American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

FROM THE AMERICAN ACADEMY OF PEDIATRICS

Guidance for the Clinician in Rendering Pediatric Care

CLINICAL REPORT

Collaborative Role of the Pediatrician in the Diagnosis and Management of Bipolar Disorder in Adolescents

Benjamin N. Shain, MD, PhD and COMMITTEE ON ADOLESCENCE

KEY WORDS
adolescent bipolar disorder, interview guidelines, psychiatric diagnosis, psychotropic medication, collaboration

ABBREVIATIONS
ADHD—attention-deficit/hyperactivity disorder
DSM-IV-TR—*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*
FDA—US Food and Drug Administration
OCD—obsessive-compulsive disorder
SMD—severe mood dysregulation

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

www.pediatrics.org/cgi/doi/10.1542/peds.2012-2756

doi:10.1542/peds.2012-2756

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

abstract

FREE

Despite the complexity of diagnosis and management, pediatricians have an important collaborative role in referring and partnering in the management of adolescents with bipolar disorder. This report presents the classification of bipolar disorder as well as interviewing and diagnostic guidelines. Treatment options are described, particularly focusing on medication management and rationale for the common practice of multiple, simultaneous medications. Medication adverse effects may be problematic and better managed with collaboration between mental health professionals and pediatricians. Case examples illustrate a number of common diagnostic and management issues. *Pediatrics* 2012;130:e1725–e1742

Pediatricians are faced with increasing numbers of patients diagnosed with bipolar disorder and taking multiple psychotropic medications. In addition, pediatricians may be seeing these patients long before they are diagnosed and treated by a child and adolescent psychiatrist or other mental health professional. Pediatric bipolar disorder, once thought to be rare in adolescents and nearly nonexistent in younger children, has been diagnosed increasingly over the past decade.[1–3] In 2004, bipolar disorder accounted for 26% of primary discharge diagnoses among psychiatrically hospitalized adolescents in the United States.[3] Bipolar spectrum disorders,[4] encompassing the several types of bipolar disorder, have an estimated prevalence of 4% of children and adolescents in the general population.[5] The diagnosis remains controversial, and there has been a shift in how the diagnosis has been defined in youth.[1]

Associated impairments may include severe depression, high risk of suicide, psychosis, impulsive and dangerous behaviors, social and cognitive deficits, and frequent comorbidity with other psychiatric disorders, including substance use disorders, attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, oppositional defiant disorder, and conduct disorder. Insight is frequently diminished, with youth vehemently blaming others for their difficulties and having little recognition of their own disruptive symptoms.[1] Management of these youth is additionally complicated by medication limitations, including troublesome adverse effects, lack of full response and the resultant common prescription of multiple medications, and incomplete prevention of relapse.[1] Not surprisingly, poor adherence to prescribed dosing is common.[6]

This report is not expected to give general pediatricians the tools necessary to diagnose and manage these complex cases independently. Some specific techniques are described with the intent of facilitating partnerships between pediatricians and child and adolescent psychiatrists and other mental health professionals. Additional goals include improved understanding of diagnosis and treatment; earlier referral of new, suspected cases, and patients with symptom relapse or worsening; and assistance in recognizing and managing medication adverse effects.

The focus of this report is diagnosis and management of adolescents with bipolar disorder. Children are mentioned as well when the subject matter applies to them.

CLASSIFICATION

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[7] describes 4 types of bipolar disorders, all without age limitations: bipolar I disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified. Manic symptoms are the key feature of these diagnoses; Tables 1, 2, and 3 provide criteria for mania, hypomania, and mixed episodes.[7] A key criterion is duration: the minimum duration for mania and mixed episodes is 7 days and for hypomania is 4 days.

Bipolar I Disorder

Bipolar I disorder is the "classic" form of the disorder and requires a current or past manic or mixed episode. At any given time, the patient may be in a manic, hypomanic, mixed, or major depressive episode or may have fully or partially recovered from the last mood episode. Notably, this is a historical diagnosis because the patient may be in any current mood state and still meet this criterion. History of a depressive episode is common but not required. Other criteria are that the mood symptoms cause significant distress or impaired functioning; are not better accounted for by schizoaffective disorder or superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified; and are not the effect of a substance (including medications) or general medical condition.

TABLE 1 Diagnostic Criteria for a Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 wk (or for any duration if hospitalization is necessary)
B. During the period of mood disturbance, 3 (or more) of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree
   1. Inflated self-esteem or grandiosity
   2. Decreased need for sleep (eg, feels rested after only 3 h)
   3. More talkative than usual or pressure to keep talking
   4. Flight of ideas or subjective experience that thoughts are racing
   5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
   7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
C. The symptoms do not meet criteria for a mixed episode
D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features
E. The symptoms are not due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication, or other treatment) or a general medical condition (eg, hyperthyroidism)

Reprinted with permission from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000.

TABLE 2 Diagnostic Criteria for a Hypomanic Episode

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 d, that is clearly different from the usual nondepressed mood
B. Same as manic episode "B" (Table 1)
C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic
D. The disturbance in mood and the change in functioning are observable by others
E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization, and there are no psychotic features
F. Same as manic episode "E" (Table 1)

DSM-IV-TR asks for specification of certain patterns, including longitudinal course as with or without full interepisode recovery and/or rapid cycling. Rapid cycling is defined as more than 4 mood changes in a year. Researchers have defined patterns that commonly apply to pediatric bipolar disorder, including ultrarapid cycling, episodes lasting a few days to a few weeks, and ultradian cycling, variation occurring within a 24-hour period.[8,9]

Bipolar II Disorder

Depression typically is the major problem in bipolar II disorder. A current or at least 1 past major depressive episode is required, and the patient must have a current or past episode of hypomania with no manic or mixed episodes at any time. That is, currently or historically, a patient with bipolar I disorder has big "ups" (mania) and may or may not have "downs" (depression). A patient with bipolar II disorder has little "ups" (hypomania) plus big "downs" (major depression).

Cyclothymic Disorder

Cyclothymic disorder is characterized by relatively mild but chronic symptoms (hypomanic and depressive symptoms) that last at least 2 years (1 year with children and adolescents) before any full manic, mixed, or major depressive

TABLE 3 Diagnostic Criteria for a Mixed Episode

A. The criteria are met for both a manic episode and a major depressive episode (except for duration) nearly every day during at least a 1-wk period
B. Same as manic episode "D" (Table 1)
C. Same as manic episode "E" (Table 1)

episodes. These patients have little "ups" (hypomania) and little "downs" (dysthymia), but the disorder is chronic.

Bipolar Disorder Not Otherwise Specified

DSM-IV-TR describes the category of bipolar disorder not otherwise specified as including, "disorders with bipolar features that do not meet criteria for any specific bipolar disorder."[7] The American Academy of Child and Adolescent Psychiatry recommends using this diagnosis for youth with manic symptoms lasting hours to days or for those with chronic manic-like symptoms.[1] These youth may be significantly impaired and constitute the majority of those referred to mental health professionals.[10] Emerging evidence suggests that this disorder is on a continuum with bipolar I disorder,[11,12] and 45% of patients converted to bipolar I or bipolar II disorder at follow-up an average of 5 years later, particularly patients with a family history of bipolar disorder.[13]

Beyond DSM-IV-TR

Akiskal and Pinto described a bipolar spectrum in adults, ranging from bipolar I disorder to hyperthymic temperament.[4] The disorders and conditions on the spectrum share symptom characteristics that generally responded better to mood-stabilizing medication than to antidepressant medication.

Leibenluft et al suggested research diagnostic criteria for 3 clinical phenotypes of pediatric bipolar disorder: narrow, intermediate, and broad[14] (Tables 4, 5, and 6). These criteria are included in this report to illustrate important features of diagnosis that are not present in DSM-IV-TR; they should not be construed as generally accepted by physicians or researchers. Narrow phenotype refers to a disorder in which, for at least 1 episode, full DSM-IV-TR criteria are met, including duration criteria, and elation and/or grandiosity also is present. Elation and grandiosity were argued by Geller et al[9] to be core bipolar features. Intermediate phenotype refers to patients with episodes that met full DSM-IV-TR criteria but lacked duration criteria (episodes too short) or had mania/hypomania that was irritable rather than euphoric. This phenotype still includes mood cycling as a required feature. Broad phenotype refers to a disorder characterized by chronic irritability and hyperarousal and does not include mood cycling. Compared with their peers, children and adolescents who have the broad phenotype show markedly increased reactivity to negative emotional stimuli. The broad phenotype has been referred to as severe mood dysregulation (SMD).

TABLE 4 Research Criteria for the Narrow Phenotype of Juvenile Mania

A. Modification to the DSM-IV-TR criteria for manic episode
   a. The child must exhibit either elevated/expansive mood or grandiosity while also meeting the other DSM-IV-TR criteria for a (hypo)manic episode
B. Guidelines for applying the DSM-IV-TR criteria
   a. Episodes must meet the full duration criteria (ie, at least 7 d for mania and at least 4 d for hypomania) and be demarcated by switches from other mood states (depression, mixed state, euthymic).
   b. Episodes are characterized by a change from baseline in the patient's mood and, simultaneously, by the presence of the associated symptoms.
   c. Decreased need for sleep should be distinguished from insomnia.
   d. Poor judgment is not a diagnostic criterion unless it is in the context of "increased goal-directed activity" or "excessive involvement in pleasurable activities that have a high potential for painful consequences."

TABLE 5 Research Criteria for the Intermediate Phenotypes of Juvenile Mania

A. The child meets the criteria for the narrow phenotype except:
   a. (Hypo)manic episodes are 1to 3 d in duration OR
   b. The (hypo)manic episodes include exclusively irritable, not elevated or expansive, mood, and DSM-IV-TR duration criteria are met

SMD among children 9 to 19 years of age has a lifetime prevalence of 3.3%, with most affected children having comorbid psychiatric disorders, most frequently disruptive behavior disorders (ADHD, conduct disorder, and oppositional defiant disorder).[15] Children with SMD were 7 times more likely to develop depression as young adults compared with those without SMD. Compared with children with narrow phenotype bipolar disorder, subjects with SMD had different psychopathological measures and were less likely to have parents with bipolar disorder,[16] suggesting that SMD is a disorder distinct from narrow phenotype bipolar disorder.

Mood diagnoses continue to evolve. The development web site for the forthcoming *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* lists an additional proposed mood diagnosis of "disruptive mood dysregulation disorder,"[17] characterized by severe recurrent temper outbursts in response to common stressors and similar to the broad phenotype. Characteristics for this diagnosis as well as others on the development Web site have been changing in response to public feedback. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* is expected to be published in May 2013. Because the final version may be fairly different, this report

TABLE 6 Research Criteria for Broad Phenotype of Juvenile Mania: Severe Mood and Behavioral Dysregulation

A. Inclusion criteria
  a. Age 7–17 y, with onset of symptoms before age 12
  b. Abnormal mood present at least half of the day most days and of sufficient severity to be noticeable by people in the child's environment
  c. Hyperarousal, as defined by at least 3 of the following symptoms: insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, intrusiveness
  d. Compared with his/her peers, the child exhibits markedly increased reactivity to negative emotional stimuli that is manifest verbally or behaviorally
  e. The symptoms noted in the previous 3 items are currently present and have been present for at least 12 mo without any symptom-free periods exceeding 2 mo in duration
  f. The symptoms are severe in at least 1 setting and at least mild symptoms in a second setting
B. Exclusion criteria
  a. The individual exhibits any of the cardinal bipolar symptoms: elevated or expansive mood, grandiosity or inflated self-esteem, episodically decreased need for sleep
  b. The symptoms occur in distinct periods lasting more than 4 d
  c. The individual meets criteria for schizophrenia, schizoaffective illness, pervasive developmental disorder, or posttraumatic stress disorder
  d. The individual has met the criteria for substance abuse disorder in the past 3 mo
  e. IQ <80
  f. The symptoms are attributable to the direct physiologic effects of a drug of abuse or to a general medical or neurologic condition

does not include additional mention of diagnoses listed on the development web site.

The balance of this report refers to *DSM-IV-TR* as well as proposed research diagnoses. Pediatricians should be aware, however, of the changing classification of bipolar and related disorders.

INTERVIEWING FOR MANIA

The presence or history of mania of some sort is the determining factor for a diagnosis of bipolar disorder. Typically, depressive symptoms are also present at some point in the illness and may be the major concern, but depression is not required to be present either currently or historically for a bipolar diagnosis. Depressed patients with bipolar disorder, particularly those with the narrow or intermediate phenotype, may require different medication from those with depression alone, so it is important for the pediatrician or mental health professional to attempt to make this differentiation before initiating pharmacotherapy.

Challenges in Diagnosing Mania

At a minimum, a full psychiatric evaluation should be performed to determine diagnosis.[1] A significant problem is that the diagnosis of mania typically is historical. Even with a patient who demonstrates manic symptoms during the interview, the interviewer still needs to determine that the symptoms represent a change, interfere with functioning, and are associated with less evident manic symptoms. Much more often, however, the patient presents as depressed or euthymic, leaving it for the interviewer to tease out groups of symptoms that occur together in episodes and are different from "normal adolescence." Adolescents and parents may tend to minimize these symptoms, wanting the trouble to be something less serious or, conversely, may tend to exaggerate, grasping at a bipolar diagnosis as a means of explaining a range of difficulties. Much of the public now has some education about bipolar disorder, often just enough to produce misconceptions about the diagnosis and associated symptoms, thus complicating the job of the interviewer.

Simplifications

Without specific training in this area, the general pediatrician should not attempt initiation of treatment in newly diagnosed cases. The goal for the pediatrician in identification, therefore, should be reasonable suspicion rather than diagnosis, followed by referral or seeking an appropriate mental health professional as partner. The balance of this section discusses several historical symptoms that may be considered red flags for the diagnosis. The clear presence of any of these should be considered sufficient for reasonable suspicion.

Red Flag Symptoms

Rage Outbursts or Verbal or Physical Aggression

Rage is not a bipolar symptom per se but is common with adolescents experiencing episodic irritable mania or chronic severe mood dysregulation. In both cases, the adolescent is edgy and easily frustrated and provoked. Questions the interviewer may ask include, "Do you lose your temper?" If so, the adolescent should be asked about frequency, duration, what happens, and what the triggers are (see Table 7 for a summary of examples of interview questions).

Episodes of Requiring Little Sleep

Requiring little sleep needs to be distinguished from going to bed late and getting up late and from receiving less sleep and consequently being tired the next day. Staying up late for 1 night during a sleepover or for a concert also does not count. Adolescents with this symptom have the experience of having high energy, receiving at least 2 hours less sleep per night, and remaining full of energy often after several nights of this.[18] Questions include, "Do you ever have nights when you have lots of energy, do not need to sleep much, and do lots of things?" If so, "Are you tired the next day?"

TABLE 7 Examples of Interview Questions

Symptom	Question examples
Rage outbursts	"Do you lose your temper?" If so, ask about frequency, duration, what happens, what the triggers are.
Episodes of requiring little sleep	"Do you ever have nights when you have lots of energy, do not need to sleep much, and do lots of things?" If so, "Are you tired the next day?"
Spontaneous mood shifts	"Do you find yourself suddenly angry or extremely happy for no apparent reason?" If so, ask about frequency and duration of the moods.
Running away, sneaking out at night, spending money, hypersexuality	"Have you even run away or snuck out of the house at night?" "Do you have time when you spend a lot of money or when you feel that you cannot control your sexual urges?"
Grandiosity	"Do you have times when you feel that nothing can happen to you?" "Do you have times when you greatly overestimate your talents or abilities?"
Agitation or mania with antidepressant	"Have you ever taken medication for depression?" If so, "Did you have any side effects?" "Did you ever become very edgy or much more happy or angry than is typical for you?"

Spontaneous Mood Shifts

The adolescent experiences sudden mood shifts between euthymic, giddy, depressed, or angry, with no evident circumstantial trigger. The giddy, depressed, or angry mood state should significantly interfere with functioning, such as making concentration in school or appropriate behavior with friends much more difficult. A mood shift may happen multiple times per day. Questions include, "Do you find yourself suddenly angry or extremely happy for no apparent reason?" If so, ask about frequency and duration of the moods.

Running Away, Sneaking Out at Night, Spending Money, Hypersexuality

These activities may be categorized as "excessive involvement in pleasurable activities that have a high potential for painful consequences" (Table 1).[7] Running away also may be an example of an impulsive activity related to severe irritability. Questions include, "Have you ever run away or snuck out of the house at night?" "Do you have times when you spend a lot of money or when you feel that you cannot control your sexual urges?"

Grandiosity

Grandiosity is a grossly inflated belief in oneself having special talents or abilities, such as never being in danger regardless of the activity or being the best at a certain sport, or endless talk about a real talent. This must be a change from baseline and does not include a consistent picture of boastfulness or failure to appreciate consequences. Questions include, "Do you have times when you feel that nothing can happen to you?" "Do you have times when you greatly overestimate your talents or abilities?"

Agitation or Mania With Antidepressant

Adverse effects for a patient under the influence of antidepressant medication may be edginess, agitation, or less commonly, frank mania. By definition, a cluster of manic symptoms resulting from a medication or substance is not mania. It is, however, a risk factor for mania either continuing once the medication is withdrawn or mania at another time. Questions include, "Have you ever taken medication for depression?" If so, "Did you have any side effects?" "Did you ever become very edgy or much more happy or angry than is typical for you?"

Any or all of these symptoms may be present currently, recently, or in the more distant past.

TREATMENT

Psychotherapy

Psychotherapeutic interventions are an important component of an overall treatment plan.[1] Interventions should be targeted to the following areas.

Psychoeducation

Information is provided to patient and family on the illness, treatment options, impact on functioning, and heritability. Relapse prevention typically is an important issue. Education is provided regarding importance of treatment adherence, avoidance of precipitating factors, and early recognition of symptoms. The illness may result in a dramatic tendency to blame others and minimize one's own symptoms and limitations, making engagement in the treatment plan difficult. For some individuals and families, education regarding relapse prevention is the key intervention.

Individual Psychotherapy

Cognitive-behavioral psychotherapy and interpersonal therapy support emotional and cognitive development, coping, and symptom monitoring.

Social and Family Functioning

Interventions aimed at communication and problem solving are needed to address disruptions in family and social relationships.

Academic and Occupational Functioning

Educational planning, specialized educational programs, and occupational training and support may be needed to address disruption of functioning in

school or work from ongoing or intermittent symptoms.

Treatment of Comorbidities

Psychosocial interventions should be aimed at treatment of pre- or coexisting substance abuse disorders, behavioral disorders, anxiety disorders, learning problems, and confounding social issues.

Inpatient Psychiatric Hospitalization

Inpatient care typically is aimed at preventing imminent harm to self and others as well as allowing for treatment that could not be accomplished in a less restrictive setting.[19] A common reason for admission is suicidality, including suicidal ideation or a recent attempt. To be at high risk of suicide, the patient need not be thinking of suicide at the time of admission. Mood and behavior may have considerable day-to-day or even minute-to-minute variation; therefore, judgment as to safety should be based on recent thoughts, moods, and behaviors rather than just the current ones and on near-future projection on the basis of possible and sudden occurrence of common adolescent stressors. For example, in an adolescent with recent suicidal behavior and a history of grossly overreacting to negative circumstances, a romantic breakup could be lethal.

Other common reasons for psychiatric hospitalization for harm prevention are recent episodes of severe rage, agitation, or aggression attributable to mood symptoms or manic symptoms accompanied by severe impulsivity in areas that could inadvertently result in self-harm, such as running away or sexual activity with multiple partners. Patients with florid mania or acute psychosis typically require hospitalization even in the absence of overtly dangerous behaviors or ideation because of the high unpredictability of the behavior of afflicted individuals as well as difficulty with treatment adherence at a time when vigorous treatment is indicated.

Partial hospitalization[20] or hospital day treatment is used as a less restrictive, step-down treatment from inpatient care or as step-up treatment from mental health office services. Partial hospitalization does not afford the 24-hour monitoring and harm prevention provided with inpatient services but is less disruptive to the patient's life, less expensive, and gives the patient and family more responsibility for the patient's care while still providing intensive psychotherapeutic and medical management.

Residential treatment[21] is longer-term, 24-hour-a-day care in a less intensive, typically nonhospital setting, and may be a month to a year or more in duration. Residential care is designed for patients who cannot be safely managed otherwise despite adequate treatment or who have symptoms that require long-term behavioral intervention to effect improvement.

Psychopharmacology

Medication management is an important component of treatment of youth with bipolar disorder and is the primary treatment in cases of well-defined mania.[1,5] The primary medications used to treat patients with bipolar disorder are mood stabilizers, such as lithium; certain anticonvulsant medications, including divalproex, lamotrigine, carbamazepine, oxcarbazepine, gabapentin, and topiramate; and atypical antipsychotics, including aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, paliperidone, clozapine, asenapine, and iloperidone. Adjunctive medications include antidepressant medications and "typical" antipsychotics, as well as medications for ADHD, anxiety, and insomnia; more information is available from the American Academy of Child and Adolescent practice parameters.[1,22–25]

The American Academy of Child and Adolescent Psychiatry[1] recommends basing the medication choice on the following: evidence of efficacy, phase of illness, type of presentation (eg, with psychotic symptoms), safety and adverse effect profile, history of medication response, and patient or family preference. Medication combinations are common, with some patients on 5 or more drugs. See Kowatch et al[5] for a suggested prescribing algorithm.

Efficacy Studies

Currently, lithium, aripiprazole, risperidone, olanzapine, and quetiapine are approved by the US Food and Drug Administration (FDA) for use in adolescents with bipolar disorder (Table 8).[26] In addition, divalproex, lamotrigine, carbamazepine, oxcarbazepine, gabapentin, and topiramate have nonmental health pediatric indications, and divalproex, lamotrigine, ziprasidone, and asenapine have indications for treatment of adults with bipolar disorder. Published studies have had mixed results (Tables 9, 10, and 11). Not all studies are available, because pharmaceutical companies are not required to publish their studies even when submitted to the FDA as part of an application for an indication. Lithium, aripiprazole, and olanzapine showed efficacy in published, double-blind, placebo-controlled studies, with open-label, chart review, and comparison studies giving support for use of divalproex, lamotrigine, clozapine, risperidone, quetiapine, and carbamazepine. Notably, divalproex and oxcarbazepine each failed to show efficacy in a double-blind, placebo-controlled study, but given the heterogeneity of this disorder, 1 negative study is not conclusive. Divalproex, lamotrigine, lithium, aripiprazole,

TABLE 8 FDA Indications for Oral Formulations of Mood Stabilizers and Atypical Antipsychotics

Medication	Bipolar disorder	Schizophrenia	Irritability associated with autism	Nonmental health	All adult mental health
Mood stabilizer					
Lithium (Eskalith)	Mania, ages 12–17				Mania
Divalproex (Depakote)				Seizures, ages 0–17	Mania
Lamotrigine (Lamictal)				Seizures, ages 2–17	Bipolar maintenance
Carbamazepine (Tegretol)				Seizures, ages 0–17; trigeminal neuralgia	
Oxcarbazepine (Trileptal)				Seizures, ages 2–17	
Gabapentin (Neurontin)				Seizures, ages 3–17	
Topiramate (Topamax)				Seizures, ages 2–17	
Atypical antipsychotics					
Aripiprazole (Abilify)	Manic and mixed episodes, ages 10–17	Ages 13–17	Ages 6–17		Bipolar mania, schizophrenia, adjunctive for major depression
Risperidone (Risperdal)	Manic and mixed episodes, ages 10–17	Ages 13–17	Ages 5–16		Schizophrenia, bipolar manic and mixed episodes
Olanzapine (Zyprexa)	Manic and mixed episodes, ages 13–17	Ages 13–17			Schizophrenia, bipolar manic and mixed episodes, bipolar and resistant depression (in combination with fluoxetine)
Quetiapine (Seroquel)	Manic episodes, ages 10–17	Ages 13–17			Schizophrenia, bipolar mania, bipolar depression
Ziprasidone (Geodon)					Schizophrenia, bipolar manic and mixed episodes, bipolar maintenance
Paliperidone (Invega)					Schizophrenia, schizoaffective disorder
Clozapine (Clozaril)					Schizophrenia, schizoaffective disorder
Asenapine (Saphris)					Schizophrenia, bipolar manic and mixed episodes
Iloperidone (Fanapt)					Schizophrenia
Lurasidone (Latuda)					Schizophrenia

quetiapine, risperidone, and topiramate have shown efficacy in medication combination studies. Kowatch et al[27] found a medication combination response rate of 80% among patients who did not respond to monotherapy with a mood stabilizer.

Adverse Effects

Mood stabilizer (Table 12)[5] and atypical antipsychotic (Table 13)[28,29] medications have a variety of adverse effects, interactions, and safety concerns. Pediatricians probably need to be most aware of weight gain and metabolic effects common with the atypical antipsychotics, although weight gain is also commonly associated with valproate and, to a lesser extent, lithium. Prescription of atypical antipsychotics in youth for bipolar disorder as well as for psychosis, disruptive behavior disorders, and other mood disorders has increased drastically in recent years.[30] Children and adolescents may be more vulnerable than adults to weight gain from these medications and, thus, likely to be at higher risk of glucose and lipid abnormalities.[31] Weight management potentially can be addressed with suggestions of diet and exercise as well as changing the dose and/or type of medication. Use of metformin may be of some help.[32,33] Stable patients should be seen by their pediatrician every 4 to 6 months, with more frequent visits when there are active adverse effects, interactions, or safety issues.

The American Diabetes Association[34] published a protocol for use in monitoring for weight gain and metabolic changes in adults treated with atypical antipsychotics, including obtaining personal and family history of related disorders, determining weight and height, determining waist circumference, taking blood pressure, and measuring fasting plasma glucose and fasting lipid profile. Weight should

TABLE 9 Published Studies of Efficacy of Mood Stabilizers With Pediatric Bipolar Disorder[a]

Medication	Study	Ages	Type	Results	Comments
Divalproex	Wagner et al (2002)[41]	7–19; *n* = 40	Open-label trial	Response rate 61% with manic symptoms	Manic, mixed, or hypomanic
Divalproex	Henry et al (2003)[42]	4–18; *n* = 15	Records review	Response rate 53% after 1 y	Divalproex alone and as add-on
Divalproex	Wagner et al (2009)[43]	10–17; *n* = 150	Double-blind	No significant difference from placebo	Manic or mixed
Lamotrigine	Chang et al (2006)[44]	12–17; *n* = 20	Open-label trial	Significant decreases in depression, mania, and aggression	Lamotrigine alone and in combination with other medication
Lamotrigine	Pavuluri et al (2009)[45]	8–18; *n* = 46	Open-label trial	Response rate 72% with manic symptoms and 82% with depressive symptoms	Monotherapy
Lithium	Strober et al (1990)[46]	13–17, *n* = 37	Naturalistic prospective follow-up	Relapse rate 3 times higher when lithium discontinued	Lithium alone and in combination with other medication
Lithium	Geller et al (1998)[47]	12–18; *n* = 25	Double-blind	Significant response rate difference, 46% versus 8% of placebo group	Bipolar disorder with secondary substance dependence
Lithium	Kafantaris et al (2003)[48]	12–18; *n* = 100	Open-label trial	Response rate 63% with manic symptoms	Acute mania
Lithium	Kafantaris, et al (2004)[49]	12–18; *n* = 40	Double-blind discontinuation	No significant difference from placebo	Mania with or without psychosis or aggression
Lithium	Patel et al (2006)[50]	12–18; *n* = 27	Open-label trial	Response rate 48% with depressive symptoms	Acute bipolar depression
Oxcarbazepine	Wagner et al (2006)[51]	7–18; *n* = 116	Double-blind	No significant difference from placebo	Manic or mixed
Topiramate	Del Bello et al (2002)[52]	5–20; *n* = 26	Chart review	Response rate 73% for mania and 62% for overall illness	Outpatient with acute manic, mixed, or depressive episode; adjunctive or monotherapy
Topiramate	Barzman et al (2005)[53]	7–20; *n* = 25	Chart review	Response rate 64%	Hospitalized with acute manic, mixed, or depressive episode; adjunctive or monotherapy
Topiramate	DelBello, et al (2005)[54]	6–17; *n* = 56	Double-blind	Mixed results	Inconclusive; study stopped early when early adult studies failed to show efficacy

[a] Includes only the most recent studies of divalproex and lithium.

TABLE 10 Published Studies of Efficacy of Atypical Antipsychotics for Pediatric Bipolar Disorder

Medication	Study	Ages	Type	Results	Comments
Aripiprazole	Barzman et al (2004)[55]	5–19; *n* = 30	Chart review	Response rate 67%	Bipolar or schizoaffective; adjunctive or monotherapy
Aripiprazole	Biederman et al (2005)[56]	4–17; *n* = 41	Records review	71% improvement of manic symptoms	Aripiprazole alone and as add-on
Aripiprazole	Biederman et al (2007)[57]	6–17; *n* = 19	Open-label trial	Significant improvement	Mania
Aripiprazole	Tramontina et al (2007)[58]	8–17; *n* = 10	Open-label trial	Significant improvement	Comorbid bipolar and ADHD; improved both mania and ADHD symptoms
Aripiprazole	Findling et al (2009)[59]	10–17; *n* = 296	Double-blind	Significant response rate difference, 44% (10 mg), 64% (30 mg), 26% (placebo)	Manic or mixed
Aripiprazole	Tramontina et al (2009)[60]	8–17; *n* = 43	Double-blind	Significant response rate difference, 89% vs 52% of placebo group	Manic or mixed comorbid with ADHD
Clozapine	Masi et al (2002)[61]	12–17; *n* = 10	Open-label trial	Significant improvement	Severe treatment-resistant manic or mixed
Olanzapine	Frazier et al (2001)[62]	5–14; *n* = 23	Open-label trial	Response rate 61%	Acute mania
Olanzapine	Tohen et al (2007)[63]	13–17; *n* = 161	Double-blind	Significant response rate difference, 45% vs 19% of placebo group	Acute manic or mixed
Olanzapine	Joshi et al (2010)[64]	4–17; *n* = 52	Open-label trial; secondary analysis of 2 trials	Significantly less antimanic response with comorbid OCD	Bipolar disorder
Quetiapine	Del Bello et al (2007)[65]	12–18; *n* = 20	Single-blind, open label	Response rate 87% with mood symptoms	Patients at high risk for bipolar I
Quetiapine	Del Bello et al (2009)[66]	12–18; *n* = 32	Double-blind	No significant difference from placebo	Bipolar depression
Quetiapine	Scheffer et al (2010)[67]	6–16; *n* = 75	Open-label trial	94% much improved at 8 wk; rapid loading tolerated well	Bipolar disorder
Risperidone	Frazier et al (1999)[68]	4–17; *n* = 28	Records review	Response rate 82% with manic and aggressive symptoms	Mixed or hypomanic
Risperidone	Biederman et al (2005)[69]	6–17; *n* = 30	Open-label trial	Response rate 70% with manic symptoms	Manic, mixed, or hypomanic
Risperidone	Haas et al (2009)[70]	10–17; *n* = 169	Double-blind	Significant response rate difference, 59% (0.5–2.5 mg), 63% (3–6 mg), 26% (placebo)	Acute manic or mixed
Risperidone	Carlson et al (2010)[71]	5–12; *n* = 151	Chart review	Reduced duration or rages	Hospitalized children with possible bipolar disorder
Risperidone	Krieger et al (2011)[72]	7–17; *n* = 21	Open-label trial	Significant reduction of irritability, depression, ADHD symptoms, and global functioning	Severe mood dysregulation
Ziprasidone	Biederman et al (2007)[73]	6–17; *n* = 21	Open-label trial	Response rate 71% with manic symptoms	Mania

be reassessed monthly for 3 months and then quarterly. Lipids and fasting plasma glucose may be measured after 3 months and then every 6 months. There is no a protocol currently for children and adolescents.[28]

When medications are prescribed by a physician other than the pediatrician, the decision of which physician monitors the patient's weight and metabolic consequences of the medication may be a matter of practicality. Certain measurements, such as vital signs, height, weight, and waist size, are easily and routinely obtained in a pediatrician's office but much more difficult to obtain in a psychiatrist's office, because it typically is not set up with the proper equipment and usually does not have a nurse on staff. In addition, at times, the patients may perceive these measurements to be physically intrusive when obtained by the psychiatrist. The pediatrician should collaborate with the prescribing physician in monitoring for and managing these medication adverse effects.

Other Medication Caution

A number of medications should be used with care because they may increase mood cycling (Table 14).[18] In particular, antidepressant medications are commonly prescribed, because bipolar disorder usually includes depression, and depression is the most common reason for the initial referral for treatment. Antidepressant induction of mania may be less frequent than once thought,[35] but common practice is to start with a mood stabilizer or atypical antipsychotic (or combination) and add an antidepressant to the mix only if there is insufficient response.

Few studies have addressed the use of mood stabilizers and atypical antipsychotics with pediatric bipolar depression. Lithium and lamotrigine

TABLE 11 Published Comparison Studies of Efficacy of Mood Stabilizers and Atypical Antipsychotics With Pediatric Bipolar Disorder

Medication	Study	Ages	Type	Results	Comments
Lithium, Divalproex, Carbamazepine	Kowatch et al (2000)[74]	6–18; *n* = 42	Open-label trial	Large effect size for all 3 medications; response rate with manic symptoms of divalproex 53%, lithium 38%, and carbamazepine 38%	Manic or mixed
Quetiapine, Divalproex	Del Bello et al (2002)[75]	12–18; *n* = 30	Double-blind	Significant response rate difference, 87% vs 53% of placebo group	Manic or mixed; divalproex plus quetiapine versus divalproex plus placebo
Risperidone, Lithium, Divalproex	Pavuluri et al (2004)[76]	5–18; *n* = 37	Open-label trial	Response rate 80% for risperidone plus divalproex and 82% for risperidone plus lithium	Manic or mixed
Lithium, Divalproex	Findling et al (2005)[77]	5–17; *n* = 60	Double-blind; no placebo group	No significant difference between the groups	Stabilized on lithium plus divalproex and then compared maintenance monotherapy with one or the other
Quetiapine, Divalproex	Del Bello et al (2006)[78]	12–18; *n* = 50	Double-blind, no placebo group	Significant improvement in both groups; no significant difference in amount of improvement but significantly faster improvement in quetiapine group	Manic or mixed; compared quetiapine and divalproex
Risperidone, Divalproex	MacMillan et al (2008)[79]	5–14; *n* = 28	Records review	Risperidone group showed significantly faster decrease of symptoms than divalproex group	More wt gain with risperidone
Risperidone, Divalproex	Pavuluri et al (2010)[80]	8–18; *n* = 66	Double-blind, no placebo group	More rapid improvement in risperidone group but no difference in final scores	No significant wt gain in either group; better retention of subjects in risperidone group

have shown efficacy in open-label trials (Table 9) and quetiapine was not significantly better than placebo (Table 10).

Medication Combinations

Adolescents with bipolar disorder may have a range of symptoms within the disorder, including symptoms of mania or hypomania, depression, and psychosis, and commonly have comorbidities with a variety of other psychiatric disorders, including ADHD, generalized anxiety disorder, obsessive-compulsive disorder (OCD), posttraumatic stress disorder, and others.[5] These comorbidities can lead to a complexity of symptoms and often difficult choices for medication management. As a result, use of multiple medications is common in treating adolescents with bipolar disorder, who often are prescribed 2 to 5, or more, simultaneous medications. Even in a research setting using algorithms designed to limit the number of medications, only 28% of patients were able to remain on monotherapy for >6 months.[36]

Reasons for combining medications include the following:

- Partial response. A group of symptoms, such as expansive mood, grandiosity, and pleasure-seeking behaviors, may have improved with a particular medication (with adequate dose and time), but symptoms continue sufficiently to cause distress and/or impairment of functioning. A second (or sometimes third) medication is then added as an "augmentation agent" to improve response. Another type of partial response is when some symptoms improve and others do not (eg, symptoms of mania improve but the patient still suffers from intermittent or persistent depression).
- Target specific symptom. There may be a particular troublesome and/or easily treated symptom, such as

TABLE 12 Adverse Effects and Possible Monitoring of Mood Stabilizers

Medication	Summary of adverse effects	Suggested monitoring
Lithium	Reduced renal function, hypothyroidism, nausea, diarrhea, abdominal distress, sedation, tremor, polyuria, wt gain, acne, cardiac conduction problems, hypoparathyroidism	Baseline: serum electrolytes, creatinine, BUN, calcium, CBC count, TFTs, EKG, pregnancy test (sexually active female patients)
	Wt gain may be additive when combined with an atypical antipsychotic[28]	Ongoing: lithium level, renal function, thyroid function, calcium
	Toxic levels may produce confusion, ataxia, dysarthria, seizures, coma, death	
Divalproex	Polycystic ovaries, nausea, increased appetite, wt gain, sedation, thrombocytopenia, hair loss, tremor, vomiting, rare pancreatitis or liver failure	Baseline: height and wt, pregnancy test (sexually active female patients), liver function tests, CBC
	Wt gain may be additive when combined with an atypical antipsychotic[28]	Every 6 mo: divalproex level, liver function tests, CBC
Carbamazepine	Multiple medication interactions (decrease or increase the other medication levels including oral contraceptive failure), sedation, ataxia, dizziness, blurred vision, nausea, vomiting, aplastic anemia, hyponatremia, Stevens-Johnson	Baseline: CBC Every 6 mo: carbamazepine level, CBC
Lamotrigine	Severe cutaneous reactions (risk 3 times greater <16), dizziness, tremor, sedation, asthenia, headache, interactions with oral contraceptives; case reports of leucopenia, agranulocytosis, hepatic failure, multiorgan failure	Baseline: CBC and liver function tests
Oxcarbazepine	Hyponatremia, oral contraceptive failure, cutaneous reactions, cognitive symptoms, sedation, coordination difficulties, nausea, vomiting, asthenia, headache, dizziness[26]	Baseline and periodic: serum sodium
Gabapentin	Mostly benign; most common are sedation, dizziness, tremor, headache, ataxia, fatigue, wt gain	None
Topiramate	Oral contraceptive failure, sedation, fatigue, impaired concentration, psychomotor slowing, word-finding difficulties, nephrolithiasis	Baseline and periodic: serum bicarbonate

BUN, blood urea nitrogen; CBC, complete blood cell (count); EKG, electrocardiogram; TFT, thyroid function test.

insomnia, that is treated with a medication just for that symptom.

- Cross-taper. When a medication is thought to be working poorly or not at all, a decision may be to replace it with another medication. The cleanest way to do so is to taper down the dose of the first medication, wait for a period of time for medication "wash out," and then start the second medication at a low dose with subsequent appropriate increases. This approach may be problematic at times if, in retrospect, the first medication is discovered to have been more effective than previously thought, but regardless, the patient goes longer without an effective medication. The likelihood of a relapse is higher, and depending on the patient's history, relapse may be debilitating or life-threatening or may interfere with a planned transition, such as starting school or leaving the hospital. The way to decrease the likelihood of relapse and treat current symptoms more quickly is to "cross-taper," for example, starting the second medication with the full dose of the first medication, and then, if the second medication is tolerated and appears to be adding incremental benefit, the second medication gradually is increased while the first medication is decreased.
- Treat comorbid disorders. Additional medications may be used to treat symptoms of comorbid disorders, such as inattentiveness with ADHD or worrying with an anxiety disorder.

PRESCRIBING GUIDELINES

The process of medicating is stepwise, with few patients having a full, lasting response to all symptoms with the first dose of the first medication. Each step is the opportunity for the physician to make a change (add or stop a medication or change a dose) or continue the current regimen as is (eg, the patient is stable or improving or needs a longer amount of time for a medication to work or for an adverse effect to resolve). Each patient becomes an individual study, with the result sometimes being good efficacy with odd-appearing or counterintuitive medication combinations. A number of issues may guide the decision at each step:

- **One Change at a Time.** With multiple medications, knowing which medication is causing positive effects or adverse effects may be difficult. Making 1 change at a time and then observing the effect can help deal with this problem, although this guideline may be discontinued at times for the sake of urgency or when there is little expected overlap in effects and

TABLE 13 Adverse Effects and Possible Monitoring of Atypical Antipsychotics

Adverse effect	Time course	Suggested monitoring	Medications most likely to cause
Anticholinergic	Early		Clozapine, olanzapine
Acute parkinsonism	Early	During titration, at 3 mo and annually	Paliperidone, risperidone
Akathisia	Early/intermediate	During titration, at 3 mo and annually	Aripiprazole
Cardiovascular events	Not known	EKG at baseline if taking ziprasidone or clozapine and during titration if taking ziprasidone	
Diabetes	Late	Fasting blood glucose at 3 mo and then every 6 mo	Clozapine, olanzapine (but problem for all)
Increased lipids	Early?	Lipids at 3 mo and then every 6 mo	Clozapine, olanzapine (but problem for all)
Neutropenia	Most likely within first 6 mo	Clozapine registry recommended CBC monitoring	Clozapine
Orthostasis	Early	Orthostatic blood pressure and pulse if symptomatic; blood pressure and pulse at 3 mo and annually	Clozapine, olanzapine, quetiapine
Increased prolactin and sexual dysfunction	Early	Sexual history during titration and then every 3 mo; prolactin level only if symptomatic	Paliperidone, risperidone, olanzapine
Decreased prolactin	Early	Prolactin level only if symptomatic	Aripiprazole
Increased QTc interval	Not known	EKG at baseline if taking ziprasidone or clozapine and during titration if taking ziprasidone	Ziprasidone
Sedation	Early	Each visit	Clozapine, olanzapine, quetiapine (but problem for all)
Seizures	During titration		Clozapine
Tardive dyskinesia	Late	At 3 mo and annually (abnormal involuntary movement scale)	Lower risk compared with first generation antipsychotics
Withdrawal dyskinesia	Early during fast switch	During titration	Aripiprazole, paliperidone
Wt gain	First 3–6 mo	Height, wt, BMI percentile, BMI *z* score each visit	All, but clozapine and olanzapine highest and aripiprazole and ziprasidone least
Other laboratories		Electrolytes, CBC, renal function test annually, and liver function tests at 3 mo and annually	

TABLE 14 Medications That May Increase Mood Cycling in Children and Adolescents

Antidepressants
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Serotonin-norepinephrine reuptake inhibitors
Aminophylline
Oral or intravenous corticosteroids
Sympathomimetic amines (eg, pseudoephedrine)
Antibiotics (eg, clarithromycin, erythromycin, and amoxicillin)

adverse effects of medications in a particular combination.

- **Important Cluster of Symptoms.** When a group of symptoms is causing severe impairment and distress, such as full-fledged mania or acute psychosis, it must be addressed first.
- **Treat the Most Troublesome Symptoms First.** A more common situation is that there is no group of symptoms that is overwhelming. In that case, first treat the group of symptoms that is causing the most distress or impairment. For example, moderate depression is treated before mild to moderate inattentiveness.
- **Opportunity to Reduce the Number of Medications That Eventually Will Be Needed.** A medication may be used that may not be the best for any particular group of symptoms but has the potential to treat ≥2 groups of symptoms.
- **Manage an Adverse Effect.** Depending on the urgency of the need for clinical effect and the troublesomeness of the adverse effect, an adverse effect may temporarily halt the search for an effective regimen until it can be resolved or reduced to an acceptable level.
- **Treat a "Lynchpin" Symptom.** At times, a symptom seems to be the basis for other symptoms, for example, an anxious and inattentive adolescent who goes into a rage

attempting to complete homework. As an alternative to using a medication that works to reduce rage, using a medication to reduce anxiety or to increase attentiveness may be at least as effective (of course, the prescriber may choose to do both to potentially increase the effect).

- **Preference for a Medication That Works Quickly.** At times, a medication is chosen over another one for a particular effect because it works quickly. The thinking is that if it then does not work, less time is lost in pursuing the other medication, thus increasing the chance of finding an effective medication in a given period of time.

An example that illustrates the use of several of these guidelines is a patient with insomnia in the context of depression. Choices for the first medication(s) include (1) a mood agent to treat the depression (the more impairing symptom) while waiting for the insomnia to resolve as the depression improves, (2) a hypnotic to treat the insomnia because the response is likely to be quick and the patient's mood may improve once he or she no longer is sleep deprived, (3) combination of a hypnotic with an optimal mood agent for this patient, or (4) a sedating mood agent that may treat both the depression and the insomnia. For a particular patient, these may all be reasonable options, or there may be other factors, such as treatment history, that favor one option over others.

CONCURRENT MEDICAL CONDITIONS

Scheffer and Linden[37] divided medical conditions concurrent with pediatric bipolar disorder into 4 types: (1) conditions related to bipolar disorder or its treatment, (2) conditions that mimic mania, (3) conditions that occur more commonly in patients with bipolar disorder that appear unrelated to its treatment, and (4) conditions related to risk behaviors associated with bipolar disorder. The authors noted that little has been published specifically with regard to pediatric bipolar disorder and concurrent medical conditions, but a number of reports that focused on adults included pediatric subjects.

Tables 12 and 13 summarize medical adverse effects from medications commonly used to treat bipolar disorder. Pediatricians should familiarize themselves with these and monitor for them. Lithium treatment can result in hypothyroidism and, regardless of the cause, hypothyroidism can make bipolar disorder more difficult to treat.[37] Elevated prolactin levels, typically from certain atypical antipsychotics, are associated with low bone mass for chronologic age, sexual dysfunction, menstrual irregularities, gynecomastia, galactorrhea, and retrograde ejaculation. Cardiovascular disease[38] and type 2 diabetes mellitus[39] may be associated with the illness itself. Conditions that may mimic mania are listed in Table 15.[5,37] Unrelated conditions more common in patients with bipolar disorder[37] include migraine headaches, epilepsy, and at least in 1 large family, autosomal dominant medullary cystic kidney disease. Conditions associated with bipolar risk behaviors[37] include complications of substance use and abuse, sexually transmitted diseases, and traumatic brain injury.

CASE VIGNETTES

The following fictitious cases are conglomerates based on the authors' clinical experience and are designed to illustrate common diagnostic and treatment issues.

Case 1

Mary is a 16-year-old girl who presents for admission to psychiatry inpatient after sudden onset 1 week previously of euphoric and giddy mood, talking rapidly and jumping from topic to topic, and little sleep with almost none over the past 3 days. She has spent most of her time since then at her health club trying to "pick up" male patrons, a behavior very out of character for her. Before age 14, she was high achieving and well adjusted, earning mostly A's in school, socially active, and described by her parents as a "model daughter." At age 14, she broke up with a boyfriend and became severely depressed, responding after 2 months to a combination of sertraline and psychotherapy. She discontinued both treatments 4 months later because she had been doing well. She continued to do well until 1 year ago, when she developed an episode similar to the current one, but her behavior was controlled, and she was managed outside the hospital, responding after 2 weeks to a combination of lithium and psychotherapy. She had difficulty with moodiness and functioning in school for the next 6 months and again stopped the treatments. She then continued about the same until this current episode.

Mary is diagnosed with bipolar I disorder, current episode manic, severe, and without psychotic features. She has the narrow phenotype. She is restarted on lithium and also is started on quetiapine for sleeping, calming, and additional mood stabilization. Lithium is chosen because of her past response to this medication. Her psychiatrist decides to combine this with quetiapine immediately, despite treatment algorithms suggesting starting with monotherapy,[5,18] for 2 reasons: (1) previous treatment with lithium yielded a good acute response but only a partial response long-term, even before she stopped the medication and (2)

TABLE 15 Medical Conditions That May Mimic Mania

Hyperthyroidism
Closed or open head injury
Temporal lobe epilepsy
Multiple sclerosis
Systemic lupus erythematosus
Fetal alcohol spectrum disorder/alcohol-related neurodevelopmental disorder
Wilson disease
HIV
Lyme disease
Dementia
Fibromyalgia
Niemann-Pick disease
Familial leukoencephalopathy

lithium can easily take 1 week or more to be effective, and Mary needs something with more immediate effect for calming and sleeping.

Mary is in a relatively consistent (abnormal) mood state. The primary treatment goals are, therefore, to help her out of this state, return her to a euthymic mood, and prevent the next mood episode. If her current mood state were depression instead of mania, mood-stabilizing medication would still be the first choice, but often, antidepressant medication is cautiously added should the depression prove resistant to the mood stabilizing medication alone. The caution is related to the possibility that the antidepressant could make it easier for her to go into a manic episode, even when combined with the mood-stabilizing medication. In addition, during the time she is in a manic state, an antidepressant is generally not recommended.

Case 2

Charles is a 15-year-old boy who presents to the psychiatrist's office for his first mental health visit with the complaint of increasing, severe depression over the past month. He feels that the depression started 3 years ago when his parents divorced and he moved with his mother and siblings to a new city and new school. Additional questions reveal that depression probably existed on and off for quite some time before the divorce. Furthermore, the depression is not continuous. Even over the past week, he reports having 1 or 2 days at a time of feeling great and "energized," spending most of the night playing an online game with little fatigue the next day, talking more, having racing thoughts, and having a more difficult time focusing on school work. He has other times, up to 2 days at a time, of being easily angered, punching a wall at times, ruminating about slights from peers and parents, and generally feeling "edgy."

Charles is diagnosed with bipolar disorder not otherwise specified and the intermediate phenotype. He does not meet duration criteria for mania (7 days) or hypomania (4 days). Key features are the spontaneous and frequent changes of mood symptoms, unrelated or only very loosely related to environmental circumstances, and the lack of distinct, continuous manic or hypomanic states for even 4 days.

Medication management for Charles is similar to that for Mary in case 1; the primary initial objective is mood stabilization with ≥1 mood stabilizers and/or atypical antipsychotics. A difference is that Charles's mood symptoms are not stable. He only has to wait a few days or less to switch to a different group of symptoms. Despite depression being the primary concern, antidepressants may make his condition worse by increasing the frequency or intensity of mood changes or undermining the effects of the mood-stabilizing medication. Even for treating the depression symptoms, the preference is typically to find more effective mood stabilizing medication rather than add an antidepressant. Exceptions are common, however, with the treatment of bipolar illness.

Cases 1 and 2 illustrate the findings of a recent study showing that in 90% of cases the first mood episode in pediatric bipolar disorder is depression.[40]

Case 3

Dan is a 17-year-old boy who presents for psychiatric inpatient admission after damaging his father's car with a crow bar and threatening to kill his parents and then himself after parents took away his cell phone. The patient reports having had difficulty with temper outbursts for years. This is the worst such episode, but the patient commonly yells or leaves the house when upset and tends to overreact to his parents' attempts to set limits. Both patient and parents report that he does "fine" most of the time and just overreacts to frustration. He was diagnosed with ADHD in the third grade and has been on and off treatment for that (currently off). He has had mild to moderate depression at times but not recently. On interview, the patient reports that the incident with the car was "not a big deal" and says that he currently feels "fine," although he appears quite edgy and becomes frustrated with the interviewer for "asking too many questions."

The patient is diagnosed with mood disorder not otherwise specified and meets criteria for bipolar spectrum broad phenotype or severe mood dysregulation. He shows no evidence for mood cycling, except for the history of depression, but his mood changes quickly with minor provocation, and he is highly sensitive to frustrating circumstances.

Common practice is to treat the rage symptoms and edginess with mood stabilizers and/or atypical antipsychotics. Treatment of rage and edginess in this population has been poorly studied, but risperidone and aripiprazole are approved by the FDA for the treatment of irritability associated with autism (Table 8). With some patients, these symptoms may respond to ≥1

medications for depression, anxiety, or ADHD.

Case 4

Claire is a 13-year-old girl who presents to the psychiatrist's office because of daily episodes of rage, which have been present for years but increasing over the past year. She has the rage only at home and does well academically and socially. She denies any history of significant depression, although she does report a strong tendency to worry and has had this for most of her life. With further questioning, she reports multiple different ritualistic behaviors, such as needing to touch the doorframe in a certain way before going through it and needing to do household tasks in groups of 3. She becomes enraged when parents inadvertently interfere with her ability to complete a behavior.

Claire is diagnosed with OCD as well as generalized anxiety disorder. She does not have a mood disorder despite the rage outbursts. The rage would probably diminish with a mood stabilizer or atypical antipsychotic, but a better treatment is medication and psychotherapy for OCD and anxiety.

Case 5

George is a 14-year-old boy who presents to the pediatrician having recently moved from another state. According to his mother, he has been doing fairly well for the past 6 months and has been diagnosed with bipolar disorder and ADHD. He is currently taking lithium, methylphenidate, quetiapine, aripiprazole, sertraline, and clonazepam. He last saw his previous psychiatrist 2 months ago, and the mother requests a refill for his medications, because he does not have a psychiatrist currently. George's mother said that he has been in general good health but gained 40 pounds over the past year. George's mother attributes this to the medication. In addition to her routine for a new patient visit, the pediatrician does the following:

- Asks more questions to confirm clinical stability, such as potential adverse effects of the medications and clinical course, including depression, suicidality, and behavioral problems.
- Asks about medication dosing adherence.
- Contacts the previous psychiatrist to confirm medications and doses, obtain history, and obtain the psychiatrist's opinion on recent stability.
- Orders laboratory studies, including lithium concentration 12 hours after last dose, electrolytes, thyroid studies, calcium, lipids, and glucose (a fasting glucose may be ordered later if the random one is abnormal).
- Performs physical examination, including vital signs, height, and weight, and calculates BMI percentile.
- Refers George to a local child and adolescent psychiatrist for ongoing mental health care and arranges to partner with the out-of-state psychiatrist for care in the meantime.
- Renews the current medications unless there is a compelling reason otherwise. Given 6 months of stability, a slow medication taper may be safe, but this should be conducted under psychiatric supervision. Not renewing the medications is dangerous, because it may precipitate a major relapse as well as withdrawal symptoms.
- Refers George to a dietitian, recommends an exercise program, and plans to work with the psychiatrist on adjusting medications to reduce weight.

If it were determined that George may not be stable in some respect, resources include phone consultations with the out-of-state psychiatrist (and the out-of-state therapist, if there was one), urgent referral to a local child and adolescent psychiatrist, urgent referral to a local psychologist or other therapist for psychotherapy, and evaluation at a local hospital emergency department.

SUMMARY

Pediatricians have a collaborative role in diagnosis and management of adolescents with bipolar disorder, a common and often debilitating illness. Interviewing for current or past mania or hypomania, the defining feature of bipolar disorder, may be challenging but may be simplified by asking about red flag symptoms that, when present in the history, signal reasonable suspicion of bipolar disorder. In suspected or previously diagnosed cases of bipolar disorder, patients with current or recent symptoms or impairments should be referred for treatment. Pediatricians can actively monitor for and manage medication adverse effects, particularly weight gain, hyperlipidemia, and diabetes mellitus.

ADVICE FOR PEDIATRICIANS

1. Have some familiarity with diagnostic criteria and different types of bipolar disorder.
2. Maintain communication with child and adolescent psychiatrists and other mental health professionals.
3. Maintain familiarity with adverse effects and suggested monitoring protocols for mood-stabilizing and atypical antipsychotic medications.
4. Assist in monitoring for and managing medication adverse effects, particularly weight gain, hyperlipidemia, and diabetes mellitus.
5. Carefully and thoroughly document all recommendations, including referrals, medications prescribed, and instructions for observing and reporting adverse reactions.

LEAD AUTHOR

Benjamin Shain, MD, PhD

COMMITTEE ON ADOLESCENCE, 2011–2012

Paula K. Braverman, MD, Chairperson
William P. Adelman, MD
Cora C. Breuner, MD, MPH
David A. Levine, MD
Arik V. Marcell, MD
Pamela J. Murray, MD, MPH
Rebecca F. O'Brien, MD

LIAISONS

Loretta E. Gavin, PhD, MPH – *Centers for Disease Control and Prevention*
Rachel J. Miller, MD – *American College of Obstetricians and Gynecologists*
Hatim A. Omar, MD – *AAP Section on Adolescent Health*
Jorge L. Pinzon, MD – *Canadian Pediatric Society*
Benjamin Shain, MD, PhD – *American Academy of Child and Adolescent Psychiatry*

STAFF

Karen Smith
Mark Del Monte, JD

REFERENCES

1. American Academy of Child and Adolescent Psychiatry. Practice parameters for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2007;46(1):107–122
2. Carlson GA. Early onset bipolar disorder: clinical and research considerations. *J Clin Child Adolesc Psychol.* 2005;34(2):333–343
3. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. *Biol Psychiatry.* 2007;62(2):107–114
4. Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. *Psychiatr Clin North Am.* 1999;22(3):517–534, vii
5. Kowatch RA, Fristad MA, Findling RL, eds. *Clinical Manual for Management of Bipolar Disorder in Children and Adolescents.* Washington, DC: American Psychiatric Publishing Inc; 2009
6. Drotar D, Greenley RN, Demeter CA, et al. Adherence to pharmacological treatment for juvenile bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2007;46(7):831–839
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).* Washington, DC: American Psychiatric Association; 2000
8. Kramlinger KG, Post RM. Ultra-rapid and ultradian cycling in bipolar affective illness. *Br J Psychiatry.* 1996;168(3):314–323
9. Geller B, Williams M, Zimerman B, Frazier J, Beringer L, Warner KL. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. *J Affect Disord.* 1998;51(2):81–91
10. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry.* 2005;44(9):846–871
11. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry.* 2006;63(10):1139–1148
12. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry.* 2006;63(2):175–183
13. Axelson DA, Birmaher B, Strober MA, et al. Course of subthreshold bipolar disorder in youth: diagnostic progression from bipolar disorder not otherwise specified. *J Am Acad Child Adolesc Psychiatry.* 2011;50(10):1001.e3–1016.e3
14. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry.* 2003;160(3):430–437
15. Brotman MA, Schmajuk M, Rich BA, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biol Psychiatry.* 2006;60(9):991–997
16. Brotman MA, Kassem L, Reising MM, et al. Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation. *Am J Psychiatry.* 2007;164(8):1238–1241
17. American Psychiatric Association. D 00 disruptive mood dysregulation disorder. DSM-5 Development. Available at: www.dsm5.org/ProposedRevision/Pages/proposedrevision.aspx?rid=397#. Accessed February 14, 2012
18. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M; Child Psychiatric Workgroup on Bipolar Disorder. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2005;44(3):213–235
19. Sederer LI, Summergrad P. Criteria for hospital admission. *Hosp Community Psychiatry.* 1993;44(2):116–118
20. Kiser LJ, Heston JD, Millsap PA, Pruitt DB. Treatment protocols in child and adolescent day treatment. *Hosp Community Psychiatry.* 1991;42(6):597–600
21. Teich JL, Ireys HT. A national survey of state licensing, regulating, and monitoring of residential facilities for children with mental illness. *Psychiatr Serv.* 2007;58(7):991–998
22. Connolly SD, Bernstein GA; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. *J Am Acad Child Adolesc Psychiatry.* 2007;46(2):267–283
23. Birmaher B, Brent D, Bernet W, et al; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry.* 2007;46(11):1503–1526
24. Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2007;46(7):894–921
25. American Academy of Child and Adolescent Psychiatry. Practice parameter on the use of psychotropic medication in children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 2009;48(9):961–973
26. US Food and Drug Administration. Drugs@FDA [database]. Available at: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed February 14, 2012
27. Kowatch RA, Sethuraman G, Hume JH, Kromelis M, Weinberg WA. Combination pharmacotherapy in children and adolescents with bipolar disorder. *Biol Psychiatry.* 2003;53(11):978–984
28. Correll CU. Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: a systematic review and pooled analysis of short-term trials. *J Am Acad Child Adolesc Psychiatry.* 2007;46(6):687–700
29. Correll CU. Antipsychotic use in children and adolescents: minimizing adverse

effects to maximize outcomes. *J Am Acad Child Adolesc Psychiatry*. 2008;47(1):9–20

30. Olfson M, Blanco C, Liu L, Moreno C, Laje G. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry*. 2006;63(6):679–685
31. Patel NC, Hariparsad M, Matias-Akthar M, et al. Body mass indexes and lipid profiles in hospitalized children and adolescents exposed to atypical antipsychotics. *J Child Adolesc Psychopharmacol*. 2007;17(3):303–311
32. Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. *Am J Psychiatry*. 2006;163(12):2072–2079
33. Shin L, Bregman H, Breeze JL, Noyes N, Frazier JA. Metformin for weight control in pediatric patients on atypical antipsychotic medication. *J Child Adolesc Psychopharmacol*. 2009;19(3):275–279
34. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry*. 2004;65(2):267–272
35. Goldberg JF. Antidepressants in bipolar disorder: 7 myths and realities. *Curr Psychiatry*. 2010;9(5):41–48
36. Pavuluri MN, Henry DB, Devineni B, Carbray JA, Naylor MW, Janicak PG. A pharmacotherapy algorithm for stabilization and maintenance of pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2004;43(7):859–867
37. Scheffer RE, Linden S. Concurrent medical conditions with pediatric bipolar disorder. *Curr Opin Psychiatry*. 2007;20(4):398–401
38. Weeke A. Juel Knud, Vaerth M. Cardiovascular death and manic-depressive psychosis. *J Affect Disord*. 1987;13(3):287–292
39. Taylor V, MacQueen G. Associations between bipolar disorder and metabolic syndrome: A review. *J Clin Psychiatry*. 2006;67(7):1034–1041
40. Duffy A, Alda M, Hajek T, Grof P. Early course of bipolar disorder in high-risk offspring: prospective study. *Br J Psychiatry*. 2009;195(5):457–458
41. Wagner KD, Weller EB, Carlson GA, et al. An open-label trial of divalproex in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2002;41(10):1224–1230
42. Henry CA, Zamvil LS, Lam C, Rosenquist KJ, Ghaemi SN. Long-term outcome with divalproex in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol*. 2003;13(4):523–529
43. Wagner KD, Redden L, Kowatch RA, et al. A double-blind, randomized, placebo-controlled trial of divalproex extended-release in the treatment of bipolar disorder in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2009;48(5):519–532
44. Chang K, Saxena K, Howe M. An open-label study of lamotrigine adjunct or monotherapy for the treatment of adolescents with bipolar depression. *J Am Acad Child Adolesc Psychiatry*. 2006;45(3):298–304
45. Pavuluri MN, Henry DB, Moss M, Mohammed T, Carbray JA, Sweeney JA. Effectiveness of lamotrigine in maintaining symptom control in pediatric bipolar disorder. *J Child Adolesc Psychopharmacol*. 2009;19(1):75–82
46. Strober M, Morrell W, Lampert C, Burroughs J. Relapse following discontinuation of lithium maintenance therapy in adolescents with bipolar I illness: a naturalistic study. *Am J Psychiatry*. 1990;147(4):457–461
47. Geller B, Cooper TB, Sun K, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry*. 1998;37(2):171–178
48. Kafantaris V, Coletti DJ, Dicker R, Padula G, Kane JM. Lithium treatment of acute mania in adolescents: a large open trial. *J Am Acad Child Adolesc Psychiatry*. 2003;42(9):1038–1045
49. Kafantaris V, Coletti DJ, Dicker R, Padula G, Pleak RR, Alvir JM. Lithium treatment of acute mania in adolescents: a placebo-controlled discontinuation study. *J Am Acad Child Adolesc Psychiatry*. 2004;43(8):984–993
50. Patel NC, DelBello MP, Bryan HS, et al. Open-label lithium for the treatment of adolescents with bipolar depression. *J Am Acad Child Adolesc Psychiatry*. 2006;45(3):289–297
51. Wagner KD, Kowatch RA, Emslie GJ, et al. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. *Am J Psychiatry*. 2006;163(7):1179–1186
52. DelBello MP, Kowatch RA, Warner J, et al. Adjunctive topiramate treatment for pediatric bipolar disorder: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2002;12(4):323–330
53. Barzman DH, DelBello MP, Kowatch RA, et al. Adjunctive topiramate in hospitalized children and adolescents with bipolar disorders. *J Child Adolesc Psychopharmacol*. 2005;15(6):931–937
54. Delbello MP, Findling RL, Kushner S, et al. A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2005;44(6):539–547
55. Barzman DH, DelBello MP, Kowatch RA, et al. The effectiveness and tolerability of aripiprazole for pediatric bipolar disorders: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2004;14(4):593–600
56. Biederman J, McDonnell MA, Wozniak J, et al. Aripiprazole in the treatment of pediatric bipolar disorder: a systematic chart review. *CNS Spectr*. 2005;10(2):141–148
57. Biederman J, Mick E, Spencer T, et al. An open-label trial of aripiprazole monotherapy in children and adolescents with bipolar disorder. *CNS Spectr*. 2007;12(9):683–689
58. Tramontina S, Zeni CP, Pheula GF, de Souza CK, Rohde LA. Aripiprazole in juvenile bipolar disorder comorbid with attention-deficit/hyperactivity disorder: an open clinical trial. *CNS Spectr*. 2007;12(10):758–762
59. Findling RL, Nyilas M, Forbes RA, et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2009;70(10):1441–1451
60. Tramontina S, Zeni CP, Ketzer CR, Pheula GF, Narvaez J, Rohde LA. Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: a pilot randomized clinical trial. *J Clin Psychiatry*. 2009;70(5):756–764
61. Masi G, Mucci M, Millepiedi S. Clozapine in adolescent inpatients with acute mania. *J Child Adolesc Psychopharmacol*. 2002;12(2):93–99
62. Frazier JA, Biederman J, Tohen M, et al. A prospective open-label treatment trial of olanzapine monotherapy in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol*. 2001;11(3):239–250
63. Tohen M, Kryzhanovskaya L, Carlson G, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry*. 2007;164(10):1547–1556
64. Joshi G, Mick E, Wozniak J, et al. Impact of obsessive-compulsive disorder on the antimanic response to olanzapine therapy in youth with bipolar disorder. *Bipolar Disord*. 2010;12(2):196–204
65. DelBello MP, Adler CM, Whitsel RM, Stanford KE, Strakowski SM. A 12-week single-blind trial of quetiapine for the treatment of mood symptoms in adolescents at high risk for developing bipolar I disorder. *J Clin Psychiatry*. 2007;68(5):789–795

66. DelBello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disord*. 2009; 11(5):483–493
67. Scheffer RE, Tripathi A, Kirkpatrick FG, Schultz T. Rapid quetiapine loading in youths with bipolar disorder. *J Child Adolesc Psychopharmacol*. 2010;20(5):441–445
68. Frazier JA, Meyer MC, Biederman J, et al. Risperidone treatment for juvenile bipolar disorder: a retrospective chart review. *J Am Acad Child Adolesc Psychiatry*. 1999;38 (8):960–965
69. Biederman J, Mick E, Wozniak J, Aleardi M, Spencer T, Faraone SV. An open-label trial of risperidone in children and adolescents with bipolar disorder. *J Child Adolesc Psychopharmacol*. 2005;15(2):311–317
70. Haas M, Delbello MP, Pandina G, et al. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. *Bipolar Disord*. 2009;11(7):687–700
71. Carlson GA, Potegal M, Margulies D, Basile J, Gutkovich Z. Liquid risperidone in the treatment of rages in psychiatrically hospitalized children with possible bipolar disorder. *Bipolar Disord*. 2010;12(2):205–212
72. Krieger FV, Pheula GF, Coelho R, et al. An open-label trial of risperidone in children and adolescents with severe mood dysregulation. *J Child Adolesc Psychopharmacol*. 2011;21(3):237–243
73. Biederman J, Mick E, Spencer T, Dougherty M, Aleardi M, Wozniak J. A prospective open-label treatment trial of ziprasidone monotherapy in children and adolescents with bipolar disorder. *Bipolar Disord*. 2007; 9(8):888–894
74. Kowatch RA, Suppes T, Carmody TJ, et al. Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2000;39(6):713–720
75. Delbello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *J Am Acad Child Adolesc Psychiatry*. 2002; 41(10):1216–1223
76. Pavuluri MN, Henry DB, Carbray JA, Sampson G, Naylor MW, Janicak PG. Open-label prospective trial of risperidone in combination with lithium or divalproex sodium in pediatric mania. *J Affect Disord*. 2004;82(suppl 1): S103–S111
77. Findling RL, McNamara NK, Youngstrom EA, et al. Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2005;44(5):409–417
78. DelBello MP, Kowatch RA, Adler CM, et al. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. *J Am Acad Child Adolesc Psychiatry*. 2006;45(3):305–313
79. MacMillan CM, Withney JE, Korndörfer SR, Tilley CA, Mrakotsky C, Gonzalez-Heydrich JM. Comparative clinical responses to risperidone and divalproex in patients with pediatric bipolar disorder. *J Psychiatr Pract*. 2008;14(3):160–169
80. Pavuluri MN, Henry DB, Findling RL, et al. Double-blind randomized trial of risperidone versus divalproex in pediatric bipolar disorder. *Bipolar Disord*. 2010;12(6): 593–605

Collaborative Role of the Pediatrician in the Diagnosis and Management of Bipolar Disorder in Adolescents

Benjamin N. Shain and COMMITTEE ON ADOLESCENCE

Pediatrics 2012;130;e1725
DOI: 10.1542/peds.2012-2756 originally published online November 26, 2012;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Collaborative Role of the Pediatrician in the Diagnosis and Management of Bipolar Disorder in Adolescents

Benjamin N. Shain and COMMITTEE ON ADOLESCENCE

Pediatrics 2012;130;e1725
DOI: 10.1542/peds.2012-2756 originally published online November 26, 2012;