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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 "Expanded Treatment Options May Address Unmet Needs in Bipolar Depression and Addressing Unmet Needs in the Diagnosis and Treatment of Bipolar I Disorder," which was held on May 6, 2022. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by educational grants from Alkermes, Inc., and Intra-Cellular Therapies, Inc.

The teleconference was chaired by **Joseph F. Goldberg, MD**, Icahn School of Medicine at Mt. Sinai, New York, New York. The faculty were **Melissa P. DelBello, MD, MS**, University of Cincinnati College of Medicine, Cincinnati, Ohio; and **Holly A. Swartz, MD**, University of Pittsburgh, Pittsburgh, Pennsylvania.

CME Objectives
After studying this article, you should be able to:

- Screen patients with major depressive episodes for bipolar I and II disorder (bipolar depression)
- Accurately diagnose patients with bipolar I disorder with manic or mixed episodes
- Select a treatment regimen (monotherapy or combination treatment) to alleviate bipolar depression without causing the patient an undue side effect burden
- Use measurement-based care in long-term bipolar disorder management
- Provide efficacious and tolerable treatment for acute episodes of bipolar I disorder
- Evaluate evidence-based treatments available for the maintenance of bipolar I disorder, including mood stabilizers, psychotherapy, and novel therapies

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Expanded Treatment Options and Addressing Unmet Needs in the Diagnosis and Treatment of Bipolar Disorder

Joseph F. Goldberg, MD; Melissa P. DelBello, MD, MS; and Holly A. Swartz, MD

Bipolar I disorder has a lifetime prevalence rate of 1%, although some studies estimate a prevalence rate of 2.6%–6%.[1] Bipolar disorder (BD) is often misdiagnosed, with an average delay from symptom onset to diagnosis of 10 to 15 years.[1] Patients who are misdiagnosed or receive a delayed diagnosis either go untreated or receive inappropriate treatment and experience persistent or worsening symptoms and comorbidities. This report is based on a series of 6 discussions between Joseph F. Goldberg, MD; Melissa P. DelBello, MD, MS; and Holly A. Swartz, MD, and will address how to diagnose BD and select the most appropriate treatment strategy for each patient.

See all 6 bipolar disorder activities

SCREENING AND ACCURATE DIAGNOSIS OF PATIENTS WITH BD TYPE I AND TYPE II

Dr Goldberg opened the first discussion by addressing the challenge that clinicians face in differentiating between depression and the types of BD due to the spectrum-like nature of the disease. He noted that recognizing the polarity, frequency, and duration of symptoms of BD can aid in diagnosis.[2] Early diagnosis of BD is key to increasing better outcomes in patients with BD. Dr Goldberg stated that the average delay from symptom onset to diagnosis is 10 years, and more than half of patients see 3 or more clinicians before receiving an accurate diagnosis.[1,3,4,5] A delayed diagnosis increases the risk of inappropriate treatment and comorbidities. Existing comorbidities such as attention-deficit/hyperactivity disorder (ADHD) and substance use also present challenges in making accurate diagnoses.[5] Special screenings, including the Mood Disorder Questionnaire, the Hypomania/Mania Symptom Checklist, and a number of depression rating scales and questionnaires, as well as charting and taking a comprehensive longitudinal history, are important tools in assessing BD in patients.[4,5]

The majority of patients with BD initially present with a depressive episode, and a diagnosis of unipolar depression would be indicated.[4,5] It is not until they polarity-convert that a diagnosis of BD can be made. This initial misdiagnosis can potentially lead to inappropriate treatment strategies, particularly antidepressants.[4,5,6] Dr Swartz emphasized that treating BD with antidepressants risks the occurrence of switching, or triggering

mania or hypomania, as well as ineffectively treating bipolar depression.[4,5]

Differentiating between the types of BD requires attention to the severity and duration of symptoms. BD I is defined by manic episodes that last 1 week or require hospitalization. BD I usually includes depressive episodes that last 2 weeks or include depressive episodes with mixed features, meaning having depressive and manic symptoms at the same time.[2] BD II is defined by hypomanic and depressive episodes, with hypomania described as less extreme with shorter duration and less functional impairment than mania.[2] Cyclothymia includes periods of hypomanic symptoms and depressive symptoms that last at least 2 years, or 1 year for children and adolescents,[2] and symptoms do not last long enough to constitute full episodes of either hypomania or major depression.

Dr DelBello offered many insights into the presentations, diagnoses, treatment, and comorbidities of BD in children and adolescents. The spectrum model of BD applies in the pediatric setting as well, and symptom presentations are many times described as unspecified, subsyndromal, or prodromal, without explicit unipolar depression or manic manifestations.[7] Taking a family history, noting the presence of substance use and other comorbidities such as ADHD as well as adverse reactions to antidepressants, can provide key indicators of the risk of BD in children and adolescents.[7] Misdiagnosis and inappropriate treatment, particularly with antidepressants, can risk unmasking or accelerating the onset of the disease.[8] The recommended treatments for BD, mood stabilizers and second-generation antipsychotics, also increase the risk of metabolic side effects in children and adolescents.[9]

Patient Perspective

"When I'm manic, I tend to lose control of myself and my activities. I also experience psychosis, which is when you lose touch with reality. When I'm hypomanic, I'm very energetic. I'm impulsive. I'm risk-taking. I can be irresponsible in my decisions. . . . You can treat mania pretty quickly when you catch it. But the depression lasts for months and for years. It's the most debilitating part of the illness. And it's very, very discouraging. It's very demotivating. You can't function during the day. You can't pursue recovery, and recovery is what we want. But we lack the motivation to pursue these goals. And I like to say it's the mania that gets you into to trouble, but it's the depression that can kill you."

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Review Process

The faculty members agreed to provide a balanced and evidence-based presentation and discussed the topics and CME objectives 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.

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Case Practice Question

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

Case 1. Richard is a 26-year-old patient who presents with depression. He reports having been very active in the past 4 days, completing several tasks in the same day, feeling happier than he has ever felt, and not needing as much sleep. What steps do you take?

a. Prescribe the patient an antidepressant.

b. Use the CAGE questionnaire.

c. Take a comprehensive history of the patient.

d. Ask the patient if he feels better and can drive himself home.

TREATMENT OPTIONS FOR BD I AND BD II

Dr Swartz helped kick off episode 2 by introducing the 3 categories of mood stabilizing medications typically used in treating BD, which include antipsychotics, anticonvulsants, and lithium (Table 1). Swartz described mood stabilizers as "managing BD 101." "Mood stabilizers help individuals ideally maintain a constant euthymic baseline state, either addressing depression or addressing mania, or in the maintenance phase of the disorder."

Lithium is considered the gold standard of treatment for BD, particularly in patients with a mania-predominant course of illness or who have a family history of responding to the compound.[10] Second-generation antipsychotics, or atypical antipsychotics, used to treat bipolar depression include olanzapine-fluoxetine combination, quetiapine, lurasidone, cariprazine, and the newly approved lumateperone. According to Dr Swartz, these drugs have shown robust data in treating bipolar depression and have agent-specific effects regarding polarity.[12]

Dr Goldberg described the mechanism of action of two of the newer second-generation antipsychotics approved for BD, cariprazine and lumateperone. "If in your brain there are dopamine tracks that are overactive, let's say your mesolimbic pathway when you're manic, [cariprazine will] bring down dopamine," Goldberg pointed out. "And in tracks in the brain where there's underactivity, like the mesocortical pathway, where you can get depression or inattention, you might actually raise dopamine."[10] Lumateperone binds to the 5-HT_{2A} and the D_2 receptors and is thought to indirectly modulate glutamate transmission. It received recent approval to treat both bipolar I and II depression, an exciting prospect in that there are limited data in the treatment of BD II depression.[13]

The anticonvulsants divalproex, lamotrigine, and carbamazepine have demonstrated some efficacy in treating BD. Specifically, lamotrigine has an FDA indication as a maintenance treatment for BD while also showing off-label efficacy in the treatment of bipolar depression both as a monotherapy and as an adjunct therapy.[10] The combination of the atypical antipsychotic olanzapine with the opioid antagonist samidorphan is indicated for the acute treatment of manic or mixed episodes as a monotherapy or an adjunct therapy with lithium or valproate in BD I as well as a maintenance monotherapy. As an opioid antagonist, samidorphan combined with olanzapine is effective in mitigating weight gain associated with olanzapine, leading to better tolerance and adherence.[14]

Table 1. General Classes of Pharmacotherapy for Bipolar Disorder[a]

Treatment	Features
Lithium salts (as carbonate, hydroxide monohydrate, and citrate salts)	Dose adjustment to therapeutic serum levels (0.6–1.2 mEq/L); monitor for signs of lithium toxicity (diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness); monitor thyroid function (hypothyroidism and case reports of hyperthyroidism have been observed); monitor kidney function; maintain adequate fluid and salt intake due to potential for sodium depletion with lithium therapy
Divalproex and valproic acid	Potential to cause hepatotoxicity; liver function must be monitored; increased risk for pancreatitis
Antipsychotics	Potential for treatment emergent tremor/extrapyramidal symptoms; weight gain/metabolic syndrome; treatment emergent depression; must monitor periodically for possible emerging signs of tardive dyskinesia during long-term use
Lamotrigine	Maintenance treatment for BD; start/stop gradually for potential Stevens-Johnson syndrome; slower titration when used with divalproex and potentially other inhibitors of UGT glucuronidation

[a]Data from Yatham et al[10] and Derry et al.[11]

Non-racemic amisulpride (SEP-4199) is in phase 3 clinical trials for the treatment of bipolar I depression,[15] and *S*-ketamine, which is approved to treat unipolar depression, is also being studied for bipolar depression.[16] There are limited agents approved for bipolar depression in the pediatric arena, which, for the most part, only include lurasidone and the combination treatment olanzapine/fluoxetine. "We don't use a ton of lamotrigine because of all [the] complicating factors," Dr DelBello said. "[With] lithium there are some data, not great data, as an adjunctive treatment for bipolar depression and depressive symptoms."

Dr Goldberg re-emphasized the risks of treating patients with antidepressants. In an analysis of treatment-emergent mania across 10,098 depressed patients with BD across 51 studies, the pooled occurrence was 18.8%.[17]

"I guess we can't leave out psychotherapy," Dr Goldberg said. Dr Swartz responded with positive data from the Systematic Treatment Enhancement Program for Bipolar

Table 2. Bipolar Depression Treatment NNT/NNH[a]

	Olanzapine-Fluoxetine	Quetiapine	Lurasidone	Cariprazine
Number needed to treat (NNT) for 1 additional response	4 (3–8)	6 (5–8)	5 (4–8) (as monotherapy) 7 (4–24) (with lithium or valproate)	10 (7–21)
Number needed to harm (NNH) 1 additional adverse event leading to discontinuation	No difference; lower rate of discontinuation with treatment	10 (8–13)	No difference; lower rate of discontinuation with treatment	100 (no significant difference)

[a]Data from Citrome.[34]

Disorder (STEP-BD) study, citing that the receipt of any psychotherapy, including cognitive behavioral therapy (CBT), family-focused therapy (FFT), interpersonal and social rhythm therapy (IPSRT), and others was associated with shorter time to recovery.[18]

CBT helps identify and modify maladaptive cognitions and behaviors related to mood symptoms or episodes. Psychoeducation provides information about BD and treatments, helping individuals develop mastery of their illness and promoting better treatment adherence. FFT includes family members or significant others in the interventions and aids in improving communication and improving outcomes related to mood. IPSRT is designed to help individuals entrain underlying disturbances in circadian rhythms by paying attention to daily routines, schedules, and social rhythms. Lastly, peer support pairs patients with peers to decrease stigma, create a sense of empowerment, and facilitate validation.[18]

ACUTE AND MAINTENANCE TREATMENT STRATEGIES FOR BIPOLAR DEPRESSION

Current guidelines for managing BD include the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the National Institute for Clinical Excellence (NICE), which recommend lithium, lamotrigine, second-generation antipsychotics, and second-generation antipsychotics combined with lithium or valproate. Guidelines advise against the use of antidepressants as a monotherapy.[10,19]

The two novel atypical antipsychotics cariprazine and lumateperone were both approved in 2019 for the treatment of BD depression and are showing promising drug profiles.[10,13] Cariprazine treats both mania and depression in BD I as well as mixed episodes or mixed symptoms, and its dopamine agonist effects may help to treat dysfunction in cognition and attention.[10,20,21] Lumateperone was approved for the treatment of depressive episodes associated with BD I or II, both as monotherapy and as adjunctive therapy in combination with lithium and valproate.[13] In a 6-week, randomized, double-blind, placebo-controlled, multicenter study in adult patients with depressive episodes associated with BD I or II, lumateperone monotherapy versus placebo showed an improvement in the least-squares mean Montgomery-Asberg Depression Rating Scale (MADRS) total score versus placebo as monotherapy –16.7 points vs –12.1 points. Improvement was statistically significant as early as week 1.[22]

Clinicians treating their patients with BD with atypical antipsychotics should see improvements in symptoms at 2 weeks,[23] a timeframe that helps the clinician forecast for the patient. Otherwise, if they are seeing no efficacy, they may want to change course or even consider increasing the dosage. However, many times an increase in dosage will have no effect. "Sometimes there's clearly a subtherapeutic dose," Dr Goldberg said. "It may have more to do with reaching a threshold. . . . There's sometimes a reflexive perception on the part of clinicians [that we] have to titrate up. Maybe that's just in our DNA somehow."

Lumateperone is recommended at a fixed dose of 42 mg per day.[13,22] As a monotherapy and in combination with lithium or valproate, there was no single adverse reaction leading to discontinuation that occurred at a rate of > 2% in lumateperone-treated patients. The most common adverse reactions are somnolence/sedation, dizziness, nausea, and dry mouth.[13,22] Overall, 6% of the patients who received cariprazine discontinued treatment due to an adverse reaction, compared with 5% of placebo-treated patients in bipolar depression trials, with the most common adverse reactions being nausea, akathisia, restlessness, and extrapyramidal symptoms.[24] Drs Goldberg, DelBello, and Swartz agree that tolerability is an important factor when considering therapeutic strategies for patients. "Having an open communication, telling patients what the side effects might be, and if they're particularly sensitive . . . or types of side effects are particularly problematic . . . then that is definitely something to consider," Dr DelBello said. Most atypical antipsychotics carry risks associated with metabolic profile; however, lumateperone and cariprazine have less liability to metabolic consequences.[20,22] The addition of metformin to mood stabilizers in patients with insulin resistance has demonstrated not only a reversal in insulin resistance but also a reduction in depression scores versus placebo in a randomized controlled trial.[25] "What is really interesting . . . is that targeting the insulin resistance itself might have an impact on mood," Dr Swartz said.

Dr Goldberg closed the discussion by pointing out the opportunities these advances provide in looking panoramically and systematically at treatment strategies and offering measurement-based care to optimize patient outcomes." That really means engaging with the patient overall," he said (Table 2).

SHARED DECISION MAKING: COMMUNICATING WITH PATIENTS AND FAMILIES ABOUT THE TREATMENT JOURNEY OF BIPOLAR DEPRESSION

According to the CANMAT guidelines for the management of patients with BD, "A strong therapeutic alliance is central to improve treatment adherence and outcomes. Providers should encourage individuals to actively participate in treatment planning, using a shared decision-making approach."[10] For this segment in the series, Drs Goldberg, DelBello, and Swartz explored best practices in implementing these guidelines in their clinical practice.

Clear communication is step 1 in achieving optimal results regarding the therapeutic alliance and paying close attention to the patient's priorities and desired outcomes is part and parcel to the process. "It's incumbent upon us to listen to their concerns, their experiences, and their perspectives, and use that as the guidepost," Dr Swartz said. "They're the expert. [We are] in a consultative role." The clinician must then weigh in with their own priorities as well as the family members' and try to reach a common goal. Providing scientific evidence that supports the patient's priorities in a way that is easily comprehensible is important so that the patient can be an informed decision-maker in their own health outcomes and communicate that information to others if needed.

It is also important to be prepared for situations in which the patient is experiencing an episode, their decisional capacity or insight is impaired, or no one can agree. Dr DelBello suggests starting with where the patient is; leveraging communication, negotiation, and compromise; and agreeing upon a similar goal as an initial step in building the alliance. However, in a situation in which the patient is at imminent risk, clinicians are morally obligated to ensure safety. Dr Swartz suggests developing a relapse prevention plan with the patient when they are well so that their actions can align with their personal values during a time of crisis.

"[I like] to say the clinician is a bit like a travel agent," Dr Goldberg said. "Where do you want to go? What do you want to be like when you get there? How do you want to get there? What have your past experiences been when you've traveled places?" In essence, he said, "No decision about me without me."

Patient Perspective

"The most important thing that physicians can do is give their patients hope. They need hope that they can live the life they want. They have to emphasize self-determination and they have to emphasize a strengths-based approach as opposed to a deficits-based approach. They have to empower their patients. They have to encourage them to participate in their care."

Case Practice Question

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

Case 2. Richard is a 26-year-old man with a history of bipolar episodes. He comes to your office with his wife, and the two seem to be having a disagreement. Richard appears agitated. His wife complains that he is drinking excessively. He complains of depression. Which of the following next steps is *incorrect*?

a. Use Richard's relapse prevention plan.
b. Communicate with both parties and come to a compromise.
c. Ensure all parties are safe.
d. Discontinue Richard's current medication.

ACUTE AND MAINTENANCE TREATMENT STRATEGIES FOR BD I: FOCUS ON MIXED AND MANIC EPISODES

When treating a patient with BD I with manic or mixed episodes, consulting an expert opinion can be especially useful. The CANMAT and NICE guidelines are two of the most relevant guidelines in treating BD. "They are a really nice synthesis of available evidence with the input of expert consensus," Dr Swartz said. "They incorporate into the materials . . . prose-based discussions of what the evidence tells us . . . which we can use as a guidepost to treatment." She added that "one thing we have to keep in mind about guidelines is the date they are published. Things may have changed."

Dr Goldberg offered a scenario from previous CANMAT guidelines[26] to discuss, one in which a patient presents with a first manic episode and responds well to treatment. Should the patient be prescribed a lifetime of treatment?

Dr Swartz pointed to the phenomenon of unipolar mania, which meets the criteria of BD I according to *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. Questions arise regarding the side effect burden that accompanies a lifetime of mood stabilizers to treat one manic episode of BD I. However, taking a patient off treatment with a mood stabilizer comes with its own hefty risk. The severity of the manic episode—a patient with hospitalized psychosis vs a patient with no family history of BD who remains well for a year on medication—can inform the decision. Close observation of the latter less severe case along with patient and family education could result in discontinuing medication, but the patient can never be declared free and clear. "I've not been able to get patients successfully off meds, even if they started with subsyndromal manifestations," Dr DelBello said.

Currently, the most common antimanic mood stabilizers used to treat manic or mixed episodes in patients with BD include lithium, divalproex, and carbamazepine.[27] The second-generation antipsychotic

olanzapine is approved to treat bipolar mania and mixed episodes as a monotherapy and as an adjunctive therapy to lithium or divalproex in maintenance therapy of BD I.[28] However, its metabolic burden is well-known, and it is reserved for more severe cases. The combination drug olanzapine/samidorphan has demonstrated a decrease in the metabolic side effects associated with olanzapine due to samidorphan's properties as an opioid antagonist, which are thought to reduce appetite.[29]

Two other novel agents, the approved loxapine and the anticipated dexmedetomidine, have been developed for the treatment of acute bipolar agitation. Loxapine's formulation as an inhalant has demonstrated rapid onset, and dexmedetomidine, as a sublingual agent, has been shown to contain acute agitation without the soporific effects of its predecessors.[30]

Patient Perspective

"You have to have a good relationship with your psychiatrist. Your psychiatrist has to be able to explain the medications, to explain the side effects. It's very important for a psychiatrist to take those concerns seriously and not merely suggest that the patient doesn't want to take medication, which is what happened to me when I would express concern over my medication. So, to properly address adherence issues, you have to have good relationships between your psychiatrist and patient to talk about those side effects."

THERAPEUTIC TOLERABILITY AND ADHERENCE IN BD

BD is associated with high morbidity and mortality rates, with the life expectancy reduced by 10 years or more in patients with BD.[31] It is estimated that between 25% and 60% of patients with BD will attempt suicide at least once during the course of the illness and between 4% and 19% will die from suicide.[32] Treatment adherence is key to improving these numbers, and adherence is greatly dependent on tolerability.[33]

In a survey conducted by the patient advocacy group Depression and Bipolar Support Alliance (DBSA), 90% of patients with BD reported that they discontinued taking their medication at some point. Almost 60% of patients cited weight gain as the most significant concern for nonadherence.[33] "You have to balance what tolerability and side effects are most important to [the patient] and that are most likely to impact their adherence," Dr DelBello said.

Dr Goldberg suggested making a "shopping list" with the patient regarding balancing efficacy with tolerability. Dr DelBello suggested being proactive in minimizing side effects, particularly in initiating a second medication to combat side effects concomitantly with the initial treatment. Medications like metformin or olanzapine/samidorphan can help combat weight gain.[25,14]

Patient Perspective

"We have a lot of examples in the media of people living with bipolar II, which is a bipolar type that you can function with. You don't see a lot of the severe examples of people with bipolar I. And typically, when I see those examples, they're often police encounters. And so, I deal with a lot of stigma. And that was one of the reasons that I refused to accept my diagnosis. People with mental illness don't have jobs. They're unemployed. They don't have relationships. They're unhappy. Who wants to live this life? I internalized that stigma. It's only since I've reached recovery that I'm really proud to have a mental illness. People with mental illness are very brave and courageous. They deal with very challenging life situations."

Clinical Points

- The use of rating scales, a longitudinal history, charting, and checking for the presence of comorbidities can help in the diagnosis of BD.
- Clinicians should consider patients' concerns with medication tolerability and even initiate concomitant treatments that address side effects when developing treatment strategies to ensure adherence.
- Most bipolar patients do not respond to antidepressants, and some may experience inductions of mania or cycle accelerations over time with antidepressants.
- Second-generation antipsychotics olanzapine, quetiapine, lurasidone, cariprazine, and lumateperone and the anticonvulsant lamotrigine are used to treat bipolar depression.
- Lithium; the anticonvulsants divalproex, lamotrigine, and carbamazepine; and the second-generation antipsychotic olanzapine are used to treat bipolar mania and mixed episodes.

Discussion of Case Practice Questions

Case 1: **Preferred response is c. Take a comprehensive history of the patient.**

Taking a comprehensive longitudinal history of the patient can detect previous manic or hypomanic episodes, can differentiate between the types of mania based on severity and duration of the symptoms, and can determine whether the patient has a family history of the illness.

Case 2: **Preferred response is d. Discontinue Richard's current medication.**

Clinicians should never stop a medication suddenly. Instead, developing a relapse prevention plan while the patient is well can prepare him to act on his own behalf when symptoms manifest. Starting with where a patient is and using open communication can lead to agreement upon similar goals, ensuring patient safety always comes first.

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1. **Which of the following treatments binds to the 5-HT_{2A} and the D_2 receptors and received recent approval to treat bipolar I and II depression?**
   a. Cariprazine
   b. Lumateperone
   c. Olanzapine + lithium
   d. Aripiprazole
2. **Which of the following is NOT one of the evidence-based psychotherapies that has shown efficacy for the treatment of bipolar disorder?**
   a. Psychoeducation
   b. Exercise therapy
   c. Family therapy
   d. Cognitive behavioral therapy
3. **Which of these medications can treat bipolar mania and mixed episodes as a monotherapy, can be used as an adjunctive therapy to lithium or divalproex in maintenance therapy, and addresses the side effect of weight gain?**
   a. Olanzapine/samidorphan
   b. Quetiapine
   c. Cariprazine
   d. Divalproex

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