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A primary care guide to bipolar depression treatment

Manage uncomplicated cases following guidelines on medical therapy and with adjunctive psychotherapy. Refer complicated and severe cases to Psychiatry.

PRACTICE RECOMMENDATIONS

▶ *Become knowledgeable in identifying an episode of bipolar depression and differentiating it from major depressive disorder, so as to provide effective treatment for bipolar depression.* (A)

▶ *Begin treatment of bipolar depression with one of the recommended first-line medications, especially lithium, lamotrigine, quetiapine, or lurasidone.* (A)

▶ *Treat bipolar II depression similar to the way bipolar I depression is treated: primarily, using a mood stabilizer alone or, occasionally, using a mood stabilizer plus an antidepressant.* (B)

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Bipolar disorder is a prevalent disorder in the primary care setting.^{1,2} Primary care providers therefore commonly encounter bipolar depression (BD; a major depressive episode in the context of bipolar disorder), which might be (1) an emerging depressive episode in previously undiagnosed bipolar disorder or (2) a recurrent episode during the course of chronic bipolar illness.^{3,4}

A primary care-based collaborative model has been identified as a potential strategy for effective management of chronic mental health conditions such as bipolar disorder.^{5,6} However, this collaborative treatment model isn't widely available; many patients with bipolar disorder are, in fact, treated solely by their primary care provider.

Two years ago in this journal,⁷ we addressed how to precisely identify an episode of BD and differentiate it from major depressive disorder (MDD; also known as unipolar depression). In this review, in addition to advancing clinical knowledge of BD, we provide:

- an overview of treatment options for BD (in contrast to the treatment of unipolar depression)
- the pharmacotherapeutic know-how to initiate and maintain treatment for uncomplicated episodes of BD.

We do not discuss management of manic, hypomanic, and mixed episodes of bipolar disorder.

How to identify bipolar depression

Understanding the (sometimes) unclear distinction between bipolar I and bipolar II disorders in an individual patient is key to formulating a therapeutic regimen for BD.

■ **Bipolar I disorder** consists of manic episodes, alternating (more often than not) with depressive episodes. Bipolar I usually manifests first with a depressive episode.

■ **Bipolar II disorder** manifests with depressive episodes

TABLE 1

What are the features of bipolar disorders?⁷

Disorder	Defining features of mood episodes	Average age at onset of mood episodes	Prevalence in the United States ^a
Bipolar I	≥ 1 wk of mania, with or without ≥ 2 wk of a major depressive episode	18 y	0.6%
Bipolar II	≥ 4 d of hypomania with ≥ 2 wk of a major depressive episode	Mid-20 y	0.3%
Other specified bipolar disorder	< 4 d of hypomania with ≥ 2 wk of a major depressive episode; hypomania without a major depressive episode; hypomanic episode with a major depressive episode of insufficient symptoms; < 24 mo of cyclothymia	Undetermined	Undetermined
Other unspecified bipolar disorder	Symptoms consistent with bipolar disorder causing distress or impairment without meeting criteria for other bipolar disorders	Undetermined	Undetermined

^a Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 5th ed. American Psychiatric Association Publishing; 2013.

and hypomanic episodes (but never manic episodes).

■ Depressive episodes in the bipolar disorders. Bipolar depression can be seen in the settings of both bipolar I and II disorders. When a patient presents with a manic episode, a history of depressive episodes is common (although not essential) to diagnose bipolar I; alternatively, a history of hypomania (but no prior mania) and depression is needed to make the diagnosis of bipolar II. The natural history of the bipolar disorders is therefore alternating manic and almost always depressive episodes (bipolar I) and alternating hypomanic and always depressive episodes (bipolar II).⁸

Symptoms of hypomanic episodes are similar to what are seen in manic episodes, but are of shorter duration (≥ 4 days [episodes of mania are at least of 1 week's duration]), lower intensity (no psychotic symptoms), and not associated with significant functional impairment or hospitalization. TABLE 1⁷ further describes the differentiating features of bipolar I and bipolar II. A history of an unequivocal manic or hypomanic episode makes the diagnosis of BD relatively easy. However, an unclear history of manic or hypomanic symptoms or episodes frequently leads to misdiagnosis or underdiagnosis of BD.

In both bipolar I and II, it is depressive

symptoms and episodes that place the greatest burden on patients across the lifespan: They are the most commonly experienced features of the bipolar disorders^{9,10} and lead to significant distress and functional impairment¹¹; in fact, patients with bipolar disorder spend 3 (or more) times as long in depressive episodes as in manic or hypomanic episodes.^{12,13} In addition, subthreshold depressive symptoms occur commonly between major mood episodes.

Failure to identify and adequately treat depressive episodes of the bipolar disorders can have serious consequences: Patients are at risk of a worsening course of illness, alcohol use disorder, substance use disorder, chronic disability, mixed states, rapid cycling of mood episodes, and suicide.

Guidelines for treating bipolar depression

Despite the similarity in presenting symptoms and signs of depressive episodes in bipolar disorders and MDD, treating episodes of BD is significantly different than treating MDD. Antidepressant monotherapy, a mainstay of treatment for MDD, has limited utility in BD (especially depressive episodes of bipolar I) because of its limited efficacy and potential to destabilize mood, lead to rapid cycling, and induce mania or hypomania.

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Failure to adequately treat bipolar depressive episodes can have serious consequences, including a worsening course of illness, alcohol and substance use disorder, and suicide.

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**Top
 recommended
 medications
 for bipolar
 depression
 are lithium,
 quetiapine,
 olanzapine,
 lamotrigine,
 and combined
 olanzapine/
 fluoxetine.**

Treatment options for BD include pharmacotherapy (the primary modality), psychological intervention (a useful adjunct, described later), and electroconvulsive therapy (ECT; highly worth considering in severe or treatment-resistant cases).

For this article, we searched PubMed and Google Scholar for guidelines for the management of bipolar disorders in adults that were published between July 2013 (when the US Food and Drug Administration [FDA] approved lurasidone for the treatment of BD) and March 2019. Related guideline-referenced articles and clinical trials were also reviewed.

Our search identified 6 guidelines issued during the search period, developed by the:

- Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD),¹⁴
- British Association for Psychopharmacology (BAP),¹⁵
- Japanese Society of Mood Disorders (JSMD),¹⁶
- National Institute for Health and Care Excellence (NICE),¹⁷
- International College of Neuropsychopharmacology (CINP),¹⁸ and
- Royal Australian and New Zealand College of Psychiatrists.¹⁹

How to manage an episode of bipolar depression

First-line pharmacotherapeutic agents for the management of BD in acute bipolar I are listed and described in **TABLE 2**.⁴⁻¹⁹ Compared to the number of studies and reports on the management of BD in bipolar I, few studies have been conducted that specifically examine the treatment of BD in acute bipolar II. In practice, evidence from the treatment of BD in bipolar I has been extrapolated to the treatment of bipolar II depression. CANMAT-ISBD guidelines recommend quetiapine as the only first-line therapy for BD in bipolar II; JSMD, CINP, and NICE guidelines do not make distinct recommendations for treating BD in bipolar II.

Patients who have BD can present de novo (ie, not taking any medication for bipolar disorder) or with a breakthrough epi-

sode while on maintenance medication(s). In either case, monotherapy for BD is preferred, although combinations of medications (**TABLE 2**¹⁴⁻¹⁹) can be more effective in some cases. Treatment guidelines overlap to a high degree, especially in regard to first-line treatments, but there is variation, especially beyond first-line therapeutics.²⁰

The top recommended medications for BD are lithium, quetiapine, olanzapine, lamotrigine, and combined olanzapine/fluoxetine. FDA-approved agents for treating acute BD specifically include quetiapine, lurasidone, and combined olanzapine/fluoxetine. Guidelines generally recommend a first step of adjusting the dosage of medications in any established regimen before changing or adding other agents. If clinical improvement is not seen using any recommended medications, psychiatric referral is recommended. See **TABLE 3**^{21,22} for dosing and titration guidance and highlights of both common and rare but serious adverse effects.

Recommendations, best options for acute bipolar depression

Start with lithium, lamotrigine, quetiapine, or lurasidone as the first-line medication at the dosages given in **TABLE 3**.^{21,22} Olanzapine alone, or in combination with fluoxetine, can be used when it has been determined that the medications listed above are ineffective.

Note that lithium requires regular blood monitoring (**TABLE 3**^{21,22}). However, lithium has the advantage of strong supporting evidence of benefit in all mood episodes of bipolar disorders (depressive, manic, hypomanic), as well as maintenance, prevention of recurrence, and anti-suicidal properties.

Also of note: Lurasidone is much more costly than other recommended medications because it is available only by brand name in the United States; the other agents are available as generics. Consider generic equivalents of the recommended agents when cost is an important factor, in part because of the impact that cost has on medication adherence for some patients.

Last, olanzapine should be used later in the treatment algorithm, unless rapid control of symptoms is needed or other first-line medications are ineffective or not tolerated—given

TABLE 2

Recommendations for first-line pharmacotherapy of bipolar I depression¹⁴⁻¹⁹

Organization or work group	Recommendations ^a
Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders ¹⁴	Monotherapy: Quetiapine, lithium, lamotrigine, or lurasidone For breakthrough episodes that occur during lithium therapy, add lurasidone, lamotrigine, or quetiapine
British Association for Psychopharmacology ¹⁵	Begin by adjusting the dosage of any established medication(s) If dosage adjustment is insufficient, or if the patient does not have an established medication, start: <ul style="list-style-type: none"> • monotherapy: lurasidone, quetiapine, or olanzapine • combination therapy: olanzapine plus fluoxetine
Japanese Society of Mood Disorders ¹⁶	Monotherapy: Quetiapine, lithium, olanzapine, or lamotrigine
National Institute for Health and Care Excellence ¹⁷	Begin by adjusting the dosage of any established medication(s); however, if the patient is established on lithium, dosage adjustment or addition of 1 of the following medications is recommended: <ul style="list-style-type: none"> • monotherapy: olanzapine, lamotrigine, or quetiapine • combination therapy: olanzapine plus fluoxetine Likewise, if the patient does not have an established medication, start: <ul style="list-style-type: none"> • monotherapy: olanzapine, lamotrigine, or quetiapine • combination therapy: olanzapine plus fluoxetine
International College of Neuropsychopharmacology ¹⁸	Monotherapy: Quetiapine, lurasidone, or combined olanzapine/fluoxetine
Royal Australian and New Zealand College of Psychiatrists ¹⁹	Monotherapy: Quetiapine, lurasidone, olanzapine, lithium, lamotrigine, or valproate ^b

^a Fewer studies have been conducted on the management of bipolar II depression than on bipolar I depression. Most existing guidelines recommend that bipolar II depression be treated similar to the way bipolar I depression is treated: primarily, a mood stabilizer. Some guidelines recommend a mood stabilizer with or without an antidepressant for bipolar II. The Canadian Network for Mood and Anxiety Treatments and the International Society for Bipolar Disorders recommend that first-line pharmacotherapy for bipolar II depression include monotherapy with quetiapine or extended-release quetiapine.

^b According to guidelines of the Royal Australian and New Zealand College of Psychiatrists, second-line therapy entails combination therapy with *either*:

- lithium plus *either* quetiapine, lurasidone, valproate, or lamotrigine
- valproate plus *either* lurasidone or quetiapine
- lamotrigine plus quetiapine
- olanzapine plus fluoxetine.

An antidepressant can be added to prior agents (except for lamotrigine), as long as symptoms of mania do not develop during the depressive episode; however, evidence for antidepressants is unclear, except for olanzapine plus fluoxetine, for which there is substantial evidence.

the higher propensity of the drug to produce weight gain and cause metabolic problems, including obesity and hyperglycemia.

The importance of maintenance therapy

Almost all patients with BD require maintenance

treatment to prevent subsequent episodes, reduce residual symptoms, and restore functioning and quality of life. Maintenance therapy is formulated on the basis of efficacy and tolerability in the individual patient.

As a general rule, the strongest evidence for preventing recurrent BD episodes favors

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Lithium has strong supporting evidence of benefit in mood episodes of all bipolar disorders.

TABLE 3

Medications commonly used to treat bipolar depression^{21,22}

Agent	Adult dosing and titration	Potential adverse effects	Laboratory testing and clinical examination
Lithium	<p>Initiate at 150-300 mg PO qhs</p> <p>Titrate upward gradually as needed over 1-2 mo while measuring the lithium level (target, ≤ 0.8 mEq/L for bipolar depression, unless the patient becomes stable at a lower dosage or adverse effects prevent an increase in dosage) and kidney and thyroid function</p>	<p>Common: Hypothyroidism, nausea, vomiting, and diarrhea</p> <p>More serious (but less common): Weight gain (occasional), cognitive impairment (at higher dosages), bradyarrhythmia, renal impairment, teratogenicity (especially in the first trimester), and lithium toxicity</p> <p>Careful, regular monitoring is of great help in minimizing the risk and severity of these adverse effects</p>	<p>Baseline pregnancy test</p> <p>Lithium level: When increasing the dosage; when there is suspicion that the lithium level is greater than the therapeutic target range (≤ 0.8 mEq/L); and 5-7 d after initiation or a dosage change (12 h after the previous dose); repeat measurement of the lithium level every 3-4 mo thereafter</p> <p>Thyroid function: At baseline, within 1 mo after initiation, and every 4-6 mo thereafter</p> <p>Kidney function and electrolytes: At baseline; when increasing the dosage; when toxicity is suspected; within 1 mo of initiation; and every 4-6 mo thereafter</p> <p>Complete blood count: At baseline and later if clinically indicated</p> <p>Electrocardiography: Only if clinically indicated</p> <p>24-hour creatinine clearance: If the patient has diminished renal function</p>
Lamotrigine	<p>Monotherapy: 25 mg/d for 2 wk; then, 50 mg/d for 2 wk; then, 100 mg/d for 1 wk; then, maintain at 200 mg/d</p> <p>Can be titrated upward to 400 mg/d if necessary</p> <p>As an add-on to valproate: 25 mg/d every other day for 2 wk; then, 25 mg/d for 2 wk; then, 50 mg/d for 1 wk; then, maintain at 100 mg/d</p> <p>As an add-on to an enzyme-inducing antiepileptic (eg, carbamazepine): 50 mg/d for 2 wk; then, 100 mg/d for 2 wk</p> <p>To discontinue, aim to decrease the dosage by about 50%/wk over ≥ 2 wk</p>	<p>Most serious, but uncommon: Stevens-Johnson syndrome; other serious skin conditions can develop but can be minimized by slow titration</p> <p>Rare: Renal and hepatic impairment, lethargy, weight gain</p>	<p>No special laboratory monitoring is required</p>

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lithium—and most guidelines therefore support lithium as first-line maintenance therapy. It is important to note, however, that if a medication (or medications) successfully aborted an acute BD episode in a given patient, that agent (or agents) should be continued for maintenance purposes to prevent or minimize future episodes—generally, at the same dosage.

First-line pharmacotherapeutic agents for the maintenance of bipolar disorder, and thus to prevent subsequent episodes of BD, are listed in TABLE 4.¹⁴⁻¹⁹

R antidepressants in bipolar depression?

The use of antidepressants to treat BD remains

TABLE 3

Medications commonly used to treat bipolar depression^{21,22} (cont'd)

Agent	Adult dosing and titration	Potential adverse effects	Laboratory testing and clinical examination
Quetiapine	50 mg on Day 1, 100 mg on Day 2, and 200 mg on Day 3; can be increased afterward, more gradually Can be titrated upward more slowly if poorly tolerated Target dosage for bipolar depression: 300-600 mg/d Often taken at bedtime because it causes sedation	Sedation, hypotension, weight gain, metabolic syndrome, diabetes mellitus, prolonged QT interval Rare: tardive dyskinesia, extrapyramidal syndrome, neuroleptic metabolic syndrome	Lipid profile Blood glucose (or hemoglobin A _{1c} , or both): at initiation and every 3 mo for the first year; annually thereafter Heart rate and blood pressure: At initiation and every 6 mo thereafter Measurement of abdominal girth, height and weight (body mass index): At initiation and every 3 mo thereafter
Extended-release quetiapine	50 mg, 100 mg, 200 mg, and 300 mg once/d at bedtime on Days 1 through 4, respectively (can be much slower to avoid sedation or hypotension)		
Valproate/divalproex (including the extended-release formulation)	Start at 250-500 mg qhs and increase gradually, as needed; usual target trough plasma level is 50-125 mcg/mL Maximum dosage is 60 mg/kg/d (treat the patient, not the level; a lower level is acceptable if the patient is stable at a certain level)	Asthenia, dizziness, palpitations, diarrhea, abdominal pain, nausea, vomiting	Baseline pregnancy test Valproic acid level: 1 wk after a dosage change and every 6 mo to annually Comprehensive metabolic profile: At baseline; 1 mo after initiation and at least 6 mo to annually thereafter; with a dosage increase and when any other significant dosage change has been made Complete blood count, with platelet count: At initiation; thereafter, at least every 6 mo Measure the ammonia level if clinically indicated

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a topic of ongoing deliberation. Antidepressant treatment of BD has historically raised concern for depressive relapse due to ineffectiveness and the ability of antidepressants to increase (1) the frequency of manic and hypomanic episodes²³ and (2) mood instability in the form of induction of mixed states or rapid cycling. Among most authorities, the recommendation against using antidepressants for BD in both bipolar I and II is the same; however, limited evidence allows the use of antidepressant monotherapy in select cases of BD episodes in bipolar II,^{24,25} although not bipolar I.

The consensus in the field is that medications with mood-stabilizing effects should be considered as monotherapy before adding

an antidepressant (if an antidepressant is to be added) to treat BD in bipolar II.²⁶ In other words, if an antidepressant is to be used at all, it should be combined with a mood stabilizer or atypical antipsychotic^{15,27} and should probably not be used long term. The efficacy of antidepressants in treating BD in bipolar II should be assessed periodically at follow-up.

Nonpharmaceutical treatment options

Although pharmacotherapy is the mainstay of treatment of BD, adjunctive psychotherapy can be useful for treating acute BD episodes that occur during the maintenance phase of the disorder. Psychoeducation (ie, education

TABLE 3

Medications commonly used to treat bipolar depression^{21,22} (cont'd)

Agent	Adult dosing and titration	Potential adverse effects	Laboratory testing and clinical examination
Olanzapine	5-20 mg/d	Orthostatic hypotension, obesity, hypercholesterolemia, hyperglycemia and diabetes mellitus, akathisia, asthenia, somnolence, tremor Rare: Tardive dyskinesia, extrapyramidal syndrome, neuroleptic metabolic syndrome	Lipid profile Blood glucose (or hemoglobin A _{1c} , or both): At initiation; every 3 mo during the first year; annually thereafter Heart rate and blood pressure: At initiation and every 6 mo thereafter Measurement of abdominal girth, height and weight (body mass index): At initiation and every 3 mo thereafter
Lurasidone	Initiate at 20-40 mg/d with food, to a maximum dosage of 120 mg/d	Akathisia, somnolence, nausea, vomiting, dizziness, dyslipidemia Usually weight-neutral, although diabetes and metabolic syndrome can develop Rare: Tardive dyskinesia, extrapyramidal syndrome, neuroleptic metabolic syndrome	For patients who have, or have a history of, a low white blood cell count: Complete blood count, with a differential count, during the first few months of therapy Fasting blood glucose (or hemoglobin A _{1c}) at baseline and periodically thereafter Patients prone to orthostatic hypotension: Monitor orthostatic vital signs Measure the creatinine level if clinically indicated

on psychiatric illness and the importance of medication adherence), alone or in combination with interpersonal and social rhythm therapy (IPSRT), family-focused therapy (FFT), and cognitive behavioral therapy (CBT) can add to the overall efficacy of pharmacotherapy by lowering the risk of relapse and enhancing psychosocial functioning.²⁸

■ **IPSRT** is supported by what is known as the *instability model*, which specifies that 3 interconnected pathways trigger recurrences of a bipolar episode: stressful life events, medication nonadherence, and social-rhythm disruption. IPSRT also uses principles of interpersonal psychotherapy that are applied in treating MDD, “arguing that improvement in interpersonal relationships can ameliorate affective symptoms and prevent their return.”^{29,30}

■ **FFT** focuses on communication styles between patients and their spouses and families. The goal is to improve relationship functioning. FFT is delivered to the patient and the family.

■ **Attention to social factors.** For psychotherapy to provide adequate results as an adjunct to pharmacotherapy, social stressors (eg, homelessness and financial concerns) might also need to be considered and addressed through social services or a social work consult.

NICE guidelines recommend psychological intervention (in particular, with CBT and FFT) for acute BD. CANMAT-ISBD guidelines recommend either adjunctive psychoeducation, CBT, or FFT during the maintenance phase. Again, medication is the mainstay of treatment for BD in bipolar disorders; psychotherapy has an adjunctive role—unlike the approach to treatment of MDD, in which psychotherapy can be used alone in cases of mild, or even moderate, severity.

Referral for specialty care

In the primary care setting, providers might choose to manage BD by initiating first-line pharmacotherapeutic agents or continuing established treatment regimens with necessary

TABLE 4

First-line maintenance treatment of bipolar disorder¹⁴⁻¹⁹

Organization or work group	Recommendations
Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders ¹⁴	Lithium, lamotrigine (limited efficacy in preventing mania), divalproex, olanzapine, quetiapine, LAI risperidone, aripiprazole; either lithium or divalproex with adjunctive quetiapine, LAI risperidone, aripiprazole, or ziprasidone
British Association for Psychopharmacology ¹⁵ Japanese Society of Mood Disorders ¹⁶ National Institute for Health and Care Excellence ¹⁷	Lithium
International College of Neuropsychopharmacology ¹⁸	Lithium, aripiprazole, quetiapine, risperidone (can be LAI), olanzapine, paliperidone
Royal Australian and New Zealand College of Psychiatrists ¹⁹	Predominantly depressive episodes: Lamotrigine Predominantly manic episodes: Lithium; olanzapine If neither mania nor depression is predominant: Quetiapine Combination therapy: Either lithium or valproate, with lamotrigine, quetiapine, or aripiprazole

LAI, long-acting injectable.

dosage adjustments. These patients should be monitored closely until symptoms remit.

However, it is important for the primary care provider to identify patients who need psychiatric referral. Complex presentations, severe symptoms, and poor treatment response might warrant evaluation and management by a psychiatrist. Furthermore, patients with comorbid psychotic features, catatonia, or severely debilitating depression (with or without suicidality) need referral to the emergency department.

■ **Electroconvulsive therapy (ECT).** Patients might also need referral to Psychiatry for ECT, which is recommended by CANMAT-ISBD and JSMD guidelines as a second-line option; by the Royal Australian and New Zealand College of Psychiatrists as a third-line option; and by BAP for cases that are resistant to conventional treatment, with or without a high risk of suicide; in pregnancy; and in life-threatening situations.^{15,31,32}

■ **Telemedicine.** There is a considerable shortage of mental health care professionals.^{33,34} The fact that nearly all (96%) counties in the United States have an unmet need for prescribers of mental health services (mainly psychiatrists) makes it crucial that primary care physicians be knowledgeable and prepared to

manage BD—often with infrequent psychiatry consultation or, even, without psychiatry consultation. For primary care facilities that lack access to psychiatric services, telemedicine can be used as a consultative resource.

Psychiatric consultation using telemedicine technologies has provided significant cost savings for medical centers and decreased the likelihood of hospital admission,³⁵ thereby alleviating health care costs and improving care, as shown in a rural Kansas county study.³⁶ Furthermore, the burden on emergency departments in several states has been significantly reduced with psychiatric consultations via interactive telemedicine technologies.³⁷

JFP

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