents with BD were associated with general psychopathology in the offspring. Thus, offspring of parents with BD are not only genetically at risk of developing the disorder but are also more likely to be exposed to negative life events and psychosocial stressors than are children and adolescents of normal parents. A multisite study examined the psychosocial variables in children and adolescents of extended families identified through BD probands (Petti et al., 2004). They reported an increased need for discipline and social support and an increase in negative life events as significant early indicators of BD. In addition, the family environment of children and adolescents with bipolar disorder was characterized by poor family cohesion and organization and high conflict (Chang and Ketter, 2001). These clinical factors should be considered for prevention and early intervention in high-risk populations. The pharmacotherapy study of offspring with BD with mood and/or disruptive behavior disorders indicated a 79% response rate based on Clinical Global Impressions-Improvement scores of 1 and 2 to divalproex sodium (DVPX) monotherapy (Chang et al., 2003a). In contrast, another study of offspring at genetic high risk and with either cyclothymia or BD-NOS showed no significant benefit with DVPX as compared with placebo (Findling et al., 2000). Substantial clinical benefit was noted in both arms and was attributed to intense clinical monitoring. The long-term efficacy of such an early intervention in preventing BD has yet to be shown.

TREATMENT

Pharmacotherapy

There have been few prospective studies on the efficacy and safety of psychotropic medications in the treatment of pediatric BD. Given the paucity of studies involving youths, with one exception, no psychotropic medications have been approved for pediatric BD by the U.S. Food and Drug Administration. The lone exception is lithium carbonate, which was grandfathered in for the treatment of youths older than age 13 years. All of the prospectively conducted studies with 20 or

more subjects are summarized in Table 2. With few exceptions, they are open trials. Several of these studies were conducted in community versus specialty programs, outpatient versus inpatient settings, children versus adolescents, and psychotic versus nonpsychotic samples and used discrepant interview methods. In addition, methodology was burdened with small sample sizes, variable length of trials, and different outcome criteria. Results must be interpreted with consideration to methodological differences. There are five published placebo-controlled trials. One of the earliest studies compared the effect of lithium with placebo on the severity of substance abuse in children and adolescents with a spectrum of mood disorders. Results indicated a reduction in substance abuse and improvement in general functioning (Geller and Luby, 1997). A second study of combination therapy with DVPX and quetiapine versus DVPX and placebo showed the combination to be superior to DVPX monotherapy and placebo (DelBello et al., 2002). In the third study, DVPX and Adderall were found to be superior to DVPX and placebo in treating comorbid ADHD in BD (Scheffer et al., 2005). This trial underscores the safety and efficacy of treating comorbid symptoms of ADHD that often continue to manifest themselves after mood stabilization. The fourth study was a double-blind discontinuation trial in bipolar adolescent lithium responders in which lithium or placebo was assigned over the course of 2 weeks (Kafantaris et al., 2004). Patients who continued on lithium monotherapy did not differ from the placebo group in rates of exacerbation, which were high in both groups, although the short duration of 2 weeks of follow-up may have influenced the findings. A fourth study was a maintenance study comparing DVPX and lithium for 3 months that reported no difference in time to relapse or premature discontinuation (Findling et al., 2005).

Several treatment issues are apparent on examining the published trials (Table 2). In the majority of these trials, rescue medications were needed in addition to the primary mood stabilizer to treat concomitant symptoms such as aggression, psychosis, and sleep disturbance. This finding illustrates the complexity of conducting treatment trials in BD and should not be interpreted as indicating that monotherapy is futile. In addition, there are no systematic methods to document adverse events. Although pediatric BD encompasses preadolescent and adolescent BD, not all studies examined both

age groups in a single study, and caution must be exercised in translating these scientific findings to the service of all age groups. For example, among the double-blind studies, except for the studies conducted by Scheffer et al. (2005) and Findling et al. (2005), DelBello et al., 2002; Geller et al., 1998a; Kafantaris et al., 2001a, b, 2004).

Retrospective chart reviews, although not rigorous in methodology, led to the observation that antidepressants may worsen or precipitate mania (Biederman et al., 1996). Such switching to mania was not noted in psychotic depression, however (DelBello et al., 2003). Patients included in these studies did not uniformly receive mood stabilizers before being prescribed antidepressants. Similarly, data on the effects of stimulants are variable, with some studies pointing to worsening of mania with stimulants (Biederman et al., 1999, 2000; DelBello et al., 2001; Mota-Castillo et al., 2001; Soutullo et al., 2002), and others reporting no such deterioration (Carlson, 2003; Carlson et al., 2000b; Scheffer et al., 2005). The reader is referred to an excellent series of articles edited by Carlson (2003) for more detailed understanding on the topic of pharmacotherapy-induced switching in pediatric BD. Second-generation antipsychotics (SGAs) are commonly used in treating pediatric BD. Chart review studies have shown that the SGAs may help mood, aggression, and psychosis in children and adolescents with BD (Frazier et al., 1999, 2001; Schreier, 1998).

In summarizing the published findings, the combination of SGAs and mood stabilizers appears to be effective in the acute treatment of pediatric BD (DelBello et al., 2002; Findling et al., 2003; Kafantaris et al., 2001a, b, 2004), as well as for continued stabilization during a 6-month period (Kowatch et al., 2003; Pavuluri et al., 2004a,e). Combination therapy of mood stabilizer and stimulant also appears promising for youths with BD and comorbid ADHD (Scheffer et al., 2005). Preliminary study of maintenance treatment with mood stabilizer monotherapy indicated a median survival of <4 months in an 18-month follow-up study (Findling et al., 2005) that again calls for maintenance studies examining either alternative agents that are likely to be effective or combination strategies for longer-term treatment. No research exists on the treatment of pediatric bipolar depression and treatment of comorbid conditions such as anxiety disorders. Preliminary results of a systematic pharmacotherapy algorithm illustrates the need to

TABLE 2
Pharmacotherapy Trials in Pediatric Bipolar Disorder

Ref. ^a	Diagnosis/State of Disorder/Age	Design Setting/Duration	Drugs/Dose or Drug Levels	No. at Entry/No. Retained	Outcome Measures
Monotherapy trials of mood stabilizer: short-term treatment					
Kowatch et al., 2000	BD I and II/mixed, manic or hypomanic/8–18 yr, mean age 11.4 yr	Open label, randomized to 3 arms; outpatient/2-wk screening + 6-wk trial period	DVPX, Li, CBZ/ 85–110 µg/mL, 0.8–1.2 mEq/L, 7–10 µg/mL, respectively	42/3 completed all 8 wk	Weekly YMRS, CGI-I score
Wagner et al., 2002	BD I and II/manic, hypomanic, mixed/ YMRS score ≥14/7–19 yr, mean age 12.1 ± 3.62 yr	Open-label study/2–8 wk depending on clinical response followed by double-blind, placebo-controlled trial (8 wk), outpatient	DVPX/813 mg/d, 45–125 µg/mL	40/20 completed 35 days; 12 completed open trial of 56 days; 3 completed the blind trial	YMRS, MSS, BIS, BPRS, CGI-S, Ham-D
Pavuluri et al., 2005	BD II/mixed mania/ YMRS score ≥20/5–18 yr, mean age 12.3 ± 3.7 yr	Prospective open-label trial/6 mo	DVPX/950 ± 355 mg/d, 109 ± 33 µg/mL	Mean length of follow-up, 5.05 ± 3.36 mo	YMRS, CGI-S, CDRS
Monotherapy trials of SGAs: short-term treatment					
Frazier et al., 2001	BD I or II/mixed, manic, hypomanic/5–14 yr, mean age 10.3 ± 2.9 yr	Open trial, outpatients/8 wk	Olanzapine/9.6 ± 4.3 mg/d	23/22	YMRS, CGI-S, BPRS, CDRS
Biederman et al., in press	BD I, II, or NOS/6–17 yr, mean age 10.1 ± 0.5 yr	Open trial, outpatients/8 wk	Risp/1.25 ± 1.5 mg/d	30/22	YMRS, CGI-S, BPRS, CDRS
Combination therapy trials of mood stabilizer and atypical antipsychotic					
Kafantaris et al., 2001a	BD I/manic episode with YMRS ≥16/12–18 yr, mean age 15.40 ± 1.14 yr in psychotic group, 14.20 ± 0.84 in nonpsychotic group	Combination therapy in psychotic patients for 1 wk, otherwise, 4-wk open Li monotherapy for all followed by double-blind discontinuation of antipsychotic, inpatient/6 wk	In psychotic mania, Li + haloperidol for 1 wk followed by Li monotherapy for 4 wk and in nonpsychotic mania, Li monotherapy for 4 wk/Li = 1,560 mg/d, 0.93 mEq/ L; haloperidol = 5 ± 5 mg/d	Psychotic mania = 5/nonpsychotic mania = 5/psychotic mania = 2/nonpsychotic = 4	YMRS, Ham-D, BPRS

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TABLE 2 (Continued)

Ref. ^a	Diagnosis/State of Disorder/Age	Design Setting/Duration	Drugs/Dose or Drug Levels	No. at Entry/No. Retained	Outcome Measures
Kafantaris et al., 2001b	BD I/acute mania with psychosis/12–18 yr	Open trial of combination therapy of Li + antipsychotic followed by Li monotherapy; 88.1% were in patients at enrollment/4 wk of open combination trial +4 wk of Li monotherapy	Li and antipsychotic; haloperidol (till 1997) and risperidone (as first line) or alternatives that included olanzapine, quetiapine, thiothixene, chlorpromazine if first-line meds failed (from 1998)	35/28 completed 4 wk of open trial; 8 were successfully weaned off anti psychotics and maintained on Li monotherapy	YMRS, CGI-I, Ham-D, CGAS
DelBello et al., 2002	BD type I/manic or mixed/12–18 yr	DVPX + quetiapine vs. DVPX + placebo, DVPX + quetiapine = 104 mg/dL + 432 mg/d, DVPX + placebo = 102 dL + 432 mg/d, respectively	DVPX open trial, with randomized, double-blind, placebo- controlled strategy for augmentation. Inpatients at study entry and followed as outpatients 6 wk	30, 15 in each arm/ 22; 14 on DVPX + quetiapine and 8 on DVPX + placebo	YMRS, PANSS-P, CDRS, CGAS
Pavuluri et al., 2004e	BD I/manic or mixed/12.1 ± 3.5 yr	Prospective open trial, initial randomization/6 mo followed by consecutive assignment, out patients/6 mo	Li + Risp vs. DVPX + Risp; mean Risp doses in Li + Risp group and DVPX + Risp group = 0.75 ± 0.75 mg and 0.70 ± 0.67 mg, respectively. DVPX mean dose was 925 ± 325 mg (106 µg/dL) and Li mean dose = 750 ± 400 mg (0.9 mEq/L)	Li + Risp = 20, DVPX + Risp = 20/In Li + Risp group, 3 dropped out in first month, 7 completed all 6 mo/In DVPX + Risp group, all completed at least 5 mo	YMRS, CDRS-R, CGI-I, CGAS
Combination trial of 2 mood stabilizers Findling et al., 2003	BD I and II/heterogeneous cohort; episode can be mixed, manic, depressed, hypomanic, euthymic/5–17 yr	Initial phase of stabilization (toward future multiphase study), out patient/1–20 wk, average 11.3 ± 5.3 wk	DVPX + Li; DVPX = 20 mg/kg/d (50–100 µg/mL), Li = 30 mg/kg/d (0.6–1.2 mmol/L) at the end of 2 wk. DVPX = 862 ± 397.5 mg/d and 79.8 µg/mL; Li = 923 ± 380.2 mg/d (0.9 mmol/L)	109 enrolled, 94 received meds ever/90 for >1 wk of follow-up	YMRS, CDRS-R, CGI-S, CGI-I, CGAS

Kowatch et al., 2003	BD I ($n = 17$), BD II ($n = 18$)/mean age 11 ± 2.8 yr	Seminaturalistic follow-up or extension phase of acute trial, outpatient/extension of 16 wk (6–8 wk acute trial + 16 wk follow-up study phase = 24 wk altogether)	Augmentation of any 3 MS primarily used in acute trial with another MS (if bipolar) or antipsychotic (if psychotic) or stimulant (if ADHD is predominant) or AD (if depressed, SSRI or Wellbutrin) if no response to monotherapy with initial MS ($n = 20/35$)	35/35; 20 of 35 required combination therapy in follow-up phase	YMRS, CGI-BP, CGAS
Comorbidity studies					
Geller et al., 1998a	BD I ($n = 12$), BD II ($n = 5$), MDD with BD predictors ($n = 8$) + substance abuse (alcohol and marijuana mostly)/state not specified/ 16.3 ± 1.2 yr	Double-blind, placebo-controlled, pharmacokinetically dosed, out patient/6 wk	Li: $1,769 \pm 401$ mg (0.98 ± 0.33 mEq/L)	25/21	Weekly random Li levels and urine samples for drug assays, C-GAS score ≥ 65
Scheffer et al., 2005	BD I (77.5%), BD II (22.5%) and ADHD/mean age 11.4 yr	8-wk open trial of DVPX followed by a 2-wk randomized, double-blind, placebo-controlled study followed by a blinded 2-wk crossover trial, outpatient/12 wk	DVPX followed by DVPX + placebo vs. DVPX + mixed amphetamine salt (Adderall); DVPX = 750 mg/d (82.98 μ g/mL); Adderall = 10 mg	Open trial: 40/32; placebo-controlled augmentation phase: 30/30?	YMRS, CGI-I
Discontinuation study					
Kafantaris et al., 2004	BD I (manic)/ responders to Li: 12–18 yr/ 15.28 ± 1.85 yr	Double-blind, placebo-controlled trial of Li vs. placebo, inpatient and outpatient/2 wk	Li or placebo; Li = 0.99 ± 0.21 mEq/L	40/37; 3 were removed to monitor suicidal ideation	YMRS, CGI-I, CGI-S, Ham-D, BPRS, CGAS
Maintenance study					
Findling et al., 2005	BD I and II/ euthymic, in remission as defined in Findling et al., 2003 study/5–17 yr	Double-blind, controlled trial of Li vs. DVPX, outpatient/18 mo	DVPX, Li; DVPX = 20 mg/kg/d (50–100 μ g/mL), Li = 30 mg/kg/d (0.6–1.2 mmol/L) at the end of 2 wk; DVPX = 79.8 μ g/mL; Li = 0.91 mmol/L	60 enrolled, 30 in each arm/3 in each arm completed 18-mo study	YMRS, CDRS-R, CGI-S, CGI-I, CGAS, time period until relapse

(Continued on next page)

TABLE 2 (Continued)

Ref. ^a	Diagnosis/State of Disorder/Age	Design Setting/Duration	Drugs/Dose or Drug Levels	No. at Entry/No. Retained	Outcome Measures
Algorithm-based study					
Pavuluri et al., 2004a	BD I/manic or mixed episode/11.74 ± 3.36 yr	Prospective, comparison of experimental group with the group that received treatment as usual, out patient/18.6 mo	Primary and secondary strategies for mood stabilization and tactics of specific medication choices, manual-based rules for dosing	Algorithm group = 64, treatment-as-usual group = 17 (matched with 17 subjects from the total algorithm sample)/Not reported	YMRS at baseline, pre/post measures included CGI-S, CGI-I-BP, CGAS
Ref. ^a	Concurrent Medications	Definition of Outcome/Efficacy Results	Adverse Events Measure Used/Results	Comment	
Monotherapy trials of mood stabilizer: short-term treatment					
Kowatch et al., 2000	3, one in each group received chlorpromazine	50% reduction in YMRS from baseline + CGI score ≤2/Response rate: DVPX, 53%; Li, 38%; CBZ, 38%; ES: DVPX = 1.63, Li = 1.06, CBZ = 1	No specific measure was mentioned/Nausea was the most common problem and highest in CBZ group; sedation was next common problem in both DVPX and CBZ groups	Predictors of response were examined and more severe the baseline YMRS score, the better the outcome	
Wagner et al., 2002	Li = 10% (added in open trial if no response by day 35); any others = 53%; haloperidol = 20%; others included lorazepam, stimulants, clonazepam, clonidine, guanfacine	Pre/post scores are compared on all outcome measures (reported <i>p</i> values, e.g., .001 on all measures)/22/36 (61%) showed ≥50% improvement from baseline in MRS score; ES for change in baseline to final score on YMRS was 1.12	Open-ended questioning, later categorized by coding symbols for thesaurus of adverse reaction terms (COSTART III)/Any adverse event was seen in 68%; those seen in >10% were reported; headache, nausea, vomiting, diarrhea, sedation	Dropout rate illustrated the onerous ordeal of sustaining subjects in placebo-controlled phase of trial	
Pavuluri et al., 2005	Stimulants = 13, risperidone = 17, trazodone = 5	Pre/post scores are compared on all outcome measures; reported <i>p</i> values, e.g., .001 on all subscales of CGI-I except Psychosis (<i>p</i> < .05) and YMRS and CDRS-R/73.5% showed ≥50% improvement from baseline in YMRS score and ≤40 on CDRS-R. Remission rate was 52.9% based on YMRS ≥50% change from baseline, end point CDRS-R ≤40, CGI-I ≤2 and CGAS ≥51	Pediatric side effect checklist, AIMS, physical exam and lab assessments, ECG, vital signs/ Weight gain, sedation, increased appetite, cognitive dulling, nausea and stomach pain were common side effects	Rescue paradigms appear to play significant role in maintaining subjects >6 mo	

<p>Monotherapy trials of SGAs: short-term treatment Frazier et al., 2001</p>	<p>Stimulants = 35%, lorazepam = 13%, benztropine = 9%, α-agonists</p>	<p>YMRS decrease in score by 30% from baseline + CGI-S score ≤ 3/Using the YMRS decrease in score by 30%, 61% improved/ There was significant change in all scales when baseline and endpoint scores were compared ($p < .001$)</p>	<p>Self-report, Barnes Akathisia Scale, Simpson-Angus Scale, AIMS, weight, vitals, lab tests/ Increased appetite in 60.9%, somnolence in 43.5%, abdominal pain and weight gain in 30.4%; other side effects included depression, diarrhea, infection, and fever. Two patients had akathisia</p>	<p>Not clear how % of improved outcomes were calculated on CDRS (32%), BPRS (62%), and positive psychotic symptomatology score (90%)</p>
<p>Biederman et al., in press</p>	<p>Lorazepam or benztropine were not used despite provision for use on p.r.n. basis. Stimulants were continued if they were thought to be necessary and were on stable dose for 30 days</p>	<p>YMRS decrease in score by 30% from baseline or CGI-I score ≤ 2/ Response rate on mania was 70%/There was significant change in YMRS, BPRS, and CDRS when baseline and end point scores were compared ($p < .001$)</p>	<p>Spontaneous reports of treatment-emergent adverse events, lab tests, including prolactin, glucose levels/ Colds, increased appetite, and sedation were common. No EPSs. Fourfold increase in prolactin and weight gain ($p < .001$)</p>	<p>Concomitant reduction in depressive symptoms make it attractive option for mood stabilization in pediatric BD. ADHD response is difficult to qualify given that stimulants were also administered for some subjects (number of subjects receiving them and dose of stimulants not reported)</p>
<p>Combination therapy trials of mood stabilizer and atypical antipsychotic Kafantaris et al., 2001a</p>	<p>2 of 5 required lorazepam in first 10 days in psychotic group</p>	<p>YMRS score 33% decrease from baseline and CGI-I 1 or 2/ Psychotic mania = all subjects showed some improvement on combination therapy, but none responded (3 needed combination again and 2 completed 4 wk of Li monotherapy); nonpsychotic mania = 3/5 responded to Li monotherapy</p>	<p>No specific measure was mentioned/No report on details or the list of side effects that may have occurred</p>	<p>Haloperidol was restarted as soon as worsening of symptoms was noted among subjects who dropped out of the double-blind discontinuation part of the study</p>
<p>Kafantaris et al., 2001b</p>	<p>Lorazepam (also alternative antipsychotics are allowed = 77.1%)</p>	<p>YMRS score 33% decrease from baseline and CGI-I 1 or 2/See numbers retained; 64% improved on combination; few remained stable on monotherapy</p>	<p>No specific measure was mentioned/No report on details or the list of side effects that may have occurred</p>	<p>Note the antipsychotic combination therapy in the study design</p>

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TABLE 2 (Continued)

Ref. ^a	Concurrent Medications	Definition of Outcome/Efficacy Results	Adverse Events Measure Used/Results	Comment
DelBello et al., 2002	Lorazepam/DVPX + placebo = 3, DVPX + quetiapine = 2	Response was change of $\geq 50\%$ from baseline to end point on YMRS/ Secondary response measures of change from baseline CGAS, PANSS-P, CDRS (<i>p</i> values, analyses of variance between groups)/87% in combination vs 53% in monotherapy; no difference in CDRS, PANSS-P, CGAS	Simpson-Angus, Barnes Akathisia and AIMS, open ended adverse events, questions by asking adolescents and caregivers. Baseline lab tests, ECG, slit-lamp ocular exams (baseline and end point)/ Sedation in combination group is significant. Nausea, vomiting, dizziness, and headache are noted with no group differences. Weight gain was 2.4 kg with monotherapy vs. 4.2 kg in combined group	Mixed episodes are present in 87% (<i>n</i> = 13) in monotherapy group and 67% (<i>n</i> = 10) in combined group; there were no group differences in outcome on depression, psychosis, or functioning, although both groups improved from baseline. It is not clear whether quetiapine augmentation is specifically beneficial for mania alone. It is difficult to be conclusive given the small sample size
Pavuluri et al., 2004e	Trazodone (50 mg): Li + Risp = 1, DVPX + Risp = 5. Stimulants: Li + Risp = 0, DVPX + Risp = 3; clonidine: Li + Risp = 1, DVPX + Risp = 4; benzotropine: Li + Risp = 2, DVPX + Risp = 1	Symptom response: YMRS $\geq 50\%$ change from baseline. Remitters are those who showed YMRS $\geq 50\%$ change from baseline and end point CGI-I ≤ 2 and CGAS ≥ 51 / Response rate with Li + Risp = 82.4% and DVPX + Risp = 80%. Remission was 64.7% and 60%, respectively	Pediatric side effect checklist, AIMS, physical exam and lab assessments, ECG, vital signs/ Weight gain, nausea, sedation, and gastrointestinal upset were seen in both groups, with no significant group differences	There appeared to be no advantage of one combination regimen over the other; note the low dose of Risp as an adjuvant therapy
Combination trial of 2 mood stabilizers Findling et al., 2003	Stimulants = 53%, α_2 agonists = 22%, SGAs = 19%, SSRIs = 10%; others included TCA, other AD, anticonvulsants, buspirone, typical antipsychotics, BDZ	Symptom response: YMRS $\geq 50\%$ change from baseline. Remitters are those who scored ≤ 12.5 at end point and CGI-I ≤ 2 and CGAS ≥ 51 / Remitters = 46.7%. Using YMRS $\geq 50\%$ change from baseline and end point CGI-I ≤ 2 , complete response = 70.6%. Using YMRS decrease in score by 30% from baseline + CGI-S ≤ 3 , complete response = 75.3%	Side effects were monitored by direct query from both research assistant and study physician on each visit apart from physical exam, vitals, basic lab tests, ECG/ Withdrawn due to intolerance of study medication = 16.7%; emesis, enuresis, stomach pain, tremor, thirst, headache, nausea, sedation, appetite increase, diarrhea are some of the common side effects	Naturalistic design with (1) variable length of follow-up, (2) variable types of disease states, (3) variable rescue medications, and (4) high score on CGAS (50.1); may have a role in low dropoff in subjects

Kowatch et al., 2003	Naturalistic study that allowed for combination therapy 20/35 on combination therapy	YMRS 50% improvement from baseline/80% among the 20 subjects requiring combination therapy	No specific measure was mentioned/No report on details or the list of side effects that may have occurred	Mood stabilizers were used for “predominantly bipolar subjects.” Duration on each medication combination is not specified; effectively this may be an algorithm study vs. combination therapy of subjects with the need to intervene with specific problems for entire 24 wk
Comorbidity studies Geller et al., 1998a	All subjects on therapy; not restricted from using any drugs of abuse	Of 13 on active drug, 6 were active responders (46.2%)/10% positive urine drug screen in those on Li and 40% in those on placebo	Acute Li side effects scale/Thirst, polyuria, nausea, vomiting, dizziness	YMRS was not reported probably as the patients were not in acute state of illness. This was not a study examining reduction in manic or depressive symptoms but response in substance abuse and functioning. Sample is heterogeneous in psychopathology, termed BDs Important finding is the absence of worsening of mania on amphetamine salts after initial stabilization with DVPX. Posttrial 12-wk follow-up continued to show improvement in 22/23 subjects
Scheffer et al., 2005	None reported other than study medications	Symptom response with DVPX: YMRS \geq 50% change from baseline; CGI 1 or 2 for ADHD outcome/Response on open trial of monotherapy with DVPX was 80%, but 3/40 improved on CGI-I on ADHD; significant difference between CGI scores on amphetamine salt (score of 1.7) vs. placebo (score of 3.4) ($p < .0001$)	Side Effects Form for Children and Adolescents/Rare overall; abdominal pain, increased appetite and drowsiness	Important finding is the absence of worsening of mania on amphetamine salts after initial stabilization with DVPX. Posttrial 12-wk follow-up continued to show improvement in 22/23 subjects
Discontinuation study Kafantaris et al., 2004	None permitted	YMRS score 33% decrease from baseline and CGI-I 1 or 2/52.6% (10/19) of those on Li and 61.9% (13/21) of those on placebo had exacerbation during the trial	CGI Efficacy Index/67.5% had mild adverse events, one subject had persistent diarrhea and increased appetite	Li was discontinued over a short period of 3 days without adverse events (other than exacerbation of symptoms in 62%)

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TABLE 2 (Continued)

Ref. ^a	Concurrent Medications	Definition of Outcome/Efficacy Results	Adverse Events Measure Used/Results	Comment
Maintenance study Findling et al., 2005	Stimulants = 58.3%; clonidine = while permitted, not reported	Time to mood relapse and premature discontinuation for any reason; Li and DVPX arms did not differ in time to mood relapse or time for premature discontinuation for any reason; median survival in the study was 114 days on Li and 112 days on DVPX; time for premature discontinuation for Li was 91 days and for DVPX, 56 days. Subjects with higher YMRS scores discontinued early	Side effects were monitored by direct query from both research assistant and study physician on each visit apart from physical exam, vitals, basic lab tests, ECG/With Li, emesis and enuresis were common (30% each). With DVPX, stomach pain and headache are common side effects (23.3% in each group)	Despite the aim to maintain, only 6 people completed the 18-mo trial with high dropout rate in the first 100 days
Algorithm-based study Pavuluri et al., in 2004a	Pharmacotherapy algorithm allowed for multiple tactics to treat mood, psychosis, ADHD, sleep difficulties, and attend to partial or no response	Final CGI-I BP score ≤ 2 on overall scale and the subscales/ In the entire algorithm sample, final overall CGI-I BP score ≤ 2 is seen in 68.3%; final mean C-GAS score was 56.19 ± 7.62 . The CGI-BP Overall score of ≤ 2 was seen in 94.1% in the matched algorithm group compared with none in treatment-as-usual group	No specific measure was mentioned/Weight gain (factored in medication choice) was 6.3 lb in the matched sample of algorithm and 5.7 lb in the treatment-as-usual group	Few subjects in the algorithm group were able to remain only on monotherapy >6 mo (28.1%). Stimulant use was high in treatment-as-usual group and atypical antipsychotic use was high in algorithm group

Note: AD = antidepressants; ADHD = attention-deficit/hyperactivity disorder; AIMS = Abnormal Involuntary Movements Scale; BD = bipolar disorder; BDZ = benzodiazepine; BIS = Behavior and Ideation Scale; BPRS = Brief Psychiatric Rating Scale; CBZ = carbamazepine; CDRS = Child Depression Rating Scale; CDRS-R = Child Depression Rating Scale; CGAS = Children's Global Assessment Scale; CGI-BP = Clinical Global Impressions-Bipolar Disorder; CGI-I = Clinical Global Impressions-Improvement Scale; CGI-I = Clinical Global Impressions-Severity Scale; COSTART III = Coding Symbols for Thesaurus of Adverse Reaction Terms; DVPX = divalproex sodium; ECG = electrocardiogram; EPSs = extrapyramidal side effects; ES = effect size; Ham-D = Hamilton Depression Rating Scale; Li = lithium; MDD = major depressive disorder; MRS = Mania Rating Scale; MS = mood stabilizer; MSS = Manic Syndrome Scale; PANSS-P = Positive and Negative Symptoms Scale-Positive subscale; Risp = risperidone; SGA = second-generation antipsychotic; SSRIs = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressant; YMRS = Young Mania Rating Scale.

^a Listed in each section in order of publication.

address breakthrough symptoms and comorbid conditions such as ADHD that do not subside with initial monotherapy or combination therapy (Pavuluri et al., 2004a). Often, it is necessary to use adjunctive psychosocial treatment, not only for BD but also to address associated symptoms of ODD by integrating effective strategies such as parent training.

PSYCHOTHERAPY

Given the complexity of the illness and associated burden on patients and their families, psychosocial intervention takes a critical role in treatment. There are no proven psychosocial treatment methods for pediatric BD, although there are a few published preliminary studies (Kowatch et al., 2005). Almost all of the studies in pediatric BD implemented therapy as soon as the youngster was stable enough to receive psychoeducation, although not completely recovered from mania. Child- and family-focused cognitive-behavioral therapy was specifically designed for pediatric BD (Pavuluri et al., 2004b). It integrates cognitive-behavioral therapy and interpersonal principles of psychotherapy, modifying the conventional behavior therapy and emphasizing empathic validation. This model also helps parents become aware of their own unhelpful cognitions and learn new tools to serve as “coaches” for their affected offspring. Preliminary results indicate a good symptomatic response and parent satisfaction, although the trial is limited by its open design. Fristad et al. (2002) employed a manual-driven, adjunctive, multiple family group treatment for youths 8–12 years old with bipolar and depressive spectrum disorders. This method included psychoeducation about the disorder including the role of medications and coping strategies. Although preliminary results indicated that families accrued knowledge, skills, support, and positive attitudes, the impact of the treatment on the illness itself has yet to be reported and is under investigation. Miklowitz et al. (2004) developed a manual-based version of family-focused therapy for adolescents with BD that includes assisting adolescents to make sense of their illness, accepting the disorder and mood-stabilizing medications, managing stress, and promoting a family environment conducive to long-term mood stability. This model emphasizes strategies for relapse prevention. In a year-long open trial, they showed symptomatic improvement in mania, depression, and behavior problems.

FUTURE DIRECTIONS FOR RESEARCH

Future research should focus on external validation of pediatric BD, the establishment of multi-informant measures that are reliable and valid for use in children, the refinement of methodology of imaging and genotyping, the verification of adequate sample sizes, and the conduct of double-blind, randomized, controlled pharmacotherapy and psychosocial treatments in clinical as well as community settings. The need to design treatment trials for BD with comorbid disorders is acute. Studies on genotyping demand that large sample sizes be definitive. Imaging methods require further refinement in data analytic methodology, with careful attention to medication effects in youths. Preventive efforts should focus not only on those at genetic risk but also on affectively unstable phenotypes that commonly present to clinical settings.

Placebo-controlled trials and randomized treatment algorithm studies focusing on various stages (mania, mixed, depression, hypomania) and phases (acute, maintenance) of illness will provide more conclusive evidence in the future. The use of combination therapies to treat bipolar depression and for use in maintenance therapy requires additional study. This is particularly true for the use of serotonin reuptake inhibitors, which may exacerbate suicidal behavior and trigger mania.

Three large multisite studies are under way: (1) a trial on longitudinal course of the disorder (Principal Investigator (PI): Birmaher); (2) a placebo-controlled pharmacotherapy trial with lithium and DVPX, alone and in combination in the event of nonresponse to monotherapy (PI: Kowatch); and (3) a controlled trial comparing risperidone, DVPX, and lithium as monotherapy or in combination if monotherapy is ineffective (PI: Geller). Several studies are also under way examining the symptoms and pathophysiology at baseline as well as treatment effects of pharmacotherapy using innovative methods that include molecular genetics, MRS, and functional MRI.

CONCLUSION

Despite the controversy regarding the hallmark symptoms of the BD diagnosis, there is consensus on the existence of pediatric BD. There is core agreement on the presence of narrow and broad phenotypes, but additional studies are required to conclude whether the

broader phenotypes fall into the bipolar spectrum. High comorbidity with ADHD, disruptive and anxiety disorders, chronicity, recurrence, rapid cycling, mixed episodes, psychosis, suicidality, and risk of substance abuse (in adolescents) characterize pediatric BD. Mood stabilizers and combined SGAs and mood stabilizers seem to help, but more short- and long-term randomized, controlled trials are needed.

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