

It is illegal to post this copyrighted PDF on any website.

You are prohibited from making this PDF publicly available.

CME Background

Articles are selected for credit designation based on an assessment of the educational needs of CME participants, with the purpose of providing readers with a curriculum of CME articles on a variety of topics throughout each volume. Activities are planned using a process that links identified needs with desired results.

To obtain credit, read the article, correctly answer the questions in the Posttest, and complete the Evaluation.

This ACADEMIC HIGHLIGHTS section of *The Journal of Clinical Psychiatry* presents the highlights of the teleconference series “Individualizing Treatment Selection for Pediatric and Adult Patients With Bipolar Depression,” which was held in October and November 2020. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Sunovion Pharmaceuticals Inc.

The teleconference was chaired by **Robert L. Findling, MD, MBA**, Virginia Commonwealth University School of Medicine, Richmond. The faculty member was **Joseph F. Goldberg, MD**, Icahn School of Medicine at Mount Sinai, New York, NY.

CME Objective

After studying this article, you should be able to:

- Develop an age-appropriate, evidence-based treatment plan for patients with bipolar depression
- Facilitate continuous care as pediatric patients transition to adult care

Accreditation Statement

The CME Institute of Physicians Postgraduate Press, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.



Release, Expiration, and Review Dates

This educational activity was published in September 2021 and is eligible for *AMA PRA Category 1 Credit™* through December 31, 2023. The latest review of this material was September 2021.

Financial Disclosure

All individuals in a position to influence the content of this activity were asked to complete a statement regarding all relevant personal financial relationships between themselves or their spouse/partner and any commercial interest. The CME Institute has resolved any conflicts of interest that were identified. In the past 3 years, Marlene P. Freeman, MD, Editor in Chief, has received research funding from JayMac and Sage; has been a member of the Independent Data Safety and Monitoring Committee for Janssen (Johnson & Johnson) and Novartis; and has served on advisory boards for Eliem and Sage. As an employee of Massachusetts General Hospital (MGH), Dr Freeman works with the MGH National Pregnancy Registry, which receives funding from Alkermes, Aurobindo, AuroMedics, Johnson & Johnson/Janssen, Otsuka, Sage, Sunovion, Supernus, and Teva, and works with the MGH Clinical Trials Network and Institute, which receives research funding from multiple pharmaceutical companies and the National Institute of Mental Health. No member of the CME Institute staff reported any relevant personal financial relationships. **Faculty financial disclosure appears on the next page.**

J Clin Psychiatry 2021;82(6):SU20014AH3C

To cite: Findling R, Goldberg F. Individualizing treatment selection for pediatric and adult patients with bipolar depression. *J Clin Psychiatry*. 2021;82(6):SU20014AH3C.

To share: <https://doi.org/10.4088/JCPSU20014AH3C>

© Copyright 2021 Physicians Postgraduate Press, Inc.

Individualizing Treatment Selection for Pediatric and Adult Patients With Bipolar Depression

Robert L. Findling, MD, MBA, and Joseph F. Goldberg, MD

Roughly 4.4% of US adults have bipolar disorder (BD),¹ and half to two-thirds of cases begin in childhood or adolescence.^{2,3} Approximately 60% of patients with BD who present with depression are misdiagnosed as having recurrent unipolar depression,⁴ which can lead to inappropriate or ineffective treatments and persistence or worsening of symptoms.⁵ This report, based on presentations given by Robert L. Findling, MD, MBA, and Joseph F. Goldberg, MD, will address how to diagnose bipolar depression in adults and children and select the most appropriate treatment strategy for each patient.

DIAGNOSIS AND PHARMACOTHERAPY OF BIPOLAR DEPRESSION IN PEDIATRIC PATIENTS

In his presentation, Dr Findling addressed assessing pediatric patients with depression for signs of bipolarity and providing individualized treatment. In youths, BD has a negative effect on numerous domains, including physical and emotional well-being,⁶ school and family functioning, friendships, and academic success.⁷ Dr Findling stated that timely diagnosis and treatment are crucial so that young patients can learn how to care for themselves and help to manage their illness, thereby potentially mitigating long-term consequences.

Diagnosing Bipolar Depression in Pediatric Patients

Dr Findling stated that diagnosing BD in pediatric patients can be difficult; symptom patterns are atypical compared to presentations in adults and can evolve with the patient’s age and developmental stage.^{8,9} Children of the same chronological age may be at different developmental stages, so clinicians should consider symptoms according to each child’s baseline.¹⁰

Among screening tools that are useful in clinical practice, the Children’s Depression

**Credit Designation**

The CME Institute of Physicians Postgraduate Press, Inc., designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Note: The American Nurses Credentialing Center (ANCC) and the American Academy of Physician Assistants (AAPA) accept certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*[™] from organizations accredited by the ACCME.

Financial Disclosure

Dr Findling is a consultant for Acadia, Adamas, Afecta, Akili, Alkermes, Allergan, Arbor, Axsome, Gedeon Richter, Genentech, Idorsia, Intra-Cellular, Luminopia, Lundbeck, MedAvante-ProPhase, Neurim, Noven, Nuvelution, Otsuka, PaxMedica, Q BioMed, Receptor Life Sciences, Roche, Signant Health, Sunovion, Supernus, Syneos, Takeda, Teva, and Tris; has received grant/research support from Akili, Allergan, Lundbeck, National Institutes of Health, Neurim, Patient-Centered Outcomes Research Institute, Pfizer, Roche, Sunovion, Supernus, SyneuRx, and Takeda; has received honoraria from the American Academy of Child and Adolescent Psychiatry; is a member of the speaker/advisory board for Tris; and has received other financial or material support from the American Psychiatric Press. **Dr Goldberg** is a consultant for Jazz Pharmaceuticals, Lundbeck, Otsuka, Sunovion, Sage, and BioXcel; has received honoraria from Allergan, Intra-Cellular, Web MD, and Sunovion; is a member of the speakers/advisory boards for Alkermes, Allergan, Intra-Cellular, Sunovion, Otsuka, and BioXcel; and has received royalties from American Psychiatric Publishing and Cambridge University Press.

Review Process

The faculty member(s) agreed to provide a balanced and evidence-based presentation and discussed the topic(s) and CME objective(s) during the planning sessions. The faculty's submitted content was validated by CME Institute staff, and the activity was evaluated for accuracy, use of evidence, and fair balance by the Chair and a peer reviewer who is without conflict of interest.

The opinions expressed herein are those of the faculty and do not necessarily reflect the opinions of the CME provider and publisher or the commercial supporter.

Rating Scale-Revised (CDRS-R) is considered the gold standard.^{11,12} A family history of mood disorders is an important clue to the possibility of pediatric BD.¹⁰ Common comorbidities include attention-deficit/hyperactivity disorder (ADHD), substance use disorder, and anxiety disorders.⁶

A study³ reported that among patients with onset of BD prior to age 18 years, the majority experienced depression as the polarity of the first episode (63.6% of those with onset before age 13 years and 58.7% of those with onset at ages 13–18 years), compared with 49.3% of those whose BD began in adulthood. Those with onset by age 18 years reported a greater number of mood episodes in the preceding year than those with later onset.³

In January 2021, a representative from Mental Health America (MHA) interviewed a mother of a patient with bipolar disorder, who wishes that she had received more guidance from the clinician at diagnosis:

"When she was diagnosed, I wish I had been told more about 'how do you talk to a bipolar child,' 'how do you talk to a depressed child.' I wish the psychiatrist would have suggested where I could go to find this information. It was something new to me, and parents facing this diagnosis of their child are like a deer in the headlights. If doctors could guide parents as to how to deal with the ups and the downs, what signs to look for, what triggers, it would help a lot."

Treatment for Bipolar Depression in Pediatric Patients

Dr Findling emphasized that pediatric BD often requires life-long psychopharmacologic management.¹³ However, most medications used for BD carry a risk of adverse effects that can be concerning in any patient but especially in young ones, such as metabolic abnormalities and weight gain. Dr Findling remarked that the dosing goal in children is to achieve optimum efficacy while maximizing tolerability.

Currently, 2 pharmacologic interventions have FDA approval for the treatment of bipolar I depression in patients aged 10 to 17 years: olanzapine-fluoxetine combination (OFC) and lurasidone. Quetiapine is commonly used as an off-label treatment.¹²

Olanzapine-fluoxetine combination. Dr Findling cited an 8-week study by Detke and colleagues¹⁴ in patients aged 10–17 years. Those who received OFC experienced significantly greater improvement in symptoms of bipolar depression compared with those receiving placebo ($P < .01$). They also experienced greater mean weight gain (4.4 kg versus 0.5 kg, respectively; $P < .001$), increased appetite, somnolence, hyperlipidemia, and hyperprolactinemia.

Lurasidone. A trial¹⁵ of lurasidone monotherapy in children aged 10–17 years with bipolar depression found greater response ($P < .0001$) in the active treatment group compared with the group receiving placebo. Treatment separation from placebo occurred as early as week 2 and also was recorded at week 6.¹⁵ At week 6, least squares mean change in body weight was similar for the lurasidone and placebo groups (0.74 kg versus 0.44 kg), and a similar percentage of patients taking lurasidone versus placebo had at least 7% weight gain (4.0% versus 5.3%). Another trial¹⁶ found that lurasidone was efficacious in the treatment of pediatric patients with bipolar depression who presented with subsyndromal hypomanic features.

In a study¹⁷ evaluating the pharmacokinetic profile and tolerability of lurasidone in children and adolescents with various psychiatric disorders, Dr Findling and his colleagues found that, compared with higher doses, lurasidone doses under 120 mg/d were better tolerated, especially in younger children. Adverse effects in pediatric patients were qualitatively similar to those reported in adults. A review¹³ of safety considerations in pediatric BD

It is illegal to post this copyrighted PDF on any website.

treatment notes that studies of lurasidone do not suggest significant metabolic effects, eg, weight gain. Common side effects associated with lurasidone are nausea and somnolence.¹⁵

Quetiapine. Currently approved by the FDA for the treatment of schizophrenia and bipolar mania in pediatric patients, quetiapine is commonly used as an off-label treatment for pediatric bipolar depression.¹⁸ Dr Findling noted that although quetiapine is reasonably safe and well tolerated, a systematic review¹⁸ of randomized clinical trials found no more efficacy than with placebo in pediatric bipolar depression when using the CDRS-R as the primary outcome measure. As Dr Findling and his colleagues discovered in a large multisite study,¹⁹ the mean changes in CDRS-R total score from baseline between quetiapine and placebo were similar. A review¹³ of safety considerations in pediatric BD pharmacology noted that weight gain and metabolic abnormalities are associated with quetiapine.

Mood stabilizers and antidepressants. Mood stabilizers, such as lamotrigine, lithium, and divalproex, have evidence of benefit for bipolar depression in small trials with pediatric patients, as monotherapy^{20,21} or in combination²² or as adjunctive treatment,²³ but more research is needed.²⁴ Antidepressant monotherapy should be avoided because of the risk of inducing a manic switch.²⁵

Conclusion

Dr Findling concluded by stating that clinicians can identify the presence of BD and individualize treatment by using diagnostic criteria and understanding the longitudinal, episodic course of the condition. For more information from Dr Findling, see the on-demand activity titled “Diagnosis and Pharmacotherapy of Bipolar Depression in Pediatric Patients” in this series at CME.psychiatrist.com.



Patient Perspectives

In January 2021, a representative from MHA conducted an interview with a person with bipolar disorder who described its impact as she transitioned to college life:

“One of the things that I really think could have been done differently by health providers is my transition from high school to college. I didn’t have a therapist in college until it was a crisis situation. Before I left for college, I had a therapist and a psychiatrist. But there was no communication like, ‘Hey, you should really get connected to a therapist when you get to college’—there were no transition materials or help. It seems kind of ridiculous now, looking back on it. Could I have received interventions that would have set me up for better success? I struggled so much in those first couple of years of college. It was such a different life to me. From a health care perspective, it should have been like, ‘This girl has a chronic condition, she’s going to college, we’re going to tell her that she needs to keep taking care of herself.’ I would really love to see, in the future, education for kids, or on that note, it could have been materials to my parents.”

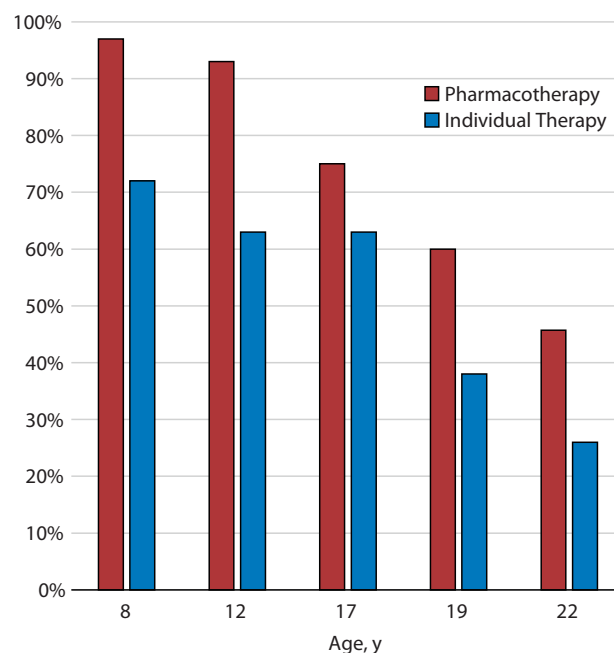
TRANSITION OF YOUNG PATIENTS FROM PEDIATRIC TO ADULT HEALTH CARE

Many young patients lose contact with health care providers as they age out of pediatric systems (Figure 1).²⁶ This is a troubling trend because this population is vulnerable to suicidality,²⁶ substance use,²⁷ and risky health behaviors.²⁸

Young adults encounter numerous barriers to care, including cessation of school-based services, changes in residence, failure of adult service providers to engage or meet the needs of younger patients, and changes in insurance.²⁶ Adult mental health services are often poorly equipped to provide youth-appropriate services.²⁸

The American Academy of Pediatrics and American College of Physicians have issued a joint report²⁸ offering a framework for the health care transition. Core elements of the transition include discussion with patients and family, assessment of the patient’s readiness, and communication among pediatric and adult clinicians before and after the initial adult visit.²⁸ Among youths with mental illness, transition planning should include active preparation and support for effective self-advocacy and community supports to bridge service gaps.^{28,29} A review³⁰ of studies of outcomes from structured transitions found that data indicated a shorter time from last pediatric visit to first adult visit, increased attendance at adult visits, and, to some extent, decreased hospitalization rates than with usual care.

Figure 1. Proportion of Youth With Bipolar Disorder Receiving at Least One Treatment Visit in a Year, by Age and Treatment Modality



Data from Hower et al.²⁶

DIAGNOSIS AND PHARMACOTHERAPY OF BIPOLAR DEPRESSION IN ADULTS

According to a meta-analysis³¹ cited by Dr Goldberg, the mean time between onset of BD and diagnosis is 6 years. Prior to receiving a diagnosis, many patients consult multiple clinicians, and over one-quarter have been misdiagnosed more than 3 times.

Screening Tools for Bipolar Disorder

Dr Goldberg stated that it is critically important to rigorously assess patients for BD. He recommended using screening tools, such as the Mood Disorder Questionnaire (MDQ),³² a self-report instrument. The items on the MDQ are keyed to the criteria in the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition*¹⁰ (DSM-5). Dr Goldberg explained that past or current substance misuse confound the reliability of MDQ self-assessment.³³ Up to 70% of people with BD have a comorbid substance use disorder. If a patient is using substances that induce either mania or depression, the clinician cannot diagnose BD. The DSM-5¹⁰ specifically states that the symptoms meeting diagnostic criteria cannot be better accounted for by another condition.

Dr Goldberg also recommended screening with the Bipolarity Index, which was developed as part of the National Institute of Mental Health Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).³⁴ The Bipolarity Index rates signs and symptoms, age at onset, course of illness, treatment response, and family history.³⁵

Another screening tool is the Bipolar Spectrum Diagnostic Scale,³⁶ which is designed to be particularly sensitive to milder BD. Dr Goldberg also made note of the Rapid Mood Screener,³⁷ a 6-question screen that differentiates bipolar I disorder from major depressive disorder (MDD) in patients with depressive symptoms.

According to Dr Goldberg, a positive screen for BD means that the clinician has identified a possible case and now must do a detailed interview to corroborate the screening results. Corroborators of a BD diagnosis include cross-sectional symptoms, family history, high recurrence, longitudinal course, and antidepressant-induced irritability. Early age at onset is also consistent with a BD diagnosis.

Diagnostic Criteria for Bipolar Disorder and Differential Diagnosis

According to the DSM-5,¹⁰ only mania, not depression, is required for a patient to meet the criteria for a diagnosis of bipolar I disorder. For a diagnosis of bipolar II disorder, the patient must have a current or past episode of hypomania and major depression.

Dr Goldberg stated that one diagnostic challenge facing clinicians is that most patients with BD experience a major depressive episode before experiencing a manic episode.³⁸ In addition, patients tend to underreport their experience of hypomanic episodes.

Comorbidity of other conditions with BD is the norm, not the exception, which presents another challenge in

making an accurate diagnosis. Dr Goldberg cited a well-known study³⁹ by McElroy et al stating that around 65% of patients with BD have at least 1 other psychiatric condition. Comorbid anxiety disorders and substance use disorders each occurred in 42% of the participants, and 5% had eating disorders. Other research corroborates that the most common comorbid conditions are anxiety disorders³⁸ and substance use disorders.⁴⁰

Dr Goldberg emphasized that, during the patient interview, the clinician should carefully weigh the differential diagnosis.⁵ For instance, while mood instability or mood shifts may be indicators of BD, they could also indicate conditions such as borderline personality disorder⁴¹ or posttraumatic stress disorder.⁴² Poor impulse control, aggression, or irritability may indicate BD but may also indicate agitated unipolar depression⁴³ or impulse-control disorders.⁴⁴ Racing thoughts or flight of ideas and distractibility may indicate the cognitive elements of mania, or they could be related to ADHD.⁴⁵

Dr Goldberg noted that a patient with depression may take an antidepressant and, in clinical terms, become manic or hypomanic. This predicament, which has been a source of great controversy, suggests the notion of a vulnerability for BD, in which it is assumed that the patient has an underlying biological predisposition that has become unmasked or catalyzed by the antidepressant. The DSM-5¹⁰ states that if, after a patient stops taking an antidepressant, the symptoms of mania or hypomania persist at a syndromal level beyond the timeframe of the physiologic effects of the drug, a diagnosis of BD can be made. In Dr Goldberg's clinical experience, if a patient is treated with a selective serotonin reuptake inhibitor, for example, and becomes wired and agitated but is back to normal 5 days after the treatment was stopped, this patient may still be a person of interest for BD and should be closely monitored.



Case Practice Question

Discussion of the best response can be found at the end of the activity.

Case. Mikala is a 24-year-old woman with recurrent major depression that has been poorly responsive to several antidepressant trials. Mikala regularly smokes cannabis and occasionally uses cocaine. Her age at onset of depressive symptoms was 13 years, and she has had 3 episodes prior to the current one. Mikala's mother has bipolar disorder. You want to use the Mood Disorder Questionnaire (MDQ) and the Bipolarity Index. Regarding assessment of Mikala for bipolar disorder, which of the following statements is true?

- The positive predictive value of the MDQ drops in the setting of active substance use.
- Mikala can be diagnosed with bipolar disorder based on the MDQ score and Bipolarity Index.
- Active substance use does not interfere with making an accurate diagnosis of bipolar disorder.
- Mikala would meet DSM-5 criteria for bipolar disorder if she became transiently hypomanic after taking an antidepressant.

It is illegal to post this copyrighted PDF on any website.

Treatment for Bipolar Depression in Adults

Dr Goldberg referred clinicians to recent guidelines provided by a collaboration between the Canadian Network for Mood and Anxiety Treatments and the International Society for Bipolar Disorders.⁴⁶

Mood stabilizers. According to Dr Goldberg, *mood stabilizer* is not a technical medical term—rather, it is a colloquialism⁴⁷ often used by clinicians. He suggested a definition of *mood stabilizer* as a pharmacologic treatment that may induce and maintain euthymia without causing either mania or depression.⁴⁸

Four medications that are considered to be mood stabilizers for BD treatment are lithium, divalproex, carbamazepine, and lamotrigine.⁴⁹ While other anticonvulsants have been studied, these 4 are the only ones that have been proven to have a “class effect” in the treatment of acute bipolar mania.⁵⁰

Lithium is considered the gold standard of mood stabilizers for the treatment of BD.^{46,51} As a meta-analysis⁵² showed, lithium exerts a larger preventative effect against manic episodes than against depressive episodes. Dr Goldberg considers lithium an antimanic mood-stabilizing drug and a better choice of treatment for patients whose illness is more mania-prone than depression-prone.

Divalproex has shown efficacy for acute bipolar depression in placebo-controlled, randomized trials.⁵³ Lithium and divalproex are among guideline-recommended first-line treatments for acute mania, but they are also used for bipolar I depression, possibly in combination with an antipsychotic.⁴⁷ According to Dr Goldberg, robust studies of carbamazepine for BD treatment apart from acute mania are lacking; a few small studies⁵⁴ exist with on-off-on designs and no placebo comparators. Therefore, insufficient evidence exists on the efficacy of carbamazepine in treating the depressed phase of BD.⁵⁵ Carbamazepine and divalproex may have teratogenic effects, which should be considered when treating women of childbearing age.⁵⁶

Lamotrigine has not been shown to treat acute mania⁵⁷ but has an antidepressant effect compared with placebo in patients with bipolar depression.⁵⁵ Lamotrigine is sometimes considered a guideline-recommended first-line therapy for bipolar I depression, whether alone or adjunctive to other agents⁴⁶; however, its use for acute depressive episodes in BD is off-label.

Antidepressants. Although depression is the most common and debilitating symptom in patients with BD,⁵⁸ traditional monoaminergic antidepressants have not shown robust efficacy for BD.⁵¹ Nevertheless, antidepressants are the most commonly prescribed treatment for people receiving outpatient care for BD.⁵⁹ No randomized, placebo-controlled trial in bipolar I depression shows an advantage for an antidepressant when added to a mood stabilizer.⁶⁰ Dr Goldberg stated that antidepressants are not recommended as monotherapy.⁴⁶ Antidepressants may be useful for a minority of depressed patients with BD, such as those who have bipolar II

disorder, those whose current depressed episode has no mixed features, those who do not experience rapid cycling, those who have not had a recent manic or hypomanic episode, those with no history of alcohol or substance abuse, and those who have a favorable initial response.⁶¹ Altshuler et al showed in a randomized trial⁶² of 83 outpatients with BD that if the patient has a robust initial response with an antidepressant, they have a 69% chance of staying well with continued treatment. In Dr Goldberg’s clinical experience, if the patient has a mediocre or poor response to an antidepressant, it is highly unlikely that they would remain depression-free or otherwise euthymic.

Antipsychotics. Some second-generation antipsychotics (SGAs) are approved by the US Food and Drug Administration (FDA) for treating bipolar depression: olanzapine-fluoxetine combination, quetiapine, lurasidone, and cariprazine.⁵⁶ A recent network meta-analysis⁶³ of SGAs for acute bipolar depression found the number needed to treat (NNT) for response was 5 for lurasidone, 6 for quetiapine, 10 for olanzapine monotherapy, and 12 for cariprazine. Risks, however, such as weight gain and sedation, vary among agents⁶³ and must be negotiated with the patient. For more information about the antipsychotics discussed by Dr Goldberg during his presentation, see the on-demand presentation activity titled “Diagnosis and Pharmacotherapy of Bipolar Depression in Adults” in this series at CME.psychiatrist.com.

Treatment-Resistant Bipolar Depression

Dr Goldberg suggested a few pharmacologic approaches for patients with treatment-resistant bipolar depression. Clinicians are advised to first confirm adherence and optimize the regimen as well as consider whether comorbid illness is interfering with treatment response.⁴⁶

Adjunctive armodafinil,⁶⁴ a wakefulness-promoting drug, has an NNT of 16 and is beneficial in patients with apathy, anergia, sluggishness, and lethargy.⁶⁵ The antiparkinsonian drug pramipexole has shown a response rate close to 50%.^{66,67} Based on Dr Goldberg’s clinical experience, he considers pramipexole effective in improving motivation and drive in purely depressed patients, but he would not prescribe it to a patient who shows psychotic, manic, agitated, or highly impulsive tendencies. Ketamine,⁶⁸ an off-label treatment option for BD that is FDA-approved (as intranasal esketamine) for unipolar depression, has shown an effect size of about 1.0 with no evidence of destabilization of mood.

Other lower-tier adjunctive options for bipolar depression in guidelines include omega-3 fatty acids, levothyroxine, *N*-acetylcysteine, transcranial magnetic stimulation, and light therapy.⁴⁶ A meta-analysis⁶⁹ provided some evidence that bipolar depressive symptoms may be improved by adjunctive use of omega-3 fatty acids. A meta-analysis⁷⁰ of the neuroprotective nutraceutical *N*-acetylcysteine used as an adjunctive treatment showed less strong evidence in bipolar depression.

You are prohibited from making this PDF publicly available.



Patient Perspectives

In January 2021, a representative from MHA conducted interviews with individuals who described their diagnostic and treatment experiences. Here, an adult patient describes the importance of “constructive” ways to cope with BD, in addition to taking medications:

“I think my doctors have been doing the best they could. But I wish all my doctors would kind of feed my spirit and my wellbeing, you know, holistic stuff, instead of just telling me to take this pill or that injection. Why don’t you suggest to me that I try some creative coping mechanisms like writing poetry or walking around in the park? That’s the only way you’re going to get through it. You got to get through this illness however you can, without being destructive though. So, you can’t do it with alcohol, you can’t do it with drugs, you can’t do it with junk food, soda, or sex. I feel like a lot of people would respond to their health care providers talking about more constructive ways to cope.”

Conclusion

Dr Goldberg concluded his presentation by noting that bipolar disorder can negatively impact a patient’s functioning and quality of life. To improve patient outcomes, he recommends using diagnostic criteria and assessment tools, and facilitating effective communication with patients about BD so that treatment (including nonpharmacologic strategies) can be individualized.



Clinical Points

- Evidence-based treatments are available for pediatric patients with bipolar depression.
- Facilitate the transition from pediatric care to adult care by communicating with patients, family members, and other practitioners before, during, and after the change.
- Use screening tools to determine possible cases of bipolar disorder in adults, and then consider cross-sectional symptoms, clinical features, and course before making a diagnosis.
- Most patients with bipolar depression do not show a robust response to antidepressants.
- Consider novel strategies for harder-to-treat forms of bipolar depression.



Discussion of Case Practice Question

Preferred response is a. The positive predictive value of the MDQ drops in the setting of active substance use.

Substance abuse confounds the reliability of MDQ self-assessment screenings. Clinical clarification of the patient’s responses via an interview will yield indicators that are more sensitive and more specific.³³

Published online: September 28, 2021.

Disclosure of off-label usage: Dr Findling has determined that, to the best of his knowledge, quetiapine, lithium, lamotrigine, and divalproex sodium are not approved by the US Food and Drug Administration (FDA) for the treatment of pediatric bipolar depression. Dr Goldberg has determined that, to the best of his knowledge, divalproex, carbamazepine, pramipexole,

ketamine, esketamine, levothyroxine, N-acetylcysteine, and transcranial magnetic stimulation are not approved by the FDA for the treatment of adults with bipolar depression, and lamotrigine is not approved to treat acute bipolar mania or acute bipolar depression.

REFERENCES

1. Bipolar Disorder. National Institute of Mental Health. Published November 2017. Accessed November 5, 2019. <https://www.nimh.nih.gov/health/statistics/bipolar-disorder>
2. Leverich GS, Post RM, Keck PE Jr, et al. The poor prognosis of childhood-onset bipolar disorder. *J Pediatr*. 2007;150(5):485–490.
3. Perlis RH, Miyahara S, Marangell LB, et al; STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1,000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry*. 2004;55(9):875–881.
4. Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. *Lancet*. 2013;381(9878):1663–1671.
5. Baldessarini RJ, Tondo L, Vázquez GH. Pharmacological treatment of adult bipolar disorder. *Mol Psychiatry*. 2019;24(2):198–217.
6. Bipolar Disorder in Children and Teens. National Institute of Mental Health. Published 2015. Accessed June 15, 2017. <https://www.nimh.nih.gov/health/publications/bipolar-disorder-in-children-and-teens>
7. Van Meter AR, Henry DB, West AE. What goes up must come down: the burden of bipolar depression in youth. *J Affect Disord*. 2013;150(3):1048–1054.
8. McClellan J, Kowatch R, Findling RL; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(1):107–125.
9. Birmaher B. Longitudinal course of pediatric bipolar disorder. *Am J Psychiatry*. 2007;164(4):537–539.
10. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
11. Mayes TL, Bernstein IH, Haley CL, et al. Psychometric properties of the Children’s Depression Rating Scale-Revised in adolescents. *J Child Adolesc Psychopharmacol*. 2010;20(6):513–516.
12. Goldstein BI, Birmaher B, Carlson GA, et al. The International Society for Bipolar Disorders Task Force report on pediatric bipolar disorder: knowledge to date and directions for future research. *Bipolar Disord*. 2017;19(7):524–543.
13. Sun AY, Woods S, Findling RL, et al. Safety considerations in the psychopharmacology of pediatric bipolar disorder. *Expert Opin Drug Saf*. 2019;18(9):777–794.
14. Detke HC, DelBello MP, Landry J, et al. Olanzapine/fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2015;54(3):217–224.
15. DelBello MP, Goldman R, Phillips D, et al. Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 2017;56(12):1015–1025.
16. Singh MK, Pikalov A, Siu C, et al. Lurasidone in children and adolescents with bipolar depression presenting with mixed (subsyndromal hypomanic) features: post hoc analysis of a randomized placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2020;30(10):590–598.
17. Findling RL, Goldman R, Chiu Y-Y, et al. Pharmacokinetics and tolerability of lurasidone in children and adolescents with psychiatric disorders. *Clin Ther*. 2015;37(12):2788–2797.
18. Srinivas S, Parvataneni T, Makani R, et al. Efficacy and safety of quetiapine for pediatric bipolar depression: a systematic review of randomized clinical trials. *Cureus*. 2020;12(6):e8407.
19. Findling RL, Pathak S, Earley WR, et al. Efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8 week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2014;24(6):325–335.
20. Findling RL. Evidence-based pharmacologic treatment of pediatric bipolar disorder. *J Clin Psychiatry*. 2016;77(suppl E1):e2.
21. Shon S-H, Joo Y, Lee J-S, et al. Lamotrigine treatment of adolescents with unipolar and bipolar depression: a retrospective chart review. *J Child Adolesc Psychopharmacol*. 2014;24(5):285–287.
22. Findling RL, McNamara NK, Gracious BL, et al. Combination lithium and divalproex sodium in pediatric bipolarity. *J Am Acad Child Adolesc Psychiatry*. 2003;42(8):895–901.
23. 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.
24. Stepanova E, Findling RL. Psychopharmacology of bipolar disorders in children and adolescents. *Pediatr Clin North Am*. 2017;64(6):1209–1222.

It is illegal to post this copyrighted PDF on any website.

You are prohibited from making this PDF publicly available.

25. Bhowmik D, Aparasu RR, Rajan SS, et al. Risk of manic switch associated with antidepressant therapy in pediatric bipolar depression. *J Child Adolesc Psychopharmacol*. 2014;24(10):551–561.
26. Hower H, Case BG, Hoepfner B, et al. Use of mental health services in transition age youth with bipolar disorder. *J Psychiatr Pract*. 2013;19(6):464–476.
27. Pottick KJ, Warner LA, Vander Stoep A, et al. Clinical characteristics and outpatient mental health service use of transition-age youth in the USA. *J Behav Health Serv Res*. 2014;41(2):230–243.
28. White PH, Cooley WC; Transitions Clinical Report Authoring Group; American Academy of Pediatrics; American Academy of Family Physicians; American College of Physicians. Supporting the health care transition from adolescence to adulthood in the medical home. *Pediatrics*. 2018;142(5):e20182587.
29. McManus M, White P. Transition to adult health care services for young adults with chronic medical illness and psychiatric comorbidity. *Child Adolesc Psychiatr Clin N Am*. 2017;26(2):367–380.
30. Gabriel P, McManus M, Rogers K, et al. Outcome evidence for structured pediatric to adult health care transition interventions: a systematic review. *J Pediatr*. 2017;188:263–269.e15.
31. Dagani J, Signorini G, Nielssen O, et al. Meta-analysis of the interval between the onset and management of bipolar disorder. *Can J Psychiatry*. 2017;62(4):247–258.
32. Hirschfeld RM, Williams JB, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry*. 2000;157(11):1873–1875.
33. Goldberg JF, Garakani A, Ackerman SH. Clinician-rated versus self-rated screening for bipolar disorder among inpatients with mood symptoms and substance misuse. *J Clin Psychiatry*. 2012;73(12):1525–1530.
34. Bowden CL, Perlis RH, Thase ME, et al. Aims and results of the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *CNS Neurosci Ther*. 2012;18(3):243–249.
35. Aiken CB, Weisler RH, Sachs GS. The Bipolarity Index: a clinician-rated measure of diagnostic confidence. *J Affect Disord*. 2015;177:59–64.
36. Nassir Ghaemi S, Miller CJ, Berv DA, et al. Sensitivity and specificity of a new bipolar spectrum diagnostic scale. *J Affect Disord*. 2005;84(2-3):273–277.
37. McIntyre RS, Patel MD, Masand PS, et al. The Rapid Mood Screener (RMS): a novel and pragmatic screener for bipolar I disorder. *Curr Med Res Opin*. 2021;37(1):135–144.
38. Merikangas KR, Jin R, He J-P, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry*. 2011;68(3):241–251.
39. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry*. 2001;158(3):420–426.
40. Hunt GE, Malhi GS, Cleary M, et al. Comorbidity of bipolar and substance use disorders in national surveys of general populations, 1990–2015: systematic review and meta-analysis. *J Affect Disord*. 2016;206:321–330.
41. Sanches M. The limits between bipolar disorder and borderline personality disorder: a review of the evidence. *Diseases*. 2019;7(3):49.
42. Cogan CM, Paquet CB, Lee JY, et al. Differentiating the symptoms of posttraumatic stress disorder and bipolar disorders in adults: utilizing a trauma-informed assessment approach. *Clin Psychol Psychother*. 2021;28(1):251–260.
43. Gosek P, Heitzman J, Stefanowski B, et al. Symptomatic differences and symptoms stability in unipolar and bipolar depression: medical charts review in 99 inpatients. *Psychiatr Pol*. 2019;53(3):655–672.
44. Powers RL, Russo M, Mahon K, et al. Impulsivity in bipolar disorder: relationships with neurocognitive dysfunction and substance use history. *Bipolar Disord*. 2013;15(8):876–884.
45. Asherson P, Young AH, Eich-Höchli D, et al. Differential diagnosis, comorbidity, and treatment of attention-deficit/hyperactivity disorder in relation to bipolar disorder or borderline personality disorder in adults. *Curr Med Res Opin*. 2014;30(8):1657–1672.
46. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97–170.
47. Malhi GS, Porter R, Irwin L, et al. Defining a mood stabiliser: novel framework for research and clinical practice. *BJPsych Open*. 2018;4(4):278–281.
48. Fava GA, Guidi J. The pursuit of euthymia. *World Psychiatry*. 2020;19(1):40–50.
49. Bourin M, Prica C. The role of mood stabilisers in the treatment of the depressive facet of bipolar disorders. *Neurosci Biobehav Rev*. 2007;31(6):963–975.
50. Rosa AR, Fountoulakis K, Siamouli M, et al. Is anticonvulsant treatment of mania a class effect? data from randomized clinical trials. *CNS Neurosci Ther*. 2011;17(3):167–177.
51. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *Lancet*. 2020;396(10265):1841–1856.
52. Geddes JR, Burgess S, Hawton K, et al. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry*. 2004;161(2):217–222.
53. Bond DJ, Lam RW, Yatham LN. Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. *J Affect Disord*. 2010;124(3):228–234.
54. Ballenger JC, Post RM. Carbamazepine in manic-depressive illness: a new treatment. *Am J Psychiatry*. 1980;137(7):782–790.
55. Bahji A, Ermacorra D, Stephenson C, et al. Comparative efficacy and tolerability of pharmacological treatments for the treatment of acute bipolar depression: A systematic review and network meta-analysis. *J Affect Disord*. 2020;269:154–184.
56. Wang D, Osser DN. The Psychopharmacology Algorithm Project at the Harvard South Shore Program: an update on bipolar depression. *Bipolar Disord*. 2020;22(5):472–489.
57. Goldsmith DR, Wagstaff AJ, Ibbotson T, et al. Lamotrigine: a review of its use in bipolar disorder. *Drugs*. 2003;63(19):2029–2050.
58. Rolin D, Whelan J, Montano CB. Is it depression or is it bipolar depression? *J Am Assoc Nurse Pract*. 2020;32(10):703–713.
59. Rhee TG, Olfson M, Nierenberg AA, et al. 20-Year trends in the pharmacologic treatment of bipolar disorder by psychiatrists in outpatient care settings. *Am J Psychiatry*. 2020;177(8):706–715.
60. Goldberg JF. Determining patient candidacy for antidepressant use in bipolar disorder. *Psychiatr Ann*. 2019;49(9):386–391.
61. Gitlin MJ. Antidepressants in bipolar depression: an enduring controversy. *Int J Bipolar Disord*. 2018;6(1):25.
62. Altshuler LL, Post RM, Helleman G, et al. Impact of antidepressant continuation after acute positive or partial treatment response for bipolar depression: a blinded, randomized study. *J Clin Psychiatry*. 2009;70(4):450–457.
63. Kadakia A, Dembek C, Heller V, et al. Efficacy and tolerability of atypical antipsychotics for acute bipolar depression: a network meta-analysis. *BMC Psychiatry*. 2021;21(1):249.
64. Tsapakis EM, Preti A, Mintzas MD, et al. Adjunctive treatment with psychostimulants and stimulant-like drugs for resistant bipolar depression: a systematic review and meta-analysis. *CNS Spectr*. 2020;1–12.
65. Nunez NA, Singh B, Romo-Nava F, et al. Efficacy and tolerability of adjunctive modafinil/armodafinil in bipolar depression: a meta-analysis of randomized controlled trials. *Bipolar Disord*. 2020;22(2):109–120.
66. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry*. 2004;161(3):564–566.
67. Zarate CA Jr, Payne JL, Singh J, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol Psychiatry*. 2004;56(1):54–60.
68. Jha MK, Murrrough JW. Psychopharmacology and experimental therapeutics for bipolar depression. *Focus Am Psychiatr Publ*. 2019;17(3):232–237.
69. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. *J Clin Psychiatry*. 2012;73(1):81–86.
70. Kishi T, Miyake N, Okuya M, et al. N-acetylcysteine as an adjunctive treatment for bipolar depression and major depressive disorder: a systematic review and meta-analysis of double-blind, randomized placebo-controlled trials. *Psychopharmacology (Berl)*. 2020;237(11):3481–3487.

For the CME Posttest, see next page.



POSTTEST

To obtain credit, go to PSYCHIATRIST.COM to complete the Posttest and Evaluation.

1. **Raj is 14 years old and presents with a major depressive episode. By conducting screening and a full evaluation, you determine that he has no current or past use of substances, has a history of manic features, and has a family history of mood disorders. You diagnose Raj with bipolar I disorder. To provide Raj with a medication that has demonstrated efficacy in the acute treatment of bipolar depression in adolescents, which of the following agents would you choose?**
 - a. Lithium
 - b. Lamotrigine
 - c. Lurasidone
 - d. Quetiapine

2. **Katelynn is your 17-year-old patient who has responded well to medication and counseling for bipolar disorder over the past few years. She has been accepted to a college that is not local. Among your considerations as Katelynn makes the transition from adolescence into young adulthood, which of the following statements is *false*?**
 - a. These patients are more likely to receive care as they age from pediatric health systems into adult mental health service settings because both sets of clinicians usually collaborate
 - b. As the change in residence for Katelynn is a barrier to continuity of care, transition planning should include finding support at her new campus
 - c. Continuity of care into young adulthood is important as many of these patients may be at risk for risky health behaviors, substance use, and suicidality
 - d. Data indicate that structured transitions are associated with a shorter time from last pediatric visit to first adult visit and increased attendance at adult visits compared with usual care

You are prohibited from making this PDF publicly available.