Practice Parameter for the Assessment and Treatment of Children and Adolescents With Bipolar Disorder

ABSTRACT

This practice parameter reviews the literature on the assessment and treatment of children and adolescents with bipolar disorder. The parameter focuses primarily on bipolar 1 disorder because that is the type most often studied in juveniles. The presentation of bipolar disorder in youth, especially children, is often considered atypical compared with that of the classic adult disorder, which is characterized by distinct phases of mania and depression. Children who receive a diagnosis of bipolar disorder in community settings typically present with rapid fluctuations in mood and behavior, often associated with comorbid attention-deficit/hyperactivity disorder and disruptive behavior disorders. Thus, at this time it is not clear whether the atypical forms of juvenile mania and the classic adult form of the disorder represent the same illness. The question of diagnostic continuity has important treatment and prognostic implications. Although more controlled trials are needed, mood stabilizers and atypical antipsychotic agents are generally considered the first line of treatment. Although patients may respond to monotherapy, combination pharmacotherapy is necessary for some youth. Behavioral and psychosocial therapies are also generally indicated for juvenile mania to address disruptive behavior problems and the impact of the illness on family and community functioning. *J. Am. Acad. Child Adolesc. Psychiatry*, 2007;46(1):107–125.
Key Words: bipolar disorder, mood stabilizers, practice parameter, practice guideline.

The number of children and adolescents receiving a diagnosis of bipolar disorder has increased markedly during the past decade in the United States. Bipolar disorder was once thought to occur only rarely in youths, especially children (see Carlson, 2005). However, there has been a shift in how the disorder is defined in juveniles. There are also similar debates about how broadly to define the disorder in adults (Baldessarini, 2000; Judd and Akiskal, 2003). In general, the field has shifted from diagnostic practices based on pattern recognition or template (i.e., the syndrome is defined by characteristic patterns of symptom and clinical presentations, including an episodic course) to one in which individual symptom criteria are considered as evidence of the disorder. Inasmuch, more individuals, children and adults, are

Accepted August 15, 2006.

This parameter was developed by Jon McClellan, M.D., Robert Kowatch, M.D., Robert L. Findling, M.D., and the Work Group on Quality Issues: William Bernet, M.D., and Oscar Bukstein, M.D., Co-Chairs, and Joseph Beitchman, M.D., R. Scott Benson, M.D., Joan Kinlan, M.D., Ulrich Schoettle, M.D., Jon Shaw, M.D., Saundra Stock, M.D., and Heather Walter, M.D. AACAP Staff: Kristin Kroeger Ptakowski. A group of invited experts also reviewed the parameter: Janet Wozniak, M.D., Ellen Leibenluft, M.D., Melissa DelBello, M.D., David Axelson, M.D., Gabrielle Carlson, M.D., and Eric Youngstrom, Ph.D.

This parameter was reviewed at the member forum in October 2004 at the annual meeting of the American Academy of Child and Adolescent Psychiatry.

During August 2005, a consensus group reviewed and finalized the content of this practice parameter. The consensus group consisted of representatives of relevant AACAP components as well as independent experts: Oscar Bukstein, M.D., Work Group Co-Chair; Jon McClellan, M.D., author; John Hamilton, M.D., and Ulrich Schoettle, M.D., members of the Work Group on Quality Issues; Marilyn Benoit, M.D., Eugene Beresin, M.D., and Ellen Sholevar, M.D., Council Representatives; Guy Palmes, M.D., Sherry Barron-Seabrook, M.D., and Syed Naqvi, M.D., Assembly of Regional Organizations Representatives; David Axelson, M.D., and Gabrielle Carlson, M.D., independent expert reviewers, and Kristin Kroeger Ptakowski, Director of Government Affairs and Clinical Practice. Members of the consensus group were asked to identify any conflicts of interest they may have with respect to their role in reviewing and finalizing the content of this practice parameter.

This practice parameter was approved by AACAP Council on June 17, 2006.

This practice parameter is available on the Internet (www.aacap.org).

Reprint requests to the AACAP Communications Department, 3615 Wisconsin Avenue, NW, Washington, DC 20016.

0890-8567/07/4601-0107©2006 by the American Academy of Child and Adolescent Psychiatry.

DOI: 10.1097/01.chi.0000242240.69678.c4

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

characterized as having subthreshold or "atypical cases" based on periods of elated, expansive, or irritable mood (Carlson, 2005). This atypical but common presentation of mania in children appears to be caused by developmental differences in manic symptom expression and the evolving picture of this disorder in children.

Although current *DSM-IV-TR* nosology does not distinguish age-specific criteria for bipolar disorder (American Psychiatric Association, 2000), the patterns of illness and symptom definition described in children often vary from the classic description of the disorder in adults (i.e., a cyclical illness characterized by distinct phases of mania and depression). Youths in community settings who present with outbursts of mood lability, irritability, reckless behavior, and aggression are now receiving a diagnosis of bipolar disorder. Published reports of juvenile mania describe either youths with a pattern of illness of very rapid, brief, recurrent episodes lasting hours to a few days (Geller et al., 2000, 2004) or youths with chronic mania, including those with mania as their baseline functioning (Wozniak et al., 1995). Thus, whether these presentations are bipolar disorder and/or represent the same condition classically described in adults has become an area of controversy and scientific debate (Pavuluri et al., 2005). The continuity of juvenile mania with the classic adult disorder has important clinical implications because assumptions about the diagnosis lead to treatment decisions based primarily on the adult literature. There are also implications for etiological research, genetic counseling, and family educational interventions because all of these areas often assume continuity of the disorder.

This parameter does not attempt to resolve this debate. Only continued research will accomplish that goal. The intent of the parameter is to describe what is known of the disorder in juveniles, where areas of controversy lie, and what constitutes acceptable practices and appropriate care.

METHODOLOGY

The literature review process was performed using the National Library of Medicine database. Key words included *adolescents, children,* and *bipolar disorder,* with supplemental searches to address other relevant topics (e.g., specific medications). The *Medline* search was updated several times, most recently in January 2005. This process identified several hundred abstracts. Relevant papers identified through this process were reviewed in detail. Pertinent books and review articles were also used. Finally, the authors drew from their own work in this area. Experts in the field were also consulted. Their comments, including additions and clarifications of the literature review, were incorporated into the parameter. An asterisk in the reference section notes key articles from which recommendations were primarily based.

DEFINITIONS

The following definitions are derived from *DSM-IV-TR* unless otherwise specified:

Bipolar I disorder: Bipolar I disorder requires the occurrence of a manic (or mixed) episode with duration of at least 7 days, unless hospitalization is required. Episodes of depression are not required, but most patients experience major or minor episodes of depression during their life span. In comparison, the *ICD-10* (World Health Organization, 1992), the diagnostic system used by much of the world, describes bipolar I disorder as an episodic illness with bouts of mania and depression and requires that manic episodes last 1 week or more. Both *DSM-IV-TR* and *ICD-10* stipulate that the episodes represent a significant departure from the individual's baseline function and note that the typical age at onset is young adulthood. Thus, these definitions are consistent with the classic conceptualization of the disorder. The definition of mania is a critical issue in the pediatric literature. Many of the published studies used *DSM-III-R* criteria, which did not specify duration criteria for mania. Therefore, brief outbursts of manic-like symptoms could be classified as mania.

Mixed episode: A period lasting 7 days or more in which symptoms for both a manic and depressive episode are met.

Bipolar II disorder: This illness requires periods of major depression and hypomania (episodes lasting at least 4 days) but no full manic or mixed manic episodes.

Rapid cycling: The occurrence of at least four mood episodes in 1 year. Per *DSM-IV-TR,* rapid cycling episodes still must meet the prerequisite duration criteria (e.g., 7 days for a manic episode). Note that this definition is different from that used in some

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

published studies of youths, in which cycling refers to mood changes within an episode (Geller et al., 2004).

Bipolar disorder not otherwise specified (NOS): This term is used for cases that do not meet full criteria for other bipolar diagnoses. This term also has been recommended to describe the large number of youths who receive a diagnosis of bipolar disorder who do not have the classic adult presentation (NIMH, 2001).

Definitions currently used in the juvenile bipolar literature, but not provided in *DSM-IV-TR*, include the following:

Ultrarapid cycling: Ultrarapid cycling refers to brief, frequent manic episodes lasting hours to days, but less than the 4-day prerequisite for hypomania. Geller et al. (2000) define ultrarapid cycling as having 5 to 364 cycles per year.

Ultradian cycling: Ultradian cycling refers to repeated brief (minutes to hours) cycles that occur daily. Geller et al. (2000) use the definition of greater than 365 cycles per year.

These terms were originally proposed by Kramlinger and Post (1996) to describe a small number of adult patients with rapid mood shifts, but they have not been adopted as part of *DSM-IV-TR*. The use of different descriptors makes it difficult to compare descriptions of adult and juvenile cases.

HISTORICAL REVIEW

Kraepelin (1921) observed that mania occurred rarely in children and that the onset of first episodes increased significantly after puberty. However, early-onset mania generally went unrecognized in the first part of the 20th century. Although Anthony and Scott (1960) reported cases of manic-depressive psychosis in children, the clinical bias that mania did not occur in youths persisted until large-scale studies of bipolar adults found that approximately one fifth of cases retrospectively had evidence of the illness before age 19 years (Carlson et al., 1977; Joyce, 1984; Loranger and Levine, 1978). Even though many adults with bipolar disorder describe the onset of mood symptoms during childhood (Lish et al., 1994; Perlis et al., 2004), the presenting symptoms are most often depression and hyperactivity, with episodes of mania developing later.

Historically, diagnostic confusion between schizophrenia and bipolar disorder led to misdiagnosis in adolescents. Mania during adolescence often presents with psychosis (McGlashan, 1988). Carlson and Strober (1978) reported that bipolar disorder in six adolescents was originally misdiagnosed as schizophrenia, a diagnostic tendency noted in subsequent studies (Bashir et al., 1987; Joyce, 1984; McClellan et al., 1993; Werry et al., 1991). This problem appears to be less of an issue given better adherence to *DSM* criteria (Carlson et al., 1994; Schwartz et al., 2000).

Although historically considered rare, childhood-onset bipolar disorder is now being diagnosed much more commonly, including in preschoolchildren (Wilens et al., 2003). This remains an area of controversy (NIMH, 2001), as discussed in greater detail below.

EPIDEMIOLOGY

The estimated lifetime prevalence of bipolar I disorder in the general population ranges from 0.4% to 1.6%, with ≈0.5% having bipolar II (American Psychiatric Association, 2000). The National Comorbidity Survey Replication study found the combined prevalence of bipolar I and II disorders to be 2.6% (Kessler et al., 2005). However, some studies of adults suggest rates as high as ≈6% when including subthreshold or "spectrum" cases (Judd and Akiskal, 2003). Epidemiological surveys of childhood psychiatric disorders have generally not addressed the illness (Costello, 1989). In a study of predominantly rural youths, ages 9, 11, and 13 years, no cases of mania were found (Costello et al., 1996). A community school survey of older adolescents (14–18 years) found the lifetime prevalence rate to be ≈1% (Lewinsohn et al., 1995), although only 0.1% had mania. Most of the identified cases had hypothymia or cyclothymia. An additional 5.7% had subthreshold symptomatology. Carlson and Kashani (1988), in an epidemiological survey of 14- to 16-year-old youth, found that the estimated lifetime prevalence of mania was 0.6%. Rates rose to 13.3% depending on whether duration and severity criteria were accounted for. Although overall bipolar disorder affects both sexes equally, early-onset cases are predominantly male, especially in cases with onset before age 13 years.

Historically, large surveys of adults with bipolar disorder noted that onset before age 10 years occurred in only 0.3% to 0.5% of patients (Goodwin and Jamison, 1990; Kraepelin, 1921; Loranger and Levine,

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

1978), leading to the assumption that childhood-onset bipolar disorder was rare. However, subsequent surveys of adults with the disorder (Lish et al., 1994; Perlis et al., 2004) note that a large proportion describe mood symptoms (most often depression) beginning in childhood. As the definition of bipolarity has broadened in both juveniles and adults, some experts suggest that the disorder may be as prevalent as 1% in youths (Geller and Luby, 1997).

RISK FACTORS

In the adult literature, twin, adoption, and family history studies support a strong genetic component, with a four- to sixfold increased risk of disorder in first-degree relatives of affected individuals (Nurnberger and Foroud, 2000). The degree of familiality appears even higher in early-onset, highly comorbid cases (Faraone et al., 2003). More studies are needed, including those that examine the offspring of parents with other psychiatric illnesses (e.g., substance abuse, major depression), to assess specificity.

Dysthymic, cyclothymic, or hyperthymic (irritable, driven) temperaments may presage eventual bipolar disorder (Akiskal, 1995). Offspring of parents with bipolar disorder display more symptoms suggestive of risk for the disorder than those of normal controls, including mood lability, anxiety, attention difficulties, hyperarousal, depression, somatic complaints, and school problems (Chang et al., 2003; Egeland et al., 2003). Egeland et al. (2003) noted that these symptoms presented in an episodic pattern, consistent with the classic adult presentation, but in contrast to other reports of bipolarity in children.

Premorbid psychiatric problems are common in early-onset bipolar disorder, especially difficulties with disruptive behavior disorders, irritability, and behavioral dyscontrol (Carlson, 1990; Fergus et al., 2003; Geller et al., 2002a; McClellan et al., 2003; Werry et al., 1991; Wozniak et al., 1995). Premorbid history may vary by age at onset. Rates of prior disruptive behavior disorders vary in studies of teenagers with bipolar disorder, with some youths having normal premorbid histories (Kafantaris et al., 1998; Kutcher et al., 1998; McClellan et al., 2003), whereas most childhood cases are associated with attention-deficit/hyperactivity disorder (ADHD; Findling et al. 2001; Geller et al., 2002a; Wozniak et al., 1995). The estimated rate of childhood hyperactivity in adults with bipolar disorder is approximately 10% to 20% (Carlson et al., 2000a, Nierenberg et al., 2005; Winokur et al., 1993). Although many children with bipolar disorder have histories of disruptive behavior disorders, the reverse is not necessarily true. Follow-up studies of youths with ADHD have not shown that they have an increased rate of classic bipolar disorder as adults (Carlson et al., 2000b; Mannuzza et al., 1998; Weiss et al., 1985).

Premorbid anxiety and dysphoria are also common, including in those whose first mood episode is a depressive disorder. Approximately 20% of youths with major depression go on to experience manic episodes by adulthood (Geller et al., 1994, 2001; Kovacs, 1996; Rao et al., 1995; Strober and Carlson, 1982). Similar to findings in adults, factors that predict the eventual development of mania in depressed children and adolescents include (1) a depressive episode characterized by rapid onset, psychomotor retardation, and psychotic features; (2) a family history of affective disorders, especially bipolar disorder; and (3) a history of mania or hypomania after treatment with antidepressants (Strober and Carlson, 1982). Youths with psychotic depression are presumed to be at greater risk for switching to mania with antidepressant therapy, although not all studies have found this (DelBello et al., 2003).

CLINICAL PRESENTATION

In adults, the disorder is considered to be cyclical in nature, with episodes of illness representing a significant departure from an individual's baseline functioning and mental status examination (Goodwin and Jamison 1990; World Health Organization, 1992). Mood changes characteristic of mania include marked euphoria, grandiosity, and irritability, with associated racing thoughts, increased psychomotor activity, and mood lability (Cassidy and Carroll, 2001). Paranoia, confusion, and/or florid psychosis may also be present. Marked sleep disturbance is a hallmark sign. Significant depressive symptoms may precede, occur conjointly (mixed episodes), or follow those of mania within the same episode. Depressive episodes in adults with bipolar disorder are typically characterized by psychomotor retardation and hypersomnia, significant suicide attempts, and often psychotic symptoms (Goodwin and Jamison, 1990). Severe cases may progress to catatonia.

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

Mania in adolescents is frequently associated with psychotic symptoms, markedly labile moods, and/or mixed manic and depressive features (Pavuluri et al., 2004a,b,c,d, 2005). The early course of bipolar disorder in adolescents appears to be more chronic and refractory to treatment than adult onset (Perlis et al., 2004), whereas the long-term prognosis is either similar to that of adults (Carlson et al., 1977; McClellan et al., 1993; McGlashan, 1988; Werry et al., 1991) or worse (Carter et al., 2003). Comorbidity predicts functional impairment, whereas age at onset predicts duration of episodes (Carlson et al., 2000a, 2002). Jairam et al. (2004) found that 96% of subjects ($n = 25$) with juvenile mania (onset <16 years) recovered from their index episode, but that 64% relapsed after a mean period of 18 months despite ongoing mood stabilizer therapy. McClellan et al. (1999), in a comparison study of youths, primarily young adolescents, with early-onset psychotic disorders (onset <18 years), found that subjects with bipolar disorder tended to have a cyclical course similar to reports in adults.

Juvenile mania, especially in younger children, often is characterized by symptom presentations and patterns of illness that vary from the classic descriptions of bipolar disorder in adults (Bowring and Kovacs, 1992). Changes in mood, energy levels, and behavior are often markedly labile and erratic rather than persistent. Irritability, belligerence, and mixed manic-depressive features are more common than euphoria. High rates of comorbid disruptive disorders are commonly found. Studies vary somewhat in their descriptions of early-onset cases. Findling et al. (2001) found that bipolar disorder in both children and adolescents is cyclical, had high rates of rapid cycling, and had low rates of 3interepisode recovery. In a series of studies by Biederman and colleagues (Biederman et al., 2004a,b; Wozniak et al., 1995), children with juvenile mania most often present with mixed episodes (primarily irritability and explosiveness), with chronic impairment, including some patients for whom the illness represents their baseline functioning. Children with bipolar depression present with both anger and dysphoria and are more likely to have comorbid conduct, anxiety, and substance abuse problems than youths with unipolar depression (Wozniak et al., 2004).

Geller et al. (2000, 2002a, 2004) published a series of reports examining bipolar disorder in children. This group has characterized a prepubertal and early-adolescent bipolar disorder (PEA-BP) phenotype for this research study, with the development of a structured diagnostic interview to identify cases (Geller et al., 2000, 2002a). Using the investigators' criteria that require the presence of elation and grandiosity, a cycle of manic symptoms may be as short as 4 hours, with at least one cycle daily for 2 weeks defined as meeting *DSM-IV* criteria for mania. Of the youths with PEA-BP, 10% had ultrarapid cycling and 77% had ultradian cycling (Geller et al., 2000). On average, the youths were described as having 3.7 ± 2.1 cycles per day (Geller et al., 2002a). The average age at onset was 7.3 ± 3.5 years, with a duration of episode of 3.6 ± 2.5 years (an episode is defined as the duration of the illness, which differs from the adult literature convention; Geller et al., 2000). There was also a high rate of comorbid ADHD and other disruptive behavior disorders (Tillman et al., 2003). This sample, with chronic continuous rapid cycling, long durations of episodes, and a high rate of ADHD, may be similar to youths described by Wozniak et al. (1995) as having chronic baseline mania. The PEA-BP phenotype has been reported to be reliable, with stability over follow-up assessments at 6 months and 1, 2, and 4 years (Geller et al., 2001a, 2002b, 2004). Unfortunately, there were high rates of chronicity and relapse during the 4-year follow-up period despite community treatment (Geller et al., 2002b). Low ratings of maternal warmth predicted a shorter time to relapse, whereas psychosis was associated with greater chronicity (Geller et al., 2004). Participation in community treatment (including mood stabilizers) did not appear to improve outcome at year 2 (Geller et al., 2002b). Symptoms of mania and hypomania persisted in this sample over a 4-year period. However, this study does not resolve the questions as to whether these children will develop more classic bipolar disorder, continue to demonstrate atypical presentations, and/or develop other psychiatric disorders.

DIAGNOSTIC CONTROVERSY

The debate and controversy over juvenile bipolar disorder are not whether there are a significant number of youths who are explosive, dysregulated, and emotionally labile or whether these youths suffer significant impairment or are at risk for a variety of adverse outcomes, including substance abuse. These

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

difficulties and concerns are commonplace, especially in community mental health settings and systems of care that deal with at-risk youths (e.g., juvenile justice, foster care). The debate is whether these problems in youths are best characterized as bipolar disorder and, more important, whether juvenile mania is the same illness as that classically described in adults (Kent and Craddock 2003; Kim and Miklowitz, 2002; Leibenluft et al., 2003; McClellan, 2005). Mood dysregulation in children and adolescents is often associated with features of borderline personality disorder (McClellan and Hamilton, 2006). This raises questions of diagnostic specificity and the overlap between mood and personality disorders, while also generating concerns regarding the validity of personality disorder diagnoses in youths. A related debate occurs in the adult literature, in which "bipolarity" overlaps with a broad array of mood and anxiety problems, including difficulties attributed to personality disorders or substance abuse (see Baldessarini, 2000).

Reports of juvenile mania challenge several preexisting notions about the classic descriptions of the illness in adults. Differences in symptom presentation and pattern of illness raise questions of diagnostic continuity. Rather than being a cyclical disorder with an acute onset of clearly demarcated phases of mania and/or depression, bipolar disorder typically presents in youths as chronic difficulties regulating their moods, emotions, and behavior. Such outbursts are erratic and explosive, often lasting just minutes to hours and yet represent fairly stable baseline patterns of response to stress, conflict, or interpersonal negotiations (thus the description of chronic mania by Wozniak et al. [1995] or the description of long duration of episode and lack of remission by Geller et al. [2004]). Furthermore, a marked reduction in the need for sleep is considered a pathognomonic sign of mania in adults (American Psychiatric Association, 1994; Goodwin and Jamison, 1990), whereas in published studies of juvenile mania, only $\leq$50% of cases had sleep disturbance (Biederman et al., 1998; Geller et al., 1999).

Another challenge is reconciling the noted high rates of juvenile mania described in some samples with the apparently contradictory adult epidemiological findings. In the general population, the overall prevalence is $\approx$1%, with rates increasing with age. The peak ages at onset range from 15 to 30 years (American Psychiatric Association, 2000). However, the early-onset bipolar literature suggests that perhaps 1% of youths have the illness, based presumably on the percentage of children with ADHD who receive a diagnosis of juvenile mania (Geller and Luby, 1997). Thus, these two rates are basically the same, which is counterintuitive because bipolar disorder is generally considered a lifelong condition and thus the rates should increase over time. The apparent discrepancies between the adult and child prevalence literature could be caused by several factors: the age at onset has shifted markedly downward (or the ability to recognize the illness earlier has improved), the adult prevalence rates are grossly underestimated, and/or the overall prevalence of the disorder is increasing at a remarkable rate. Conversely, these findings may imply that some children diagnosed with bipolar disorder do not have the same illness that is classically described in adults.

Other factors to consider when evaluating whether bipolar disorder in children and adolescents represents the same entity as in adults includes evidence of heritability and whether the early-onset form eventually evolves into the more classic adult presentation. Faraone et al. (1997) found that youths with juvenile mania have increased family histories of bipolar disorder. However, this study also found higher than expected rates of bipolar disorder in relatives of controls, raising questions about the specificity of how the diagnosis is being applied (see Klein et al., 1998). With regard to long-term outcome, although symptoms of early-onset bipolar disorder appear stable over time (Biederman et al., 2004b; Geller et al., 2004), juvenile mania has not yet been shown to progress into the classic adult disorder. Furthermore, because early childhood problems with ADHD and conduct problems also tend to persist long term (Shaw et al., 2005), it is not clear whether outcomes are attributable to the early-onset bipolar disorder versus its associated comorbidities.

Lewinsohn et al. (2000) found that bipolar disorder during later adolescence predicted continuity of the disorder at age 24 years. However, subsyndromal cases, which may include youths otherwise characterized as bipolar disorder NOS, had an increase in psychopathology and adverse outcomes as young adults, but not an increase in bipolar disorder. Both the bipolar

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

and subsyndromal cases had an increased risk of antisocial and borderline personality symptoms. Hazell et al. (2003), in a 6-year follow-up study, found that manic symptoms in boys with ADHD did not persist, nor did they evolve into *DSM-IV*–defined bipolar disorder. Studies that did find continuity (Carlson, 1990; Jairam et al., 2004; McClellan et al., 1993, 1999; McGlashan, 1988; Werry et al., 1991) used the classic adult definition of the illness and thus likely did not include cases more recently described as juvenile mania.

This debate is driven in part by a fundamental dilemma inherent to child and adolescent psychiatry: how to extrapolate adult diagnostic criteria for use with children and adolescents. *DSM* criteria for mania specify that the distinct periods of elevated mood may include irritability. Therefore, how do clinicians distinguish irritable mania from more commonplace anger problems, especially given the high rate of comorbidity with disruptive behavior disorders? Hallmark manic symptoms of grandiosity, psychomotor agitation, and reckless behavior must be differentiated from those of other more common childhood disorders such as hyperactivity, irritability, dangerous play, and inappropriate sexualized activity, as well as from the normal childhood phenomena of boasting, imaginary play, overactivity, and youthful indiscretions. To address these concerns, Geller et al. (2002a) required that either elation or grandiosity occur but did not specify how long these symptoms had to persist to be rated as significantly abnormal. Although the investigators provided examples of elated or grandiose symptoms suggestive of childhood mania (Geller et al., 2002a), the descriptions still raise questions. Many behaviors characterized as elation (excessive silliness and giggling) or grandiosity (a child saying it is not wrong for him to steal after getting caught, a child believing he or she can grow up to be a famous athlete even though he or she is not good at sports) are commonplace among youths with disruptive behavior problems (Harrington and Myatt, 2003). The lack of a gold standard, independent of diagnostic criteria, for confirming a diagnosis remains the major challenge. This is a problem for all psychiatric research because ultimately the application of diagnostic criteria is dependent on the clinician's or investigator's views as to what constitutes a symptom (see McClellan and Werry, 2000 for a more extensive review of these issues).

Although some studies have attempted to validate the diagnosis by examining other diagnostic tools (e.g., symptom rating scales), these measures generally assess the same types of symptoms and therefore may not be truly independent. For example, juvenile mania is proposed to have a specific profile on the Child Behavior Checklist, with elevations in scales for inattention/hyperactivity, depression/anxiety, and aggression (Mick et al., 2003). However, it is questionable whether this represents a unique profile versus a greater severity of psychopathology across multiple domains (Youngstrom et al., 2005a,b). Poor rates of agreement are found among reports of manic symptoms made by children, parents, and teachers (Thuppal et al., 2002). Parent report appears to be more useful than teacher or youth report for discriminating cases (Youngstrom et al., 2004). Children for whom there is good agreement between parents and teachers regarding manic symptoms are more likely to have a complicated, refractory course of illness (Carlson and Youngstrom, 2003). Manic symptoms may be nonspecific markers for emotionality and severity rather than true indicators of a classic manic disorder (Carlson et al., 1998; Hazell et al., 2003; Thuppal et al., 2002).

Finally, this debate raises important issues regarding the implications of labeling children with a major psychiatric disorder, especially one that warrants treatment with aggressive pharmacotherapy. This is especially pertinent given the recent public concerns about the increasing use of psychotropic agents in youths, including preschoolchildren (Zito et al., 2000). Anecdotally, the diagnosis of bipolar disorder is now being applied to very young children. In a survey of members of the Child and Adolescent Bipolar Foundation, 24% of the respondents' affected children (n = 854) were between the ages of 1 and 8 years (Hellander, 2002). Wilens et al. (2003) noted that 26% of preschoolchildren with ADHD have bipolar disorder, a rate significantly higher than that found in their comparison school-age sample. Others (Dilsaver and Akiskal, 2004; Scheffer and Niskala Apps, 2004) have also described bipolar disorder in preschoolers, whereas Speltz et al. (1999) found no cases using similar diagnostic methodologies in a sample referred for disruptive behavior disorders. Reports of very early onset bipolar disorder raise questions about the applicability and developmental appropriateness of

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

applying adult criteria to toddlers. The validity of diagnosing bipolar disorder in preschoolchildren has not been established. A consensus conference of experts advised the U.S. Food and Drug Administration (FDA) to only extend medication treatment studies down to age 10 years, given concerns about the challenge of accurate diagnosis in younger children (Carlson et al., 2000). Until the validity of the diagnosis is established in preschoolers, caution should be taken before making the diagnosis in anyone younger than age 6 years.

The evidence is not yet sufficient to conclude that most presentations of juvenile mania are continuous with the classic adult disorder (Harrington and Myatt, 2003). It is possible that juvenile bipolar disorder evolves into the broader subthreshold subtypes described in adults (Judd and Akiskal, 2003). This issue has not been sufficiently studied. Furthermore, a major dilemma in the existing literature is that the term bipolar disorder is used differently by different investigators to describe what may be diverse clinical populations. Thus, Leibenluft et al. (2003) proposed subdividing juvenile mania into three phenotypes: narrow (classically defined *DSM-IV-TR* mania), intermediate (well-demarcated periods of mania or hypomania lasting 1–3 days), and broad (chronic difficulties with irritability and hyperarousal). Such an approach acknowledges the potential differences in the disorder as it is being applied in juveniles. The term bipolar disorder NOS has been recommended to characterize some of the published reports of juvenile mania (NIMH, 2001). Further study is needed to confirm that this represents a discrete diagnostic group (versus a mixture of emotional and behavioral disturbances at the severe end of the spectrum), and what, if any, relationship this syndrome has to narrowly defined *DSM-IV-TR* mania.

RECOMMENDATIONS

Each recommendation in this parameter is identified as falling into one of the following categories of endorsement, indicated by an abbreviation in brackets following the statement. These categories indicate the degree of importance or certainty of each recommendation.

[MS] *Minimal standards* are recommendations that are based on rigorous empirical evidence (e.g., randomized, controlled trials) and/or overwhelming clinical consensus. Minimal standards are expected to apply >95% of the time (i.e., in almost all cases).

[CG] *Clinical guidelines* are recommendations that are based on empirical evidence and/or strong clinical consensus. Clinical guidelines apply ≈75% of the time (i.e., in most cases). These practices should almost always be considered by the clinician, but there are significant exceptions to their universal application.

[OP] *Options* are practices that are acceptable, but not required. There may be insufficient empirical evidence and/or clinical consensus to support recommending these practices as minimal standards or clinical guidelines.

[NE] *Not endorsed* refers to practices that are known to be ineffective or contraindicated.

The recommendations of this parameter are based on a thorough review of the literature as well as clinical consensus. The following coding system is used to indicate the nature of the research that supports the recommendations.

[rdb] *Randomized, double-blind clinical trial* is a study of an intervention in which subjects are randomly assigned to either treatment or control groups and both subjects and investigators are blind to the assignments.

[rct] *Randomized clinical trial* is a study of an intervention in which subjects are randomly assigned to either treatment or control groups.

[ct] *Clinical trial* is a prospective study in which an intervention is made and the results are followed longitudinally.

SCREENING

Recommendation 1. Psychiatric Assessments for Children and Adolescents Should Include Screening Questions for Bipolar Disorder [MS].

Screening questions include inquiries about distinct, spontaneous periods of mood changes associated with sleep disturbances and psychomotor activation. Histories of depression and family histories of mood disorders are also important to assess. Symptoms of irritability, reckless behaviors, or increased energy are important to assess, but they occur in a number of different conditions and therefore lack specificity. Because emotional and behavioral difficulties in children are often context dependent, it is important to assess symptom reports in perspective given family, school, peer, and other psychosocial factors, rather than simply using a checklist to identify psychopathology.

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

ASSESSMENT

Recommendation 2. The *DSM-IV-TR* Criteria, Including the Duration Criteria, Should Be Followed When Making a Diagnosis of Mania or Hypomania in Children and Adolescents [MS].

Manic-like symptoms of irritability and emotional reactivity may be found in a number of conditions, including disruptive behavior disorders, posttraumatic stress disorder, and pervasive developmental disorders. Manic grandiosity and irritability present as marked changes in the individual's mental and emotional state, rather than reactions to situations, temperamental traits, negotiation strategies, or anger outbursts. The pattern of illness, duration of symptoms, and association with psychomotor, sleep, and cognitive changes are important diagnostic clues. The illness represents a marked departure from baseline functioning, and it should be evident and impairing in different realms of the child's life (i.e., not isolated to one setting). Acute psychosis in an adolescent may be the first presentation of mania, and it needs to be carefully assessed for other associated features, including a marked decrease in the need for sleep, affective lability, a lack of negative symptoms, and/or a positive family history.

The diagnostic assessment needs to incorporate both current and past history regarding symptomatic presentation, treatment response, psychosocial stressors, and family psychiatric history. It is helpful to organize the clinical information using a life chart to characterize the course of illness, patterns of episodes, severity, and treatment response (Youngstrom et al., 2005). Using such a longitudinal perspective to conceptualize the disorder helps with diagnostic accuracy because the presenting symptoms during the acute phases often can be confused with other disorders. Cross-cultural issues may influence the expression or interpretation of symptoms and/or treatment response, and therefore must be assessed.

Structured diagnostic interviews and questionnaires are available that may be helpful for diagnosing bipolar disorder in youth, with the K-SADS and the WASH-U-KSADS being the most commonly used diagnostic tools in published research (Geller et al., 2001; Wozniak et al., 1995). The Young Mania Rating Scale (YMRS; Youngstrom et al., 2003) is commonly used in research to assess the severity of manic symptoms, and assess treatment response. However, the YMRS is not a diagnostic instrument. There are no biological tests, including imaging or genetic studies, that are helpful in making the diagnosis of a bipolar disorder.

Recommendation 3. Bipolar Disorder NOS Should Be Used to Describe Youths With Manic Symptoms Lasting Hours to Less Than 4 Days or for Those With Chronic Manic-Like Symptoms Representing Their Baseline Level of Functioning [CG].

Children with manic symptoms lasting hours to less than 4 days, or with chronic manic-like symptoms are significantly impaired. Until it is clear that this condition is really continuous with adult-type bipolar disorder for which the treatment literature applies, such youths should be characterized as classified as having bipolar disorder NOS, with the recognition that is a scant evidence base from which to extrapolate treatment recommendations. Youths characterized as having bipolar disorder NOS typically have high rates of comorbid disorders including ADHD, disruptive behavior disorders, posttraumatic stress disorder, anxiety disorders, and developmental disorders. Their mood states are generally volatile and reactive. It is important to examine for environmental triggers, patterns of events that reinforce the outbursts, significant pragmatic language impairment, and risk factors (e.g., history of maltreatment).

Recommendation 4. Youths With Suspected Bipolar Disorder Must Also Be Carefully Evaluated for Other Associated Problems, Including Suicidality, Comorbid Disorders (Including Substance Abuse), Psychosocial Stressors, and Medical Problems [MS].

A thorough workup can rule out other confounding illnesses and identify comorbid disorders that need to be addressed as part of a comprehensive treatment plan. Adolescents with bipolar disorder are reported to have high rates of suicide attempts (Strober et al., 1995) and are clearly at risk of completed suicides. Rates of substance abuse are high in this population (Findling et al., 2001; McClellan et al., 1999; Wilens et al., 2004). Assessments for developmental, cognitive, or speech and language disorders also may be indicated.

Recommendation 5. The Diagnostic Validity of Bipolar Disorder in Young Children Has Yet to Be Established. Caution Must Be Taken Before Applying This Diagnosis in Preschoolchildren [MS].

Preschool children who present with mood and behavioral concerns must be carefully assessed for other

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

contributing factors, including developmental disorders, psychosocial stressors, parent–child relationship conflicts, and temperamental difficulties. The interpretation of adult diagnostic criteria in very young children is a major challenge. There are no definitive studies outlining a developmentally valid method for assessing manic symptoms in this age group, including grandiosity, flight of ideas, and attention that is too easily drawn to irrelevant stimuli. Moreover, patterns of disrupted sleep and energy must be assessed in the context of the developmental period. Highly volatile and reactive toddlers need assessment and intervention, but whether such youths have bipolar disorder, as defined by the adult literature, has not been established. The diagnosis of a bipolar spectrum disorder in very young children potentially exposes them to aggressive pharmacotherapy. There are reports describing the use of mood stabilizers (Scheffer and Niskala Apps, 2004; Tumuluru et al., 2003) and atypical antipsychotics (Biederman et al., 2005a,b) in this age group. The short- and long-term safety of mood stabilizers and atypical antipsychotic agents for this indication in young children has not been established. It is particularly important with preschoolers that intervention strategies address environmental, developmental, temperamental, and social factors that may relate to symptom presentation.

TREATMENT

Because there are limited studies in youths, most of the treatment recommendations for early-onset bipolar disorder are derived from the adult literature for acute mania. Traditional mood stabilizers (e.g., lithium, valproate) and/or atypical antipsychotic medications are the primary treatment, with other psychotropic agents and psychotherapies generally used as adjunctive therapy or to address comorbid conditions and problems. Although the term *mood stabilizer* is widely used, most agents only have clearly demonstrated efficacy for treating acute manic symptoms in adults, thus the term *antimanic* may be a more accurate description. There are considerably fewer data in adults on the treatment of bipolar depression and the prevention of new mood episodes. No single agent is approved by the FDA for the treatment of all phases of bipolar disorder (acute mania, acute depression, and maintenance treatment to prevent new manic and/or depressive episodes). The adult literature is rapidly evolving, and new evidence on the potential efficacy of medications for bipolar depression and maintenance treatment is likely to emerge soon.

The adult literature appears to be appropriate for those cases with more classic presentation (primarily found in adolescents). The effectiveness and safety of mood-stabilizing regimens for the earlier-onset cases of juvenile mania have not yet been established. Youths with significant emotional and behavioral dysregulation likely need intensive behavioral and parenting interventions in addition to medication therapy (Fristad et al., 2003). Furthermore, the safety of these agents has not been established in youths and is an area of concern given the recent upsurge in prescriptions written for younger children, including preschool children.

A comprehensive treatment plan, combining medications with psychotherapeutic interventions, is needed to address the symptomatology and confounding psychosocial factors present in children and adolescents with bipolar disorder. Cultural issues must be appropriately incorporated into the treatment plan. The goal of therapy is to ameliorate symptoms, provide education about the illness, and promote adherence to treatment, thus working to prevent relapse, reduce long-term morbidity, and promote normal growth and development. This guideline focuses primarily on the treatment of mania and mixed episodes.

SOMATIC TREATMENTS

Recommendation 6. For Mania in Well-Defined *DSM-IV-TR* Bipolar I Disorder, Pharmacotherapy Is the Primary Treatment [MS].

Standard therapy, based on the adult literature, typically includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (Kowatch et al., 2005; Suppes et al., 2002). The choice of medication(s) should be made based on (1) evidence of efficacy, (2) the phase of illness, (3) the presence of confounding presentations (e.g., rapid cycling mood swings, psychotic symptoms), (4) the agent's side effect spectrum and safety, (5) the patient's history of medication response, and (6) the preferences of the patient and his or her family. A history of treatment response in parents may predict response in offspring (Duffy et al., 2002). Pharmacokinetic parameters of psychotropic agents may vary in

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

different ethnic groups, with a potential impact on side effects, blood levels, efficacy, and cultural expectations. Although multiple agents are often required, care should be taken to avoid unnecessary polypharmacy.

Treatment should begin with an agent that is approved by the FDA for bipolar disorder in adults, recognizing that the evidence of the efficacy for these agents in children and adolescents is sparse at best, including the following:

- Lithium is approved down to age 12 years for acute mania and maintenance therapy.
- Aripiprazole, valproate, olanzapine, risperidone, quetiapine, and ziprasidone are approved for acute mania in adults. Chlorpromazine is also approved for acute mania in adults, but it is generally not used as a first-line agent.
- Both lamotrigine and olanzapine are approved for maintenance therapy in adults.
- The combination of olanzapine and fluoxetine is approved for bipolar depression in adults.

Other agents with some support for efficacy in adult studies include carbamazepine and antipsychotic agents (American Psychiatric Association, 2002). Controlled studies in adults have not found gabapentin or topiramate to be helpful (Calabrese et al., 2002), whereas the one study of topiramate in children and adolescents was equivocal (DelBello et al., 2005). Clozapine is generally reserved for treatment-refractory cases because of its side-effect profile; it should be used only when the diagnosis is well established. Benzodiazepines are used in adult studies to stabilize the acute agitation and sleep disturbance associated with mania but may cause disinhibition in younger children. Antidepressants (selective serotonin reuptake inhibitors [SSRIs] or nontricyclics) may be useful adjuncts for depression as long as the patient is also taking at least one mood stabilizer. Caution must be taken, however, because antidepressants may destabilize the patient's mood or incite a manic episode. It is important to note that a manic episode precipitated by an antidepressant is characterized as substance induced per *DSM-IV-TR* (American Psychiatric Association, 2000). Manic symptoms associated with an SSRI may represent the unmasking of the disorder or disinhibition secondary to the agent. Clinicians should also be aware of the concerns regarding the efficacy and safety (included suicidality) of antidepressants in youths (see Vitiello and Swedo, 2004).

The only agent with FDA approval for bipolar disorder in youths (age 12 years and older) is lithium, although that decision was made historically based on the adult literature. All of the mood stabilizers and antipsychotic agents are commonly used for early-onset bipolar disorder in clinical settings, although none of the agents has been well studied in juveniles. The few double-blind, placebo-controlled studies of lithium (Carlson et al., 1992; Delong and Aldershof, 1987; Geller et al., 1998a; Gram and Rafaelsen, 1972; McKnew et al., 1981 [all rdb]) are generally positive, but they are limited by small sample sizes and diagnostic variability. However, one controlled discontinuation trial randomized adolescents acutely stabilized on lithium to either ongoing lithium therapy or placebo (Kafantaris et al., 2004 [rdb]). High rates of relapse were found in both groups in patients stabilized on lithium, raising questions about its ongoing efficacy. Other studies include a positive, large, open-label trial (although many subjects in this trial were also taking antipsychotic agents; Kafantaris et al., 2003 [ct]) and a trial demonstrating benefit for comorbid substance abuse (Geller et al., 1998a [rdb]). Finally, lower rates of relapse for adolescents with acute psychotic mania were reported when antipsychotic medication was maintained for at least 4 weeks in combination with lithium (Kafantaris et al., 2001 [ct]).

There are few studies to date that document the efficacy of the anticonvulsants for bipolar disorder in youths. Open-label trials, case reports, and retrospective chart reviews describe the effectiveness of valproate (Davanzo et al., 2003; Papatheodorou et al., 1995 [ct]; State et al., 2004; Wagner et al., 2002 [ct], West et al., 1994 [ct]), carbamazepine (Hsu, 1986), and topiramate (as an adjunctive agent; DelBello et al., 2002) for juvenile mania, and lamotrigine for adolescents with bipolar depression (Chang et al., 2006). Kowatch et al. (2000 [ct]) found valproate, lithium, and carbamazepine helpful for mania and mixed episodes in 40 children and adolescents, with response rates of 53%, 38%, and 38%, respectively. Combinations of mood stabilizers in youths with bipolar disorder have also been found to be beneficial and safely tolerated for mania and hypomania (Findling et al., 2003 [ct], 2006 [ct]; Kowatch et al. 2003 [ct]).

Open-label trials and retrospective chart reviews also support the effectiveness of olanzapine (Frazier et al., 2001 [ct]; Soutullo et al., 1999), risperidone (Frazier

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

et al., 1999), quetiapine (Marchand et al., 2004), and aripiprazole (Barzman et al., 2004; Biederman et al., 2005a,b) for pediatric bipolar disorder. Risperidone in combination with either lithium or valproate appeared to be effective in an open-label, prospective trial (Pavuluri et al., 2004b [ct], 2006 [ct]). A double-blind, controlled trial found that quetiapine plus valproate worked better than valproate alone for adolescent mania (DelBello et al., 2002 [rdb]). When used as mood stabilizers, the atypical antipsychotic agents are prescribed with the same dose ranges and have the same spectrum of side effects as when used for psychotic illnesses. Weight gain has been a particular concern for this class of agents, especially in youths.

Pavuluri et al. (2004c [ct]) developed a pharmacotherapy algorithm to systematically assign patients with pediatric bipolar disorder to mood stabilizers and/or atypical antipsychotics based on clinical presentation. Youths treated using the algorithm demonstrated greater improvements in global functioning, aggression, and mania than those receiving treatment as usual. In community settings, anticonvulsants and atypical antipsychotics appear to be the agents used most often in youths (Bhangoo et al., 2003; Hellander, 2002). Polypharmacy is common, with some youths taking five or more drugs (Duffy et al., 2005). Geller et al. (2002b) reported that treatment in the community, including mood stabilizers and antipsychotic agents, did not influence outcome over a 24-month period, but the adequacy of treatment was not assessed. Biederman et al. (1999) noted that mood stabilizers and antipsychotic agents appeared to help juvenile mania, whereas stimulants and antidepressants did not. In this report, response to therapy was low and rates of relapse were high. Comorbid disruptive behavioral disorders (Masi et al., 2004) and ADHD (State et al., 2004) predict a poorer response to treatment. Thus, although the medications used in adults may be helpful, youths may be more difficult to treat and likely also need additional interventions in conjunction with pharmacotherapy.

For patients with clearly defined bipolar disorder, stimulant medications may be helpful for addressing ADHD symptoms once the patient's mood symptoms are adequately controlled on a mood stabilizer regimen. A randomized, controlled trial of 40 bipolar children and adolescents with ADHD demonstrated that treatment with low-dose mixed amphetamine salts was safe and effective for the treatment of comorbid ADHD once the child's mood symptoms were stabilized with divalproex (Scheffer et al., 2005).

Recommendation 7. Most Youths With Bipolar I Disorder Will Require Ongoing Medication Therapy to Prevent Relapse; Some Individuals Will Need Lifelong Treatment [CG].

In the adult literature, >80% of patients with a manic episode will have at least one episode of relapse (American Psychiatric Association, 1994). Withdrawal of maintenance lithium therapy has been associated with an increased risk of relapse, especially within the 6-month period following lithium discontinuation (American Psychiatric Association, 1994).

Strober et al. (1990) prospectively studied 37 adolescents with bipolar disorder for 18 months; they found that >90% of those who were noncompliant with their lithium treatment relapsed (12 of 13 cases). The relapse rate for those who were compliant with treatment was 37.5%. Findling et al. (2003 [rct]), using a sample of children and adolescents with bipolar disorder stabilized on the combination of valproate and lithium, randomized subjects to receive either lithium or valproate alone as maintenance monotherapy. The majority of subjects relapsed after the switch to monotherapy (median time to relapse was ≈3 months), with no difference in relapse rates between the two agents. The use of stimulants for comorbid ADHD did not affect relapse rates. Thus, although more definitive studies are needed, current evidence suggests that the regimen needed to stabilize acute mania should be maintained for 12 to 24 months. Maintenance therapy is often needed for youths with bipolar disorder, with some individuals needing lifelong therapy when the benefits of continued treatment outweigh the risks. This should be decided on a case-by-case basis after discussing the risks and benefits of continued treatment (Kowatch et al., 2005).

Until more definitive information is available about the long-term effects of mood stabilizers and antipsychotics, the clinician must balance the potential deleterious impact of symptom reoccurrence versus that of the side effects of the medications. Any attempts to discontinue prophylactic therapy should be done gradually, while closely monitoring the patient for relapse. Furthermore, patients and families must be thoroughly educated as to the early signs and symptoms of mood episodes so that, if necessary, resumption of

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

treatment occurs as soon as possible. Diagnostic status should also be reviewed over time to ensure that the course of medication therapy is justified.

Recommendation 8. Psychopharmacological Interventions Require Baseline and Follow-up Symptom, Side Effect (Including Patient's Weight), and Laboratory Monitoring as Indicated [MS].

Medication trials should be as systematic as possible, with the duration of trials sufficient to determine the agent's effectiveness (Kowatch et al., 2005). In general, a 6- to 8-week trial of a mood-stabilizing agent is recommended, using adequate doses, before adding or substituting other mood stabilizers. Phase of illness is an important consideration when choosing a medication. Care should be taken to avoid unnecessary polypharmacy, in part by discontinuing agents that have not demonstrated significant benefit.

Before the initiation of lithium therapy, baseline laboratory assessment should include complete blood cell counts; thyroid function tests; urinalysis; blood urea nitrogen, creatinine, and serum calcium levels; and a pregnancy test in female adolescents (Kowatch and DelBello, 2003). Once a stable lithium dose is obtained, lithium levels, renal and thyroid function, and urinalyses should be monitored regularly (every 3–6 months; Kowatch and DelBello, 2003). For valproate, baseline liver function tests, complete blood cell counts, and pregnancy tests are recommended (Kowatch and DelBello, 2003). Serum drug levels, plus hepatic and hematological indices, should be monitored periodically (every 3–6 months). However, it is also important to advise patients and families about presenting symptoms of potential adverse effects because periodic monitoring does not ensure that abnormalities will be readily identified. Finally, clinicians should be aware of the concerns raised regarding valproate and the development of polycystic ovary disease in females (Rasgon, 2004).

The atypical antipsychotics as a class are associated with significant weight gain and other metabolic problems (e.g., type 2 diabetes, hyperlipidemia). Thus, the American Dietetic Association's recommendations for managing weight gain for patients taking antipsychotics should be followed (American Psychiatric Association, 2004). This includes baseline body mass index, waist circumference, blood pressure, fasting glucose, and a fasting lipid panel. The body mass index should be followed monthly for 3 months and then quarterly. Blood pressure, fasting glucose, and lipids should be followed up after 3 months and then yearly. Some agents have additional monitoring requirements (e.g., white blood cell counts with clozapine). Extrapyramidal side effects, including tardive dyskinesia, may occur with atypical agents and need to be monitored.

Recommendation 9. For Severely Iimpaired Adolescents With Manic or Depressive Episodes in Bipolar I Disorder, Electroconvulsive Therapy (ECT) May Be Used If Medications Either Are Not Helpful or Cannot Be Tolerated [OP].

In adults, ECT is an effective treatment for mania, but it is generally offered only for patients who have not responded to standard medication treatment (Suppes et al., 2002). ECT is safe as long as modern methods are used (i.e., appropriate anesthesia, alterations in the delivery of the electrical stimulus, the selected use of unilateral treatment, and cardiopulmonary monitoring). ECT is generally considered the treatment of choice for bipolar disorder in the following clinical situations: (1) pregnancy, (2) catatonia, (3) neuroleptic malignant syndrome, and (4) any other medical condition in which more standard medication regimens are contraindicated (American Psychiatric Association, 1990).

Case reports indicate that ECT may be beneficial for youths with bipolar disorder (including mania, rapid cycling, and depressed phases), although the literature at this time is extremely limited (American Academy of Child and Adolescent Psychiatry, 2004). ECT should only be considered for adolescents with well-characterized bipolar I disorder who have severe episodes of mania or depression and are nonresponsive (or unable to take) standard medication therapies. ECT should not be considered an option for cases best described as bipolar disorder NOS or the atypical presentations of juvenile mania. Potential side effects include short-term cognitive impairment, anxiety reactions, disinhibition, and altered seizure threshold.

PSYCHOTHERAPEUTIC INTERVENTIONS

Recommendation 10. Psychotherapeutic Interventions Are an Important Component of a Comprehensive Treatment Plan for Early-Onset Bipolar Disorder [MS].

The development of bipolar disorder during childhood or adolescence disrupts ongoing developmental

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

processes, including academic, social, and family functioning (Kowatch et al., 2005). Therefore, a comprehensive, multimodal treatment approach that combines psychopharmacology with adjunctive psychosocial therapies is almost always indicated for early-onset bipolar disorder. Although medications help with the core symptoms of the illness, they do not necessarily address the associated functional and developmental impairments and the frequent need for support and skills building. Preexisting behavior disorders, substance abuse disorders, learning problems, and confounding psychosocial issues may require additional and specific treatments related to those problems once the affective episode is stabilized. Psychotherapeutic interventions are needed to promote medication compliance and avoid relapse. Finally, interventions are needed to help youths and families cope with the developmental impact on peer relationships, academic performance, and psychological health.

In the adult literature, psychoeducational, family, and individual interpersonal and social rhythm therapies are the best supported adjuncts to medications (Craighead and Miklowitz, 2000). Research examining expressed emotion suggests that family dynamics have a moderating effect on treatment response and relapse rates (Miklowitz, 2004). Family-focused therapy stresses the importance of treatment compliance and positive family relationships and enhances problem-solving and communication skills (Miklowitz et al., 2000). Interpersonal and social rhythm therapy (Frank et al., 1997, 2000) focuses on reducing stress and vulnerability by stabilizing social and sleep routines. Combining individual and family interventions appears to help decrease relapse and lessen depressive symptoms (Miklowitz et al., 2003).

For pediatric bipolar disorder, controlled data on psychosocial interventions are starting to emerge. Miklowitz et al. (2004 [ct]) modified their family-focused therapy for adolescents and demonstrated positive results in a preliminary open trial. Pavuluri et al. (2004a,b,c,d [ct]) developed child- and family-focused cognitive-behavioral therapy, adapting strategies from adult therapeutic models, including functional family therapy (Miklowitz et al., 2000). The treatment uses psychoeducational, affect regulation, and interpersonal functioning strategies. Preliminary outcomes in 34 youths with bipolar disorder were positive. Others have also noted that psychoeducational approaches appear to be helpful in this population (Fristad et al., 2003).

Thus, extrapolation from the adult literature plus preliminary studies suggests several areas in which psychotherapeutic interventions should be directed:

1. *Psychoeducational therapy*. Information should be provided to both the patient and family regarding the symptoms and course of the disorder, treatment options, the potential impact of the illness on psychosocial and family functioning, and the heritability of the disorder.
2. *Relapse prevention*. Education should be provided to the patient and family regarding the impact of noncompliance with medications, the recognition of emergent relapse symptoms, and other factors that may precipitate relapse (e.g., sleep deprivation, substance abuse). Stress reduction and the promotion of stable social and sleep habits may be particularly helpful areas to target, especially for adolescents. Medication noncompliance is a major contributor to relapse. Therefore, efforts must be made to educate both the patient and family about the importance of ongoing treatment as well as dealing with psychological resistance to taking medication. Establishing a strong therapeutic relationship and providing regular follow-up assessments are important in maintaining compliance.
3. *Individual psychotherapy*. Based on studies of cognitive-behavioral therapy and interpersonal therapy in adults as well as clinical consensus of therapy with bipolar youths, individual psychotherapies support psychological development, skill building, and close monitoring of symptoms and progress.
4. *Social and family functioning*. Bipolar disorder significantly affects social, family, academic, and developmental functioning. Therefore, in addition to efforts directed at reducing further episodes, psychosocial interventions are needed to address the myriad of disruptions that emerge in the wake of the disorder. Efforts to enhance family and social relationships, including therapies directed at communication and problem-solving skills, are likely to be helpful. Cultural issues must be taken into account when devising psychotherapeutic strategies.
5. *Academic and occupational functioning*. The educational needs of youths with bipolar disorder must

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

be adequately addressed to help promote long-term academic growth, especially given the high rates of comorbid disruptive behavior disorders. School consultation and an individual educational plan are often necessary to help develop an appropriate educational environment. Some youths will need specialized educational programs, including day treatment or partial hospitalization programs. For older teenagers, vocational training and occupational support may also be important needs to address.

6. *Community consultation*. Consultation may be needed with other involved community, juvenile justice, and/or social welfare programs. Some youths, because of either the severity of their symptoms or confounding environmental stressors, will need referral for intensive community-based services to maintain them at home. Alternatively, some patients may need foster care or residential services. Finally, patients and families often receive benefit by participating in community support and advocacy programs.

Recommendation 11. The Treatment of Bipolar Disorder NOS Generally Involves the Combination of Psychopharmacology With Behavioral/Psychosocial Interventions [CG].

Strategies for treating bipolar disorder NOS are not well defined because it is not clear how well the adult bipolar treatment literature extrapolates to this population. Intervention strategies should be based on the specific symptom presentations of the child, comorbid conditions, and family needs rather than initiating standard protocols for bipolar I disorder. Evidence-based therapies for behavioral difficulties should be used (see McClellan and Werry, 2003). Dialectical behavioral therapy may be helpful for youths with mood and behavioral dysregulation (Katz et al., 2004).

Mood stabilizers and atypical antipsychotics are often used to help control severe mood lability and explosive outbursts. In general, although open trials have supported efficacy for juvenile mania (Kowatch et al., 2000 [ct]), the impact of medication treatment on outcome remains in question (Biederman et al., 1999; Geller et al., 2002b). The specificity of the treatment response is unclear because these agents also help in the treatment of aggression, with risperidone being the agent best studied to date (Steiner et al., 2003).

Other medications, including stimulants and antidepressants, may be used to treat comorbid ADHD or associated depression. Perhaps the most common dilemma is whether and when to use stimulants in children when there is a question of whether one is dealing with mania/hypomania or ADHD with mood lability and low frustration tolerance. Two studies (Carlson and Kelly, 2003; Carlson et al., 2000; Galanter et al., 2003) found that boys with ADHD plus manic-like symptoms responded as well as those without manic symptoms to methylphenidate and that stimulant treatment did not precipitate progression to bipolar disorder. These data challenge existing beliefs that the failure to respond to stimulants is diagnostic of mania or that stimulant treatment may predispose children to the development of bipolar disorder. Of course, these data also raise the question of whether manic symptoms equate to true mania. Because stimulants and SSRIs can cause irritability and disinhibition, distinguishing medication side effects from an emerging manic episode is a potential challenge. One retrospective review found that 58% of youths with juvenile bipolar disorder (n = 82) had experienced an emergence of manic symptoms after exposure to a mood-elevating agent, most often antidepressants (Faedda et al., 2004). The development of activation secondary to mood-elevating agents does not equate to a diagnosis of bipolar disorder (Carlson et al., 2000). If this were the case, then high rates of bipolar disorder would be evident in the follow-up studies of children with ADHD in those subjects who did not respond well to stimulants.

SCIENTIFIC DATA AND CLINICAL CONSENSUS

Practice parameters are strategies for patient management, developed to assist clinicians in psychiatric decision making. American Academy of Child and Adolescent Psychiatry practice parameters, based on evaluation of the scientific literature and relevant clinical consensus, describe generally accepted approaches to assess and treat specific disorders or to perform specific medical procedures. These parameters are not intended to define the standard of care, nor should they be deemed inclusive of all proper methods of care or exclusive of other methods of care directed at obtaining the desired results. The ultimate judgment regarding the care of a particular patient must be made by the clinician

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

in light of all of the circumstances presented by the patient and his or her family, the diagnostic and treatment options available, and available resources.

Disclosure: Dr. McClellan has received a research grant from Pfizer. Dr. Findling receives or has received research support, acted as a consultant, and/or served on the speakers' bureau of Abbott, AstraZeneca, Bristol-Myers Squibb, Celltech-Medeva, Forest, Glaxo SmithKline, Johnson & Johnson, Lilly, New River, Novartis, Otsuka, Pfizer, Sanofi-Aventis, Shire, Solvay, and Wyeth. Dr. Kowatch has no financial relationships to disclose.

REFERENCES

References marked with an asterisk are particularly recommended.

Akiskal HS (1995), Developmental pathways to bipolarity: are juvenile-onset depressions pre-bipolar? *J Am Acad Child Adolesc Psychiatry* 34:754–763

American Academy of Child and Adolescent Psychiatry (2004), Practice parameter for the use of electroconvulsive therapy with adolescents. *J Am Acad Child Adolesc Psychiatry* 43:1521–1539

American Psychiatric Association (1994), American psychiatric association practice guideline for the treatment of patients with bipolar disorder. *Am J Psychiatry* 151:1–36

American Psychiatric Association (2000), *Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association

American Psychiatric Association (2002), Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 159(Suppl 4):1–50

American Psychiatric Association (2004), Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 161:1–56

American Psychiatric Association Task Force on ECT (1990), The practice of ECT: recommendations for treatment, training, and privileging. *Convuls Ther* 2:85–120

Anthony EJ, Scott P (1960), Manic-depressive psychosis in childhood. *J Child Psychol Psychiatry* 1:53–72

Baldessarini RJ (2000), A plea for integrity of the bipolar disorder concept. *Bipolar Disord* 2:3–7

Barzman DH, DelBello MP, Kowatch RA et al. (2004), The effectiveness and tolerability of aripiprazole for pediatric bipolar disorders: a retrospective chart review. *J Child Adolesc Psychopharmacol* 14:593–600

Bashir M, Russell J, Johnson G (1987), Bipolar affective disorder in adolescence: a 10 year study. *Aust N Z J Psychiatry* 21:36–43

Bhangoo RK, Lowe CH, Myers FS, et al. (2003), Medication use in children and adolescents treated in the community for bipolar disorder. *J Child Adolesc Psychopharmacol* 13:515–522

Biederman J, Faraone SV, Wozniak J, Mick E, Kwon A, Aleardi M (2004), Further evidence of unique developmental phenotypic correlates of pediatric bipolar disorder: findings from a large sample of clinically referred preadolescent children assessed over the last 7 years. *J Affect Disord* 82:S45–S58

Biederman J, McDonnell MA, Wozniak J et al. (2005), Aripiprazole in the treatment of pediatric bipolar disorder: a systematic chart review. *CNS Spectr* 10:141–148

Biederman J, Mick E, Bostic JQ et al. (1998), The naturalistic course of pharmacologic treatment of children with manic like symptoms: a systematic chart review. *J Clin Psychiatry* 59:628–637

Biederman J, Mick E, Faraone SV, Van Patten S, Burback M, Wozniak J (2004), A prospective follow-up study of pediatric bipolar disorder in boys with attention-deficit/hyperactivity disorder. *J Affect Disord* 82:S17–S23

Biederman J, Mick E, Hammerness P et al. (2005), Open-label, 8-week trial of olanzapine and risperidone for the treatment of bipolar disorder in preschool-age children. *Biol Psychiatry* 58:589–594

Biederman J, Mick E, Prince J et al. (1999), Systematic chart review of the pharmacologic treatment of comorbid attention deficit hyperactivity disorder in youth with bipolar disorder. *J Child Adolesc Psychopharmacol* 9:247–256

Biederman J, Mick E, Spencer TJ, Wilens TE, Faraone SV (2000), Therapeutic dilemmas in the pharmacotherapy of bipolar depression in the young. *J Child Adolesc Psychopharmacol* 10:185–192

Brent DA (1993), Depression and suicide in children and adolescents. *Pediatr Rev* 14:380–388

Bowring MA, Kovacs M (1992), Difficulties in diagnosing manic disorders among children and adolescents. *J Am Acad Child Adolesc Psychiatry* 31:611–614

Calabrese JR, Shelton MD, Rapport DJ, Kimmel SE (2002), Bipolar disorders and the effectiveness of novel anticonvulsants. *J Clin Psychiatry* 63:5–9

Carlson GA (1990), Child and adolescent mania: diagnostic considerations. *J Child Psychol Psychiatry* 31:331–342

*Carlson GA (2005), Early onset bipolar disorder: clinical and research considerations. *J Clin Child Adolesc Psychol* 34:333–443

Carlson GA, Bromet EJ, Driessens C, Mojtabai R, Schwartz JE (2002), Age at onset, childhood psychopathology, and 2-year outcome in psychotic bipolar disorder. *Am J Psychiatry* 159:307–309

Carlson GA, Bromet EJ (2000), Phenomenology and outcome of subjects with early-and adult-onset psychotic mania. *Am J Psychiatry* 157:213–219

Carlson GA, Davenport YB, Jamison K (1977), A comparison of outcome in adolescent and late-onset bipolar manic-depressive illness. *Am J Psychiatry* 134:919–922

Carlson GA, Fennig S, Bromet EJ (1994), The confusion between bipolar disorder and schizophrenia in youth: where does it stand in the 1990's? *J Am Acad Child Adolesc Psychiatry* 33:453–460

Carlson GA, Kashani JH (1988), Phenomenology of major depression from childhood through adulthood: analysis of three studies. *Am J Psychiatry* 145:1222–1225

Carlson GA, Kelly KL (2003), Stimulant rebound: how common is it and what does it mean? *J Child Adolesc Psychopharmacol* 13:137–142

Carlson GA, Loney J, Salisbury H, Kramer JR (2000), Stimulant treatment in young boys with symptoms suggesting childhood mania: a report from a longitudinal study. *Child Adolesc Psychopharmacol* 10:175–184

Carlson GA, Loney J, Salisbury H, Volpe RJ (1998), Young referred boys with DICA-P manic symptoms vs. two comparison groups. *J Affect Disord* 51:113–121

Carlson GA, Rapport MD, Kelly KL, Pataki CS (1992), The effects of methylphenidate and lithium on attention and activity level. *J Am Acad Child Adolesc Psychiatry* 31:262–270

Carlson GA, Strober M (1978), Manic-depressive illness in early adolescence. A study of clinical and diagnostic characteristics in six cases. *J Am Acad Child Adolesc Psychiatry* 17:138–153

Carlson GA, Youngstrom EA (2003), Clinical implications of pervasive manic symptoms in children. *Biol Psychiatry* 53:1050–1058

Carter TD, Mundo E, Parikh SV, Kennedy JL (2003), Early age at onset as a risk factor for poor outcome of bipolar disorder. *J Psychiatr Res* 37:297–303

Cassidy F, Carroll BJ (2001), Frequencies of signs and symptoms in mixed and pure episodes of mania: implications for the study of manic episodes. *Prog Neuropsychopharmacol Biol Psychiatry* 25:659–665

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

Chang K, Steiner H, Ketter T (2003), Studies of offspring of parents with bipolar disorder. *Am J Med Genet* 123C:226–235

Costello E (1989), Developments in child psychiatric epidemiology. *J Am Acad Child Adolesc Psychiatry* 28:836–846

Costello EJ, Angold A, Burns BJ et al. (1996), The Great Smoky Mountains Study of Youth. Goals, design, methods, and the prevalence of DSM-III-R disorders. *Arch Gen Psychiatry* 53:1129–1136

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

Craighead WE, Miklowitz DJ (2000), Psychosocial interventions for bipolar disorder. *J Clin Psychiatry* 61:58–64

Craney JL, Geller B (2003), A prepubertal and early adolescent bipolar disorder-I phenotype: review of phenomenology and longitudinal course. *Bipolar Disord* 5:243–256

Davanzo P, Gunderson B, Belin T et al. (2003), Mood stabilizers in hospitalized children with bipolar disorder: a retrospective review. *Psychiatry Clin Neurosci* 57:504–510

DelBello MP, Carlson GA, Tohen M, Bromet EJ, Schwiers M, Strakowski SM (2003), Rates and predictors of developing a manic or hypomanic episode 1 to 2 years following a first hospitalization for major depression with psychotic features. *J Child Adolesc Psychopharmacol* 13: 173–185

DelBello MP, Findling RL, Kushner S et al. (2005), A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44:539–547

DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM (2002), A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 41:1216–1223

DeLong GR, Aldershof AL (1987), Long-term experience with lithium treatment in childhood: correlation with clinical diagnosis. *J Am Acad Child Adolesc Psychiatry* 26:389–394

Dilsaver SC, Akiskal HS (2004), Preschool-onset mania: incidence, phenomenology and family history. *J Affect Disord* 82:S35–S43

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

Duffy FF, Narrow WE, Rae DS et al. (2005), Concomitant pharmacotherapy among youths treated in routine psychiatric practice. *Child Adolesc Psychopharmacol* 15:12–25

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

Faedda GL, Baldessarini RJ, Glovinsky IP, Austin NB (2004), Treatment-emergent mania in pediatric bipolar disorder: a retrospective case review. *J Affect Disord* 82:149–158

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

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

Fergus EL, Miller RB, Luckenbaugh DA et al. (2003), Is there progression from irritability/dyscontrol to major depressive and manic symptoms? A retrospective community survey of parents of bipolar children. *J Affect Disord* 77:71–78

Findling R, Calabrese J, Youngstrom E (2003), Divalproex sodium vs. lithium carbonate in the treatment of children and adolescents with bipolar disorder. *Bipolar Disord* 5:23

Findling RL, Gracious BL, McNamara NK et al. (2001), Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. *Bipolar Disord* 3:202–210

Findling RL, McNamara NK, Stansbrey R et al. (2006), Combination lithium and divalproex sodium in pediatric bipolar symptom re-stabilization. *J Am Acad Child Adolesc Psychiatry* 45:142–148

Frank E, Hlastala S, Ritenour A et al. (1997), Inducing lifestyle regularity in recovering bipolar disorder patients: results from the maintenance therapies in bipolar disorder protocol. *Biol Psychiatry* 41:1165–1173

Frank E, Swartz HA, Kupfer DJ (2000), Interpersonal and social rhythm therapy: managing the chaos of bipolar disorder. *Biol Psychiatry* 48: 593–604

Frazier JA, Biederman J, Tohen M et al. (2001), A prospective open-label treatment trial of olanzapine monotherapy in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol* 11:239–250

Frazier JA, Meyer MC, Biederman J et al. (1999), Risperidone treatment for juvenile bipolar disorder: a retrospective chart review. *J Am Acad Child Adolesc Psychiatry* 38:960–965

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

Galanter CA, Carlson GA, Jensen PS et al. (2003), 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* 13:123–136

Geller B, Cooper TB, Sun K et al. (1998), Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry* 37:171–178

Geller B, Cooper TB, Zimerman B et al. (1998), Lithium for prepubertal depressed children with family history predictors of future bipolarity: a double-blind, placebo-controlled study. *J Affect Disord* 51:165–175

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

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

Geller B, Luby J (1997), Child and adolescent bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry* 36:1168–1176

Geller B, Reising D, Leonard HL, Riddle MA, Walsh BT (1999), Critical review of tricyclic antidepressant use in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 38:513–516

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

Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL (2001), Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. *Am J Psychiatry* 158:125–127

Geller B, Zimerman B, Williams M et al. (2000), Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol* 10:157–164

Geller B, Zimerman B, Williams M, Delbello MP, Frazier J, Beringer L (2002a), 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* 12:3–9

Ghaemi S, Nassir K, James Y, Goodwin FK (2001), The bipolar spectrum and the antidepressant view of the world. *J Psychiatr Pract* 7:287–297

Goodwin FK, Jamison KR (1990), *Manic Depressive Illness*. New York: Oxford University Press

Gram LF, Rafaelsen OJ (1972), Lithium treatment of psychotic children and adolescents. *Acta Psychiatr Scand* 48:253–260

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

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

Hellander I (2002), A review of data on the health sector of the United States January 2002. *Int J Health Serv* 32:579–599

Hsu LK (1986), Lithium-resistant adolescent mania. *J Am Acad Child Adolesc Psychiatry* 25:280–283

Jairam R, Srinath S, Girimaji SC, Seshadri SP (2004), A prospective 4-5 year follow-up of juvenile onset of bipolar disorder. *Bipolar Disord* 6:386–394

Joyce PR (1984), Age of onset in bipolar affective disorder and misdiagnosis as schizophrenia. *Psychol Med* 14:145–149

Judd LL, Akiskal HS (2003), 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* 73:123–131

Kafantaris V, Coletti DJ, Dicker R, Padula G, Kane JM (2001), Adjunctive antipsychotic treatment of adolescents with bipolar psychosis. *J Am Acad Child Adolesc Psychiatry* 40:1448–1456

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

Kafantaris V, Coletti DJ, Dicker R, Padula G, Kane JM (2003), Lithium treatment of acute mania in adolescents: a large open trial. *J Am Acad Child Adolesc Psychiatry* 42:1038–1045

Kafantaris V, Coletti DJ, Dicker R et al. (2004), Lithium treatment of acute mania in adolescents: a placebo controlled discontinuation study. *J Am Acad Child Adolesc Psychiatry* 43:984–993

Kafantaris V, Coletti DJ, Dicker R, Padula G, Pollack S (1998), Are childhood psychiatric histories of bipolar adolescents associated with family history, psychosis, and response to lithium treatment? *J Affect Disord* 51:153–164

Katz LY, Cox BJ, Gunasekara S, Miller AL (2004), Feasibility of dialectical behavior therapy for suicidal adolescent inpatients. *J Am Acad Child Adolesc Psychiatry* 43:276–282

Keck PJ, Mendlwicz J, Calabrese J et al. (2000), A review of randomized, controlled clinical trials in acute mania. *J Affect Disord* 59:S31–S37

Kent L, Craddock N (2003), Is there a relationship between attention deficit hyperactivity disorder and bipolar disorder? *J Affect Disord* 73:211–221

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE (2005), Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62:617–627

Kim EY, Miklowitz DJ (2002), Childhood mania, attention deficit hyperactivity disorder and conduct disorder: a critical review of diagnostic dilemmas. *Bipolar Disord* 4:215–225

Klein RG, Pine DS, Klein DF (1998), Resolved: mania is mistaken for ADHD in prepubertal children: negative rebuttal. *J Am Acad Child Adolesc Psychiatry* 37:1091–1096

Kovacs M (1996), Presentation and course of major depressive disorder during childhood and later years of the life span. *J Am Acad Child Adolesc Psychiatry* 35:705–715

Kowatch RA, DelBello MP (2003), The use of mood stabilizers and atypical antipsychotics in children and adolescents with bipolar disorders. *CNS Spectr* 8:273–280

*Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M (2005), Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44:213–235

Kowatch RA, Sethuraman G, Hume JH, Kromelis M, Weinberg WA (2003), Combination pharmacotherapy in children and adolescents with bipolar disorder. *Biol Psychiatry* 53:978–984

Kowatch RA, Suppes T, Carmody TJ et al. (2000), Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 39:713–720

Kraepelin E (1921), *Manic-Depressive Insanity and Paranoia*. Edinburgh: Livingstone

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

Kutcher S, Robertson HA, Bird D (1998), Premorbid functioning in adolescent onset bipolar I disorder: a preliminary report from an ongoing study. *J Affect Disord* 51:137–144

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

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

Lewinsohn PM, Klein DN, Seeley JR (2000), Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord* 2:281–293

Lewinsohn PM, Seeley JR, Klein DN (2003), Bipolar disorders during adolescence. *Acta Psychiatr Scand* 418:47–50

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

Loranger AW, Levine PM (1978), Age at onset of bipolar affective illness. *Arch Gen Psychiatry* 35:1345–1348

Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M (1998), Adult psychiatric status of hyperactive boys grown up. *Am J Psychiatry* 155:493–498

Marchand WR, Wirth L, Simon C (2004), Quetiapine adjunctive and monotherapy for pediatric bipolar disorder: a retrospective chart review. *J Child Adolesc Psychopharmacol* 14:405–411

Masi G, Perugi G, Toni C et al. (2004), Predictors of treatment nonresponse in bipolar children and adolescents with manic or mixed episodes. *J Child Adolesc Psychopharmacol* 14:395–404

McClellan J (2005), Commentary: treatment guidelines for child and adolescent bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44:236–239

McClellan J, Breiger D, McCurry C, Hlastala S (2003), Premorbid functioning in early onset psychotic disorders. *J Am Acad Child Adolesc Psychiatry* 42:666–672

McClellan J, McCurry C, Snell J, DuBose A (1999), Early onset psychotic disorders: course and outcome over a two-year period. *J Am Acad Child Adolesc Psychiatry* 38:1380–1389

McClellan J, Werry J (2000), Introduction—research psychiatric diagnostic interviews for children and adolescents. *J Am Acad Child Adolesc Psychiatry* 39:19–27

McClellan JM, Hamilton JD (2006), An evidence-based approach to an adolescent with emotional and behavioral dysregulation. *J Am Acad Child Adolesc Psychiatry* 45:489–493

McClellan JM, Werry JS (2003), Evidence-based treatments in child and adolescent psychiatry: an inventory. *J Am Acad Child Adolesc Psychiatry* 42:1388–1400

McClellan JM, Werry JS, Ham M (1993), A follow-up study of early onset psychosis: comparison between outcome diagnoses of schizophrenia, mood disorders, and personality disorders. *J Autism Dev Disord* 23:243–262

McGlashan TH (1988), Adolescent versus adult onset of mania. *Am J Psychiatry* 145:221–223

McKnew DH, Cytryn L, Buchsbaum MS (1981), Lithium in children of lithium responding parents. *Psychiatr Res* 4:171–180

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

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

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

Miklowitz DJ, Richards JA, George EL et al. (2003), Integrated family and individual therapy for bipolar disorder: results of a treatment development study. *J Clin Psychiatry* 64:182–191

Miklowitz DJ, Simoneau TL, George EL et al. (2000), Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. *Biol Psychiatry* 15:582–592

Nierenberg AA, Miyahara S, Spencer T et al. (2005), 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* 57:1467–1473

*NIMH (2001), National Institute of Mental Health research roundtable on prepubertal bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 40:871–878

Nurnberger JI Jr, Foroud T (2000), Genetics of bipolar affective disorder. *Curr Psychiatry Rep* 2:147–157

Papatheodorou G, Kutcher SP, Katic M, Szalai JP (1995), The efficacy and safety of divalproex sodium in the treatment of acute mania in adolescents and young adults: an open clinical trial. *J Clin Psychopharmacol* 15:110–116

Pavuluri MN, Birmaher B, Naylor MW (2005), Pediatric bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry* 44:846–871

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

Pavuluri MN, Henry DB, Carbray JA, Sampson G, Naylor MW, Janicak PG (2004b), Open-label prospective trial of risperidone in combination with

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.

lithium or divalproex sodium in pediatric mania. *J Affect Disord* 82(suppl 1):S103–S111

Pavuluri MN, Henry DB, Carbray JA, Sampson GA, Naylor MW, Janicak PG (2006), A one-year open-label trial of risperidone augmentation in lithium nonresponder youth with preschool-onset bipolar disorder. *J Child Adolesc Psychopharmacol* 16:336–350

Pavuluri MN, Henry DB, Devineni B, Carbray JA, Naylor MW, Janicak PG (2004c), A pharmacotherapy algorithm for stabilization and maintenance of pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 43:859–867

Pavuluri MN, Herbener ES, Sweeney JA (2004), Psychotic symptoms in pediatric bipolar disorder. *J Affect Disord* 80:19–28

Perlis RH, Miyahara S, Marangell LB et al, STEP-BD Investigators (2004), 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* 55:875–881

Rao U, Ryan ND, Birmaher B et al. (1995), Unipolar depression in adolescents: clinical outcome in adulthood. *J Am Acad Child Adolesc Psychiatry* 34:566–578

Rasgon N (2004), The relationship between polycystic ovary syndrome and antiepileptic drugs: a review of the evidence. *J Clin Psychopharmacol* 24:322–334

Scheffer R, Kowatch R, Carmody T, Rush A (2005), A randomized placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder following mood stabilization with divalproex sodium. *Am J Psychiatry* 162:58–64

Scheffer RE, Niskala Apps JA (2004), The diagnosis of preschool bipolar disorder presenting with mania: open pharmacological treatment. *J Affect Disord* 82:S25–S34

Schwartz JE, Fennig S, Tanenberg-Karant M et al. (2000), Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. *Arch Gen Psychiatry* 57:593–600

Shaw DS, Lacourse E, Nagin DS (2005), Developmental trajectories of conduct problems and hyperactivity from ages 2 to 10. *J Child Psychol Psychiatry* 46:931–942

Soutullo CA, Sorter MT, Foster KD, McElroy SL, Keck PE (1999), Olanzapine in the treatment of adolescent acute mania: a report of seven cases. *J Affect Disord* 53:279–283

Speltz M, McClellan J, Deklyen M, Jones K (1999), Preschool boys with oppositional defiant disorder: clinical presentation and diagnostic change over a two year period. *J Am Acad Child Adolesc Psychiatry* 38:838–846

State RC, Frye MA, Altshuler LL et al. (2004), Chart review of the impact of attention-deficit/hyperactivity disorder comorbidity on response to lithium or divalproex sodium in adolescent mania. *J Clin Psychiatry* 65:1057–1063

Steiner H, Saxena K, Chang K (2003), Psychopharmacologic strategies for the treatment of aggression in juveniles. *CNS Spectr* 8:298–308

Strober M, Carlson G (1982), Bipolar illness in adolescents with major depression: clinical, genetic and psychopharmacologic predictors in a 3–4 year prospective follow-up investigation. *Arch Gen Psychiatry* 39:549–555

Strober M, Morrell W, Lampert C, Burroughs J (1990), Relapse following discontinuation of lithium maintenance therapy in adolescents with bipolar I illness: a naturalistic study. *Am J Psychiatry* 147:457–461

Strober M, Schmidt-Lackner S, Freeman R, Bower S, Lampert C, DeAntonio M (1995), Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. *J Am Acad Child Adolesc Psychiatry* 34:724–731

Suppes T, Dennehy EB, Swann AC et al. (2002), Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder. Report of the Texas Consensus Conference Panel on medication treatment of bipolar disorder. *J Clin Psychiatry* 63:288–299

Thuppal M, Carlson GA, Sprafkin J, Gadow KD (2002), Correspondence between adolescent report, parent report, and teacher report of manic symptoms. *J Child Adolesc Psychopharmacol* 12:27–35

Tillman R, Geller B, Bolhofner K, Craney JL, Williams M, Zimerman B (2003), Ages of onset and rates of syndromal and subsyndromal comorbid DSM-IV diagnoses in a prepubertal and early adolescent bipolar disorder phenotype. *J Am Acad Child Adolesc Psychiatry* 42:1486–1493

Tumuluru RV, Weller EB, Fristad MA, Weller RA (2003), Mania in six preschool children. *J Child Adolesc Psychopharmacol* 13:489–494

Vitiello B, Swedo S (2004), Antidepressant medications in children. *N Engl J Med* 350:1489–1491

Wagner KD, Weller EB, Carlson GA et al. (2002), An open-label trial of divalproex in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 41:1224–1230

Weiss G, Hechtman L, Milroy T, Perlman T (1985), Psychiatric status of hyperactives as adults: a controlled prospective 15-year follow-up of 63 hyperactive children. *J Am Acad Child Adolesc Psychiatry* 24:211–220

Werry JS, McClellan J, Chard L (1991), Early-onset schizophrenia, bipolar and schizoaffective disorders: a clinical and follow-up study. *J Am Acad Child Adolesc Psychiatry* 30:457–465

West SA, Keck PE Jr, McElroy SL et al. (1994), Open trial of valproate in the treatment of adolescent mania. *J Child Adolesc Psychopharmacol* 4:263–267

Wilens TE, Biederman J, Forkner P et al. (2003), Patterns of comorbidity and dysfunction in clinically referred preschool and school-age children with bipolar disorder. *J Child Adolesc Psychopharmacol* 13:495–505

Wilens TE, Biederman J, Kwon A et al. (2004), Risk of substance use disorders in adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 43:1380–1386

Winokur G, Coryell W, Endicott J, Akiskal H (1993), Further distinctions between manic-depressive illness (bipolar disorder) and primary depressive disorder (unipolar depression). *Am J Psychiatry* 150:1176–1181

World Health Organization (1992), *ICD-10 Classification of Mental and Behavioural Disorders*. Geneva: World Health Organization

*Wozniak J, Biederman J, Kiely K et al. (1995), Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry* 34:867–876

Wozniak J, Spencer T, Biederman J et al. (2004), The clinical characteristics of unipolar vs. bipolar major depression in ADHD youth. *J Affect Disord* 82:S59–S69

Youngstrom EA, Findling RL, Calabrese JR et al. (2004), 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* 43:847–858

Youngstrom EA, Findling RL, Youngstrom JK, Calabrese JR (2005), Toward an evidence-based assessment of pediatric bipolar disorder. *J Clin Child Adolesc Psychol* 34:433–448

Youngstrom EA, Gracious BL, Danielson CK, Findling RL, Calabrese J (2003), Toward an integration of parent and clinician report on the Young Mania Rating Scale. *J Affect Disord* 77:179–190

Youngstrom E, Youngstrom JK, Starr M (2005), Bipolar diagnoses in community mental health: Achenbach Child Behavior Checklist profiles and patterns of comorbidity. *Biol Psychiatry* 58:569–575

Zito JM, Safer DJ, dos Reis S, Gardner JF, Boles M, Lynch F (2000), Trends in the prescribing of psychotropic medications in preschoolers. *JAMA* 283:1025–1103

Copyright © 2007 American Academy of Child and Adolescent Psychiatry. Unauthorized reproduction of this article is prohibited.