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THERAPY IN PRACTICE

Bipolar Depression in Pediatric Populations

Epidemiology and Management

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Abstract Depression in children and adolescents with bipolar disorder is more commonly observed than mania or hypomania, and is associated with significant functional disability in multiple environmental realms. Optimal management of pediatric bipolar depression is often defined by its multimodal nature with emphasis on both psychopharmacological and psychosocial treatment. This article provides a brief overview of the epidemiology and clinical course of pediatric bipolar depression, a clinically-oriented guide to the evidence-based psychopharmacological and psychosocial management of bipolar depression in youth, and suggestions on how best to integrate medication and therapy. Recommended treatment for bipolar depression in pediatric populations usually includes both medication and psychosocial interventions given a paucity of double-blind, placebo-controlled psychopharmacological studies. Lithium and lamotrigine are feasible and tentatively efficacious options; however, treatment with quetiapine monotherapy may be no better than placebo. Furthermore, some youth may be at heightened risk for developing manic symptoms after treatment with selective serotonin reuptake inhibitors (SSRIs). Psychotherapy, either alone or adjunctively with medications, provides practitioners with a safe and feasible alternative. Interpersonal and Social Rhythm Therapy for Adolescents (IPSRT-A), Child- and Family-Focused Cognitive Behavioral Therapy (CFF-CBT), Dialectical Behavior Therapy for Adolescents (DBT-A), family psychoeducation, and Family Focused Therapy for Adolescents (FFT-A) are evidence-based treatments available to clinicians treating youth with bipolar depression.

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1 Introduction

Early onset of bipolar disorder typically presents with a severe, unremitting course replete with mixed episodes, psychosis, and suicidal thoughts and behaviors [1–3]. While much literature has concentrated on defining and treating the manic phase of the disorder in youth, bipolar depression in youth is actually more commonly observed than mania or hypomania and can be equally debilitating [4]. Without adequate treatment, youth with bipolar depression may demonstrate compromised development in both environmental and neurobiological dimensions [5, 6]. After succinctly reviewing what is currently known about its epidemiology and clinical course, this article will provide a brief, clinically oriented guide to the optimal treatment of pediatric bipolar depression. It will conclude by emphasizing the need for a multimodal (i.e. psychopharmacological, psychosocial) treatment plan for pediatric bipolar depression.

2 Epidemiology and Clinical Course

The rates of diagnosis and treatment of bipolar disorders in children and adolescents have soared in recent years [7]. Office-based visits for youth with a diagnosis of bipolar disorder increased 40-fold between the mid-1990s and 2003 [7]. A recent meta-analysis of epidemiologic studies suggests that the overall rate of bipolar spectrum disorders in community samples is about 1.8 % in youth [8]. Although extensive scientific investigation and clinical interest has focused on mania and hypomania in younger populations [9, 10], youth may spend as much time experiencing depressive symptoms as adults with bipolar disorder [11].

2.1 How Common is Bipolar Depression in Youth?

Depression occurring for the first time in childhood may represent a unipolar major depressive episode or a bipolar depressive episode. In some cases, first episode bipolar depression will be misdiagnosed as unipolar depression. While a family history positive for bipolar disorder is a good indicator of possible bipolar depression [12], a bipolar diagnosis is not often confirmed until symptoms of mania later emerge. Research suggests that children diagnosed with unipolar depression before puberty may be at elevated risk for later meeting diagnostic criteria for a bipolar spectrum illness [13]. One study suggests that close to 50 % of children with unipolar depression go on to experience mania or hypomania [14].

Because a first manic episode is often what precedes the initiation of formal treatment (i.e. outpatient psychiatry/psychology visit, hospitalization, etc.) for youth with bipolar disorder, it is difficult to conclude with certainty the incidence of bipolar depression in children and adolescents. While bipolar depression has been less studied than mania in pediatric bipolar disorder, a study involving over 400 children and adolescents with bipolar disorder found that greater than 50 % of youth diagnosed with a bipolar spectrum disorder (I, II, or not otherwise specified [NOS]) reported at least one lifetime major depressive episode [15]. Furthermore, more than 70 % endorsed lifetime suicidal ideation, a core clinical symptom of depression [15].

2.2 Clinical Presentation and Course

Pediatric patients with bipolar disorder may experience full depressive episodes or subsyndromal depressive symptomatology. Common symptoms of bipolar and unipolar depression include feelings of sadness and unhappiness, loss of interest or pleasure in normal activities, troublesome sleeping patterns, slowed thinking or body movements, distractibility, fatigue, and frequent thoughts of death and dying. Irritability, commonly observed in pediatric depression, has garnered particular attention because it tends to occur within the contexts of both bipolar depression and mania [16]. In pediatric bipolar depression, irritability may occur without any accompanying elation or high mood [17].

It is worth noting that mixed episodes occur commonly in pediatric bipolar disorder. In a 4-year prospective study of youth diagnosed with mania at baseline, individuals met criteria for mixed diagnoses (e.g. mania and major depression, hypomania and major depression, mania and dysthymia, or cyclothymia) during nearly 40 % of the follow-up period [18]. Mixed presentations in youth with bipolar disorder have been linked to an increased likelihood of attempting suicide [19].

Youth diagnosed with bipolar disorder may be more likely to relapse into a major depressive episode than into hypomanic, manic, or mixed episodes. In a 4-year follow-up of more than 400 children and adolescents diagnosed with bipolar I, II, and NOS disorder, youth were more likely to relapse into depressive or mixed episodes than manic episodes [20, 21]. Furthermore, polarity of index episode appeared to predict polarity of recurrent episodes. In other words, youth diagnosed with bipolar disorder and whose first mood episode is depressive in nature may go on to experience more subsequent episodes of depression than mania.

3 Psychopharmacological Management

In recent years, several reviews have provided an analysis of the evidence-based psychopharmacological management of pediatric bipolar disorder [22–24]. Evidence-based research has primarily informed clinicians on treating mania in children and adolescents. In many cases, inclusion in randomized, controlled trials for pediatric bipolar disorder has depended on symptoms of mania, and the primary outcome measure of remission has frequently been the Young Mania Rating Scale (YMRS) [25]. Few controlled trials of medications specifically for pediatric bipolar depression exist [26]; thus, there is an immediate need for more open-label and placebo-controlled trials of medications in this population. Sections 3.1, 3.2, 3.3, 3.4 intend to briefly survey the specific evidence base for medications indicated in the treatment of pediatric bipolar depression, and provide clinically relevant recommendations.

3.1 Selective Serotonin Reuptake Inhibitors and Other Antidepressants

For the treatment of unipolar depression in youth, selective serotonin reuptake inhibitors (SSRIs) are considered a safe, first-line treatment for moderate to severe depressive symptoms [27]. However, the use of SSRIs and other classes of antidepressants for the treatment of bipolar depression in youth is complicated by evidence in the adult literature that a switch between affective poles may occur in more than one-third of adults treated with antidepressants [28–30]. A recent review of the existing literature concluded that while SSRIs may improve depressive symptomatology in youth with bipolar disorder, they may also induce symptoms of mania in some children [31]. Because of this risk, the American Academy of Child and Adolescent Psychiatry practice parameters recommends use of SSRIs and other antidepressants only in conjunction with antimanic or mood-stabilizing agents [32]. However,

there is no empirical data to support the efficacy or safety of antidepressants in youth with bipolar depression.

From a practical perspective, depressive symptoms experienced by youth with pediatric bipolar disorder can be exceptionally disabling. Frequently, anhedonia and psychomotor retardation are severe enough to preclude a child's socializing with friends, participating in extracurricular activities, or attending school. The risk of potentially inducing mania as a result of treatment with SSRIs or other antidepressants must be weighed against the potential therapeutic benefits as well as the very real suicide risk that often accompanies severe depression [33]. Clinicians treating pediatric bipolar depression with antidepressants should do so with high vigilance. In general, it is recommended that other options, discussed below in Sects. 3.2, 3.3, 3.4 and 4.1, 4.2, 4.3, 4.4, 4.5, are considered first.

3.2 Lithium

Because of its well-established antimanic properties and potential for antidepressant effects, lithium is considered by many to anchor the psychopharmacological management of bipolar disorder in adults [34]. Although lithium was the first medication approved by the US FDA for the treatment of pediatric bipolar disorder in children over 12 years of age, relatively few studies have examined its efficacy using controlled designs [35]. One open-label study examined the effectiveness and tolerability of lithium for the treatment of depression in 27 adolescents aged 12–18 years with bipolar I disorder [36]. Side effects were moderate and did not lead to abnormally high attrition. Response, defined by a $\geq$50 % reduction in Children's Depression Rating Scale-Revised (CDRS-R) [37] scores from baseline to endpoint, was reported for 48 % of subjects, suggesting plausible effectiveness in pediatric bipolar depression. Placebo-controlled studies would be necessary to conclusively determine whether lithium's antidepressant properties are robust in pediatric bipolar disorder. Clinicians should currently consider using lithium to treat pediatric bipolar depression.

3.3 Quetiapine

Because of durable evidence supporting quetiapine in the treatment of adult bipolar depression [38], the efficacy of quetiapine monotherapy was investigated in 32 adolescents aged 12–18 years diagnosed with bipolar I disorder and currently experiencing a depressive episode in the first, published, double-blind, placebo-controlled trial in pediatric bipolar depression [39]. Quetiapine and placebo groups did not significantly differ in change from baseline to endpoint CDRS-R scores, suggesting that quetiapine alone may be no better than placebo treatment in its therapeutic effects on pediatric bipolar depression. While quetiapine was generally well tolerated, high rates of gastrointestinal-related adverse events and increased levels of triglycerides were associated with quetiapine treatment. This was a small, two-site study reporting a high placebo response rate (67 %), so eliminating quetiapine as a viable treatment option for pediatric bipolar depression will require more rigorous examination with larger, double-blind studies. However, given the gold standard nature of this double-blind study, prescribing clinicians considering quetiapine as a feasible treatment option should do so only after consulting this study's findings.

3.4 Lamotrigine

In the last decade, lamotrigine has emerged as a first-line treatment for the management of bipolar depression in adults [40]. Lamotrigine was studied as adjunctive or monotherapy in youth aged 12–17 years with bipolar depression [41] using an 8-week, open-label design. Sixty-three percent of subjects showed at least a 50 % reduction in CDRS-R scores by 8 weeks of lamotrigine treatment. Since this was an open study, bias affecting mood ratings was a distinct possibility. Lamotrigine was well-tolerated, and minimal weight gain was observed. While placebo-controlled studies of lamotrigine in children and adolescents are needed to unambiguously determine its efficacy in young populations, this open trial offers some preliminary evidence that lamotrigine may be a feasible alternative in treating pediatric bipolar depression.

4 Management with Psychosocial Intervention

Since the National Institutes of Mental Health convened a roundtable to reach an expert consensus regarding how to define prepubertal bipolar disorder in 2001 [42], psychosocial treatments have been developed and adapted to meet the needs of a younger group of patients with bipolar spectrum disorders [43]. Many therapeutic components of protocol-driven, psychosocial interventions for the treatment of pediatric bipolar disorder may be particularly useful for management of bipolar depression in youth. Multiple psychosocial interventions are reviewed below and, when available, the evidence base for treating depression is briefly discussed.

4.1 Interpersonal and Social Rhythm Therapy for Adolescents (IPSRT-A)

Interpersonal and Social Rhythm Therapy (IPSRT) was initially developed as a maintenance treatment in adult bipolar disorder and intended to lengthen time between

episodes by reducing interpersonal stress. Two large-scale studies in adults have demonstrated its efficacy in acute and maintenance treatment of bipolar depression [44, 45]. Adjunctive IPSRT for Adolescents (IPSRT-A) was adapted from IPSRT for adults to be developmentally sensitive to adolescents with bipolar disorder [46]. Like its adult counterpart, resolution of interpersonal problem areas and regulation of sleep and social rhythms are the focus of IPSRT-A. It has been shown to be feasible and well accepted in an open trial with adolescents [47].

The premise of IPSRT and IPSRT-A is that bipolar disorder is at least in part precipitated by a vulnerability of biological systems to dysregulation and sensitivity to interpersonal stressors. IPSRT-A addresses interpersonal problem areas within the context of adolescent development. Discussion is usually focused on interpersonal disputes with parents and difficulties in transitioning between childhood and young adulthood via sexual and emotional maturation. Results from a small open trial showed that in addition to being feasible and well tolerated by adolescents with bipolar disorder, IPSRT-A treatment resulted in significant decreases in depressive symptoms [47].

Developmental theory points to interpersonal factors such as negative feedback from parents, parenting styles, peer rejection, and peer victimization as playing appreciable roles in the evolution of cognitive vulnerability to depression [48]. Directly addressing problematic interpersonal situations with youth with bipolar depression using IPSRT-A may bolster a child's arsenal of coping skills, staving off the development or return of depressive symptoms in response to conflict. Additionally, children and adolescents practice regulating sleep, eating, and general body rhythms, examining positive benefits on psychosocial functioning in school and mood.

4.2 Child- and Family-Focused Cognitive Behavioral Therapy (CFF-CBT)

Many elements of Child- and Family-Focused Cognitive Behavioral Therapy (CFF-CBT) make it an especially relevant treatment for bipolar depression in youth. CFF-CBT, originally developed as an individual treatment for children aged 8–12 years and their parents, amalgamates approaches from cognitive-behavioral and interpersonal psychotherapies to maximize a child's ability to function in the world—with his family, at school, and with friends. Thus, it places equal emphasis on ameliorating mood symptoms and improving functioning within the family as well as within other social contexts. One feature of CFF-CBT is that parents and children learn about the illness and its impact on psychosocial functioning [49].

Formal individual CFF-CBT consists of 12 weekly, 1-hour sessions mostly involving both parents and child together. CFF-CBT has also been modified into a group format, consisting of 12 weekly, 1.5-hour group sessions that run in parallel for parents and children. Key components of CFF-CBT consist of developing regular daily routines, regulating affect, refining coping skills, reducing negative thoughts, developing a balanced lifestyle, learning how to better solve problems, and developing ways to get support [49]. Learning about healthy routines around activities such as eating and sleeping and developing balance both fall under the purview of psychoeducation, which has been shown to lengthen time to relapse when delivered in conjunction with psychopharmacological treatment in adults with bipolar disorder [50]. Similarly, learning skills that aid in reducing negative thoughts and solving problems are within the scope of cognitive behavioral therapy, a widely accepted treatment for treating depressive symptoms in children and adolescents [51].

Open trials of individual CFF-CBT have demonstrated significant reductions in acute symptoms of depression as well as protracted remission of depressive symptoms when maintenance CFF-CBT booster sessions were administered intermittently for up to 3 years [49, 52]. A recent small pilot study showed the feasibility and acceptability of group CFF-CBT for families with a child struggling with bipolar disorder [53]. While measurable improvements were observed in manic but not depressive symptoms, children who received CFF-CBT reported greater levels of psychosocial functioning after treatment, and their parents reported an enhanced ability to cope with the reality of the illness [53]. With greater coping abilities, parents may feel more hopeful about their child's future, feel empowered to provide better care, and advocate for better treatment. The specific effect, therefore, on depressive symptoms is not clear, but as children may benefit from access to better treatment and positive perception of parental messages, CFF-CBT could lead to a reduction in depressive symptoms associated with pediatric bipolar disorder [54].

4.3 Dialectical Behavior Therapy for Adolescents (DBT-A)

Dialectical Behavior Therapy (DBT) was originally developed to treat adults with borderline personality disorder [55]. DBT therapists validate an individual's efforts to make positive changes in his/her life, impede troublesome behaviors, and encourage good behaviors in an effort to help individuals create a life worth living defined by more than their mood symptoms. DBT is often particularly useful for teaching individuals how to regulate their mood as well as preventing self-injurious behaviors and suicide attempts. The usefulness and feasibility of DBT for treating adolescents with suicidal and self-injurious behavior was demonstrated in two recent uncontrolled trials [56, 57].

Statistically significant improvement in suicidality, non-suicidal self-injurious behavior, emotional dysregulation, and depressive symptoms was reported in a pilot study of ten adolescents diagnosed with bipolar disorder and treated with DBT [58]. Formally, DBT adapted for adolescents (DBT-A) with bipolar disorder has been designed to be delivered over a 1-year period, but like IPSRT-A it can be easily adapted to a variety of treatment settings. DBT-A is hypothesized to work by helping children to regulate their responses to emotional stimuli. Like DBT for adults, DBT-A clients are encouraged to attend both a skills training group as well as individual therapy, where they learn to apply skills in their own lives at school and home [58].

Since children and adolescents with pediatric bipolar depression may be at elevated risk of experiencing suicidal ideation and attempting or completing suicide [59, 60], DBT-A may be a clinically appropriate choice for bipolar youth with substantial suicidal tendencies or a history of attempts. Furthermore, both irritable mood and mood lability are well-documented symptoms of pediatric bipolar depression [16] that may be effectively targeted with DBT-A emotion regulation skills.

4.4 Family Psychoeducation

Providing education about bipolar depression may help parents and other family members better understand the illness and empathize with the affected child. Since pediatric bipolar depression is often characterized by extreme irritability [61], family members may become easily frustrated with the affected child unless they receive appropriate education about the typical clinical presentation of bipolar depression in youth. Delivering psychoeducation is an active component of many psychotherapies that treat bipolar and unipolar depression in adults and youth [62, 63]. Fristad and colleagues have shown that providing psychoeducation to the family of a child with bipolar disorder, as well as to the affected child in a multi-family group format, may not only enhance a family's understanding of mood disorders[64] but may also lead to lower levels of depression [65].

Formal multi-family group psychoeducation as designed by Fristad et al. consists of eight 90-minute, concurrent sessions for parents and children [66]. The first two sessions emphasize signs and symptoms of childhood mood disorders as well as medication treatment options. The remaining sessions underscore family dynamics, problem-solving techniques, coping mechanisms, and verbal and non-verbal communication [67]. However, disseminating education about mood symptoms and triggers need not be done in a multi-family format to be effective. Clinicians treating children and adolescents with bipolar depression should include psychoeducational elements into routine treatment sessions.

4.5 Family-Focused Therapy for Adolescents (FFT-A)

Parental and sibling relationships within a family, and how conflict is negotiated within a particular family, may impact the course of a child's bipolar depression [68]. Building on the family group psychoeducation approach, family-focused therapy (FFT) aims to decrease overall stress for the child by building and strengthening family relationships, potentially precipitating fewer mood symptoms and episode relapses. Originally designed for adults, FFT was shown to be effective for decreasing depressive symptoms in a randomized, controlled trial in adults with bipolar disorder [69, 70].

Miklowitz and colleagues adapted FFT for adolescents with bipolar disorder (FFT-A) [71]. FFT-A consists of three modules that help families build a repository of skills. In the first module entitled Psychoeducation, therapists provide education to the family tailored to the young person's individual experience of the bipolar disorder. Therapists work with children and their families to understand the frequent need for psychiatric medication as well as to illuminate environmental (e.g. conflict with family members, academic stress, etc.) and biological (e.g. sleep, eating) factors that trigger mood episodes. In Communication Enhancement Training, family members practice communicating with one another by listening actively, expressing positive feelings, making positive requests for change, and expressing negative emotions about specific behaviors. Finally, in the Problem Solving phase, families identify, agree upon, and generate solutions for common problem areas within the family using communication skills developed in the previous weeks.

FFT-A may be particularly useful for treating pediatric bipolar depression. In a 2-year randomized trial comparing FFT-A with an education control in youth aged 12–17 years, FFT-A effectively stabilized symptoms of bipolar depression [71, 72]. FFT-A may also be helpful in preventing symptoms of bipolar disorder from evolving in youth already at high risk for bipolar disorder (e.g. parent with bipolar disorder and subsyndromal mood symptoms [73].

5 Future Directions: Alternative Approaches to Management

As the search for effective treatments for the management of pediatric bipolar depression continues, researchers have begun to consider therapeutic alternatives that have shown potency in other areas of psychiatry [74]. For example, some research suggests that levels of omega-3 fatty acids are linked with better outcome in mood disorders [75–77]. Results from one small, open-label trial suggest that

omega-3 fatty acid monotherapy may lead to improvement in manic symptoms in pediatric bipolar disorder [78]. However, supplementation of psychiatric treatment with omega-3 fatty acid during a small, randomized, placebo-controlled study did not lead to manic or depressive symptom improvement in children and adolescents with bipolar I or II disorder [79].

Electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) are two other alternative or supplementary treatment options available for children and adolescents with bipolar depression. While ECT is generally considered safe and effective for adults with mood disorders [80], it is usually only administered in youth after all other options have been exhausted and symptoms are crippling [81]. Although controlled trials examining ECT in pediatric bipolar depression do not exist, experts recommend considering ECT when other options have proven ineffective [26]. rTMS, has shown a moderate effect on treatment of depression in adults [82], and there is increasing interest in using rTMS to treat depression in youth [83]. Given its non-invasive nature, rTMS may prove a valid alternative treatment for pediatric bipolar depression and warrant further investigation [84].

6 Conclusions: Multimodal Approach to Management

The treatment of bipolar depression has not been as thoroughly studied as treatments for mania and hypomania in children and adolescents. Although the continuity between pediatric and adult bipolar psychopathology is debated among experts [85, 86], a child accurately diagnosed with bipolar disorder is likely to experience one or more major depressive episodes during his or her lifetime. Such episodes are debilitating and potentially dangerous given that depression is associated with elevated levels of psychosocial disability as well as suicide attempts and completed suicides.

Given high morbidity and risk of suicide in pediatric bipolar depression, medication treatment should be initiated when depressive symptoms are moderate to severe. Despite limited data, a trial with lamotrigine is currently considered first-line, and lithium second. Should neither agent prove efficacious, clinicians may wish to consider quetiapine. Open-label data supports tolerability and tentative efficacy of lamotrigine and lithium for the clinical management of pediatric bipolar depression, although more rigorous scrutiny of these agents is needed to fully understand their utility. The only double-blind study of a medication for pediatric bipolar depression sheds doubt on the efficacy of quetiapine monotherapy over placebo. Given the high placebo response rate in that study, it may be that adolescents with bipolar depression respond well to psychosocial interventions in general.

Although there is an absence of efficacy data and some evidence that they may induce mania in youth with bipolar disorder [87], antidepressants are often considered on a case-by-case basis when no family history of antidepressant-induced mania is evident and trials with lithium, quetiapine, and/or lamotrigine have not been successful. However, bupropion treatment may be considered before other antidepressants since evidence from the adult literature suggests lower rates of switches to mania or hypomania [88].

Psychotherapy, on the other hand, offers a comparatively safe alternative as an adjunct to psychopharmacological intervention. Psychotherapy should be instituted regardless of the decision whether to treat bipolar depression with addition medications. In cases of mild depression, psychotherapy could be initiated first-line to see if there is an adequate response to psychosocial intervention before adding a medication. For patients with moderate to severe depression that is functionally disabling, a combination of medications and psychotherapy is currently the recommended treatment of choice. With such an aggregate, families benefit from the possibility that a child with pediatric bipolar depression will benefit from one or two treatments as well as from the interaction with multiple treatment providers.

Several available psychotherapeutic approaches may be particularly applicable to depressive symptoms in pediatric bipolar disorder. Randomized trial data supports the use of family psychoeducation and FFT as adjunctive treatments for bipolar depression in youth, and open data suggests that IPSRT-A, DBT-A, and CFF-CBT may also be efficacious as adjunctive treatments. Psychotherapeutic components such as psychoeducation and skills training (e.g. interpersonal, emotional, cognitive, etc.), common to multiple treatment modalities, may be attractive to parents who are eager to shepherd their children toward productive and healthy adulthoods.

Given the insufficient number of existing randomized, double-blind, placebo-controlled trials specifically examining psychotropic agents in the treatment of pediatric bipolar depression, a multimodal approach to treatment is recommended, including medication and psychosocial interventions. Additionally, combining psychopharmacological and psychotherapeutic management strategies for pediatric bipolar depression may be particularly germane given the frequency of mixed presentations in youth, which, although common, we do not discuss separately in this review as treatment of mixed states are often lumped together with manic states. For example, many randomized, controlled trials for the treatment of mania include data from youth in mixed as well as manic states. But specific tools from psychosocial interventions can be safe, appropriate and useful for the management of manic,

hypomanic, and depressive symptoms. With fluctuating or mixed symptom presentations, alterations to medication may become necessary. In such cases, appropriate management with protocol-driven psychotherapies may protect children and adolescents from severe symptom relapses.

Depression in youth where there is a strong family history of bipolar disorder is a special case. Children and adolescents who fall into this category may constitute a unique group at elevated risk for developing bipolar disorder [89]. Treatment approaches for this specialized group are beyond the scope of this article but have been previously reviewed in the existing literature [31, 90]

Clinical acumen surrounding pediatric bipolar disorder has advanced in leaps and bounds in recent years [91]. However, current treatment recommendations for pediatric bipolar depression are primarily informed by a small number of open psychopharmacological and psychosocial treatment studies and by even fewer randomized, controlled studies. As research continues to inform clinical practice, clinicians will gain access to additional psychopharmacological and psychosocial treatment options.

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References

1. Geller B, Zimerman B, Williams M, et al. Six-month stability and outcome of a prepubertal and early adolescent bipolar disorder phenotype. J Child Adolesc Psychopharmacol. 2000;10(3):165–73.
2. 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(6):927–33.
3. Leverich GS, Post RM, Keck PE, et al. The poor prognosis of childhood-onset bipolar disorder. J Pediatr. 2007;150(5):485–90.
4. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry. 2005;44(9):846–71.
5. Miklowitz DJ, Cicchetti D. Toward a life span developmental psychopathology perspective on bipolar disorder. Dev Psychopathol. 2006;18(4):935–8.
6. Kloos A, Weller EB, Weller RA. Biologic basis of bipolar disorder in children and adolescents. Curr Psychiatry Rep. 2008;10(2):98–103.
7. Moreno C, Laje G, Blanco C, et al. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Arch Gen Psychiatry. 2007;64(9):1032–9.
8. Van Meter AR, Moreira ALR, Youngstrom EA. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. J Clin Psychiatry. 2011;72(9):1250–6.
9. Stringaris A, Baroni A, Haimm C, et al. Pediatric bipolar disorder versus severe mood dysregulation: risk for manic episodes on follow-up. J Am Acad Child Adolesc Psychiatry. 2010;49(4):397–405.
10. Horwitz SM, Demeter CA, Pagano ME, et al. Longitudinal Assessment of Manic Symptoms (LAMS) study: background, design, and initial screening results. J Clin Psychiatry. 2010;71(11):1511–7.
11. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002;59(6):530–7.
12. Akiskal HS. Developmental pathways to bipolarity: are juvenile-onset depressions pre-bipolar? J Am Acad Child Adolesc Psychiatry. 1995;34(6):754–63.
13. Weissman MM, Wolk S, Wickramaratne P, et al. Children with prepubertal-onset major depressive disorder and anxiety grown up. Arch Gen Psychiatry. 1999;56(9):794–801.
14. 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(1):125–7.
15. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry. 2006;63(10):1139–48.
16. Youngstrom EA, Birmaher B, Findling RL. Pediatric bipolar disorder: validity, phenomenology, and recommendations for diagnosis. Bipolar Disord. 2008;10(1 Pt 2):194–214.
17. Stringaris A, Zavos H, Leibenluft E, et al. Adolescent irritability: phenotypic associations and genetic links with depressed mood. Am J Psychiatry. 2012;169(1):47–54.
18. 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):459–67.
19. Goldstein TR, Birmaher B, Axelson D, et al. History of suicide attempts in pediatric bipolar disorder: factors associated with increased risk. Bipolar Disord. 2005;7(6):525–35.
20. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry. 2006;63(2):175–83.
21. 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.
22. Hamrin V, Iennaco JD. Psychopharmacology of pediatric bipolar disorder. Expert Rev Neurother. 2010;10(7):1053–88.
23. Liu HY, Potter MP, Woodworth KY, et al. Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. J Am Acad Child Adolesc Psychiatry. 2011;50(8):749–62.e39.
24. Thomas T, Stansifer L, Findling RL. Psychopharmacology of pediatric bipolar disorders in children and adolescents. Pediatr Clin. N Am 2011; 58 (1): 173–87, xii.
25. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429–35.
26. Kowatch RA, Fristad M, Birmaher B, et al. Treatment guidelines for children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2005;44(3):213–35.
27. Taurines R, Gerlach M, Warnke A, et al. Pharmacotherapy in depressed children and adolescents. World J Biol Psychiatry. 2011;12(Suppl. 1):11–5.
28. Henry C, Sorbara F, Lacoste J, et al. Antidepressant-induced mania in bipolar patients: identification of risk factors. J Clin Psychiatry. 2001;62(4):249–55.

29. Truman CJ, Goldberg JF, Ghaemi SN, et al. Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Clin Psychiatry. 2007;68(10): 1472–9.
30. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. Bipolar Disord. 2003;5(6):407–20.
31. Goldsmith M, Singh M, Chang K. Antidepressants and psychostimulants in pediatric populations: is there an association with mania? Paediatr Drugs. 2011;13(4):225–43.
32. 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 (10 Suppl.): 157–76S.
33. Joseph MF, Youngstrom EA, Soares JC. Antidepressant-coincident mania in children and adolescents treated with selective serotonin reuptake inhibitors. Future Neurol. 2009;4(1):87–102.
34. Nivoli AMA, Murru A, Vieta E. Lithium: still a cornerstone in the long-term treatment in bipolar disorder? Neuropsychobiology. 2010;62(1):27–35.
35. Washburn JJ, West AE, Heil JA. Treatment of pediatric bipolar disorder: a review. Minerva Psichiatr. 2011;52(1):21–35.
36. 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):289–97.
37. Poznanski E, Freeman L, Mokros H. Children's depression rating scale-revised. Psychopharmacol Bull. 1985;21:979–89.
38. Janicak PG, Rado JT. Quetiapine monotherapy for bipolar depression. Expert Opin Pharmacother. 2011;12(10):1643–51.
39. 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):483–93.
40. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br J Psychiatry. 2009;194(1):4–9.
41. 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.
42. National Institute of Mental Health research roundtable on prepubertal bipolar disorder. J Am Acad Child. Adolesc Psychiatry. 2001;40(8):871–8.
43. West AE, Pavuluri MN. Psychosocial treatments for childhood and adolescent bipolar disorder. Child Adolesc Psychiatr Clin N Am. 2009; 18 (2): 471–82, x–xi.
44. Miklowitz DJ, Otto MW, Frank E, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. Arch Gen Psychiatry. 2007;64(4):419–26.
45. Frank E, Kupfer DJ, Thase ME, et al. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Arch Gen Psychiatry. 2005;62(9):996–1004.
46. Hlastala SA, Frank E. Adapting interpersonal and social rhythm therapy to the developmental needs of adolescents with bipolar disorder. Dev Psychopathol. 2006;18(4):1267–88.
47. Hlastala SA, Kotler JS, McClellan JM, et al. Interpersonal and social rhythm therapy for adolescents with bipolar disorder: treatment development and results from an open trial. Depress Anxiety. 2010;27(5):457–64.
48. Hankin BL, Oppenheimer C, Jenness J, et al. Developmental origins of cognitive vulnerabilities to depression: review of processes contributing to stability and change across time. J Clin Psychol. 2009;65(12):1327–38.
49. Pavuluri MN, Graczyk PA, Henry DB, et al. Child- and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: development and preliminary results. J Am Acad Child Adolesc Psychiatry. 2004;43(5):528–37.
50. Colom F, Lam D. Psychoeducation: improving outcomes in bipolar disorder. Eur Psychiatry. 2005;20(5–6):359–64.
51. Spirito A, Esposito-Smythers C, Wolff J, et al. Cognitive-behavioral therapy for adolescent depression and suicidality. Child Adolesc Psychiatr Clin N Am. 2011;20(2):191–204.
52. West AE, Henry DB, Pavuluri MN. Maintenance model of integrated psychosocial treatment in pediatric bipolar disorder: a pilot feasibility study. J Am Acad Child Adolesc Psychiatry. 2007;46(2):205–12.
53. West AE, Jacobs RH, Westerholm R, et al. Child and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: pilot study of group treatment format. J Can Acad Child Adolesc Psychiatry. 2009;18(3):239–46.
54. Stark KD, Schmidt KL, Joiner TE Jr. Cognitive triad: relationship to depressive symptoms, parents' cognitive triad, and perceived parental messages. J Abnorm Child Psychol. 1996;24(5):615–31.
55. Lynch TR, Trost WT, Salsman N, et al. Dialectical behavior therapy for borderline personality disorder. Annu Rev Clin Psychol. 2007;3:181–205.
56. Fleischhaker C, Böhme R, Sixt B, et al. Dialectical Behavioral Therapy for Adolescents (DBT-A): a clinical trial for patients with suicidal and self-injurious behavior and borderline symptoms with a one-year follow-up. Child Adolesc Psychiatry Ment Health. 2011;5(1):3.
57. Perepletchikova F, Axelrod SR, Kaufman J, et al. Adapting dialectical behaviour therapy for children: towards a new research agenda for paediatric suicidal and non-suicidal self-injurious behaviours. Child Adolesc Ment Health. 2011;16(2):116–21.
58. 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):820–30.
59. Algorta GP, Youngstrom EA, Frazier TW, et al. Suicidality in pediatric bipolar disorder: predictor or outcome of family processes and mixed mood presentation? Bipolar Disord. 2011; 13(1):76–86.
60. Goldstein TR. Suicidality in pediatric bipolar disorder. Child Adolesc Psychiatr Clin N Am. 2009; 18 (2): 339–52, viii.
61. Hunt J, Birmaher B, Leonard H, et al. Irritability without elation in a large bipolar youth sample: frequency and clinical description. J Am Acad Child Adolesc Psychiatry. 2009;48(7):730–9.
62. McCarty CA, Weisz JR. Effects of psychotherapy for depression in children and adolescents: what we can (and can't) learn from meta-analysis and component profiling. J Am Acad Child Adolesc Psychiatry. 2007;46(7):879–86.
63. Miklowitz DJ, Goodwin GM, Bauer MS, et al. Common and specific elements of psychosocial treatments for bipolar disorder: a survey of clinicians participating in randomized trials. J Psychiatr Pract. 2008;14(2):77–85.
64. Fristad MA, Goldberg-Arnold JS, Gavazzi SM. Multifamily psychoeducation groups (MFPG) for families of children with bipolar disorder. Bipolar Disord. 2002;4(4):254–62.
65. 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): 1013–21.
66. Fristad MA, Gavazzi SM, Mackinaw-Koons B. Family psychoeducation: an adjunctive intervention for children with bipolar disorder. Biol Psychiatry. 2003;53(11):1000–8.
67. Fristad MA. Psychoeducational treatment for school-aged children with bipolar disorder. Dev Psychopathol. 2006;18(4): 1289–306.
68. Miklowitz DJ, Johnson SL. Social and familial factors in the course of bipolar disorder: basic processes and relevant interventions. Clin Psychol (New York). 2009;16(2):281–96.

69. Miklowitz DJ, George EL, Richards JA, et al. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry. 2003;60(9):904–12.
70. Miklowitz DJ, Simoneau TL, George EL, et al. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biol Psychiatry. 2000;48(6):582–92.
71. Miklowitz DJ, George EL, Axelson DA, et al. Family-focused treatment for adolescents with bipolar disorder. J Affect Disord. 2004;82(Suppl. 1):S113–28.
72. Miklowitz DJ, Axelson DA, Birmaher B, et al. Family-focused treatment for adolescents with bipolar disorder: results of a 2-year randomized trial. Arch Gen Psychiatry. 2008;65(9):1053–61.
73. Potter M, Moses A, Wozniak J. Alternative treatments in pediatric bipolar disorder. Child Adolesc Psychiatr Clin N Am. 2009; 18 (2): 483–14, xi.
74. Miklowitz DJ, Chang KD, Taylor DO, et al. Early psychosocial intervention for youth at risk for bipolar I or II disorder: a one-year treatment development trial. Bipolar Disord. 2011;13(1): 67–75.
75. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J Clin Psychiatry. 2006;67(12):1954–67.
76. Hibbeln JR. Fish consumption and major depression. Lancet. 1998;351(9110):1213.
77. Parker G, Gibson NA, Brotchie H, et al. Omega-3 fatty acids and mood disorders. Am J Psychiatry. 2006;163(6):969–78.
78. Wozniak J, Biederman J, Mick E, et al. Omega-3 fatty acid monotherapy for pediatric bipolar disorder: a prospective open-label trial. Eur Neuropsychopharmacol. 2007;17(6–7):440–7.
79. Gracious BL, Chirieac MC, Costescu S, et al. Randomized, placebo-controlled trial of flax oil in pediatric bipolar disorder. Bipolar Disord. 2010;12(2):142–54.
80. Fink M. Electroconvulsive therapy resurrected: its successes and promises after 75 years. Can J Psychiatry. 2011;56(1):3–4.
81. Walter G, Rey JM. An epidemiological study of the use of ECT in adolescents. J Am Acad Child Adolesc Psychiatry. 1997; 36(6):809–15.
82. Loo CK, Mitchell PB. A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. J Affect Disord. 2005;88(3):255–67.
83. Croarkin PE, Wall CA, Lee J. Applications of transcranial magnetic stimulation (TMS) in child and adolescent psychiatry. Int Rev Psychiatry. 2011;23(5):445–53.
84. Stein D, Weizman A, Bloch Y. Electroconvulsive therapy and transcranial magnetic stimulation: can they be considered valid modalities in the treatment of pediatric mood disorders? Child Adolesc Psychiatr Clin N Am. 2006; 15 (4): 1035–56, xi.
85. Chang K. Adult bipolar disorder is continuous with pediatric bipolar disorder. Can J Psychiatry. 2007;52(7):418–25.
86. Carlson GA. Diagnostic stability and bipolar disorder in youth. J Am Acad Child Adolesc Psychiatry. 2011;50(12):1202–4.
87. Baumer FM, Howe M, Gallelli K, et al. A pilot study of antidepressant-induced mania in pediatric bipolar disorder: characteristics, risk factors, and the serotonin transporter gene. Biol Psychiatry. 2006;60(9):1005–12.
88. Post RM, Altshuler LL, Leverich GS, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry. 2006;189:124–31.
89. Goldstein BI, Shamseddeen W, Axelson DA, et al. Clinical, demographic, and familial correlates of bipolar spectrum disorders among offspring of parents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2010;49(4):388–96.
90. McNamara RK, Nandagopal JJ, Strakowski SM, et al. Preventative strategies for early-onset bipolar disorder: towards a clinical staging model. CNS Drugs. 2010;24(12):983–96.
91. Goldstein BI. Recent progress in understanding pediatric bipolar disorder. Arch Pediatr Adolesc Med. 2012;166(4):362–71.