Diagnosis and Treatment of Bipolar Disorder in Children and Adolescents

Karen Dineen Wagner, M.D., Ph.D.

Bipolar disorder is a serious illness in children that adversely affects social, academic, emotional, and family functioning. Its prevalence in adolescents is estimated to be as high as 1%. The diagnosis of bipolar disorder in young children is often a challenge, largely because the symptoms may differ from those exhibited in late adolescence and adulthood. The occurrence of comorbid disorders such as attention-deficit/hyperactivity disorder also may complicate the diagnosis. Despite the significant severity and chronicity of this disorder in youths, very few controlled data are available to guide treatment decisions in children and adolescents. The treatment literature consists largely of open studies, case series, and case reports. Therefore, a pressing need exists for controlled trials to determine whether medications commonly used to treat the disorder in children are significantly superior to placebo, as well as to determine whether initial monotherapy or combination treatment is warranted. This article will review the epidemiology, diagnosis, course of illness, and treatment of bipolar disorder in children and adolescents. *(J Clin Psychiatry 2004;65[suppl 15]:30–34)*

The prevalence of bipolar disorder in young children has not been assessed adequately. In a community sample of adolescents, the prevalence of bipolar disorder was found to be approximately 1%; however, the prevalence rate was 5% for subsyndromal bipolar disorder in this sample.[1]

DIAGNOSIS

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[2] criteria for diagnosing bipolar disorder in children and adolescents are the same as those for diagnosing the disorder in adults. According to these criteria, manic episodes are characterized by an elevated, expansive, or irritable mood of at least 1 week's duration accompanied by symptoms such as grandiosity, decreased need for sleep, pressured speech, flight of ideas, distractibility, increased goal-directed activity, and excessive involvement in activities with potentially harmful consequences.

Although these criteria are used to diagnose bipolar disorder in the pediatric population, there is controversy about the clinical presentation of the disorder in prepubertal children. Often these children do not meet full DSM-IV criteria for bipolar disorder, but have significant mood instability and consequent impairment in functioning. Young children may not have the clear-cut episodes of mania and depression that characterize adult bipolar disorder.

Recently, 4 clinical phenotypes of pediatric mania have been proposed[3]: a narrow phenotype, 2 intermediate phenotypes, and a broad phenotype. A child with the narrow phenotype would exhibit full DSM-IV criteria for mania or hypomania, with elevated/expansive mood or grandiosity and full symptom-duration criteria. This phenotype is similar to the presentation of adulthood mania. For the intermediate phenotypes, there are clear mood episodes, but the mood episode duration is short (i.e., 1 to 3 days). In these intermediate phenotypes, the mood state may be either elevated or irritable. The broad phenotype is characterized by severe mood and behavioral dysregulation. The mood state is chronic and nonepisodic, with severe irritability, hyperarousal, and increased reactivity to negative emotional stimuli. The reliability and validity of these 4 phenotypes for childhood mania have yet to be determined and require further investigation, particularly to assess

From the University of Texas Medical Branch, Galveston.

Based in part on a presentation at the National Summit Meeting of the Bipolar Care OPTIONS initiative, which was held September 4–6, 2003, in Washington, D.C., and supported by an unrestricted educational grant from Janssen Medical Affairs, L.L.C.

Dr. Wagner has served on the speakers or advisory boards of Abbott, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Novartis, Otsuka, Pfizer, UCB Pharma, Wyeth-Ayerst, and the National Institute of Mental Health (NIMH) Advisory Council. She has been a consultant for or received research support from Abbott, Bristol-Myers Squibb, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Organon, Novartis, Otsuka, Pfizer, UCB Pharma, Wyeth-Ayerst, and NIMH.

Corresponding author and reprints: Karen Dineen Wagner, M.D., Ph.D., Dept. of Psychiatry and Behavioral Sciences, University of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0188 (e-mail: kwagner@utmb.edu).

whether the course of illness and treatment response differs among them.

The clinical characteristics of prepubertal and early adolescent bipolar disorder were investigated by Geller and colleagues.[4] In a sample of 93 outpatients ranging in age from 7 to 16 years (mean age = 11 years) with bipolar disorder I or II, the mean age at onset was 7 years. The study found that the mean episode duration was 3.5 years. The clinical symptoms exhibited in this sample included mixed mania (55%), rapid cycling (87%), grandiose delusions (50%), and suicidality (25%). The most common comorbid disorder was attention-deficit/hyperactivity disorder (ADHD), which occurred at a rate of 87%. The youths who exhibited comorbid ADHD tended to be younger (aged 10.4 years vs. 13.8 years in children without ADHD comorbidity) and male (98.3% in males vs. 69.4% in females).

Given the significant comorbidity between bipolar disorder and ADHD in children, it is important to be able to distinguish between the 2 disorders, which are marked by significantly different courses of illness and treatments. Geller et al.[5] examined the clinical characteristics that distinguish bipolar disorder from ADHD in youth. In this sample, there were 93 outpatient children with bipolar disorder (mean age = 10.9 years), 81 outpatient children with ADHD (mean age = 9.7 years), and 94 community controls (mean age = 11 years). All of these children received thorough clinical assessments, including interviews with the child and mother as well as review of diagnostic instruments, school reports, agency reports, and pediatrician's charts. The symptoms that most distinguished children with bipolar disorder from children with ADHD were, respectively, elevated mood (89% vs. 14%), grandiosity (86% vs. 5%), flight of ideas or racing of thoughts (71% vs. 10%), decreased need for sleep (40% vs. 6%), and hypersexuality (43% vs. 6%). The symptoms that did not distinguish between bipolar disorder and ADHD were distractibility and being hyperenergetic.

A strong family history of bipolar disorder may be another potential clue to differentiating it from ADHD. However, it is important to recognize that children of parents with bipolar disorder may have ADHD and not develop bipolar disorder. The psychiatric diagnoses of children of parents with bipolar disorder were investigated by Chang and colleagues[6] in a study of 37 families with 60 offspring (mean age = 11 years) who had a least 1 parent with bipolar disorder. The study found that 51% of the offspring had a psychiatric disorder. The most common disorders in the offspring were ADHD (27%), bipolar disorder (15%), and major depression (15%). Importantly, the earlier the age of onset of parental bipolar disorder, the greater the risk for bipolar disorder in the offspring.

Children who have a prepubertal onset of major depression may be at significant risk of having a subsequent diagnosis of bipolar disorder. Geller et al.[7] followed into young adulthood a sample of 72 children with prepubertal major depression who had participated in a nortriptyline study and compared them with 28 normal controls. By young adulthood, 33% of these previously depressed prepubertal children had developed bipolar I disorder compared with 0% of the controls. Bipolar spectrum disorder (including bipolar disorder I and II and bipolar disorder not otherwise specified) occurred in 48% of the prepubertal major depression group compared with 7% of the normal controls.

Comorbid Disorders

Although ADHD is the comorbid disorder most commonly associated with childhood bipolar disorder, a number of other psychiatric disorders also may occur concomitantly with bipolar disorder. Conduct disorder; oppositional defiant disorder; anxiety disorders, especially panic disorder; and substance abuse frequently are comorbid with childhood bipolar disorder.[8–13] Children who have bipolar disorder and ADHD tend to have a more severe course of illness compared with children with bipolar disorder alone.[14] The former children frequently present with psychosis, comorbid depression, and school failure and often require psychiatric hospitalization. However, for children with a primary diagnosis of ADHD and comorbid mania, Hazell et al.[15] found that manic symptoms did not persist over time.

Course of Illness

There is recent evidence of the chronicity and severity of the course of childhood bipolar disorder. In a 2-year follow-up study of 89 children and adolescents (mean age = 10.9 years) with bipolar disorder, it was found that 65% had recovered from mania. The mean time to recovery was 36 weeks. However, of those who had recovered from mania, 55% relapsed after recovery, and the mean time to relapse was 28 weeks. A predictor of recovery was an intact biological family, while relapse was associated with a low level of maternal warmth.[16] In a 5-year prospective follow-up study of 54 adolescents who had been hospitalized for bipolar disorder, the recovery rate was 96%. However, during this follow-up period, 44% relapsed and 20% attempted suicide.[17] A community study of adolescents diagnosed with bipolar disorder found that 27% had a recurrence of illness by age 24 years.[18]

TREATMENT

To date, only a limited amount of controlled data is available regarding the efficacy and safety of mood stabilizers in children and adolescents.[19] The majority of information on pharmacologic treatment of bipolar disorder in children and adolescents relies on open studies, case series, and case reports. No medications have been approved by the U.S. Food and Drug Administration (FDA)

for the treatment of bipolar disorder in children, and only lithium has FDA approval for use in adolescents.

Lithium

Lithium has been the most extensively studied pharmacologic agent used in the treatment of childhood bipolar disorder. In case series and case reports, response rates to lithium have ranged from 50% to 100%.[19] In a recent, large, 4-week open study of 100 adolescent inpatients with bipolar I mania who received lithium treatment and, if needed, adjunctive antipsychotic medication, it was found that 63% of the adolescents had a positive response. Response was defined as ≥ 33% improvement on the Young Mania Rating Scale (YMRS),[20] and scores of much or very much improved on the Clinical Global Impressions scale (CGI).[21,22]

The only double-blind, placebo-controlled study of lithium treatment for adolescent bipolar disorder and substance dependence was conducted by Geller and colleagues.[23] Subjects in this study had diagnoses of bipolar type I, bipolar type II, or bipolar depression or a predictor of bipolarity such as delusions or switching from major depressive disorder to bipolar disorder during treatment with a tricyclic antidepressant. In this study, 25 adolescents ranging in age from 12 to 18 years were randomly assigned to either lithium or placebo for a 6-week trial. Lithium produced significantly greater improvement for bipolar disorder and substance use than did placebo. Outcome measures included the Schedule for Affective Disorders and Schizophrenia for School Age Children (KSADs), Children's Global Assessment Scale (CGAS), and DSM-IV-TR criteria for substance dependence.

Valproate

A multisite, open-label study[24] of divalproex treatment for 40 children and adolescents, ages 7 to 19 years, with bipolar disorder was conducted over a 2- to 8-week period. Subjects were enrolled based on a Mania Rating Score (MRS) of ≥ 14 and had manic, hypomanic, or mixed symptoms. Sixty-one percent of the patients showed improvement from baseline to endpoint, as defined by a 50% or greater reduction in the MRS score. Twenty-three patients (58%) discontinued the study. Of those who discontinued, 16 had a comorbid diagnosis such as ADHD, oppositional defiant disorder, or conduct disorder.

In an active comparator trial,[25] 42 children and adolescent outpatients, ages 8 to 18 years, with bipolar disorder were randomly assigned to divalproex, lithium, or carbamazepine for a 6- to 8-week treatment period. Among the inclusion criteria were a YMRS score > 14. The mean serum divalproex level was 82.8 μg/L, the mean serum lithium level was 0.9 mEq/L, and the mean serum carbamazepine level was 7.1 μg/L. The response rates for divalproex, lithium, and carbamazepine were 53%, 38%, and 38%, respectively, using a definition of 50% or greater reduction in the YMRS score from baseline to endpoint and a score of 1 or 2 on the Bipolar Clinical Global Impressions scale (CGI-BP). However, there were no statistically significant differences in response rates among these agents.

Carbamazepine

The data available on the use of carbamazepine in childhood bipolar disorder is limited to case reports, case series, and the aforementioned active comparator study. As described above, of 14 children and adolescents treated openly with carbamazepine in a randomized 6-week treatment trial, 38% had at least a 50% improvement in their symptoms of mania.[26]

Oxcarbazepine

In a retrospective chart review[27] of adjunctive treatment with oxcarbazepine for 44 children and adolescents, ages 6 to 18 years, with bipolar disorder, depression, or anxiety disorder, 86% had clinical improvement defined as much or very much improved on the CGI.

A number of studies, summarized below, have examined the roles of atypical and conventional antipsychotics, as well as non–mood-stabilizing antiepileptic drugs, in treating child and adolescent patients.

Olanzapine

There is 1 open-label study[28] of 23 children and adolescents, ages 5 to 14 years, who received olanzapine treatment for 8 weeks. Inclusion criteria included a YMRS score ≥ 15. Sixty-one percent of the patients responded to treatment based on a definition of response of ≥ 30% reduction in the YMRS.

Risperidone

There is 1 open-label study[29] of 30 outpatient children and adolescents, ages 6 to 17 years, with bipolar disorder who received risperidone for 8 weeks. To participate, the children had to have a YMRS score ≥ 15. The dose range for children up to age 12 years was 0.25 to 2 mg per day; for older youths, the dose range was 0.5 mg to 4 mg per day. Significant reduction in YMRS scores from baseline to endpoint was found.

Quetiapine

Quetiapine as an adjunctive treatment to divalproex was studied in a double-blind, placebo-controlled trial.[30] Thirty adolescents, ages 12 to 18 years, who were hospitalized with a manic or mixed episode, received divalproex 20 mg/kg per day. These patients were randomized concurrently to quetiapine or placebo for a 6-week treatment period. With response defined as a ≥ 50% reduction in the YMRS score, there was a significantly greater response in the group treated with divalproex and quetiapine (87%) than in the divalproex and placebo group (53%).

Topiramate

A retrospective chart review of 26 children and adolescents, ages 5 to 21 years, with bipolar disorder who received adjunctive topiramate over a 1- to 30-month period, found that 73% showed improvement in mania, defined as a ≥ 50% reduction in the YMRS score.[31]

Lamotrigine

The effectiveness of adjunctive lamotrigine treatment for 22 adolescents with refractory bipolar disorder was assessed in an open 6-week study.[32] The lamotrigine dose was either 50 or 100 mg/day. Sixteen (72%) of the adolescents had a positive response to a combination of lamotrigine and divalproex, with response defined as a ≥ 50% reduction in the Hamilton Rating Scale for Depression score from baseline.

Clozapine

Clozapine has been studied in an open trial[33] of 10 hospitalized adolescents, ages 12 to 17 years, with severe acute mania or mixed episodes who had failed prior trials of mood stabilizers and antipsychotics. Clozapine (in doses of 75 to 300 mg/day) was administered either as monotherapy or in combination with a mood stabilizer. Significant improvement in mood symptoms based on scores on the MRS, Brief Psychiatric Rating Scale, CGAS, and CGI-Severity of Illness scale was found within a few weeks of clozapine treatment.

Combination Medication Treatment

Although many clinicians use monotherapy initially to treat a child with bipolar disorder, some children may require a combination medication regimen. To address this issue, Kowatch and colleagues[34] conducted an open extension study for children and adolescents with bipolar disorder who had received 6 to 8 weeks of acute treatment with a single mood stabilizer (lithium, divalproex, or carbamazepine). Depending on the clinical response during the 16-week extension phase, the patients could have their acute-phase mood stabilizer switched or augmented with another mood stabilizer, a stimulant, an antidepressant, or an antipsychotic agent. Fifty-eight percent (20 of 35) of these youths required treatment with more than 1 medication over the course of the 16-week trial. With combination treatment, there was an 80% response rate for subjects who previously had not responded to monotherapy with a mood stabilizer. Importantly, the addition of a stimulant for comorbid ADHD improved overall functioning.

Combination treatment with divalproex and lithium for childhood bipolar disorder also has been investigated.[35] Ninety child and adolescent outpatients, ages 5 to 17 years, with bipolar disorder I or II received lithium and divalproex treatment. At week 8, there was significant improvement in all outcome measures (YMRS, Children's Depression Rating Scale-Revised, and CGAS). Only 7 youths (9%) failed to respond during the combination treatment trial.

Duration of Medication Treatment

There are no available controlled data examining maintenance treatment to help determine adequate treatment duration for a child who presents with an episode of mania. In an 18-month prospective study[36] of 37 adolescents with bipolar disorder who had received lithium treatment, the rate of relapse was 37% in the treatment-compliant patients compared with 92% in the treatment noncompliant patients. Therefore, in clinical practice, it is recommended to continue medication for a minimum of 18 months following a child's or adolescent's recovery from a manic episode.[37] Other researchers have recommended continuing lithium therapy without interruption throughout adolescence.[36]

Psychoeducation

Researchers are investigating the efficacy of psychoeducation as a treatment modality for children and adolescents with bipolar disorder. Fristad and colleagues[38] have examined multifamily groups in which there are eight 90-minute sessions that begin and end with a family component, with a middle portion to meet with the parent(s) and the child separately. Training is provided in communication, cognitive behavioral interventions, and social problem-solving strategies. The psychoeducation group also can be conducted with individual families. Pilot studies have reported that parents had increased positive attitudes toward their children and that the children experienced increased social support from parents and improved peer support.[39]

Family-focused therapy also has been investigated for the treatment of adolescent bipolar disorder. This approach is based on a model of psychosocial treatment for families of adults with bipolar disorder. Components of family-focused therapy include education about coping with illness and training in communication and problem-solving skills. Family-focused therapy currently is being modified for families with an adolescent with bipolar disorder.[40]

CONCLUSION

It is important for clinicians to recognize the clinical symptoms of bipolar disorder in children. This is a serious, chronic illness that adversely affects a child's development; social, academic, and family functioning; and relationships with peers. Unfortunately, there are very limited controlled data to guide medication selection. Medications typically used in clinical practice to treat this disorder include traditional mood stabilizers such as lithium, divalproex, and carbamazepine, as well as the atypical antipsychotics. Controlled studies comparing the efficacy of

medications with each other, as well as controlled studies of combination medication treatments, are needed. In addition, the role of psychoeducation added to medication treatment requires further investigation. Overall, it is important to determine whether early treatment intervention affects the course of illness and reduces the likelihood of its occurrence in adulthood.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril and others), divalproex (Depakote), lamotrigine (Lamictal), lithium (Eskalith and others), nortriptyline (Aventyl and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax).

REFERENCES

1. 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
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Press; 1994
3. Leibenluft E, Charney DS, Towbin KE, et al. Defining clinical phenotypes of juvenile mania. Am J Psychiatry 2003;160:430–437
4. Geller B, Zimerman B, Williams M, et al. Diagnostic characteristics of 93 cases of prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 2000;10:157–164
5. Geller B, Zimerman B, Williams M, et al. DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. J Child Adolesc Psychopharmacol 2002;12:11–25
6. Chang KD, Steiner H, Ketter TA. Psychiatric phenomenology of child and adolescent bipolar offspring. J Am Acad Child Adolesc Psychiatry 2000;39:453–460
7. Geller B, Zimerman B, Williams M, et al. Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. Am J Psychiatry 2001;158:125–127
8. Kovacs M, Pollock M. Bipolar disorder and comorbid conduct disorder in childhood and adolescence. J Am Acad Child Adolesc Psychiatry 1995;34:715–723
9. Carlson GA, Kelly KL. Manic symptoms in psychiatrically hospitalized children: what do they mean? J Affect Disord 1998;51:123–135
10. Masi G, Toni C, Perugi G, et al. Anxiety disorders in children and adolescents with bipolar disorder: a neglected comorbidity. Can J Psychiatry 2001;46:797–802
11. Birmaher B, Kennah A, Brent D, et al. Is bipolar disorder specifically associated with panic disorder in youths? [CME] J Clin Psychiatry 2002;63:414–419
12. West SA, Strakowski SM, Sax KW, et al. Phenomenology and comorbidity of adolescents hospitalized for the treatment of acute mania. Biol Psychiatry 1996;39:458–460
13. Wilens TE, Biederman J, Millstein RB, et al. Risk for substance use disorders in youths with child- and adolescent-onset bipolar disorder. J Am Acad Child Adolesc Psychiatry 1999;38:680–685
14. Wozniak J, Biederman J, Mundy E, et al. A pilot family study of childhood-onset mania. J Am Acad Child Adolesc Psychiatry 1995;34:1577–1583
15. Hazell PL, Carr V, Lewin TJ, et al. Manic symptoms in young males with ADHD predict functioning but not diagnosis after 6 years. J Am Acad Child Adolesc Psychiatry 2003;42:552–560
16. Geller B, Craney JL, Bolhofner K, et al. Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype. Am J Psychiatry 2002;159:927–933
17. Strober M, Schmidtlackner S, Freeman R, et al. Recovery and relapse in adolescents with bipolar affective-illness: a 5-year naturalistic, prospective follow-up. J Am Acad Child Adolesc Psychiatry 1995;34:724–731
18. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. Bipolar Disord 2000;2:281–293
19. Wagner KD. Management of bipolar disorder in children and adolescents. Psychopharmacol Bull 2002;36:151–159
20. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–435
21. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
22. Kafantaris V, Coletti DJ, Dicker R, et al. Lithium treatment of acute mania in adolescents: a large open trial. J Am Acad Child Adolesc Psychiatry 2003;42:1038–1045
23. 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
24. Wagner KD, Weller E, Carlson G, et al. An open-label trial of divalproex in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2002;41:1224–1230
25. 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
26. Kowatch RA, Carmody TJ, Suppes T, et al. Acute and continuation pharmacological treatment of children and adolescents with bipolar disorders: a summary of two previous studies. Acta Neuropsychiatrica 2000;12:145–149
27. Reimherr JP, Rosen SJ, Leahy LF. Oxcarbazepine treatment in child and adolescent mood and anxiety disorders. Paper presented at the annual meeting of the US Psychiatric Congress; October 28–31, 2002; Las Vegas, Nev
28. 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
29. Biederman J. Open-label study of risperidone in children with bipolar disorder. Presented at the 16th annual meeting of the European Neuropsychopharmacology Congress; September 20–24, 2003; Prague, Czech Republic. Abstract P.2.079
30. DelBello MP, Schwiers ML, Rosenberg HL, et al. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. J Am Acad Child Adolesc Psychiatry 2002;41:1216–1223
31. Ryback RS, Brodasky L, Munasifi F. Gabapentin in bipolar disorder. J Neuropsychiatry Clin Neurosci 1997;9:301
32. Kusumakar V, Yatham LN. An open study of lamotrigine in refractory bipolar depression. Psychiatry Res 1997;72:145–148
33. Masi G, Mucci M, Millepiede S. Clozapine in adolescent inpatients with acute mania. J Child Adolesc Psychopharmacol 2002;12:93–99
34. Kowatch RA, Sethuraman G, Hume JH, et al. Combination pharmacotherapy in children and adolescents with bipolar disorder. Biol Psychiatry 2003;53:978–984
35. Findling RL, McNamara NK, Gracious BL, et al. Combination lithium and divalproex sodium in pediatric bipolarity. J Am Acad Child Adolesc Psychiatry 2003;42:895–901
36. Strober M, Morrell W, Lampert C, et al. Relapse following discontinuation of lithium maintenance therapy in adolescents with bipolar I illness: a naturalistic study. Am J Psychiatry 1990;147:457–461
37. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder [Revision]. Am J Psychiatry 2000;159:1–50
38. Fristad MA, Gavazzi SM, Mackinaw-Koons B. Family psychoeducation: an adjunctive intervention for children with bipolar disorder. Biol Psychiatry 2003;53:1000–1008
39. Fristad MA, Goldberg-Arnold JS, Gavazzi SM. Multi-family psychoeducation groups in the treatment of children with mood disorders. J Marit Fam Ther 2003;29:491–504
40. Taylor DO, Miklowitz DJ, George EL, et al. Modifying focused family therapy for adolescents with bipolar disorder. Presented at the annual meeting of the Fifth International Conference on Bipolar Disorder; June 12–14, 2003; Pittsburgh, Pa. Abstract 199