CNS Spectrums (2013), **18**, 209–213. © Cambridge University Press 2013
doi:10.1017/S1092852913000217

REVIEW ARTICLE

Bipolar depression in children and adolescents

Melissa S. DeFilippis,[1]* and Karen Dineen Wagner[1,2]

[1] *Department of Child and Adolescent Psychiatry, The University of Texas Medical Branch, Galveston, Texas, USA*
[2] *Department of Psychiatry, The University of Texas Medical Branch, Galveston, Texas, USA*

Children and adolescents with bipolar disorder may have depression as the presenting mood state. It is important for clinicians to distinguish between unipolar and bipolar depression in youth. Depressive episodes are common during the course of bipolar illness in children and adolescents. Evidence-based treatments are needed to guide clinicians' treatment decisions for youth with bipolar depression. This article reviews the prevalence, diagnosis, course, and treatment of bipolar depression in youth, and emphasizes the need for large, controlled treatment studies in the pediatric population.

Received 18 December 2012; Accepted 14 February 2013; First published online 10 April 2013

Key words: Bipolar disorder, depression, children, adolescents.

CLINICAL IMPLICATIONS

- Bipolar disorder in children and adolescents is a chronic condition with a high risk of severe depressive episodes.
- It is important for clinicians to distinguish unipolar depression from bipolar depression in youth.
- Lamotrigine and lithium have shown benefit in small open trials but large controlled trials for pediatric bipolar depression are needed.
- Psychosocial therapies show promise in the treatment of bipolar disorder in children and adolescents, but current evidence is not specific to bipolar depression.

Introduction

The prevalence of bipolar disorder was found to be approximately 1% in a community sample of 1,709 adolescents aged 14–17 years.[1] The majority of youths with bipolar disorder in this sample experienced a depressive episode as the onset mood episode, and the mean age of onset of this first episode was 11.75 years. The National Comorbidity Survey Replication—Adolescent Supplement (NCS-A) surveyed 10,123 adolescents aged 13–18 years along with their parents.[2] The prevalence of bipolar disorder (bipolar I and bipolar II disorder) in this community sample was 2.9%. The prevalence of bipolar disorder increased with age, with a nearly twofold increase from the 13- to 14-year age group to the 17- to 18-year age group. The lifetime prevalence of mania/hypomania with major depression was 2.5% within the entire sample.[3] Many prevalence studies do not differentiate between bipolar I and II disorder. A review article by Merikangas and Lamers[4] reports lifetime prevalence rates of bipolar II disorder in adolescents to be 1.5%.

*Address for correspondence: Melissa S. DeFilippis, MD, 301 University Blvd., Galveston, TX 77555-0188, USA.
(Email: msdefili@utmb.edu)

Diagnosis

Youth with bipolar disorder may have varying mood states at onset of bipolar illness. In a retrospective chart review of 82 youth with bipolar disorder, 52% of youth presented with manic symptoms, 31% with mixed symptoms, and 17% with depressed symptoms.[5] Notably, within the group with manic symptoms at onset, the majority of youth experienced a dysphoric mania (65%) versus a classic euphoric mania (35%).

Since depression is a common presentation in child and adolescent clinical settings, it is important to determine whether the depressive symptoms are evidence of unipolar or bipolar depression. For example, in a study of 247 adolescent outpatients presenting to a community mental health clinic with a major depressive episode, 41% met criteria for bipolar disorder I or II.[6] The *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) criteria for a depressive episode do not differ between unipolar depression and bipolar depression, so these are not helpful in the distinction between unipolar and bipolar depression.[7]

Wozniak *et al*[8] examined a group of 280 children and adolescents with either unipolar or bipolar depression and compared depressive symptoms. Youth with bipolar depression had a more severe depressive episode with suicidality, hopelessness, and anhedonia compared to youth with unipolar depression. Bipolar depression in adolescents has greater clinical severity than unipolar depression, as evidenced by earlier age of onset, more depressive episodes, and more severe depression.[3] Youth with

bipolar depression were also found to have more comorbid disorders, more hospitalizations, and lower functioning than with unipolar depression.[8]

The clinician should do a thorough assessment for prior or current symptoms of mania or hypomania in children and adolescents who present with symptoms of depression. Diagnostic criteria for bipolar disorder are the same in children and adolescents as for adults. Screening instruments may be helpful in identifying bipolar depression, especially for youth who present with depressive symptoms only. The Mood Disorder Questionnaire—Adolescent version (MDQ-A) aids in identifying prior and current episodes of mania.[9] Other useful screening instruments are the 10-item short form of the Parent General Behavior Inventory (PGBI-SF10) and the Child Mania Rating Scale (CMRS).[10,11]

Course of Illness

Bipolar disorder in children has a chronic course, with a high percentage of youth experiencing relapse of symptoms. In a 4-year prospective follow-up study of 78 youth with bipolar I disorder, ages 6–17, only 6.4% of youths were considered to be in remission without pharmacotherapy at the end of the 4-year follow up.[12] Seventy-three percent continued to meet diagnostic criteria for bipolar I disorder. Over 5% of study participants experienced significant depressive symptoms at the end of the 4-year follow up period.

A prospective 4–5 year follow-up study examined the course of bipolar I disorder in 25 youth, ages 9–16 years, who presented with a diagnosis of mania at initial assessment.[13] All youth experienced recovery from the index episode, with a mean time to recovery of 44 days. Sixteen youth (64%) relapsed during the course of the study, with a mean period of 18 months to relapse. Polarity at time of relapse was manic (58%), depression (23%), mixed (16%), and hypomanic (3%). The youth who experienced relapse were more likely to have had a prior depressive episode. One subject committed suicide during the course of the study while in a depressive episode.

In the Course and Outcome of Bipolar Youth (COBY) study, 413 youths, ages 7–17 years, with bipolar spectrum disorder were followed over 4 years to assess the course of their illness, including recovery and remission rates.[14] After a median time of 12 weeks, 81.4% of the study participants experienced a full recovery. Of these recovered youths, 62.5% experienced a syndromal recurrence a median of 71 weeks after recovery. The most common polarity observed in recurrence was depression (60%), followed by hypomania (21%), mania (15%), and mixed (5%). This large study highlights the significance of bipolar depression in the pediatric population, since the majority of mood symptoms experienced by participants during the 4-year follow-up period were depressive symptoms. Similarly, in a 4-year follow-up of 86 youth ages 7–16 years with bipolar I disorder, manic or mixed, the mean number of weeks that youth were depressed was 99. Switch rates to depression were 1.1 times per year.[15]

Youth with bipolar disorder may experience depressive episodes into young adulthood. Of 115 children and adolescents with bipolar I disorder, manic or mixed, followed over 8 years, 20% had depressive episodes by young adulthood.[16]

Treatment

Pharmacotherapy

There are no U.S. Food and Drug Administration (FDA)–approved medications for the treatment of bipolar depression in children and adolescents. Quetiapine and olanzapine/fluoxetine combination have FDA approval for treatment of adults with bipolar depression. Lithium and lamotrigine are also commonly used in the treatment of adults with bipolar disorder. Medications to treat bipolar depression in children and adolescents are frequently those used to treat adults; however there is a very limited evidence base for their use in pediatric bipolar depression.

Quetiapine

There is one double-blind, placebo-controlled, 8-week trial that examined the efficacy of quetiapine for bipolar depression in 32 adolescents, ages 12–18 years.[17] The dose range of quetiapine was 100–600 mg/day with a mean of 403 mg/day. The primary outcome measure was change in the Children's Depression Rating Scale–Revised (CDRS-R) scores from baseline to endpoint. Response was defined as a $\geq 50\%$ reduction in CDRS-R score from baseline to endpoint, and remission was defined as a CDRS-R score ≤ 28. There was no statistically significant difference between quetiapine and placebo in change in CDRS-R scores from baseline to endpoint. Similarly, response rates (71% vs 67%) and remission rates (35% vs 40%) did not differ between the quetiapine group and the placebo group. These findings are in contrast to the positive adult bipolar depression studies.

Lamotrigine

An 8-week, open-label study examined the efficacy of lamotrigine either as monotherapy or adjunctive treatment for bipolar depression in 20 adolescents, ages 12–17 years.[18] Seven study participants had a diagnosis of bipolar I disorder, 6 had bipolar II disorder, and 7 had bipolar disorder not otherwise specified (NOS).

https://doi.org/10.1017/S1092852913000217 Published online by Cambridge University Press

The primary efficacy measure for response was a score ≤2 on the Clinical Global Impressions Improvement scale (CGI-I), and the secondary measure for response was a ≥50% decrease in the CDRS-R score from baseline to endpoint. Nineteen youth completed the study, and of those, 84% were considered responders using primary criteria, and 63% were responders based on secondary criteria. There was no difference among youth with bipolar I, II, or NOS in response rate, using secondary criteria. Remission was defined as a CDRS-R score ≤28 and a CGI Severity scale (CGI-S) score of ≤2; 58% of the youth in the study met remission criteria. The mean dose of lamotrigine at the end of the study was 131.6 mg/day. The most common side effects reported were headache (84%), fatigue (58%), nausea (53%), and sweating (47%). There were no significant rashes reported, and no youth discontinued the study due to adverse effects.

A 12-week, prospective, open-label trial examined the efficacy of lamotrigine in 39 children and adolescents, ages 6–17 years, with bipolar disorder in a manic, hypomanic, or mixed episode.[19] The majority of the study participants had a diagnosis of bipolar I disorder (90%), 1 had bipolar II disorder (2%), and 3 (8%) had bipolar disorder NOS. There was a significant improvement of depressive symptoms from baseline to endpoint, using change in CDRS-R score as a measure for depressive symptom response. A CGI-I score of ≤2 for depressive symptoms was found for 46% of youth. Thirteen youth reported skin rashes, and 6 youth discontinued lamotrigine as a result of skin rashes. However, no Steven–Johnson syndrome was reported in any of the youth.

A restrospective chart review examined the response to adjunctive lamotrigine in 5 adolescents with bipolar depression.[20] One youth was diagnosed with bipolar I disorder, 1 with bipolar II disorder, and 3 with bipolar disorder NOS. The mean dose of lamotrigine was 100 ± 87.5 mg/day, and the mean duration of treatment was 28 weeks. All 5 patients were taking a mood stabilizer (lithium, carbamazepine, and/or valproate) and an antipsychotic (olanzapine, risperidone, or quetiapine) before adding lamotrigine. Response was retrospectively rated using the CGI-I scale, and the mean CGI scores significantly improved from 5 (markedly ill) at baseline to 3 (mildly ill) at endpoint. The one youth with bipolar II disorder showed minimal improvement on CGI from baseline to endpoint compared to responses of either much or very much improved in the other two youths (bipolar I or NOS). No significant rashes were reported.

Lithium

A 6-week, open-label study examined the effectiveness of lithium in bipolar I depressed youth, ages 12–18.[21] Lithium was titrated up to a dose yielding a therapeutic serum level of 1.0–1.2 mEq/L. There was a significant reduction from baseline to endpoint in the CDRS-R scores.[22] Response was defined as a ≥50% reduction in the CDRS-R score from baseline to endpoint, and 48% of youth met this criteria. Remission was defined as a CDRS-R endpoint score ≤28, and a Clinical Global Impressions Improvement Scale for Bipolar Disorder (CGI-BP) score of 1 or 2; 30% of study participants met criteria for remission.[23]

Antidepressants

In a chart review of 42 outpatient youth with bipolar disorder in a depressive episode, depressive symptoms were 6.7 times more likely to improve for youth who received selective serotonin reuptake inhibitors (SSRIs) than those who did not.[24] However, youth on SSRIs were 3 times more likely to have emergence or worsening manic symptoms than youth not on SSRIs.

A case report of a 17-year-old girl with bipolar disorder stable on valproate and olanzapine described deterioration of mood with emergence of manic symptoms two days after duloxetine was prescribed for a depressive episode.[25] Her symptoms included decreased sleep, euphoria, grandiosity, and excessive speech, with cycling between euphoria and sadness every four days. Duloxetine was discontinued, the valproate dose was increased, and the manic symptoms subsequently resolved.

A review article examined the potential of antidepressants to induce manic episodes in bipolar youth.[26] The studies reviewed showed evidence of an increased risk of mania in bipolar youth treated with antidepressants. Placebo-controlled studies are needed to clarify the efficacy and safety of adding antidepressants to existing mood stabilizers in bipolar depressed youth.

Alternative Treatments

A 16-week, double blind, randomized-controlled trial examined the efficacy of adjunctive or monotherapy flax oil in youth, ages 6–17 years, with bipolar I or bipolar II disorder, manic, hypomanic, mixed, or depressed.[27] The youth were randomized to either an olive oil placebo or flax oil [550 mg of omega-3 fatty acid α-linolenic acid (α-LNA)]. The dose was titrated to 12 capsules per day as tolerated over 16 weeks. There were no differences between the two groups when comparing scores on all the efficacy measures, including the CDRS-R, which was the primary depression efficacy measure used in this study.

Psychotherapy

The efficacy of adjunctive cognitive-behavioral therapy (CBT) for 16 adolescents with bipolar I, II, NOS, or

https://doi.org/10.1017/S1092852913000217 Published online by Cambridge University Press

cyclothymia was assessed in a 12 week randomized study.[28] Twelve study participants had a diagnosis of bipolar I disorder, 3 had bipolar II disorder, and 1 had cyclothymia. Eight adolescents received individual CBT along with pharmacological treatment, and 8 adolescents received no adjunctive psychosocial interventions. The group receiving CBT showed a significant decrease in depressive symptoms on the parent-rated General Behavior Inventory (GBI). No significant change in symptoms was reported on the child-rated GBI or on interview-administered measures of depression using the Inventory of Depressive Symptoms (IDS).

Ten adolescents, with bipolar I, II, or NOS, manic, mixed, or depressed received adjunctive dialectical behavioral therapy in an open study.[29] Seven study participants had a diagnosis of bipolar I disorder, 2 had bipolar II disorder, and 1 had bipolar disorder NOS. The course of treatment included 24 weekly sessions over 6 months, then 12 sessions tapering in frequency through 1 year. Sessions included family skills training and individual therapy. Significant improvements in suicidality, emotional dysregulation, and depressive symptoms were found.

One randomized controlled trial examined the efficacy of multifamily psychoeducational psychotherapy for mood symptoms in 165 children.[30] Seventy percent of the subjects had some form of bipolar disorder, and 30% had a depressive disorder. The primary outcome measure was the Mood Severity Index, calculated from a combination of CDRS-R and the Mania Rating Scale ratings at each assessment.[31] Subjects randomized to the multifamily psychoeducational psychotherapy plus treatment as usual showed significant improvement in mood severity scores from baseline to endpoint when compared to subjects in the wait list control plus treatment as usual group, with a decrease in their mean MSI score of 6.48 more than the control group.

Conclusion

Bipolar disorder in children and adolescents has a chronic course, marked by relapse of symptoms in a high percentage of patients. Youth with bipolar disorder spend a significant amount of time in depressive episodes during the course of their illness. They also experience more frequent depressive episodes and lower functioning than those with unipolar depression. Bipolar depression in this population is more likely to present with more severe depressive symptoms than unipolar depression, including a higher risk of suicidality. However, evidence-based pharmacological treatment for bipolar depression in children and adolescents is limited to mostly small open studies, and evidence for psychosocial interventions is not specific to bipolar depression. Large controlled studies are needed to examine the efficacy of pharmacological and psychotherapy treatments for bipolar depression in the pediatric population.

Disclosures

Dr. DeFilippis has nothing to disclose. Dr. Wagner for the period 3/2012 to 3/2013 has received honoraria from UBM Medica, American Psychiatric Association, Slack Inc., Las Vegas Psychiatric Society, Partners Healthcare, Brain and Behavior Research Foundation, NAC CME, and the University of Wisconsin.

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**(4): 454–463.
2. Merikangas KR, He JP, Burstein M, *et al*. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*. 2010; **49**(10): 980–989.
3. Merikangas KR, Cui L, Kattan G, *et al*. Mania with and without depression in a community sample of US adolescents. *Arch Gen Psychiatry*. 2012; **69**(9): 943–951.
4. Merikangas K, Lamers F. The "true" prevalence of bipolar II disorder. *Curr Opin Psychiatry*. 2011; **25**(1): 19–23.
5. Faedda GL, Baldessarini RJ, Glovinsky IP, *et al*. Pediatric bipolar disorder: phenomenology and course of illness. *Bipolar Disord*. 2004; **6**(4): 305–313.
6. Dilsaver SC, Benazzi F, Akiskal HS. Mixed states: the most common outpatient presentation of bipolar depressed adolescents? *Psychopathology*. 2005; **38**(5): 268–272.
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text rev. Washington, DC: American Psychiatric Association; 2000.
8. Wozniak J, Spencer T, Biederman J, *et al*. The clinical characteristics of unipolar vs. bipolar major depression in ADHD youth. *J Affect Disord*. 2004; **82**(Suppl 1): S59–S69.
9. Wagner KD, Findling RL, Emslie GJ, *et al*. Validation of the Mood Disorder Questionnaire for Bipolar Disorders in Adolescents. *J Clin Psychiatry*. 2006; **67**: 827–830.
10. Youngstrom EA, Frazier TW, Findling RL, *et al*. Developing a ten item short form of the Parent General Behavior Inventory to assess for juvenile mania and hypomania. *J Clin Psychiatry*. 2008; **69**: 831–839.
11. Pavuluri MN, Henry DB, Devineni B, *et al*. Child mania rating scale: development, reliability, and validity. *J Am Acad Child Adolesc Psychiatry*. 2006; **45**: 550–560.
12. Wozniak J, Petty CR, Schreck M, *et al*. High level of persistence of pediatric bipolar-I disorder from childhood onto adolescent years: a four year prospective longitudinal follow-up study. *J Psychiatr Res*. 2011; **45**(10): 1273–1282.

13. Jairam R, Srinath S, Girimaji SC, *et al*. A prospective 4–5 year follow-up of juvenile onset bipolar disorder. *Bipolar Disord*. 2004; **6**(5): 386–394.
14. Birmaher B, Axelson D, Goldstein B, *et al*. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. *Am J Psychiatry*. 2009; **166**(7): 795–804.
15. Geller B, Tillman R, Craney JL, *et al*. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. *Arch Gen Psychiatry*. 2004; **61**(5): 459–467.
16. Geller B, Tillman R, Bolhofner K, *et al*. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. *Arch Gen Psychiatry*. 2008; **65**(10): 1125–1133.
17. DelBello MP, Chang K, Welge JA, *et al*. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disord*. 2009; **11**(5): 483–493.
18. Chang K, Saxena K, Howe M. An open-label study of lamotrigine adjunct or monotherapy for the treatment of adolescents with bipolar depression. *J Am Acad Child Adolesc Psychiatry*. 2006; **45**(3): 298–304.
19. Biederman J, Joshi G, Mick E, *et al*. A prospective open-label trial of lamotrigine monotherapy in children and adolescents with bipolar disorder. *CNS Neurosci Ther*. 2010; **16**(2): 91–102.
20. Soutullo CA, Díez-Suárez A, Figueroa-Quintana A. Adjunctive lamotrigine treatment for adolescents with bipolar disorder: retrospective report of five cases. *J Child Adolesc Psychopharmacol*. 2006; **16**(3): 357–364.
21. Patel NC, DelBello MP, Bryan HS, *et al*. Open-label lithium for the treatment of adolescents with bipolar depression. *J Am Acad Child Adolesc Psychiatry*. 2006; **45**(3): 289–297.
22. Poznanski EO, Freman LN, Mokros HB. Children's Depression Rating Scale–Revised. *Psychopharmacol Bull*. 1985; **21**: 979–989.
23. Spearing MK, Post RM, Leverich GS, *et al*. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res*. 1997; **73**(3): 159–171.
24. Biederman J, Mick E, Spencer TJ, *et al*. Therapeutic dilemmas in the pharmacotherapy of bipolar depression in the young. *J Child Adolesc Psychopharmacol*. 2000; **10**(3): 185–192.
25. Desarkar P, Bakhla A, Sinha VK. Duloxetine-induced ultrarapid cycling in an adolescent with bipolar depression. *J Clin Psychopharmacol*. 2007; **27**(1): 115–116.
26. Goldsmith M, Singh M, Chang K. Antidepressants and psychostimulants in pediatric populations: is there an association with mania? *Pediatr Drugs*. 2011; **13**(4): 225–243.
27. Gracious BL, Chirieac MC, Costescu S, *et al*. Randomized, placebo-controlled trial of flax oil in pediatric bipolar disorder. *Bipolar Disord*. 2010; **12**(2): 142–154.
28. Feeny NC, Danielson CK, Schwartz L, *et al*. Cognitive-behavioral therapy for bipolar disorders in adolescents: a pilot study. *Bipolar Disord*. 2006; **8**(5): 508–515.
29. Goldstein TR, Axelson DA, Birmaher B, *et al*. Dialectical behavior therapy for adolescents with bipolar disorder: a 1-year open trial. *J Am Acad Child Adolesc Psychiatry*. 2007; **46**(7): 820–830.
30. Fristad MA, Verducci JS, Walters K, *et al*. Impact of multifamily psychoeducational psychotherapy in treating children aged 8 to 12 years with mood disorders. *Arch Gen Psychiatry*. 2009; **66**(9): 1013–1021.
31. Young RC, Biggs JT, Ziegler VE, *et al*. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978; **133**: 429–435.