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

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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

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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 study[3] 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]

Family Perspectives

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 colleagues[14] 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 trial[15] 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 trial[16] found that lurasidone was efficacious in the treatment of pediatric patients with bipolar depression who presented with subsyndromal hypomanic features.

In a study[17] 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 review[13] of safety considerations in pediatric BD

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 review[18] 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 review[13] 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 combination[22] 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."

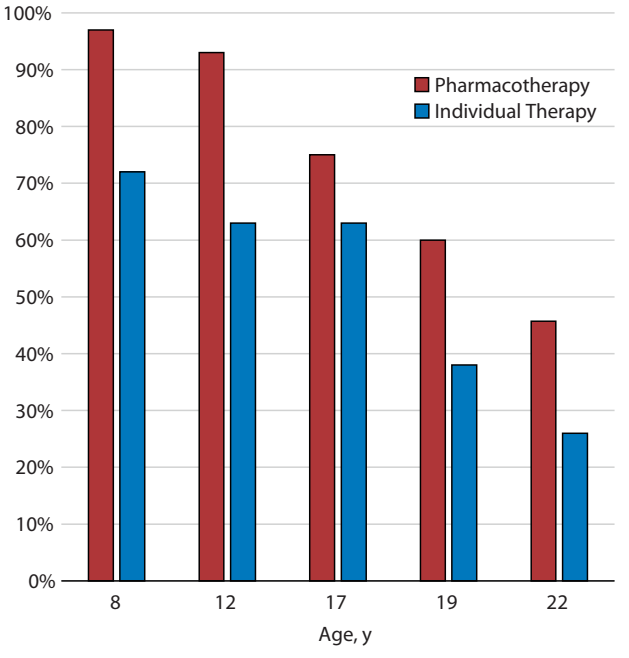
TRANSITION OF YOUNG PATIENTS FROM PEDIATRIC TO ADULT HEALTH CARE

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 report[28] 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 review[30] 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-analysis[31] 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-5*[10] 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 study[39] 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 disorders[38] 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 disorder[41] or posttraumatic stress disorder.[42] Poor impulse control, aggression, or irritability may indicate BD but may also indicate agitated unipolar depression[43] 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-5*[10] 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?

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

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 colloquialism[47] 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-analysis[52] 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 studies[54] 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 mania[57] 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 agents[46]; 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 trial[62] 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-analysis[63] 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 agents[63] 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-analysis[69] provided some evidence that bipolar depressive symptoms may be improved by adjunctive use of omega-3 fatty acids. A meta-analysis[70] of the neuroprotective nutraceutical *N*-acetylcysteine used as an adjunctive treatment showed less strong evidence in bipolar depression.

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]

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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.

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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