

Child and Adolescent Bipolar Disorder: Focus on Differential Diagnosis and Management

A Monograph for Continuing Medical Education Credit

Guest Editors

Karen Dineen Wagner, MD, PhD
Robert A. Kowatch, MD



Sponsored by:
ACCESS Medical Group
Department of Continuing Medical Education
Arlington Heights, Illinois

© Copyright 2001 by ACCESS Medical Group
Department of Continuing Medical Education
3395 North Arlington Heights Road, Suite A
Arlington Heights, Illinois 60004-1566

All rights reserved. This monograph is protected by copyright. No part of it may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or utilizing any information storage and retrieval system, without written permission from the copyright owner, ACCESS Medical Group.

The opinions expressed in this monograph, *Child and Adolescent Bipolar Disorder: Focus on Differential Diagnosis and Management*, should not be construed as those of the publisher or grantor. The views in this monograph are based on clinical practice and literature. However, the information may be subject to change as new information and additional research data become available. A portion of the monograph may include the use of drugs for unlabeled indications. Use of drugs outside of labeling should be considered experimental, and physicians are advised to consult current prescribing information for the approved indications of those drugs. Regulations do allow physicians to use drugs outside of labeling at their discretion when supportive literature is available.

Child and Adolescent Bipolar Disorder: Focus on Differential Diagnosis and Management

A Monograph for Continuing Medical Education Credit

Guest Editors

Karen Dineen Wagner, MD, PhD

Clarence Ross Miller Professor and Vice Chair
Department of Psychiatry and Behavioral Sciences
Director, Division of Child and Adolescent Psychiatry
University of Texas Medical Branch
Galveston, Texas

Robert A. Kowatch, MD

Professor of Psychiatry and Pediatrics
University of Cincinnati Medical Center
Children's Hospital Medical Center
Cincinnati, Ohio

Sponsored by: ACCESS Medical Group, Department of Continuing Medical Education

This monograph is funded by an unrestricted educational grant from Abbott Laboratories.

Date of release: December 1, 2001. Version 1.0

Child and Adolescent Bipolar Disorder: Focus on Differential Diagnosis and Management

Accreditation

ACCESS Medical Group is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education (CME) for physicians. ACCESS Medical Group takes responsibility for the content, quality, and scientific integrity of this CME activity.

Designation of Credit

ACCESS Medical Group designates this continuing medical education activity as meeting the criteria for **2 credit hours** in category 1 of the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent on the educational activity.

CME Credit

It has been determined that this monograph and post-test can be read and completed in 2 hours. Two hours of credit has been designated for this material. The accompanying post-test allows you the opportunity to assess your knowledge of the information presented in the monograph and to earn continuing medical education credit. Additional information regarding credit can be found in the post-test section at the end of this monograph.

This monograph for CME credit has a release date of December 1, 2001, and is valid for three years. Credit requests must be received by November 30, 2004. This CME activity was produced in accordance with the ACCME Essentials and Guidelines.

Target Audience

This monograph is intended for physicians interested in learning about management of pediatric patients with mood disorders.

Purpose and Objectives

The purpose of this monograph is to educate physicians about bipolar disorder and its diagnosis, comorbidities, treatment strategies, and outcomes in child and adolescent patients.

After reading this monograph, you should be able to:

- Use *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria to make an appropriate diagnosis of bipolar disorder in children and adolescents
- Identify pediatric patients at high risk for the development of bipolar disorder
- Recognize the features of bipolar disorder that are common in pediatric populations, including mixed mania, rapid cycling, and chronicity of episodes
- Distinguish between bipolar disorder, attention deficit/hyperactivity disorder (ADHD), and other conditions in child and adolescent patients
- Identify different pharmacologic and nonpharmacologic options used in clinical practice for the treatment of child and adolescent patients with bipolar disorder
- Understand patient outcomes associated with discontinuation of therapy in child and adolescent bipolar patients

Child and Adolescent Bipolar Disorder: Focus on Differential Diagnosis and Management

Disclosure Statement

Current Guidelines state that participants in CME activities should be made aware of any affiliation or financial interest that may affect the editors' contributions. The editors have completed a statement of disclosure, which includes funding sources other than the honorarium received for this program. The editors have provided the following information on sources of funding that may be perceived as a potential conflict of interest.

Karen Dineen Wagner, MD, PhD reports that she has provided consultation services to GlaxoSmithKline, Pfizer Inc., Abbott Laboratories, Eli Lilly and Company, Janssen Pharmaceutica, Bristol-Myers Squibb, Forest Laboratories, Wyeth-Ayerst Laboratories, Organon Inc., and Novartis AG.

Robert A. Kowatch, MD reports that he has provided consultation services to Abbott Laboratories.

Inquiries Should be Directed to

ACCESS Medical Group
Department of Continuing Medical Education
3395 N. Arlington Heights Road, Suite A
Arlington Heights, IL 60004-1566
Phone: 847-392-2227

Child and Adolescent Bipolar Disorder: Focus on Differential Diagnosis and Management

Introduction

Bipolar disorder is a common mood disorder that has a highly variable age of onset. It is most commonly diagnosed in persons between the age of 18 and 24, but as many as 59% of adult patients with bipolar disorder experienced their first episode before the age of 18.¹ The expression of bipolar symptoms is developmentally variable among children and adolescents. Youth may experience a variety of overlapping, comorbid conditions, such as attention deficit/hyperactivity disorder (ADHD) or substance abuse. Confusion with other conditions and a limited understanding of the incidence of bipolar disorder among patients with early onset (adolescent onset) and very early onset (child onset) contribute to the under-diagnosis and undertreatment of this disease by physicians.² The purpose of the present monograph is to provide current information related to bipolar disorder in children and adolescents to help improve the identification and treatment of young people.

Diagnosis and Epidemiology

Diagnostic Criteria

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* uses the same criteria for the diagnosis of bipolar disorder for all patients regardless of age.³ However, physicians should consider developmental issues when evaluating children and adolescents, because manifestations of bipolar symptoms are often highly dependent on age.⁴ During the course of bipolar disorder, patients experience cycles of mood that include manic and depressive episodes over time, with some periods of normal mood, or euthymia.

Manic Episode. A manic episode is a distinct period of abnormally and persistently elevated, expansive, and/or irritable mood that represents a severe change from previous emotional condition. According to the *DSM-IV*, a manic episode is diagnosed if the following criteria are met:³

- Any of the following moods are experienced for at least 1 week (or any duration of hospitalization is necessary): feeling irritable or silly/elated, high self-esteem, increased talking, decreased need for sleep, distractibility, or disregard of risk.
- During the period of mood disturbance, the patient must display at least 3 (or 4, if the mood is irritable) of the following symptoms: grandiosity, decreased sleep, pressured speech, racing thoughts, distractibility, increased goal-directed activity, and/or excessive involvement in reckless activities.

As many as 59% of adult patients with bipolar disorder experienced their first episode before the age of 18.¹

Major Depressive Episode. According to the *DSM-IV*, a major depressive episode is a change from previous functioning over a 2-week period that includes either a depressed mood or a loss of interest or pleasure. In addition, at least 4 of the following symptoms must be present: difficulty sleeping or sleeping too much; loss of appetite or eating too much; difficulty concentrating or making decisions; feelings of being slowed down or agitated; feeling worthless or having low self esteem; or having thoughts of suicide or death.³

To meet the criteria for either a manic or major depressive episode, the mood disturbance must impair normal, healthy functioning, and it must not be due to the physiologic effects of a substance or a general medical condition, or be part of a mixed episode (see below).³

Mixed Episode. A mixed episode is diagnosed when the child or adolescent patient meets criteria for both a manic episode and a major depressive episode over at least a 1-week period. The requirement for significant impairment and the exclusion of organic causes are the same as for a manic episode.³

Hypomanic Episode. A hypomanic episode is a mild form of mania that has symptoms similar to a manic episode, but of lesser severity and duration. In a hypomanic episode, none of the following characteristics are present: hospitalization, psychotic features, or marked deterioration in functioning. The symptoms, however, produce an observable change in the patient's functioning and persist 4 days or longer. Hypomania is sometimes predictive of future symptom escalation to mania or major depression.³

Clinical Subtypes

If a patient experiences at least 4 episodes of major depression, mania, mixed mania, or hypomania within a 12-month period, a subtype of rapid cycling should be established.³ Prevalence of rapid cycling in prepubertal bipolar patients has been reported to be as high as 75%.^{5,6} Methods for tracking and diagnosing rapid cycling among children and adolescent patients include the retrospective life charting method⁷ and the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) method.⁸ Results with both of these methods have shown high rates of rapid, continuous cycling (eg, complex cycling) among children and adolescents.

Clinical Characteristics

Because manifestations of bipolar disorder vary with age, it is important for physicians to understand the disease from a developmental perspective. Some youths who express rapid cycling and hypomania may not precisely fit adult bipolar criteria; however, early diagnosis and treatment of such patients is imperative because early intervention can lead to improved outcomes.^{9,10}

In addition to rapid cycling, several other features differentiate early-onset bipolar disorder from adult onset. Patients with very early onset (younger than 13 years of age) often exhibit atypical and subthreshold forms of bipolar disorder. In addition to rapid cycling, symptoms may include less discrete episodes of mania or depression, mixed states, chronicity, and emotionally labile behavior.¹¹ Children often experience explosive outbursts that are out of proportion to the stimulus.¹² Changes in mood may appear to be erratic and continuous, rather than episodic, in course.^{6,13,14} Irritability during episodes, rather than euphoria, often characterizes mania in young children.^{6,13,14}

Some youths who express rapid cycling and hypomania may not precisely fit adult bipolar criteria; however, early diagnosis and treatment of such patients is imperative because early intervention can lead to improved outcomes.^{9,10}

Geller et al recently described the characteristics of 93 child and adolescent outpatients diagnosed with bipolar disorder.¹⁵ Patients in this group were between 7 and 16 years of age, with a mean age of 10.9 years. Mean episode duration was 3.6 years (manic or depressive), and patients were 7.3 years at early age of onset. In this patient sample, 87.1% experienced comorbid ADHD. Prepubertal boys were significantly more likely to exhibit comorbid ADHD than older, adolescent girls ($P<0.001$).¹⁵ High rates of comorbidity between ADHD and bipolar disorder are often reported among young patients, even when strict diagnostic criteria were applied. Other characteristics expressed within the study group included mixed mania (54.8%), rapid cycling (87.1%), grandiose delusions (50.5%), and suicidality (24.7%). In this study, differences in disease manifestation among patients were found largely to reflect normal development.¹⁵ Geller et al has also reported a mixed mania rate of 57.7% in children compared with a 30% rate observed in adults.⁶

Adolescent patients who develop bipolar disorder usually experience symptoms similar to adult patients with bipolar disorder. Unlike younger children, adolescents may experience distinct periods of mania and depression with rapid onset of symptoms.¹⁶ While younger patients may experience subthreshold symptoms that are difficult to diagnose, adolescent patients are more likely to exhibit classical symptoms of mania and are more likely to be diagnosed with bipolar disorder. Associated behavioral problems and psychotic features may lead to the misdiagnosis of conduct disorder or schizophrenia in bipolar adolescents.¹⁷ Table 1 summarizes differences in bipolar disorder based on age of onset.

Table 1

HYPOTHESIZED CLINICAL COURSE BY AGE OF ONSET		
	Prepubertal and Young Adolescent	Older Adolescent and Adult
Initial episode	Major depressive disorder	Mania
Episode type	Rapid-cycling, mixed	Discrete with sudden onsets and clear offsets
Duration	Chronic, continuous cycling	Weeks
Interepisode functioning	Nonepisodic	Improved functioning

Reprinted with permission from the American Academy of Child and Adolescent Psychiatry.¹⁸ Copyright 1997, American Academy of Child and Adolescent Psychiatry.

Children and adolescents with bipolar disorder often express comorbid ADHD, along with mixed mania, rapid cycling, grandiose delusions, and suicidality.¹⁵

Comorbidity and Differential Diagnosis

Diagnosis of bipolar disorder within pediatric populations is often complicated because symptoms that overlap may be difficult to distinguish from other disorders. Common comorbid disorders with bipolar disorder in youths may include ADHD, substance abuse, anxiety disorder, and conduct disorder. Diagnosis is further complicated by the range of symptoms (which may include a behavioral dimension) associated with younger patients who have abnormal mood. As a result, bipolar disorder is often confused with conditions that have similar features, such as schizophrenia, schizoaffective disorder, agitated depression, and posttraumatic stress disorder (PTSD). A summary of comorbid conditions and differential diagnoses by age group is shown in Table 2.

Table 2

DIFFERENTIAL DIAGNOSES AND/OR COMORBID CONDITIONS IN PATIENTS WITH BIPOLAR DISORDER

	Child	Adolescent	Adult
Specific language disorders	X		
Attention deficit/hyperactivity disorder	X	X	
Oppositional defiant disorder	X	X	
Conduct disorder	X	X	
Sexual abuse/posttraumatic stress disorder	X	X	
Schizophrenia		X	X
Substance abuse		X	X
Antisocial personality			X

Reprinted with permission from the American Academy of Child and Adolescent Psychiatry.¹⁸ Copyright 1997, American Academy of Child and Adolescent Psychiatry.

Bipolar Disorder and ADHD

A significant proportion of children with bipolar disorder also meet established criteria for ADHD. Wozniak et al studied 43 children under the age of 13 years who had bipolar disorder with *DSM III* established mania.¹⁴ Of these children, 94% also met the criteria for ADHD. Most other studies have found comorbidity rates of bipolar disorder and ADHD to be between 57% and 86%.^{19,20} More studies are required to determine whether high comorbidity rates between ADHD and bipolar disorder in children are primarily the result of taxonomical overlap and diagnostic methodology, or if these disorders, as currently defined, truly exist as distinct conditions.^{21,22} Patients who have been diagnosed with comorbid ADHD and bipolar disorder tend to exhibit psychotic grandiosity, comorbid depression, psychiatric hospitalization, and school failure.¹⁴ Children with ADHD who have a parent with bipolar disorder are at the highest risk for bipolar disorder.²³

Bipolar disorder is often confused with conditions that have similar features, such as schizophrenia, schizoaffective disorder, agitated depression, and posttraumatic stress disorder (PTSD).

In an attempt to distinguish between the characteristics of bipolar disorder and ADHD, Geller et al used a list of 16 items to assess the characteristics of outpatient children who had been diagnosed with exclusively ADHD (n=60) or bipolar disorder (n=60).^{24,25} Children with bipolar disorder but not ADHD experienced greater elevated mood, grandiosity, hypersexuality, racing thoughts, and a decreased need for sleep ($P<0.05$). Hypersexuality is especially characteristic of bipolar disorder.²⁶ Features common to both bipolar disorder and ADHD include hyperenergy and distractability.^{24,25}

In children who fulfill the criteria of both bipolar disorder and ADHD, treatment of the mood disorder should be the first priority.² Future course, family genetic, and symptom clusters may be required to further differentiate ADHD from bipolar disorder.²⁷

Bipolar Disorder and Substance Abuse

During teenage years, substance abuse often emerges as an important comorbid factor in bipolar patients.¹³ The most predictive factor for the development of substance abuse among bipolar teenagers is age of bipolar onset. Teenagers who developed bipolar disorder before puberty are much less likely to develop substance abuse than teenagers who developed bipolar disorder after puberty.²⁸ After controlling for age, gender, conduct disorder, and other psychiatric comorbidity, patients with adolescent-onset bipolar disorder are 8.8 times more likely to develop substance abuse than patients with child-onset bipolar disorder ($P<0.02$).²⁸ Patients who developed bipolar disorder after the age of 13 years should be evaluated for possible substance abuse.

High rates of mania and alcohol or marijuana dependence have been found among juvenile offenders.²⁹ Before a diagnosis of bipolar disorder is made, physicians should rule out the possibility of substance abuse as a differential cause of mood episodes. For example, the use of amphetamines may result in behaviors that mimic periods of rapid cycling, and euphoria or fits of laughing may occur following the use of marijuana.¹⁸

Bipolar Disorder and Schizophrenia/Schizoaffective Disorder

As many as 50% of all cases of early-onset bipolar disorder are misdiagnosed as schizophrenia.^{13,30,31} Psychotic features associated with pediatric-onset mania include auditory hallucinations, persecutory delusions, passive feelings of mind control, and cognitive disorganization with loosening of associations and incoherence.³² In addition, symptoms commonly associated with adult-onset bipolar disorder (eg, hypersexuality, grandiosity, and inappropriate behavior) also occur in schizophrenic and bipolar adolescents. In as many as half of juvenile patients with bipolar disorder and psychotic thinking, psychotic features were incongruent with the patient's prevailing mood.³³

Psychotic features in bipolar disorder are influenced by age and gender factors. Delusional thoughts tend to occur more frequently in patients with onset of bipolar disorder before the age of 20 years than in patients with an older age of onset.³⁴ Few studies have evaluated gender differences regarding comorbidity of schizophrenia and bipolar disorder. However, among hospitalized adolescent bipolar patients, more psychotic features have been found in males than females.³⁵

Children with bipolar disorder but not ADHD experienced greater elevated mood, grandiosity, hypersexuality, racing thoughts, and a decreased need for sleep ($P<0.05$). Features common to both bipolar disorder and ADHD include hyperenergy and distractability.^{24,25}

Strict use of DSM-IV criteria has been shown to improve the accuracy of the physician's differential diagnosis between schizophrenia and bipolar disorder.³⁶

Because adolescent-onset bipolar disorder often presents with associated psychotic features, physicians should be methodical when determining whether a patient should be diagnosed with schizophrenia or bipolar disorder.³¹ Strict use of *DSM-IV* criteria has been shown to improve the accuracy of the physician's differential diagnosis between schizophrenia and bipolar disorder.³⁶

Schizoaffective disorder is diagnosed if a patient has a period of illness that fulfills *DSM-IV* criteria for a significant mood disorder (eg, depression, mania, or mixed episode) and schizophrenia.³ Psychotic symptoms occur for at least a 2-week duration in the absence of mood disorder, and mood symptoms must occur for a substantial length of the overall illness. Few studies have been performed in younger patients with this condition. Diagnosis occurs infrequently and is often associated with severe impairment of the patient.³⁷

Other Differential Diagnoses

Other important diagnostic considerations among children and adolescents who meet the criteria for bipolar disorder include conduct disorder, agitated depression, PTSD, and mood disorders caused by a medical condition.³⁷ Substantial overlap exists between patients with bipolar disorder and conduct disorder; as many as 40% of adolescent patients in either group belong to both groups.³⁸ Adolescent patients with emerging bipolar disorder often may appear unipolar when presenting with depression for the first time.³⁹ Also, patients with agitated depression may appear to have a mixed episode at times due to increased psychomotor activity. Rating scales have been developed to differentiate between agitated depression and mania in adults.⁴⁰ Youths with traumatic histories may present with mood instability and other symptoms of PTSD that may be confused with mixed or manic episodes. Comorbidity between bipolar disorder and PTSD has been reported.⁴¹ Other common comorbidities may include anxiety disorders (eg, a patient refuses to allow blood to be drawn) and oppositional defiant disorder (eg, patient is hostile and antagonistic). Lastly, symptoms of mania have been associated with medical conditions, such as neurological disorders, systemic conditions, and prescribed medications.⁴² A diagnosis of bipolar disorder should only be made on the basis of a thorough physical evaluation that includes results from laboratory, neuroimaging, psychiatric, pediatric, and neurological examinations.³⁷

Cultural Issues

Physicians should be aware that the expression of bipolar symptoms and behaviors may be influenced by cultural context. One study of Old Order Amish patients found that expression of manic symptoms (ie, grandiosity) among Amish youths was diminished by religious and community ties. Young Amish patients with bipolar disorder did not express conventional symptoms of the illness because the cultural context did not create the same messages, behavioral models, and opportunities as those of children from other social, ethnic, or racial backgrounds.⁴³ Studies have shown that ethnic minorities and children from lower socioeconomic backgrounds have a greater risk of misdiagnosis of schizophrenia than other patients with bipolar disorder because manic episodes are more likely to include psychotic behavior in this population.⁴⁴ In addition, racial differences may influence treatment patterns. One study of treatment patterns found that African American adolescents with bipolar disorder were twice as likely as Caucasian adolescents to receive treatment with an antipsychotic ($P=0.006$).⁴⁵ Differences in treatment patterns were associated with misinterpretation of disease symptoms. Early treatment of bipolar disorder with appropriate pharmacologic agents is crucial for successful outcomes. Because misdiagnosis may lead to inappropriate pharmacologic choices, physicians should be especially aware of how cultural factors may influence the diagnosis of bipolar disorder among younger patients.

Prevalence

Estimating the prevalence of bipolar disorder among children and adolescents is difficult because few epidemiological studies have been performed within this population. Historically, bipolar disorder was believed to occur rarely among children and adolescents. From the 1930s through the 1960s, mood disorders were believed to be caused by dysfunction of the postpubertal superego during late adolescence. For this reason, bipolar disorder was not thought to be possible in prepubertal patients, and disordered mood in children and adolescents was usually associated with schizophrenia.^{32,37} Bipolar disorder is now recognized to occur in children and adolescents, but the prevalence of child-onset bipolar disorder remains an area of controversy.⁴⁶ Prevalence rates may vary, depending on diagnostic criteria used.⁴⁷ Because manifestation of child and adolescent bipolar disorder differs from adult-type bipolar disorder, specific diagnostic criteria are necessary for the recognition of this disorder in children.

Lewinsohn et al performed a series of diagnostic interviews among 1709 American high school students aged 14 to 18 years to determine the prevalence of bipolar disorder in this patient population. Lifetime prevalence among these adolescents was 1.0%.⁴⁸ Most of these patients were identified with bipolar II disorder. A much larger group of adolescents (5.7%) was found to have subthreshold, rather than threshold, phenomenology, or bipolar not otherwise specified (NOS).⁴⁸ A prevalence rate of 1% compares with similar prevalence rates observed in adult populations. While bipolar disorder affects males and females equally in general, studies have shown that emerging bipolar characteristics may occur years earlier among boys than among girls. For example, while women are at a higher risk than men for depressive disorders, depressive features occur more frequently in boys than girls.⁴⁹

In summary, bipolar disorder is a condition that is commonly underdiagnosed and misdiagnosed among children and adolescents. Youth-specific traits, such as rapid cycling and mixed mania, often complicate the diagnosis of bipolar disorder. In addition, overlapping and comorbid symptoms may obscure differential diagnoses among children and adolescents meeting *DSM-IV* criteria for bipolar disorder. Further age-specific studies may produce diagnostic criteria specific to younger age groups.

Current Concepts in Patient Management

Goals of Management

Primary objectives of treatment include improving patient symptoms and preventing relapse while reducing long-term morbidity and promoting normal growth and development.³⁷ The most common medications used to achieve these goals include lithium, divalproex, and carbamazepine, as shown in [Table 3](#). Controlled medication trials with these therapies in younger patients are limited. To date, only 1 double-blind, placebo-controlled trial of bipolar disorder with lithium has been completed in children or adolescents, and no double-blind, placebo-controlled trials have been completed with any other mood stabilizers. Medication strategies for children and adolescents with bipolar disorder are largely based on clinical experience with bipolar adults. Because manifestation of bipolar disorder in youths does not appear to mimic adult-type bipolar disorder, further age-specific, controlled studies are warranted to determine which therapies are most appropriate for youths.¹⁸

Before initiating psychopharmacological intervention, current practice guidelines recommend that physicians obtain appropriate informed consent and assess the patient's phase of illness and the estimated length of treatment.³⁷ Recognition of illness phase is important when determining medication choice and progression of symptoms. Guidelines recommend that choice of medication should be based on the following priorities:³⁷

- Evidence of medication efficacy
- Patient's phase of illness
- Presence of complicated presentations (eg, rapid-cycling, mood swings, or psychotic symptoms)
- Side effect spectrum of agent
- Patient's history of medication response
- Preferences of family and patients

Physicians should be aware that the use of antidepressant medication to treat depression in a person with bipolar disorder may induce manic symptoms if taken without a mood stabilizer, such as lithium or valproate.³⁷

Because manifestation of bipolar disorder in youths does not appear to mimic adult-type bipolar disorder, further age-specific, controlled studies are warranted to determine which therapies are most appropriate for youths.¹⁸

Table 3

PHARMACOLOGIC TREATMENT OF ADOLESCENT BIPOLAR DISORDER			
Medication	Starting Dosage	Maintenance Dosage (range)	Comments
Lithium	30 mg/kg/d	5-40 mg/kg/d in divided doses	Monitor serum concentration; dermatologic problems (acne, psoriasis), weight gain, tremor, and cognitive impairment more pronounced in this population.
Divalproex	15 mg/kg/d in divided doses	15-60 mg/kg/d	Divalproex generally better tolerated than valproic acid; side effects include nausea, gastrointestinal discomfort, and sedation.
Carbamazepine	100 mg/d	400-800 mg/d Titrate to efficacy	Monitor for neurological side effects/manic induction

Reprinted with permission from the National Alliance for the Mentally Ill (NAMI).⁵⁰ Copyright 1996-2001, NAMI.

It may be difficult to predict which depressed children will experience manic episodes. Children with a family history of bipolar disorder have a higher likelihood of developing bipolar disorder. If manic symptoms worsen during the use of an antidepressant or stimulant in a child or adolescent who is bipolar, mood stabilization therapy should be initiated. Consultation with a child psychiatrist may be useful in determining whether antidepressant or mood stabilization therapy is most appropriate. Families of depressed children should be educated to identify symptoms of bipolar disorder so that they can be reported immediately.³⁷

While multiple agents are often required to control bipolar disorder, physicians should avoid the unnecessary use of polypharmacy.³⁷ Additionally, cultural issues should be considered in any treatment plan.

Lithium

Based largely on open studies and clinical experience, lithium is considered a first-line medication for the treatment of bipolar disorder in children and adolescents. In adults, lithium has been shown to treat acute manic and depressive episodes, prevent recurrent manic and depressive episodes, and reduce mood instability between episodes.⁴⁴ Lithium is primarily used in children and adolescents to treat presentations of classic adult-type bipolar I disorder with euphoria.

In the only placebo-controlled, double-blind trial for children and adolescents with bipolar disorder, patients in the lithium group significantly improved their level of functioning and decreased signs of bipolar disorder.⁵¹

In the only completed placebo-controlled, double-blind trial for children and adolescents with bipolar disorder, 25 outpatients were randomized to receive lithium (n=13) or placebo (n=12) for 6 weeks.⁵¹ Patients were between the ages of 12 years and 18 years and had been diagnosed with bipolar disorder and were dependent on alcohol or marijuana. Mean age of onset for bipolar disorder was 9.6 years, and mean age onset for substance dependence was 15.3 years. Patients in the lithium group significantly improved their level of functioning and decreased signs of bipolar episodes and drug use.⁵¹ Primary psychopathology measures included intent-to-treat (n=25) and completer (n=21) analyses. Mean lithium level for responding patients was 0.9 mEq/L. Compliance with trial medication was problematic in these adolescent, bipolar patients.⁵¹

Open trials with lithium in bipolar youths have produced similar responses to those observed with adults.⁵² In addition, many case reports and smaller studies have examined the use of lithium in bipolar children and adolescents.⁵³⁻⁵⁵ Although lithium is relatively well-tolerated in children and adolescents, the therapeutic range is very narrow (0.8-1.2 mEq/L), and serum concentrations of the drug must be regularly monitored. Therefore, lithium may not be the ideal therapy if patient compliance is an issue.

Common side effects of lithium in children include nausea, diarrhea, tremor, enuresis, fatigue, ataxia, leukocytosis, and malaise. Neurological effects may be especially associated with use by children 6 years or younger.⁵⁶ Lithium levels may be affected by the use of therapies, such as carbamazepine, nonsteroidal anti-inflammatory agents, some antibiotics, and thiazide diuretics. Physicians should be aware of all potential drug interactions before administration.

Mood Stabilizing Anticonvulsants

Divalproex and carbamazepine have been studied extensively in the adult literature for the treatment of bipolar disorder.³ Divalproex is the mood stabilizer of choice for patients with rapid cycling, mixed mania, and comorbid substance abuse, conditions that are associated with poor response to lithium.⁵⁷ Successful treatment of bipolar disorder often requires treatment with more than one mood-stabilizing agent.

Divalproex is considered a first-line treatment for children and adolescents with bipolar disorder based on comparative open-label studies and clinical experience. Forty children and adolescents with bipolar disorder, aged 7 to 17 years, participated in a multisite, open-label study to determine the efficacy of divalproex. After stabilization of mood, patients were randomized to divalproex or placebo for a period of 2 to 8 weeks.⁵⁸ During the treatment phase, 61% of patients receiving divalproex showed an improvement of 50% or more on the Young-Mania Ratings Scale (Y-MRS), an 11-item scale used to assess the severity of a patient's mania. Within the enrolled population, 69% had a comorbid diagnosis, and 58% discontinued the study due to compliance issues. Response rates of patients treated with divalproex were significantly greater than response rates to placebo ($P<0.05$).

General side effects of valproate may include nausea, gastrointestinal discomfort, and sedation. Additionally, Isojärvi et al has reported an increased incidence of polycystic ovary syndrome (PCOS) among women with epilepsy under the age of 20 treated with valproate.⁵⁹⁻⁶² Major complications of PCOS include obesity, metabolic syndrome, irregular or absent menses, and abnormal growth of hair. However, follow-up studies showed that valproate may not increase the risk of PCOS among adult women. A total of 93 epileptic women, between the ages of 20 and 53 years, received valproate, carbamazepine, more than 1 antiepileptic, or no medication.⁶³ In the study, rates of PCOS were 11% in the valproate group, 10% in the carbamazepine group, 0% in the multiple antiepileptic group, and 11% in the no medication group.⁶³ A separate analysis by Genton et al found that most studies of women treated with valproate have reported low incidence rates of PCOS comparable to women who were not treated with valproate, and no studies have established a causal link between valproate and PCOS.⁶⁴ Furthermore, the Isojärvi et al study may have been biased due to retrospective patient selection.⁶⁴

Anecdotal experience suggests that carbamazepine may be an effective treatment for bipolar disorder when used in combination with lithium.⁵⁵ Though few studies exist in children with bipolar disorder, studies with adults suggest that carbamazepine may be more effective than lithium in the treatment of mixed or rapid-cycling mania.⁶⁵ Primary side effects reported among children treated with carbamazepine include untoward effects on cognitive and psychomotor performance, sedation, vertigo, ataxia, headache, and nausea.³² In addition, carbamazepine has been associated with a twofold increased rate of major congenital anomalies and birth weight reduction when administered to women during their third trimester of pregnancy.⁶⁶ Therefore, physicians should be cautious when prescribing carbamazepine to women of childbearing ages.

Kowatch et al reported the results of a prospective, open-label study in which 42 bipolar outpatients with a mean age of 11.4 years (20 with bipolar I disorder and 22 with bipolar II disorder) were randomly assigned to receive 6 to 8 weeks of treatment with either lithium, divalproex, or carbamazepine.⁶⁷ Patients received acute phase treatment during a mixed or manic episode. The primary efficacy measures included weekly Clinical Global Impression (CGI) Improvement scores and Y-MRS. Using a $\geq 50\%$ change from baseline to exit in the Y-MRS scores to define response, the effect sizes were 1.63 for divalproex, 1.06 for lithium, and 1.00 for carbamazepine. Using this same response measure with the intent-to-treat sample, response rates were 53% for divalproex, 38% for lithium, and 38% for carbamazepine. ($\chi^2=0.85$, $P=0.60$).⁶⁷

Atypical Neuroleptics

The use of polypharmacy is often necessary to control manic and depressive episodes in child and adolescent populations. Atypical neuroleptics, such as olanzapine and risperidone, may improve the symptomology of children through dopaminergic and serotonergic action. Olanzapine was studied in a small, open-label trial of 23 bipolar children who had been resistant to other therapies.⁶⁸ Patients were aged 5 to 14 years and received 2.5 mg/d to 20 mg/d olanzapine. In this patient population, 60.9% achieved an improvement of 30% or greater on Y-MRS scores. This rate may seem low compared with studies of other agents that measured Y-MRS score improvements of 50% or greater. Nonetheless, olanzapine may be an appropriate agent for patients resistant to other treatments. The only significant side effect observed in the study was weight gain (mean weight gain=4.98 kg, $P<0.001$).⁶⁸

Kowatch et al reported that 53% of patients receiving divalproex improved Y-MRS scores by $\geq 50\%$, compared with 38% receiving lithium and 38% receiving carbamazepine.⁶⁷

Risperidone is another atypical neuroleptic that has been explored in the treatment of child and adolescent bipolar disorder.⁶⁹ A recent retrospective chart review summarized the use of risperidone among 28 outpatient children and adolescents with bipolar disorder. Patients had a mean age of 10.4 years, and concurrent medications were used in all but 1 patient. The mean daily dose of risperidone was 1.7 mg. Of the patients enrolled, 82% decreased disease severity, as measured by the National Institute of Mental Health Clinical Global Impression Scale (CGI). Mean CGI severity ratings decreased from 5.4 (in the marked/severe range) to 2.9 (in the mild range) during treatment with risperidone.⁶⁹ Mean time to optimal response was 1.9 months, and 57% responded to treatment within 1 month. Treatment was well tolerated, and common side effects included weight gain, sedation, and drooling.⁶⁹

Third Generation Mood Stabilizers

Newer agents with unique mechanisms of action, such as lamotrigine and topiramate, warrant systematic study in children and adolescents. No treatment studies with these agents are currently available among younger bipolar populations. These third generation mood stabilizers should be considered if olanzapine or risperidone fail to control patient symptoms.

Physicians should be aware of potential drug interactions and side effects associated with newer antiepileptics. The hepatic metabolism of lamotrigine may be induced if used with carbamazepine, and the clearance of lamotrigine is affected by valproic acid.⁷⁰ Rare but potentially life-threatening rashes have been associated with the use of lamotrigine.⁷⁰ Topiramate's action may be lessened by the use of mood stabilizers; decreased plasma concentrations of topiramate have been associated with the use of carbamazepine, divalproex sodium, and valproic acid.⁷¹ Somnolence, fatigue, and drowsiness have been associated with the use of topiramate.⁷¹

Extended-Release Formulations

Patient compliance is vital to the successful management of child and adolescent bipolar disorder. Because extended-release (ER) formulations only require once-a-day dosing, they may improve patient compliance, which is especially important in child and adolescent bipolar patients. In addition, because ER formulations achieve higher blood serum levels than delayed-release (DR) formulations over longer periods of time, ER formulations may also decrease peak-related side effects, such as mood fluctuations, and may offer improved efficacy. Currently, lithium, carbamazepine, and divalproex are available as ER tablets. Further research into the use of ER formulations in juvenile bipolar patients is necessary to confirm expected benefits.

Psychosocial Treatments

As part of an integrated approach to patient management, physicians should offer nonpharmacologic treatment to child and adolescent bipolar patients, which should be supportive in nature. An appropriate learning environment can be developed through consultation with families and educators. In addition, patients and family members should be taught to properly manage and cope with the disease.

Importantly, patients and family members should be taught about the symptoms and course of bipolar disorder, treatment options, and its impact on social and family functioning.³⁷ Psychotherapy should be flexible to reflect the needs of the individual patient and may involve teaching the patient to predict episodic relapse based on a variety of factors (eg, seasonal or situational changes, sleep deprivation, medication noncompliance, or substance abuse).³⁷ Patients who are taught to predict episodic relapse may experience improved outcomes because of early pharmacologic intervention.

Medication Strategies

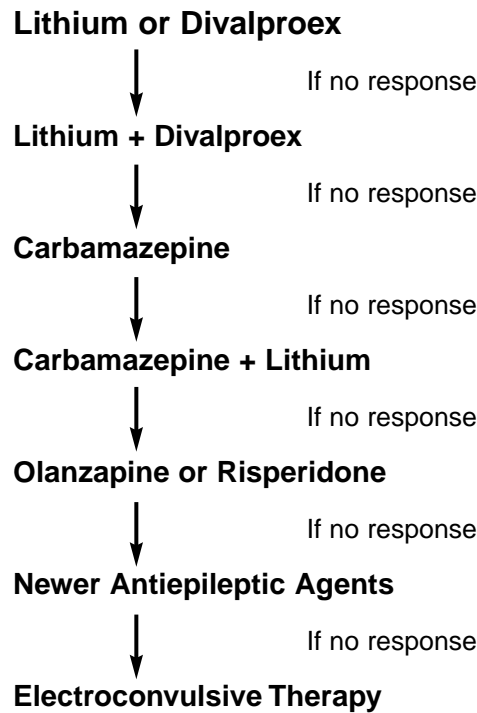
Clinicians should develop a plan of treatment soon after the diagnosis of bipolar disorder based on the patient's prior medical history and a thorough physical examination. [Figure 1](#) represents a treatment algorithm for child and adolescent patients with bipolar disorder. Mood stabilizers are often used in clinical practice as first-line treatments for child and adolescent bipolar disorder. For patients with classic adult-type euphoria, lithium is usually the medication of choice. However, patients with a prior childhood history of ADHD do not respond to lithium as well as patients with no prior history of ADHD.⁷² Divalproex is preferred for patients who exhibit mixed mania or rapid cycling. Monotherapy is not usually effective at controlling symptoms of bipolar disorder. If monotherapy with a mood stabilizer fails, patients should be administered a second mood stabilizer.

Combination therapy of divalproex and lithium is well tolerated and is often effective at controlling the symptoms of bipolar disorder. Carbamazepine may also be used in combination with lithium in nonresponding patients. If the patient does not respond to combination therapy, olanzapine or risperidone should be added. Finally, newer antiepileptics or electroconvulsive therapy (ECT) may be attempted. All pharmacologic treatment decisions should be based on whether the patient is experiencing a manic or depressive episode, the known side effects of the medication, the patient's past medication response, and whether the patient's episodes include mixed states or rapid cycling.

Clinicians should develop a plan of treatment soon after the diagnosis of bipolar disorder based on the patient's prior medical history and a thorough physical examination.

Figure 1

Treatment Algorithm for Children and Adolescents with Bipolar Disorder



Treatment of Bipolar Depression

Clinical evidence suggests that patients experiencing a bipolar depressive episode should receive medication that specifically treats the depression. A chart review was performed with 59 children and adolescents with bipolar disorder who had experienced bipolar depression.⁷³ At follow-up, symptoms of depression were evident in 42 youths, who were then prescribed one of the following therapies: tricyclic antidepressants (45%), stimulants (20%), mood stabilizers (40%), and atypical neuroleptics (10%). Of all the therapies prescribed, patients responded best if treatment involved selective serotonin reuptake inhibitors (SSRIs). Depressive symptoms were 7 times more likely to improve if the patient received SSRIs than if receiving no medication, and no significant improvement was observed among patients who had received any other medication.⁷³ Patients who received SSRIs, however, were 3 times more likely to develop manic symptoms than patients who received other medications. Patients who received SSRIs in combination with mood stabilizers, however, experienced improved manic symptoms. SSRIs, therefore, are effective treatment for bipolar depression, but should be prescribed only in combination with a mood stabilizer. Physicians should understand the risks associated with SSRI monotherapy and should balance the benefits of reducing depressive symptoms against the risk of producing manic symptoms.⁷³

Outcomes of Treatment

In addition to being aware of which medications to use, physicians treating child and adolescent bipolar disorder should understand when to initiate and when to discontinue therapy. While few studies have been performed in children and adolescents with bipolar disorder to determine the course of the disease in younger patients, these studies, as well as clinical experience, have provided useful information regarding recovery and relapse rates and disease outcomes that is relevant to treatment.

Discontinuing Therapy

To date, only 2 studies have been performed to assess the result of discontinuation of pharmacologic therapy in child and adolescent bipolar patients.^{74,75} Strober et al evaluated 37 adolescents with bipolar disorder in an 18-month prospective study. All patients had been prescribed lithium for bipolar disorder, and patient compliance was measured. The rate of episodic relapse was 92% among patients who discontinued therapy (n=13). Patients who continued to receive therapy (n=24) had a relapse rate of only 37%.⁷⁴ In a naturalistic, 5-year follow-up study, the rate of recovery was determined to vary based on polarity of episode at time of entry, with quick recovery observed in subjects with pure mania or mixed states and a protracted index episode in subjects with pure depression.⁷⁵ Multiple relapses were most often observed in subjects with mixed or cycling episodes at intake. Polarity of disease episodes, therefore, appears to be related to the rate of disease relapse following cessation of therapy.⁷⁵

Geller et al evaluated the relapse and recovery rates of bipolar disorder by interviewing 89 children (mean age=11 years) one year following the cessation of therapy.⁷⁶ Of the 89 patients, only 51% had received mood stabilizing antimanic medication for 1 year (all of whom were unipolar). The recovery rate from mania was low (37.1%) and the relapse rate after recovery was high (38.3%).⁷⁶

Clinical experience suggests that therapeutic levels of mood stabilizers should be maintained for at least 2 years following the resolution of disease symptoms. As adolescent patients age, they may request discontinuation of pharmacologic therapy. Discontinuation of therapy must occur slowly, and dosages should be tapered over a 6-month period.

Course of Bipolar Disorder

Few studies have been performed to determine the long-range course of child- and adolescent-onset bipolar disorder. Lewinsohn et al evaluated a community of 893 patients at the age of 16 years and when the patients were 24 years.⁷⁷ At the age of 16 years, 18 patients were diagnosed with bipolar disorder, 14 with bipolar NOS, and 275 with major depression. By the age of 24 years, 27% of adolescents with bipolar disorder had experienced a relapse of bipolar episodes. Lifetime prevalence of bipolar disorder within the community sample was 1%.⁷⁷ Physicians should be aware that few 16-year-old patients with unipolar depression proceed to develop bipolar disorder. Of the 275 patients diagnosed with major depression at age 16 years, fewer than 1% switched to bipolar disorder by the age of 24. Lifetime prevalence of bipolar NOS was 5%. Treatment with a mood stabilizer reduced symptoms in greater than 80% of all patients with bipolar NOS.⁷⁷

Multiple relapses were most often observed in subjects with mixed or cycling episodes at intake.⁷⁵

Conclusion

Diagnosis of bipolar disorder in children and adolescents is often complicated by the disease's complex phenomenology and course. While early intervention with pharmacologic therapy may be essential to successful patient outcomes, child and adolescent bipolar disorder is often misdiagnosed and undertreated. Strict use of *DSM-IV* criteria by physicians to diagnose bipolar disorder in children and adolescents can improve diagnostic accuracy. Also, physicians should carefully evaluate all potential differential diagnoses and comorbid disorders, including ADHD and substance abuse. In addition, physicians should attempt to understand the manifestation of symptoms within the proper cultural context of the patient.

Because few placebo-controlled studies have been performed in child and adolescent patients with bipolar disorder, treatment is largely based on the results of controlled studies in adult populations. The most commonly prescribed medications for child and adolescent bipolar disorder are lithium, divalproex, and carbamazepine. In order to reduce the recurrence of manic and depressive episodes in children and adolescents, combination pharmacotherapy, usually consisting of 2 mood stabilizers, is often necessary. Patients experiencing depressive episodes may respond to SSRIs, which should only be administered with mood stabilizing therapy. Before prescribing medications, physicians should be aware of all potential adverse reactions and drug-drug interactions. More research is required to determine the safety and efficacy of monotherapies and combination therapies within younger populations. In spite of the paucity of evidence regarding the treatment of child and adolescent bipolar disorder, physicians should be aware of the importance of early intervention and aggressive treatment in this patient population.

References

1. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *J Affect Disord.* 1994;31:281-294.
2. Cassano GB, McElroy SL, Brady K, Nolen WA, Placidi GF. Current issues in the identification and management of bipolar spectrum disorders in 'special populations'. *J Affect Disord.* 2000;59(suppl 1):S69-S79.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition. Washington, DC: American Psychiatric Association; 1994.
4. Eyberg SM, Schuhmann EM, Rey J. Child and adolescent psychotherapy research: developmental issues. *J Abnorm Child Psychol.* 1998;26:71-82.
5. Geller B, Cook EH, Jr. Ultradian rapid cycling in prepubertal and early adolescent bipolarity is not in transmission disequilibrium with val/met COMT alleles. *Biol Psychiatry.* 2000;47:605-609.
6. Geller B, Sun K, Zimmerman B, Luby J, Frazier J, Williams M. Complex and rapid-cycling in bipolar children and adolescents: a preliminary study. *J Affect Disord.* 1995;34:259-268.
7. Findling RL, Calabrese JR. Rapid-cycling bipolar disorder in children. *Am J Psychiatry.* 2000;157:1526-1527.
8. Geller B, Zimmerman B, Williams M, et al. Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. *J Am Acad Child Adolesc Psychiatry.* 2001;40:450-455.
9. Giaconia RM, Reinherz HZ, Silverman AB, Pakiz B, Frost AK, Cohen E. Ages of onset of psychiatric disorders in a community population of older adolescents. *J Am Acad Child Adolesc Psychiatry.* 1994;33:706-717.
10. Reinherz HZ, Giaconia RM, Lefkowitz ES, Pakiz B, Frost AK. Prevalence of psychiatric disorders in a community population of older adolescents. *J Am Acad Child Adolesc Psychiatry.* 1993;32:369-377.
11. Wozniak J, Biederman J, Richards JA. Diagnostic and therapeutic dilemmas in the management of pediatric-onset bipolar disorder. *J Clin Psychiatry.* 2001;62:10-15.
12. Bowring MA, Kovacs M. Difficulties in diagnosing manic disorders among children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 1992;31:611-614.
13. Carlson GA. Child and adolescent mania--diagnostic considerations. *J Child Psychol Psychiatry.* 1990;31:331-341.
14. Wozniak J, Biederman J, Kiely K, et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry.* 1995;34:867-876.
15. Geller B, Zimmerman B, Williams M, et al. 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.* 2000;10:157-164.
16. Akiskal HS, Downs J, Jordan P, Watson S, Daugherty D, Pruitt DB. Affective disorders in referred children and younger siblings of manic-depressives. Mode of onset and prospective course. *Arch Gen Psychiatry.* 1985;42:996-1003.
17. Kovacs M, Pollock M. Bipolar disorder and comorbid conduct disorder in childhood and adolescence. *J Am Acad Child Adolesc Psychiatry.* 1995;34:715-723.

18. Geller B, Luby J. Child and adolescent bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry.* 1997;36:1168-1176.
19. Milberger S, Biederman J, Faraone SV, Murphy J, Tsuang MT. Attention deficit hyperactivity disorder and comorbid disorders: issues of overlapping symptoms. *Am J Psychiatry.* 1995;152:1793-1799.
20. Faraone SV, Biederman J, Wozniak J, Mundy E, Mennin D, O'Donnell D. Is comorbidity with ADHD a marker for juvenile-onset mania? *J Am Acad Child Adolesc Psychiatry.* 1997;36:1046-1055.
21. Chang KD, Steiner H, Ketter TA. Psychiatric phenomenology of child and adolescent bipolar offspring. *J Am Acad Child Adolesc Psychiatry.* 2000;39:453-460.
22. Stein MA, Roizen NM, Leventhal BL. Bipolar disorder and ADHD. *J Am Acad Child Adolesc Psychiatry.* 1999;38:1208-1209.
23. Sachs GS, Baldassano CF, Truman CJ, Guille C. Comorbidity of attention deficit hyperactivity disorder with early- and late-onset bipolar disorder. *Am J Psychiatry.* 2000;157:466-468.
24. Geller B, Warner K, Williams M, Zimmerman B. Prepubertal and young adolescent bipolarity versus ADHD: assessment and validity using the WASH-U-KSADS, CBCL and TRF. *J Affect Disord.* 1998;51:93-100.
25. Geller B, Williams M, Zimmerman B, Frazier J, Beringer L, Warner KL. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. *J Affect Disord.* 1998;51:81-91.
26. Geller B, Bolhofner K, Craney JL, Williams M, DelBello MP, Gundersen K. Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. *J Am Acad Child Adolesc Psychiatry.* 2000;39:1543-1548.
27. Biederman J, Faraone SV, Keenan K, Tsuang MT. Evidence of familial association between attention deficit disorder and major affective disorders. *Arch Gen Psychiatry.* 1991;48:633-642.
28. Wilens TE, Biederman J, Millstein RB, Wozniak J, Hahesy AL, Spencer TJ. Risk for substance use disorders in youths with child- and adolescent-onset bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 1999;38:680-685.
29. Pliszka SR, Sherman JO, Barrow MV, Irick S. Affective disorder in juvenile offenders: a preliminary study. *Am J Psychiatry.* 2000;157:130-132.
30. Werry JS, McClellan JM, Chard L. Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: a clinical and outcome study. *J Am Acad Child Adolesc Psychiatry.* 1991;30:457-465.
31. McClellan JM, Werry JS, Ham M. A follow-up study of early onset psychosis: comparison between outcome diagnoses of schizophrenia, mood disorders, and personality disorders. *J Autism Dev Disord.* 1993;23:243-262.
32. Faedda GL, Baldessarini RJ, Suppes T, Tondo L, Becker I, Lipschitz DS. Pediatric-onset bipolar disorder: a neglected clinical and public health problem. *Harv Rev Psychiatry.* 1995;3:171-195.
33. Hsu LK, Starzynski JM. Mania in adolescence. *J Clin Psychiatry.* 1986;47:596-599.
34. Rennie T, Fowler J. Prognosis in manic-depressive psychoses. *Am J Psychiatry.* 1942;98:801-814.
35. Landolt A. Follow-up studies on circular manic-depressive reactions occurring in the young. *Bull NY Acad Med.* 1957;33:65-73.

36. Carlson GA, Fennig S, Bromet EJ. The confusion between bipolar disorder and schizophrenia in youth: where does it stand in the 1990s? *J Am Acad Child Adolesc Psychiatry*. 1994;33:453-460.
37. McClellan J, Werry J. Practice parameters for the assessment and treatment of children and adolescents with bipolar disorder. American Academy of Child and Adolescent Psychiatry. *J Am Acad Child Adolesc Psychiatry*. 1997;36(suppl):157S-176S.
38. Biederman J, Faraone SV, Chu MP, Wozniak J. Further evidence of a bidirectional overlap between juvenile mania and conduct disorder in children. *J Am Acad Child Adolesc Psychiatry*. 1999;38:468-476.
39. Kaufman J, Martin A, King RA, Charney D. Are child-, adolescent-, and adult-onset depression one and the same disorder? *Biol Psychiatry*. 2001;49:980-1001.
40. Swann AC, Secunda SK, Katz MM, et al. Specificity of mixed affective states: clinical comparison of dysphoric mania and agitated depression. *J Affect Disord*. 1993;28:81-89.
41. Borchardt CM, Bernstein GA. Comorbid disorders in hospitalized bipolar adolescents compared with unipolar depressed adolescents. *Child Psychiatry Hum Dev*. 1995;26:11-18.
42. Cummings J. *Clinical Neuropsychiatry*. Orlando, FL: Grue & Stratton; 1985.
43. Egeland JA, Hostetter AM, Pauls DL, Sussex JN. Prodromal symptoms before onset of manic-depressive disorder suggested by first hospital admission histories. *J Am Acad Child Adolesc Psychiatry*. 2000;39:1245-1252.
44. Goodwin F, Jamison K. *Manic Depressive Illness*. New York: Oxford; 1990.
45. Delbello MP, Soutullo CA, Strakowski SM. Racial differences in treatment of adolescents with bipolar disorder. *Am J Psychiatry*. 2000;157:837-838.
46. Carlson GA, Meyer SE. Bipolar disorder in youth. *Curr Psychiatry Rep*. 2000;2:90-94.
47. Carlson GA, Kashani JH. Phenomenology of major depression from childhood through adulthood: analysis of three studies. *Am J Psychiatry*. 1988;145:1222-1225.
48. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry*. 1995;34:454-463.
49. Costello EJ. Child psychiatric disorders and their correlates: a primary care pediatric sample. *J Am Acad Child Adolesc Psychiatry*. 1989;28:851-855.
50. West SA. Treating adolescent mania and bipolar disorder. Available at: http://nami.org/youth/adoles_bipolar.htm. Accessed November 1, 2001.
51. 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;37:171-178.
52. DeLong GR, Aldershof AL. Long-term experience with lithium treatment in childhood: correlation with clinical diagnosis. *J Am Acad Child Adolesc Psychiatry*. 1987;26:389-394.
53. Viesselman J, Yaylayan S, Weller E, Weller R. Antidysthymic drugs (antidepressants and antimanic). In: Werry J, Aman M, eds. *Practitioner's Guide to Psychoactive Drugs for Children and Adolescents*. New York: Plenum; 1993:239-268.
54. Alessi N, Naylor MW, Ghaziuddin M, Zubieta JK. Update on lithium carbonate therapy in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1994;33:291-304.

55. Kafantaris V. Treatment of bipolar disorder in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1995;34:732-741.
56. Ryan ND, Bhatara VS, Perel JM. Mood stabilizers in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1999;38:529-536.
57. McElroy SL, Keck PE, Jr., Pope HG, Jr., Hudson JI. Valproate in the treatment of bipolar disorder: literature review and clinical guidelines. *J Clin Psychopharmacol*. 1992;12(suppl):42S-52S.
58. Wagner PG, Welton SR, Hammond CM. Gastrointestinal adverse effects with divalproex sodium and valproic acid. *J Clin Psychiatry*. 2000;61:302-303.
59. Vainionpaa LK, Rattya J, Knip M, et al. Valproate-induced hyperandrogenism during pubertal maturation in girls with epilepsy. *Ann Neurol*. 1999;45:444-450.
60. Isojärvi JI, Tapanainen JS. Valproate, hyperandrogenism, and polycystic ovaries: a report of 3 cases. *Arch Neurol*. 2000;57:1064-1068.
61. Isojärvi JI, Laatikainen TJ, Knip M, Pakarinen AJ, Juntunen KT, Myllylä VV. Obesity and endocrine disorders in women taking valproate for epilepsy. *Ann Neurol*. 1996;39:579-584.
62. Isojärvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllylä VV. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med*. 1993;329:1383-1388.
63. Bauer J, Jarre A, Klingmuller D, Elger CE. Polycystic ovary syndrome in patients with focal epilepsy: a study in 93 women. *Epilepsy Res*. 2000;41:163-167.
64. Genton P, Bauer J, Duncan S, et al. On the association between valproate and polycystic ovary syndrome. *Epilepsia*. 2001;42:295-304.
65. Calabrese JR, Fatemi SH, Kujawa M, Woyshville MJ. Predictors of response to mood stabilizers. *J Clin Psychopharmacol*. 1996;16(suppl):24S-31S.
66. Diav-Citrin O, Shechtman S, Arnon J, Ornoy A. Is carbamazepine teratogenic?: A prospective controlled study of 210 pregnancies. *Neurology*. 2001;57:321-324.
67. 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;39:713-720.
68. 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;11:239-250.
69. 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;38:960-965.
70. Lamictal [package insert]. Philadelphia, PA: GlaxoSmithKline Pharmaceuticals; 2001.
71. Topamax [package insert]. Basel, Switzerland: Novartis Pharmaceuticals Corporation; 2000.
72. Strober M, DeAntonio M, Schmidt-Lackner S, Freeman R, Lampert C, Diamond J. Early childhood attention deficit hyperactivity disorder predicts poorer response to acute lithium therapy in adolescent mania. *J Affect Disord*. 1998;51:145-151.
73. Biederman J, Mick E, Spencer TJ, Wilens TE, Faraone SV. Therapeutic dilemmas in the pharmacotherapy of bipolar depression in the young. *J Child Adolesc Psychopharmacol*. 2000;10:185-192.

74. 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;147:457-461.
75. Strober M, Schmidt-Lackner S, Freeman R, Bower S, Lampert C, DeAntonio M. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. *J Am Acad Child Adolesc Psychiatry*. 1995;34:724-731.
76. Geller B, Craney JL, Bolhofner K, DelBello MP, Williams M, Zimmerman B. One-year recovery and relapse rates of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry*. 2001;158:303-305.
77. Lewinsohn PM, Rohde P, Farrington DP. The OADP-CDS: a brief screener for adolescent conduct disorder. *J Am Acad Child Adolesc Psychiatry*. 2000;39:888-895.

Child and Adolescent Bipolar Disorder: Focus on Differential Diagnosis and Management

Post-Test Review

To receive up to **2.0 credit hours** in category 1 of the Physician's Recognition Award of the American Medical Association, please review this monograph carefully and answer the questions that follow. Answer ALL of the questions. Complete the enrollment form and mail, along with the completed post-test and the evaluation form, to ACCESS Medical Group, Department of Continuing Medical Education, 3395 N. Arlington Heights Road, Suite A, Arlington Heights, IL 60004-1566. Your corrected post-test, a copy of the answers, and a certificate (if appropriate) will be returned to you. Should you have any questions, call 847-392-2227.

To earn credit, a minimum score of 70% must be obtained. This test may be submitted only once for credit consideration and must be received by November 30, 2004. All test results are strictly confidential and intended for self-assessment only.

CME Post-Test

1. Children with bipolar disorder are more likely than adults to experience comorbid:

- a. Substance abuse
- b. Conduct disorder
- c. Attention deficit/hyperactivity disorder
- d. All of the above
- e. None of the above

2. ADHD is a common comorbidity of children with bipolar disorder:

- a. True
- b. False

3. Similarities between bipolar disorder and ADHD include:

- a. Psychotic grandiosity
- b. Hyperenergy and distractibility
- c. Periodicity or seasonality of mood episodes
- d. All of the above
- e. None of the above

4. Patients with child-onset bipolar disorder are more likely than patients with adolescent-onset bipolar disorder to develop substance abuse as teenagers:

- a. True
- b. False

5. ***Which of the following is a primary objective of pharmacologic therapy for patients with child and adolescent bipolar disorder?***
- a. Improve patient symptoms
 - b. Prevent disease relapse
 - c. Reduce long-term morbidity
 - d. Promote normal growth and development
 - e. All of the above
 - f. None of the above
6. ***For the child or adolescent bipolar disorder patient who does not respond to a mood stabilizer, the best therapeutic choice is:***
- a. Risperidone
 - b. Olanzapine
 - c. Adding a second mood stabilizer
 - d. ECT
 - e. None of the above
7. ***When treating child and adolescent bipolar patients, risperidone should be used in high doses.***
- a. True
 - b. False
8. ***Which of the following therapies may be associated with potentially life-threatening rashes?***
- a. Divalproex
 - b. Amitriptyline
 - c. Lamotrigine
 - d. Risperidone
 - e. None of the above
9. ***Based upon clinical experience, children with bipolar depression respond best to what type of medication?***
- a. TCA
 - b. Stimulant
 - c. Mood stabilizer
 - d. SSRI
 - e. Neuroleptic
10. ***Which of the following statements regarding bipolar disorder in children and adolescents is FALSE?***
- a. Polypharmacy is usually not required
 - b. Further research is necessary
 - c. Diagnosis can be quite difficult
 - d. All of the above
 - e. None of the above

Child and Adolescent Bipolar Disorder: Focus on Differential Diagnosis and Management

Enrollment Form

(For CME Identification Purposes)

PLEASE PRINT CLEARLY

Name _____
Last First MI Degree

Address _____

City _____ State _____ Zip code _____

Specialty _____ Social Security number _____

Medical Education number _____

Year medical degree was received _____

Phone number _____ Fax number _____

E-mail _____

Accreditation

ACCESS Medical Group is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education (CME) for physicians. ACCESS Medical Group takes responsibility for the content, quality, and scientific integrity of this CME activity.

Designation of Credit

ACCESS Medical Group designates this continuing medical education activity as meeting the criteria for **2.0 credit hours** in category 1 of the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent on the educational activity.

I have read the CME monograph and completed the post-test in _____ hour(s).

(The smallest division of hours currently used by the AMA is 0.5 hours)

Participant Signature

FOR DCME USE ONLY

SCORE

CAT ___ HR

DBASE

DATE CERT. SENT

Child and Adolescent Bipolar Disorder: Focus on Differential Diagnosis and Management

Evaluation Form

After reviewing the monograph and completing the post-test, to what degree were the following objectives met?

Scale: 1 = Low, 5 = High

I am able to use *DSM-IV* criteria to make an appropriate diagnosis of bipolar disorder in children and adolescents **1 2 3 4 5**

I am able to identify pediatric patients at high risk for the development of bipolar disorder **1 2 3 4 5**

I am able to recognize the features of bipolar disorder that are unique to pediatric populations **1 2 3 4 5**

I am able to distinguish between bipolar disorder and ADHD in child and adolescent patients **1 2 3 4 5**

I am able to identify different pharmacologic and nonpharmacologic options used for the treatment of child and adolescent bipolar patients **1 2 3 4 5**

I understand patient outcomes associated with discontinuation of therapy in child and adolescent patients **1 2 3 4 5**

Did you find the information contained herein to be clinically relevant? Yes No

Did you learn anything regarding the evaluation and treatment of bipolar disorder from this CME activity? Yes No

Provide specific examples:

Can you apply this information to your clinical practice? Yes No

Provide specific examples:

What topics would you like to see in future programs? _____

How can we improve this monograph?

Would you recommend this monograph to a colleague? Yes No

