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The Diagnosis and Management of Bipolar I and II Disorders: Clinical Practice Update

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Abstract

Bipolar disorders, including bipolar I disorder (BP-I) and bipolar II disorder (BP-II), are common, potentially disabling, and, in some cases, life-threatening conditions. Bipolar disorders are characterized by alternating episodes of mania or hypomania and depression, or mixtures of manic and depressive features. Bipolar disorders present many diagnostic and therapeutic challenges for busy clinicians. Adequate management of bipolar disorders requires pharmacotherapy and psychosocial interventions targeted to the specific phases of illness. Effective treatments are available for each illness phase, but mood episode relapses and incomplete responses to treatment are common, especially for the depressive phase. Mood symptoms, psychosocial functioning, and suicide risk must, therefore, be continually reevaluated, and, when necessary, the plan of care must be adjusted during long-term treatment. Many patients will require additional treatment of comorbid psychiatric and substance use disorders and management of a variety of commonly co-occurring chronic general medical conditions.

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Bipolar disorders are serious, chronic psychiatric illnesses characterized by alternating episodes of mania or hypomania and depression, or mixtures of manic and depressive features. The annual incidence of bipolar disorders ranges from 3 to 10 cases per 100,000 population,[1] and the lifetime prevalence is estimated to be 3% to 7%.[2-5] The public health impact of bipolar disorders is profound based on well-documented adverse effects on functioning in nearly all life domains, including the ability to work.[6,7] In general, bipolar disorders can be managed with appropriate pharmacotherapy and targeted psychosocial interventions, but residual clinical symptoms and dysfunction can persist, even with active treatment.[8] Therefore, mood symptoms and functioning must be continually reevaluated when treating patients with bipolar disorders. This article provides a brief clinical guide to the diagnosis and treatment of bipolar disorders, with emphasis on bipolar I (BP-I) and bipolar II (BP-II) subtypes.

CLINICAL FEATURES

Early and accurate diagnosis of bipolar disorders is important for optimizing treatment outcomes.[9] Yet, for many patients, the time lag to accurate diagnosis of BP-I or BP-II is more than 10 years.[10] No biomarkers with sufficient diagnostic validity for use in clinical practice are currently available for bipolar disorders or other psychiatric disorders.[11] Therefore, bipolar disorders and other psychiatric illnesses are diagnosed clinically, and a high index of suspicion must be maintained. Many patients with bipolar disorders are initially diagnosed as having unipolar major depression, which is problematic because antidepressants used in the absence of mood stabilizers or selected antipsychotic drugs may not be effective and can cause a switch to mania or destabilization of their illness. These issues are discussed separately herein.

Making the Diagnosis

The first step toward the accurate diagnosis of BP-I or BP-II disorder is identifying current or past manic, hypomanic, and depressive episodes. Diagnostic criteria for these types of mood episodes, and clinical probes for identifying key symptoms, are provided in Table 1.[12] With this information, specific bipolar syndromes can then be diagnosed, including the classic bipolar disorder subtypes, BP-I and BP-II, as well as cyclothymic disorder, intermediate bipolar disorder phenotypes that are commonly encountered in clinical practice

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(other specified bipolar and related disorders), and bipolar disorders due to secondary causes (Table 2).[12] It is important to determine whether episodes of depression, mania, or hypomania are complicated by psychotic features (hallucinations or delusions) and whether the patient's long-term course meets the operational criteria for rapid cycling (having ≥4 discrete mood episodes in the preceding 12 months). These bipolar subtypes have specific treatment implications that are discussed later herein.

Onset and Course

The peak incidence of BP-I and BP-II occurs between 12 and 30 years of age.[13-15] The symptoms of bipolar disorders are persistent, particularly depressive symptoms.[16-18] Individuals with bipolar disorders die an average of 8 to 20 years sooner than general population controls.[19,20] Part of this risk can be attributed to suicide, which occurs 14 times as often in patients with bipolar disorder compared with the general population.[21] However, a much higher proportion of patients with bipolar disorder die of natural causes related to comorbid obesity, cardiovascular and metabolic diseases, other co-occurring chronic health conditions (discussed later herein), and complications related to smoking.[22,23]

Outcome

Bipolar disorders have persisting adverse clinical, social, and economic effects, even when treated.[17,24-27] Only approximately one-quarter of patients with bipolar disorders fully recover from an acute depressive episode,[28] and rates of illness relapse and disability remain high despite good treatment adherence.[29] Thus, although treatment with mood stabilizers and other medications improves the symptoms and natural course of bipolar disorders, illness relapses remain frequent, and symptomatic remission (the absence of illness symptoms) and functional recovery (return to premorbid level of functioning) are often difficult to achieve. Poor adherence to recommended treatments is a major problem, especially early in the illness course.

DIFFERENTIAL DIAGNOSIS AND COMORBIDITY

Misdiagnosis or Missed Diagnosis?

Having a low index of suspicion can lead to missing the diagnosis of bipolar disorders.[30] This is particularly true of bipolar depression, the phase of bipolar illness during which most patients seek treatment.[31] Among depressed patients who seek care in specialty and nonspecialty medical settings, there is evidence for both misdiagnosis (false-positives) and missed diagnoses (false-negatives) of bipolar disorders.[32-34] When the diagnosis is missed, patients are typically misclassified as having unipolar major depression.[35] Oppositely, certain comorbid psychiatric diagnoses occurring in depressed patients are predictive of overdiagnosing bipolar disorders, including borderline personality disorder, posttraumatic stress disorder, other anxiety disorders, and impulse control disorders.[36]

Misdiagnosis or Mixed Diagnosis?

The situation becomes particularly complex when considering mood episodes complicated by mixed features. The previous nosology used by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, defined mixed episodes as meeting the full diagnostic criteria for major depressive and manic episodes simultaneously[37]; however, such presentations are uncommon in clinical practice. This narrow definition of mixed episodes overlooked the broader spectrum of mixed mood presentations that are more commonly encountered by clinicians. Indeed, subthreshold hypomanic symptoms can occur in as many as 40% of patients with major depressive disorder.[38] Therefore, the current diagnostic classification system uses a "mixed features" specifier when (hypo)manic episodes are complicated by co-occurring depressive symptoms, and vice versa. Although major depression with mixed features is not pathognomonic of bipolar disorders, it may alert the clinician to the possibility of a bipolar spectrum disorder, and the need to carefully assess the patient for a history of manic or hypomanic episodes.[39]

Unipolar or Bipolar Depression?

A significant challenge is distinguishing between unipolar and bipolar depression. Episodes of bipolar depression and unipolar major depression have the same general diagnostic criteria.[12] However, a history of manic or hypomanic episodes distinguishes bipolar depression from unipolar depression. The search for past manic or hypomanic episodes is especially important for individuals with

TABLE 1. Diagnostic Criteria and Aids to Diagnosing the Basic Subtypes of Bipolar Mood Episodes[12]

Major depressive episode[a]

- **At least 1 essential criterion (depressed mood or anhedonia) persisting for ≥2 wk and**
- **Essential criteria and additional symptoms add up to ≥5 total diagnostic criteria being met.**

Essential criteria	**Clinical probes**
Persisting depressed mood	Have you been feeling depressed or down most of the day, nearly every day? How long has this lasted?
Persisting anhedonia	Have you lost interest or pleasure in things that you usually enjoy? How long has this lasted?
Additional symptoms criteria	**Clinical probes**
Increase or decrease in appetite or body weight	Has your appetite changed from normal during the time you have been feeling depressed? Have you started eating more/less than usual? Has your weight changed? Did you intend to gain/lose weight?
Persisting insomnia or hypersomnia	Has there been a change in the amount of your sleep while feeling depressed? How many hours a night compared to normal? Do you have problems falling asleep, staying asleep, or waking up too early (or a combination of these)?
Persisting fatigue or energy loss	Have you felt tired or run down all the time (or nearly every day) while feeling depressed?
Psychomotor agitation or slowing	Have you been so fidgety or restless that you could not sit still? Have others noticed? Have you or others noticed that you have been talking or moving more slowly than usual?
Feelings of worthlessness or excessive guilt	Have you felt like you were less deserving than other people while feeling so depressed? Why? Have you been feeling worthless on a daily or near-daily basis while feeling depressed? Have you been feeling more guilty than usual about mistakes, things you have done, or even things you have not done? How so?
Problems concentrating or making decisions	Has it been harder for you to maintain your focus or think through things while feeling depressed? Has it been harder to make everyday decisions?
Recurring thoughts of death or suicide	Have you been thinking a lot about death or that you may be better off dead? Have you been thinking of hurting yourself and how you might do that? Have you done anything to hurt yourself? Are you having these thoughts now?

Manic or hypomanic episodes[a]

- **At least 1 essential criterion persisting for ≥7 d (mania)[b] or ≥4 d (hypomania) and**
- **Essential criteria and additional symptoms add up to ≥3 diagnostic criteria being met (≥4 if mood is irritable).[c]**
- **Assess for the threshold level of severity needed to distinguish between manic and hypomanic episodes.[d]**

Essential criteria	**Clinical probes**
Persisting elevated, expansive, or irritable mood[b]	Have you had a time in your life where your mood was so excited, energized, or high that others thought you were not your normal self? What was that like? How long did it last? How about feeling so irritable or angry for several days in a row that others thought you were not your usual self? Was that different than how you normally are when you get upset? How so? How long did that last? Did you need to be in the hospital because of any of this?
Additional symptoms criteria	**Clinical probes**
Abnormally elevated self-esteem	When your mood was abnormally elevated/irritable, how did you feel about yourself? Did you feel more confident or smarter than usual? Did you think you had special capabilities or insights? What was that like? Do you recall feeling more attractive to others than usual? Do you remember having a lot more sexual energy or interest than usual?
Decreased need for sleep	When your mood was abnormally elevated/irritable, did you seem to need much less sleep than usual? How much is normal for you? How much were you getting by on when your mood was abnormally elevated/irritable? Did you still feel rested, or even more energized than usual, despite getting so little sleep?
Increased talkativeness	When your mood was abnormally elevated/irritable, were you more talkative than usual? Did others point it out to you? What did they say? Did others have problems understanding you because you talked too fast or too much? Did they have trouble interrupting you? Is that different than how you normally are or how you normally talk?

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TABLE 1. Continued

Flight of ideas or racing thoughts	When your mood was abnormally elevated/irritable, did your thoughts race or seem to go faster than normal? Did your head seem to become overcrowded with thoughts? What was that like?
Abnormal distractability	When your mood was abnormally elevated/irritable, did you have problems staying focused on one thing? Were you really prone to being distracted? What was that like? Is that different than how you normally are? How so?
Increased energy or goal-directed activity	When your mood was abnormally elevated/irritable, were you unusually hyper or wired because you had an unusual amount of energy? What was that like? Do you recall being unusually restless, not being able to sit still, or pacing excessively? Were you unusually productive (or unproductive) during that time? How so? What was a typical day for you like when your mood was abnormally elevated/irritable? How does that compare with normal?
Abnormally risky behaviors[e]	When your mood was abnormally elevated/irritable, do you think you lost control of your impulses and judgment? Did you do things that were unusually risky or caused problems for you? Can you give me some examples?

[a]Can use the diagnostic probes to guide clinical history taking from patients and collateral historians, such as family members or significant others.

[b]Psychiatric hospitalization is often needed to manage acute manic episodes to prevent patients from harming themselves or others, to prevent behaviors that could cause serious financial or legal problems, or to address psychotic symptoms. If hospitalization is required, then diagnostic criteria for a manic episode can be satisfied even if the defining symptoms have been present for less than 7 days.

[c]If the mood state (essential criterion) is irritable instead of elevated, then four or more of the eight diagnostic criteria must be met to satisfy the diagnostic criteria for a manic episode.

[d]Manic episodes are diagnosed if the defining symptoms are severe enough to result in psychiatric hospitalization, cause marked impairment in social or occupational functioning, or are associated with psychotic features (hallucinations or delusions).

[e]This can include any type of behavior stemming from a loss of impulse control or judgment. It can be helpful to provide examples of specific behaviors for patients, emphasizing that they must be behaviors that would not fall within the range of normal for that individual. These behaviors include excessive overspending, engaging in highly pleasurable but also high-risk activities (such as high-risk sexual encounters, gambling, and substance use), engaging in thrill-seeking types of behaviors (such as reckless driving or spending more money than usual), and making decisions impulsively to such a degree that it would be considered unusual for the patient.

early onset of their first depressive episode (<25 years of age), a high lifetime number of depressive episodes (≥5), a history of psychotic features during depressive episodes, and a family history of bipolar disorders. These characteristics have been shown to increase the probability of bipolar rather than unipolar major depression,[40,41] particularly among those with multiple risk factors.[42,43] Inquiring about past manic or hypomanic episodes is also important for depressed patients who fail to respond to (or worsen during) antidepressant drug treatment.[44,45]

Psychiatric Comorbidity

Psychiatric comorbidity is present in 50% to 70% of patients with bipolar disorders. The most common of these are anxiety disorders (~70% of patients) and alcohol and other substance use disorders (~40%-50% of patients).[46] The presence of these comorbidities in patients with bipolar disorder is associated with a worse longitudinal course, more frequent mood episodes and suicide attempts, and poorer quality of life and role functioning.[47-49] Although people with co-occurring bipolar and substance use disorders are more ill overall, they are not less likely to recover from a mood episode than those with bipolar disorders without substance use disorder comorbidity.[50] Other conditions that frequently co-occur with bipolar disorders include eating disorders (eg, bulimia nervosa and binge-eating disorder) and impulse control disorders (eg, attention-deficit/hyperactivity disorder).[48,51] More than one-third of patients with bipolar disorders have a comorbid personality disorder, particularly borderline personality disorder.[46] Patients with comorbid personality disorders tend to have more frequent mood episodes, shorter euthymic intervals, and higher rates of alcohol and substance use disorders and suicidality.[52] These comorbid conditions should be treated aggressively and often require integrated treatment along with managing the core symptoms of bipolar disorders.

General Medical Comorbidity

Bipolar disorders are also associated with a variety of co-occurring general medical conditions, including obesity/overweight, cardiovascular diseases, type II diabetes mellitus, autoimmune diseases, and malignancies, and with high rates

TABLE 2. Diagnostic Criteria for Major Forms of Bipolar Disorder

Bipolar I disorder	**Bipolar II disorder**	**Cyclothymic disorder (cyclothymia)**
Essential diagnostic features: a. At least 1 lifetime manic episode b. The manic episode was not due to effects of medication, substances, or medical illness Diagnostic note: an episode of depression is not required to make a diagnosis of bipolar I disorder	Essential diagnostic features: a. At least 1 lifetime hypomanic episode b. At least 1 lifetime major depressive episode c. Neither the hypomanic nor the depressive episode(s) was due to effects of medication, substances, or medical illness	Essential diagnostic features: a. Numerous hypomanic and depressive symptoms for ≥2 y b. Diagnostic criteria for hypomanic episodes and for major depressive episodes not met c. No symptom-free period lasting ≥8 wk during the 2-y period
Other specified bipolar and related disorders	**Substance/medication-induced bipolar and related disorders**	**Bipolar and related disorders due to another medical condition**
Examples include: • Major depressive episodes + short episodes of hypomanic symptoms (2-3 d) that do not meet duration criteria for hypomanic episodes • Major depressive episodes + episodes of hypomanic symptoms that do not meet symptomatic criteria for hypomanic episodes • Hypomanic episodes with no previous major depressive episodes • Short-duration cyclothymia, with symptoms persisting for <2 y	Clues to the diagnosis: • Mood disturbance (mania, hypomania, depression) develop during or soon after exposure to (or withdrawal from) the implicated substance/medication • The implicated substance/medication is capable of producing the mood disturbance • Mood disturbance abates soon after exposure to the implicated substance/medication ends • Reemergence of mood disturbance during rechallenge with the same substance/medication or a pharmacologically related alternative implicates the exposure as being causal, absent other factors	Clues to the diagnosis: • Mania, hypomania, or depression develops in the context of existing or newly diagnosed medical illness • The medical illness is capable of causing the mood disturbance

Data from American Psychiatric Association.[12]

of smoking.[53-56] Comorbid obesity and overweight are of particular concern for patients with bipolar disorders. Both are associated with a more severe and chronic bipolar illness course, poorer response to pharmacotherapy, and heightened suicide risk.[57-60] Moreover, many effective pharmacotherapies have been associated with clinically significant weight gain and adverse effects on glycemic and lipid profiles.[61] Therefore, obesity/overweight and metabolic disorders must be identified and addressed in patients with bipolar disorder, both at baseline and after initiation of pharmacotherapy, to optimize treatment outcomes.

CAUSES AND RISK FACTORS

Etiology

The etiology of bipolar disorders is unknown but is thought to involve widespread abnormalities in neuroendocrine, neurotransmitter, and intracellular signaling systems that regulate mood and neuronal functioning.[62-64] The results of genetic and other studies suggest that no single factor can adequately explain the symptoms of bipolar disorders or the variations in treatment outcomes in afflicted patients.[65] Several risk genes for bipolar disorders have been identified, but these genetic risk factors have substantial overlap with other psychiatric disorders, including schizophrenia.[66,67] Magnetic resonance imaging studies have shown abnormalities in the structure and function of prefrontal and other brain regions implicated in emotional regulation and cognition.[68,69]

Risk Factors

Although risk genes that are specific for bipolar disorders have been difficult to identify, genetic factors clearly affect the risk of developing bipolar disorders. The overall heritability—that is, the proportion of disorder risk in the population attributable to genetic variation—of bipolar disorders ranges from 73% to 93%.[70] The concordance rates for bipolar disorders is substantially higher for

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identical twins (39%-43%) than for dizygotic twins (5%-6%).[71] Adoption studies have shown that the relative risk of developing bipolar disorder is higher for adopted children with an affected biological parent than for adopted children without an affected biological parent.[72] Environmental, cognitive, and developmental factors also affect the course and expression of bipolar disorders, and their contributions to disease risk are being actively researched.[73]

CLINICAL EVALUATION

Identifying Manic and Hypomanic Episodes

The presence of manic or hypomanic episodes is a hallmark of the bipolar disorder diagnosis because it distinguishes bipolar disorders from other conditions, such as unipolar major depression. Therefore, a systematic approach to diagnosing bipolar disorders often begins with inquiring about a history of manic and hypomanic symptoms or episodes (Table 1), followed by definitive history taking, work-up, and diagnosis (outlined later herein).

Screening instruments have been developed to aid clinicians with making the eventual diagnosis of bipolar disorders. They are typically used to help identify current or past manic or hypomanic symptoms in patients seeking an evaluation, usually for depression. The Mood Disorder Questionnaire,[74] the Bipolar Spectrum Diagnostic Scale,[75,76] and the Bipolar Disorder Screening Scale are examples of such instruments.[77] Regardless of which instrument is used, positive screening results indicate only the need for additional evaluation to establish a bipolar disorder diagnosis. Likewise, the screening instruments are not very sensitive, and more than 25% of patients with bipolar disorders may have a negative screen.

Evaluation and Diagnosis

The evaluation of patients with suspected bipolar disorders begins with a psychiatric and general medical history and mental status and physical examinations. Focused laboratory and imaging studies may be obtained as clinically indicated (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org).[78-81] Psychiatric assessment includes detailed questioning about current psychiatric symptoms, including suicidal ideation, intent, or plan; the degree of functional impairment ascribable to the current psychiatric symptoms; current psychotic features and rapid cycling; past manic, mixed, hypomanic, and depressive episodes; substance use history; and past treatment responses (including treatment-limiting adverse effects). Evaluation of substance abuse, antidepressant use, and corticosteroid treatment preceding hypomanic or manic episodes is especially important. Level of insight (acceptance of diagnosis and need for treatment) and the quality of the patient's social support network should also be evaluated. Interviewing family members and other collateral informants is important because patients may not view hypomanic episodes as being problematic or recall important details of their history with sufficient accuracy.

MANAGEMENT

Treatment Approach

Treatment generally has 2 phases. Acute-phase treatment is focused on the management of the acute mood episodes (manic, hypomanic, or depressive). Maintenance-phase treatment is focused on preventing recurrences of acute episodes. Each phase is associated with specific treatment needs, and available pharmacotherapies have shown differential effectiveness according to the illness phase.[82] Regular communication between health care providers about changes in prescribed and over-the-counter medications is critical given the risk of clinically significant drug-drug interactions associated with medications used to treat bipolar disorders. Lithium levels and toxicity risk, for example, can increase when lithium is combined with commonly used medications such as nonsteroidal anti-inflammatory drugs and several antihypertensive medications.

Acute Behavioral Emergencies

In acute treatment settings, patients with bipolar disorders may present with severe agitation, violent behaviors, and psychosis. When this occurs, the goal of treatment is to control dangerous behaviors that may result in harm to the patient or others. Patients can then be safely interviewed and further evaluated. Oral or inhaled pharmacotherapy with benzodiazepines or antipsychotic drugs can be offered to

agitated but cooperative patients.[83] However, parenteral antipsychotics, with or without benzodiazepines, may be needed to quickly manage aggressive and violent behaviors.[84] Therapeutic options and doses are summarized in Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org).[84,85] Acutely suicidal patients require urgent mental health evaluation to determine their level of risk and appropriate level of care, including the need for psychiatric hospitalization.

Acute Manic or Hypomanic Episodes

Manic Episodes. Because of its severity, mania is considered a medical emergency, often requiring psychiatric hospitalization.

TABLE 3. Pharmacotherapy Options for Acute Manic or Hypomanic Episodes[a,b]

Medication name	Starting dose	Effective dose (drug level)	Treatment priority and comments
Monotherapy, mood stabilizers			
Lithium	300 mg bid-tid	Usually 900-1800 mg (0.8-1.2 mEq/L)	First line; often combined with other mood stabilizers or antipsychotics for severe or psychotic mania[c]
Divalproex	250 mg bid-tid	Usually 1250-2500 mg Loading dose 20-30 mg/kg body weight[d] (50-125 μg/mL)	First line; often combined with other mood stabilizers or antipsychotics for severe or psychotic mania[c] High priority for rapid cycling patients Usually avoided in women of reproductive age
Carbamazepine	100-200 mg bid	800-1600 mg (4-12 μg/mL)[e]	Second line[e]
Monotherapy, antipsychotic drugs—generally higher priority than mood stabilizer monotherapy for patients with psychotic symptoms, especially those with established maintenance-phase efficacy (Table 5)			
Aripiprazole	10-15 mg/d	15-30 mg/d	First line; may be higher priority for rapid cycling patients
Asenapine	5-10 mg bid	10 mg bid	First line
Cariprazine	1.5 mg/d on day 1 3 mg/d on day 2	3-12 mg/d	First line
Paliperidone extended release	3-6 mg/d	6-12 mg/d	First line
Quetiapine	50 mg bid (300 mg/d when using the extended release form)	400-800 mg/d	First line; may be higher priority for rapid cycling patients
Risperidone	0.5-1.5 mg bid	1-6 mg/d	First line[f]
Ziprasidone	40 mg bid	60-80 mg bid	First line; all doses must be taken with food
Olanzapine	10-15 mg/d	10-30 mg/d	Second line[g]
Typical antipsychotics	Haloperidol (0.5-2 mg bid-tid) Chlorpromazine (10-50 mg bid-tid)	Haloperidol (6-20 mg/d) Chlorpromazine (300-800 mg/d)	Third line[h]; usually combined with mood stabilizers for severe or psychotic mania; typically not used beyond the acute phase of treatment.
Combination therapy—generally high priority for patients with severe mania,[c] with or without psychosis, or if monotherapy is ineffective[i]; combinations that include ≥1 agent with established maintenance-phase efficacy (Table 5) are preferred, whenever possible			
Lithium + divalproex	See above guidelines regarding dosing	See above guidelines regarding dosing	First line for nonpsychotic mania
Lithium + carbamazepine	See above guidelines regarding dosing	See above guidelines regarding dosing	Second line for nonpsychotic mania

Continued on next page

TABLE 3. Continued

Medication name	Starting dose	Effective dose (drug level)	Treatment priority and comments
Combination therapy—generally high priority for patients with severe mania,[c] with or without psychosis, or if monotherapy is ineffective[i]; combinations that include ≥1 agent with established maintenance-phase efficacy (Table 5) are preferred, whenever possible, continued			
Lithium or divalproex + an antipsychotic	See above guidelines regarding dosing	See above guidelines regarding dosing	First line for severe or psychotic mania In general, a first-line atypical antipsychotic drug is preferred for combination therapy with lithium or divalproex over other antipsychotics

[a]bid = twice daily; tid = 3 times daily.

[b]Doses specified in the table are guidelines. Refer to the prescription label for specific dosing instructions for each medication. Treatment priorities (first, second, and third line) are based on the opinion of the author.

[c]Recommendation based, in part, on controlled evidence of faster onset of antimanic effects with combination therapy vs monotherapy with a mood stabilizer or antipsychotic drug alone.

[d]Can use an oral loading strategy in hospitalized patients, starting at 20 mg/kg per day in divided doses, for the first 4 to 7 days of treatment. Valproate blood levels are measured on day 4, and the medication dose can be adjusted accordingly. An alternative strategy is to administer 30 mg/kg per day in divided doses for the first 2 days of treatment, followed by 20 mg/kg per day in divided doses on treatment days 3 to 10.

[e]Therapeutic blood levels of carbamazepine for treating patients with manic or hypomanic episodes have not been established, but a range of 4 to 12 μg/mL may be a useful guide. Carbamazepine extended release is approved in the United States for the treatment of acute manic episodes in adults but is considered lower priority by the author based on the potential for clinically significant drug-drug interactions and limited maintenance-phase data. The use of carbamazepine may be considered earlier for rapid cycling patients. Although carbamazepine can be combined with divalproex, this combination can lead to an increased risk of neurotoxicity (due to raised levels of carbamazepine-epoxide metabolite and increases in free carbamazepine levels) and relapse (due to carbamazepine inducing the metabolism of both itself and divalproex).

[f]May be preferred in cases where there is a foreseeable need to switch from oral antipsychotic medication to a long-acting injectable antipsychotic drug during maintenance treatment. Long-acting injectable forms of aripiprazole and paliperidone have not yet been established as efficacious for bipolar maintenance treatment.

[g]Considered lower priority by the author based on risk of olanzapine-associated weight gain and dysmetabolic adverse effects.

[h]Considered lower priority by the author based on the risk of haloperidol-associated extrapyramidal adverse effects and the potentially limited role of all typical antipsychotic drugs during long-term treatment owing to the risk of tardive dyskinesia.

[i]Adding antipsychotic drugs to carbamazepine has not been shown to be more effective than carbamazepine monotherapy.

Goals of treatment include rapid stabilization of manic symptoms and dangerous behaviors, restoration of sleep, and, often, concurrent management of withdrawal from drugs and alcohol. Pharmacotherapeutic options for manic episodes are shown in Table 3. Key precautions, adverse effects, and drug interactions for these agents are summarized in Supplemental Table 3 (available online at http://www.mayoclinicproceedings.org).

Nearly all antipsychotic drugs and mood stabilizers are effective for treating manic episodes.[86] Antimanic treatments are selected according to a variety of factors, including severity of manic symptoms, presence of psychosis, past responses to medication, psychiatric and general medical comorbidities, and willingness to accept therapy. In general, antidepressants should be discontinued owing to their possible mood destabilizing effects in some patients (discussed later herin).

Combining a mood stabilizer (such as lithium or valproate) with an antipsychotic drug is more rapidly effective than monotherapy with either.[87] Therefore, combination pharmacotherapy with a mood stabilizer and an antipsychotic drug may be preferred in patients with severe or psychotic mania. For less severe manic episodes, monotherapy with mood stabilizers or antipsychotic drugs may be preferred, with combination pharmacotherapy being reserved for patients who respond poorly to monotherapy. Adjunctive benzodiazepines are often used in combination with mood stabilizers and antipsychotic drugs to reduce agitation and anxiety, rapidly restore sleep, and manage catatonia during acute treatment.[88]

Lithium is effective for classical forms of mania, but its onset of action is slower than that of antipsychotic drugs.[89] Lithium may be less effective for patients with mixed manic and depressive symptoms and rapid cycling than anticonvulsant mood stabilizers,[90] although results of

a recent meta-analysis suggest that the effectiveness of lithium for such patients may be no different than that of other pharmacotherapies, including anticonvulsant mood stabilizers.[91] Effective antimanic effects with lithium can usually be achieved at blood levels ranging from 0.8 to 1.2 mEq/L. To reduce the risk of toxicity, lithium-treated patients should consume 8 to 12 glasses of water daily, avoid the use of nonsteroidal anti-inflammatory drugs and other medications that may increase lithium blood concentrations (Supplemental Table 3), and temporarily halt lithium treatment during diarrheal illnesses, if vomiting, or if exposed to other causes of severe dehydration.

Divalproex is an effective antimanic agent when dosed to achieve serum levels ranging from 50 to 125 μg/mL. The antimanic effects of divalproex seem to be more robust as the dose is increased within its therapeutic range.[92] Oral loading (20-30 mg/kg per day) may result in more rapid antimanic effects than conventional dosing.[93] Divalproex is available in delayed-release and extended-release forms, both of which can be used for conventional dosing and oral loading; however, serum drug concentrations with extended-release divalproex are approximately 11% lower than those of the delayed-release form at a given daily dose.[94]

Carbamazepine is sometimes used for treating acute mania that does not respond to lithium and as a monotherapy for hypomanic episodes. Although carbamazepine is approved in the United States for treating acute mania, it is also associated with clinically significant drug-drug interactions and is less well-established for maintenance-phase treatment.[95,96] In addition, carbamazepine is associated with potentially serious hematologic adverse effects (eg, agranulocytosis and aplastic anemia) and dermatologic reactions (such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme). Patients of Asian descent with the HLA-B*1502 allele are at higher risk of potentially serious skin reactions with carbamazepine and should be tested before initiating carbamazepine therapy.[97]

Lamotrigine is a mood stabilizer that is not effective for acute mania[86]; however, lamotrigine is still often added to antimanic pharmacotherapy because of its effectiveness during maintenance treatment. Several other anticonvulsants, such as oxcarbazepine, topiramate, tiagabine, and gabapentin, are sometimes prescribed for manic episodes. However, these drugs have no proven benefit for treating bipolar disorders and are best avoided absent a clearly supported indication (oftentimes a comorbid condition) for their use.

As mentioned earlier, antipsychotic drugs are recommended when psychosis is present.[98] However, antipsychotics are effective for mania with or without psychosis and are more rapidly beneficial than monotherapy with mood stabilizers.[99] Although typical antipsychotics, eg, haloperidol, are effective for acute mania, they are not often used beyond the acute phase of treatment because of the high incidence of acute neuromuscular adverse effects, hyperprolactinemia, and long-term risk of tardive dyskinesia.[100,101]

For most patients, the acute antimanic effects of pharmacotherapy unfold over several days, and almost always within 3 weeks. Manic episodes that do not respond to conventional pharmacotherapy (including drug combinations) may benefit from clozapine (usually combined with mood stabilizers) or electroconvulsive therapy.[102,103] Some patients with refractory mania may respond to experimental tamoxifen or allopurinol when added to lithium-based pharmacotherapy.[104,105]

Hypomanic Episodes. Hypomanic episodes are not associated with either psychosis or significant dysfunction and are managed in ambulatory settings. Pharmacotherapeutic options for hypomania are similar to those for mania. Monotherapy with mood stabilizers with or without adjunctive benzodiazepines can be used for the initial treatment of hypomanic episodes (Table 3). Pharmacotherapy with an antipsychotic drug, or combination therapy with 2 mood stabilizers or mood stabilizers combined with antipsychotic drugs, is generally reserved for cases of poor response to monotherapy.

Acute Bipolar Depressive Episodes

Acute bipolar depressive episodes are generally managed in ambulatory settings. Psychiatric hospitalization is usually needed for bipolar depressed patients at imminent risk for suicide, those with severe agitation or psychotic features, or those with severe loss of functioning to the point that they can no longer

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adequately care for themselves. The goal of acute treatment for bipolar depressive episodes is remission. Because remission requires several weeks to occur, a reasonable interim goal is response, defined as a clinically significant reduction in the number and severity of mood symptoms, with resolution of suicidal ideation and psychotic features. Improvement in depressive symptoms must occur without precipitating manic episodes or rapid cycling. For those with comorbid substance use disorders, dual treatment of bipolar depression and the substance use disorder(s) is recommended. Psychosocial treatment as an adjunct to pharmacotherapy is discussed separately later herein.

BP-I Depression: New Episodes. Depressive episodes account for greater disability and adverse functional impact than manic or hypomanic episodes[18,106,107]; yet, relatively few medications have been shown to be effective for treating acute bipolar depressive episodes. Treatment options for new bipolar depressive episodes with no active pharmacotherapy are shown in Table 4. Monotherapy with quetiapine or lurasidone and combination pharmacotherapy with lithium and lamotrigine, and either quetiapine or lurasidone plus a mood stabilizer (lithium or valproate), are high-priority treatment options for acute BP-I depression.[108-110]

The effectiveness of lithium monotherapy for acute bipolar depression is less well established than that for treating acute mania or for maintenance treatment.[109] However, several studies have shown a significant effect of lithium for reducing suicide attempts and deaths in patients with bipolar disorders compared with antidepressants or other mood stabilizers.[111] Lithium's maintenance-phase efficacy is also well established.[96] Therefore, lithium can also be considered either as a monotherapy or as an adjunct for some patients with acute BP-I depression, particularly those struggling with suicidal impulses.

Some controlled but less consistent evidence also supports monotherapy with divalproex,[109,112] lamotrigine,[113] and carbamazepine.[109] An important disadvantage of lamotrigine is that it takes several weeks to achieve target doses for treating bipolar depression.

The combination of olanzapine and fluoxetine is approved for treating BP-I depression,[114] but the risk of clinically significant weight gain and associated metabolic adverse effects may be treatment limiting for some patients. This applies particularly to patients who are already overweight or obese or have abnormal glycemic or lipid profiles. Aripiprazole and ziprasidone are effective antimanic agents, but they are ineffective for bipolar depression.[115,116]

If the aforementioned pharmacotherapies are ineffective, other options with more limited empirical support can be considered. In general, recommendations at this stage of treatment are based on uncontrolled studies or expert consensus recommendations, including combining other drugs with bipolar antidepressive properties, or cautiously adding antidepressants to mood stabilizers or other atypical antipsychotics (Table 4). Electroconvulsive therapy should be considered for refractory bipolar depression or first line for treating bipolar depression with psychotic features, a high risk of suicide, or medical/nutritional complications because of poor oral intake.[117] Ketamine given intravenously or intranasally at subanesthetic doses is a promising short-term treatment for refractory nonpsychotic bipolar depression; however, it is an experimental treatment with no long-term effectiveness or safety data yet available.[118] Antidepressant monotherapy should almost always be avoided, especially for patients with BP-I.[119,120]

BP-I Depression: Breakthrough Episodes. Breakthrough depressive episodes can occur in patients with bipolar disorder who responded initially to mood-stabilizing treatment and remain on long-term pharmacotherapy. For patients with breakthrough depressive episodes despite ongoing treatment, it is important to consider the following causes of apparent loss of efficacy:

- Inadequate dose of medication
- Poor adherence to pharmacotherapy and psychosocial treatments
- Drug-drug interactions that may render medication less effective
- Use of concomitant medications (antidepressants, psychostimulants, etc) that may destabilize mood
- Changes in thyroid functioning induced by lithium therapy

- Alcohol or substance use
- Increases in psychosocial stress or major disruption of regular social rhythms and daily routines

Loss of efficacy in previously responsive patients is particularly challenging because very few randomized trials specifically address this scenario. Serum concentrations of mood stabilizers (eg, lithium, valproate) should be measured to evaluate adherence and adequacy of dosing. If the mood stabilizer dose is insufficient and the patient has had reasonably good adherence, the dose can be increased. For patients already taking lithium, some have recommended that the lithium dose be optimized to yield serum concentrations of 0.8 mEq/L or greater.[121-123] There is no evidence to support measuring serum drug concentrations of certain mood stabilizers (such as lamotrigine) or atypical antipsychotic drugs. Still, for patients taking low doses, increasing the daily medication dosage to the minimum doses found to be effective for acute bipolar depressive episodes in randomized trials is recommended (Table 4).

For many patients, adjunctive treatments will be needed, and several potential mood stabilizer augmentation strategies exist (Table 4). However, very few studies have examined the efficacy of adding a second medication to ongoing mood stabilizer treatment for breakthrough depression, with the exception of adding lamotrigine to lithium.[124] The use of other mood stabilizer combinations and augmenting mood stabilizers with atypical antipsychotic drugs with bipolar antidepressive properties (such as quetiapine, olanzapine, and lurasidone) can also be considered, but the empirical basis for these recommendations is limited.

BP-II Depression. There are very few studies focused on treatment of BP-II depression. In general, treatment options for BP-II depression are closely aligned with those for BP-I depression. There is empirical support for quetiapine monotherapy for BP-II depression from randomized trials.[125,126] Weaker support exists for the use of lithium, adjunctive antidepressants (taken with mood stabilizers or atypical antipsychotic drugs with bipolar antidepressive effects), and lamotrigine.[127]

The Use of Antidepressants. The use of antidepressants in patients with bipolar disorder is controversial. Antidepressants may be helpful for some patients when used as adjuncts to mood-stabilizing medications; however, possible risks of using antidepressants in bipolar depressed patients include increased mood cycle frequency and the development of rapid cycling.[119] Moreover, in terms of effectiveness, the results from meta-analyses of short-term (up to 26 weeks) randomized trials of antidepressants for bipolar depression are mixed.[128,129] For most patients with BP-I or BP-II depression, antidepressant monotherapy should be avoided.

On the other hand, prescribing antidepressants with antimanic drugs (eg, lithium, valproate, or second-generation antipsychotics) may reduce the risk of switching to mania/hypomania. Antidepressants can be safely used in combination with antimanic medications by patients who have responded favorably to these drugs in the past without treatment-emergent mania/hypomania or mood instability.[119,130] Antidepressants should be avoided in patients with a history of poor outcomes with antidepressant treatment, current mixed depressive symptoms or substance abuse, frequent or severe manic episodes, and manic or hypomanic episodes within the preceding 2 to 3 months.[119,131,132] If manic or hypomanic symptoms occur while taking antidepressants, the antidepressants should be stopped and antimanic treatments should be started or optimized. The risk of antidepressant-induced mania/hypomania may be higher in BP-I than BP-II depressed patients.[133]

Maintenance Pharmacotherapy

Treatments that were effective during the acute phase of treatment should be continued in an effort to prevent early relapses. Ideally, this will already include 1 or more medications with established efficacy for treatment during the maintenance phase (Table 5).

Most mood stabilizers and atypical antipsychotics are effective for preventing manic episodes.[134] Lithium, lamotrigine, quetiapine, and olanzapine are also efficacious in the prevention of depressive episodes,[135] although lithium is generally more effective at preventing manic episodes than depressive

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TABLE 4. Pharmacotherapy Options for Acute Bipolar I or II Depression[a,b]

Medication name	Starting dose	Effective dose (drug level)	Treatment priority and comments
Monotherapy, mood stabilizers			
Lamotrigine	Variable[c]	Variable[c]	Second line; but takes several weeks[d] to achieve target doses
Lithium	150-300 mg bid	900-1800 mg/d (0.6-1.2 mEq/L)	Second line; may be higher priority in patients at high risk for suicidal behavior[e]
Divalproex	250 mg bid	750-2500 mg	Second line; usually avoided in women of reproductive age
Carbamazepine	100 mg bid	800-1600 mg (4-12 μg/mL)[f]	Third line[f]
Monotherapy, antipsychotic drugs—generally higher priority than mood stabilizer monotherapy for patients with psychotic symptoms; medications with established maintenance-phase efficacy (Table 5) are preferred, whenever possible			
Quetiapine	50 mg at bedtime	300 mg at bedtime	First line
Lurasidone	20 mg/d	20-120 mg/d	First line; all doses must be taken with food
Olanzapine	5 mg at bedtime	5-12.5 mg at bedtime	Second line[g]
Cariprazine	1.5 mg/d on day 1 3 mg/d on day 2	1.5-3 mg/d	Third line monotherapy
Combination therapy—generally preferred if monotherapy is ineffective or "breakthrough" depressive episodes occur despite ongoing treatment; combinations that include ≥1 agent with established maintenance-phase efficacy (Table 5) are preferred, if possible			
Lithium + lamotrigine	See above guidelines regarding dosing	See above guidelines regarding dosing	First line
Lithium or divalproex + an atypical antipsychotic	See above guidelines regarding dosing	See above guidelines regarding dosing	First line; lithium or divalproex plus either quetiapine or lurasidone Second line; lithium or divalproex + olanzapine[g]
Olanzapine + fluoxetine	3 mg/25 mg-6 mg/25 mg at bedtime	6 mg/25 mg-12 mg/50 mg at bedtime	Second line[h]
Lithium + divalproex	See above guidelines regarding dosing	See above guidelines regarding dosing	Second line
Lithium or divalproex + an antidepressant[i]	See above guidelines regarding dosing	See above guidelines regarding dosing	Second line; higher priority in patients with a history of good response to antidepressants taken with mood-stabilizing medications
Atypical antipsychotic + an antidepressant[i]	See above guidelines regarding dosing	See above guidelines regarding dosing	Second line; antipsychotics include quetiapine, lurasidone, and olanzapine Higher priority in patients with a history of good response to antidepressants taken with mood-stabilizing medications
Lithium + carbamazepine	See above guidelines regarding dosing	See above guidelines regarding dosing	Third line
Lamotrigine + quetiapine	See above guidelines regarding dosing	See above guidelines regarding dosing	Third line

[a]bid = twice daily.

[b]Doses specified in the table are guidelines. Refer to the prescription label for specific dosing instructions for each medication. Treatment priorities (first, second, and third line) are based on the opinion of the author.

[c]If there are no interacting drugs, start at 25 mg/d for 2 weeks, then increase to 50 mg/d for 2 weeks, then increase the total daily dose by 50 mg/d every 1 to 2 weeks to an initial target dose of 200 mg/d. If taking valproic acid (and derivatives, including divalproex), a slower titration is required—start at 25 mg every other day for 2 weeks, then increase to 25 mg/d for 2 weeks, then increase the total daily dose by 25 to 50 mg/d every 1 to 2 weeks to an initial target dose of 100 mg/d. If taking carbamazepine or other enzyme-inducing drugs, a faster titration is possible—start at 50 mg/d for 2 weeks, then increase to 100 mg/d (in divided doses) for 2 weeks, then increase total daily dose by 100 mg/d every 1 to 2 weeks to an initial target dose of 400 mg (in divided doses).

[d]Rapid dose escalation should be avoided owing to the risk of precipitating potentially serious rashes with lamotrigine. Severe rashes, including Stevens-Johnson syndrome, are, fortunately, rare (0.08%-0.3% of epileptic adults who received lamotrigine treatment along with valproic acid) and nearly always occur within the first 8 to 12 weeks of treatment. However, the emergence of any skin rash during lamotrigine therapy should usually lead to discontinuation of the drug, unless the rash is clearly not drug related, because it is often not possible to predict which benign-appearing rashes will progress to life-threatening dermatologic eruptions.

[e]Recommendation is based on mainly epidemiologic evidence of lithium-associated reductions in suicide attempts and deaths in patients with diagnosed bipolar disorders. These potential benefits must be weighed against the risk of potential lethality of lithium in overdose.

[f]Therapeutic blood levels of carbamazepine for treating patients with bipolar I or II depressive episodes has not been established, but a range of 4 to 12 μg/mL may be a useful guide. Carbamazepine is considered third line for acute bipolar depressive episodes by the author based, in part, on having less consistent or lower-quality evidence of efficacy for acute bipolar I or II depressive episodes, the potential for clinically significant drug-drug interactions, and limited maintenance-phase data. The use of carbamazepine may be considered earlier for rapid cycling patients.

[g]Olanzapine monotherapy is considered a second-line treatment by the author based, in part, on olanzapine monotherapy being less effective than olanzapine + fluoxetine combination therapy in randomized trials and the risk of olanzapine-associated weight gain and dysmetabolic adverse effects. Olanzapine combined with mood stabilizers (lithium or divalproex) is considered a second-line treatment by the author based on olanzapine-associated weight gain and dysmetabolic adverse effects.

[h]The olanzapine + fluoxetine combination is approved in the United States for the treatment of acute bipolar I depressive episodes in adults but is considered second line by the author based on the risk of olanzapine-associated weight gain and dysmetabolic adverse effects.

[i]In most cases, refers to selective serotonin reuptake inhibitors (except for paroxetine) or bupropion.

episodes, and lamotrigine is more effective at preventing depressive episodes than manic episodes.[136] Combination pharmacotherapy may be superior to monotherapy for preventing relapses.[134,137] Divalproex can inhibit the metabolism of lamotrigine, which requires adjustments to the dose of lamotrigine to reduce the risk of severe dermatologic reactions to lamotrigine. The use of long-acting injectable atypical antipsychotic drugs such as risperidone may be helpful for patients with frequent relapses owing to poor treatment adherence; however, these medications are generally more effective for preventing manic episodes than depressive episodes.[138]

There is some evidence that bipolar depressed patients who respond well to and continue treatment with antidepressants combined with mood-stabilizing medications have a lower risk of depressive relapses than those

TABLE 5. Pharmacotherapy Options for Bipolar Maintenance Treatment[a,b]

Medication name	Effective dose (drug level)	Effective dose (drug level)	Comments
Monotherapy, mood stabilizers			
Lamotrigine	Continue acute -phase dose, or start the medication using dose guidelines in Table 4	Variable (Table 4)	First line; may be more effective for preventing depressive than manic relapse; often combined with other mood stabilizers or antipsychotic drugs
Lithium	Continue acute-phase dose,[c] or start at 300 mg bid-tid	Usually 900-1200 mg (0.6-1.2 mEq/L)	Second line; may be more effective for preventing manic than depressive relapse; often combined with other mood stabilizers or antipsychotic drugs
Divalproex	Continue acute-phase dose,[c] or start at 250 mg bid-tid	Usually 750-2500 mg (50-125 μg/mL)[d]	Third line; may be more effective for preventing manic than depressive relapse; often combined with other mood stabilizers or antipsychotics with more established maintenance-phase efficacy Usually avoided in women of reproductive age
Carbamazepine	Continue acute-phase dose, or start at 100-200 mg bid	800-1600 mg (4-12 μg/mL)[e]	Third line[e]
Monotherapy, antipsychotic drugs—generally higher priority than mood stabilizer monotherapy for patients with a history of psychotic symptoms			
Aripiprazole	Continue acute-phase dose, or start at 2-5 mg	5-30 mg	First line
Quetiapine	Continue acute-phase dose, or start at 50 mg	300-600 mg	First line
Risperidone long-acting injectable	25 mg IM every 2 wk (must continue oral risperidone for first 3 wk)	25-50 mg IM every 2 wk	First line for patients with frequent relapses owing to poor adherence to pharmacotherapy; more effective for preventing manic than depressive relapse
Olanzapine	10-15 mg/d	10-30 mg/d	Second line[f]
Risperidone	Continue acute-phase dose, or start at 0.5-1 mg bid	3-6 mg	Third line
Paliperidone extended release	Continue acute-phase dose, or start at 3-6 mg	6-12 mg	Third line
Combination therapy—generally high priority for patients for whom monotherapy is ineffective for preventing relapses			
Lithium or divalproex + an antipsychotic	See above guidelines regarding dosing	See above guidelines regarding dosing	First line Antipsychotics include quetiapine,[g] aripiprazole, risperidone, risperidone long-acting injection,[h] olanzapine[g]
Lithium + lamotrigine	See above guidelines regarding dosing	See above guidelines regarding dosing	First line
Lamotrigine + an antipsychotic	See above guidelines regarding dosing	See above guidelines regarding dosing	Second line

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TABLE 5. Continued

Medication name	Effective dose (drug level)	Effective dose (drug level)	Comments
Combination therapy—generally high priority for patients for whom monotherapy is ineffective for preventing relapses, continued			
Lithium + divalproex	See above guidelines regarding dosing	See above guidelines regarding dosing	Second line
Lithium + carbamazepine	See above guidelines regarding dosing	See above guidelines regarding dosing	Second line
Mood-stabilizing medication + antidepressants[i]			Use with caution[j]

[a]bid = twice daily; IM = intramuscular; tid = 3 times daily.

[b]Doses specified in the table are guidelines. Refer to the prescription label for specific dosing instructions for each medication. Treatment priorities (first, second, and third line) are based on the opinion of the author.

[c]Continue the dose of medication needed to achieve acute-phase stability or, if being started as monotherapy or being added to an existing medication regimen, follow the dosing guidelines provided in the table. In many cases, drug doses (and blood levels) for maintenance treatment may be lower than for treating acute-phase illness, especially acute mania.

[d]The target doses and blood drug levels for maintenance treatment with divalproex are not as evidence based as for treating acute mania; however, the drug doses and drug levels provided in the table may be reasonable targets.

[e]The maintenance-phase efficacy of carbamazepine is less well established than for other mood stabilizers. Dosing of carbamazepine during maintenance-phase treatment may be complicated by its cytochrome P450 enzyme induction effects, which may result in the acceleration of its own metabolism and the metabolism of other medications that patients may be taking. Dosing targets based on blood drug levels of carbamazepine have not been established for bipolar maintenance-phase treatment. However, a target of 4 to 12 μg/mL may be reasonable and may be useful for monitoring changes in drug concentration owing to accelerated metabolism via cytochrome P450 autoinduction.

[f]Olanzapine monotherapy is considered a second-line treatment by the author based, in part, on the long-term risk of olanzapine-associated weight gain and dysmetabolic adverse effects.

[g]May be higher priority for patients with predominantly depressive symptoms or relapses.

[h]May be higher priority for patients with frequent relapses owing to poor adherence to pharmacotherapy but efficacious primarily for preventing manic relapses.

[i]There is some evidence that bipolar depressed patients who respond well to and continue treatment with antidepressants combined with mood-stabilizing medications have a lower risk of depressive relapses than those who stop adjunctive antidepressants. However, the overall effectiveness of this strategy for long-term maintenance is still unclear.

[j]Possible risks of using antidepressants in bipolar depressed patients include increased mood cycle frequency and the development of rapid cycling.

who stop adjunctive antidepressant use.[139] However, meta-analyses of randomized trials of antidepressants (given for up to 50 weeks) for bipolar depression have yielded mixed results.[128,129,140] The same general principles for patient selection when using antidepressants for acute bipolar depression also apply to the use of antidepressants during bipolar maintenance treatment.

Several bipolar maintenance pharmacotherapies are associated with potentially major long-term adverse effects, and monitoring recommendations are provided in Supplemental Table 3. Long-term lithium treatment has been associated with adverse effects on thyroid, renal, and parathyroid functioning. Because of the risk of lithium-induced nephrogenic diabetes insipidus, patients should be asked frequently about changes in urinary frequency or excessive thirst. A patient's ability to renally excrete lithium is a critical factor in dosing lithium. As such, older patients almost always need lower doses. Divalproex has been associated with infrequent pancreatitis, leukopenia, thrombocytopenia, hyperammonemia, and parkinsonism. For patients taking divalproex, liver function tests and complete blood cell counts should be monitored routinely, and other tests (ammonia, pancreatic enzyme levels, etc) can be obtained as clinically indicated. The most significant longer-term risks with carbamazepine and lamotrigine include serious rashes. Carbamazepine has also been associated with liver toxicity and hematologic adverse effects, including rare agranulocytosis and aplastic anemia. Carbamazepine drug levels should also be periodically monitored early in the course of treatment and in cases of apparent loss of efficacy due to metabolic autoinduction. For patients taking atypical antipsychotic drugs, body weight should be checked at every visit, and fasting glucose and lipid levels should be periodically

monitored. Patients treated long-term with any antipsychotic medication should be monitored for neuromuscular adverse effects, including tardive dyskinesia.

Rapid Cycling Patients

For patients with rapid cycling BP-I or BP-II, quetiapine, aripiprazole, olanzapine, lithium, carbamazepine, lamotrigine, and valproate have some controlled evidence supporting their use,[141] although much of this evidence is from post hoc analyses of randomized trial data. For patients with active psychosis and rapid cycling, the use of one of the aforementioned antipsychotic drugs—either alone or combined with a mood stabilizer—can be recommended.[135] Combination therapy with medications shown to have benefit in rapid cycling BP-I or BP-II may be needed for preventing relapses in stabilized patients with a rapid cycling course. Again, this will often involve combining antipsychotic drugs with mood stabilizers or the use of 2 mood stabilizers.[135] Antidepressant drug use, substance use disorders, and thyroid disease are risk factors for rapid cycling.[142] Discontinuation of antidepressants, screening for drug abuse, and treatment of thyroid dysfunction are, therefore, recommended when managing rapid cycling BP-I or BP-II.

Psychosocial Treatments

Adding psychotherapy to medications can reduce rates of recurrence by 50% or more compared with usual care.[143] Psychotherapies for bipolar disorders optimize disease stability and psychosocial functioning by targeting important therapeutic areas that medication alone cannot address, including lack of support, acceptance of the diagnosis and treatment, improving understanding of bipolar illness and its management, optimizing medication adherence, managing interpersonal and other types of stress, and identifying and responding to early signs of mood episode relapse.[144] Important objectives of psychosocial treatments are to encourage the patient to discuss relevant issues that may operate as both risk and protective factors for illness relapse, to explore cultural aspects and effects of the illness, and to attempt to solve crucial personal, work-related, social, and other problems that the patient may be facing.

Several intensive psychotherapies have been developed—or adapted—for use in patients with bipolar disorders, particularly bipolar depression. Psychotherapies with the most supporting evidence include cognitive behavior therapy, group psychoeducation, family-focused therapy, and interpersonal-social rhythm therapy.[143,145] These intensive psychotherapies are time limited and are typically instituted after acute mood episodes have resolved. Although comparative effectiveness studies are sparse, available data suggest that one form of intensive psychotherapy is not clearly superior to other forms for bipolar depression.[146] One important limitation of intensive psychotherapies for bipolar disorders is that they are not widely available in many routine treatment settings.

Additional Considerations

Therapeutic Alliance. A cornerstone of long-term management of patients with bipolar disorders is a strong therapeutic alliance between clinicians and their patients. This is important because adherence to treatment in patients with bipolar disorders is often poor,[147] which increases the risk of poor treatment outcomes.[148] The quality of the therapeutic alliance is a strong predictor of engagement in treatment.[149] Specific clinician behaviors such as empathy, listening well, and allowing patients to participate in treatment decisions have been shown to positively influence both therapeutic relationships and treatment outcomes, including better treatment adherence, higher satisfaction with care, and reduced suicidal ideation.[150]

Other Supports. Many patients with bipolar disorders will benefit from additional services, such as case management or care coordination services to secure or maintain insurance coverage and facilitate referrals to local support groups, subsidized mental health centers, substance use treatment programs, and other community-based resources. Patients and clinicians are encouraged to consult with their local social service agencies to identify such resources.

Referral. Psychiatric referral should be considered when the diagnosis (eg, unipolar vs bipolar depression) is unclear and for

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patients with severe bipolar depression, mood symptoms that are not responding adequately to initial treatment, and comorbid psychiatric illnesses or substance use disorders. Patients who express suicidal ideation or homicidal ideation, psychotic symptoms, or bizarre behavior indicative of psychosis require emergency mental health evaluation. Some will need psychiatric hospitalization. Obtaining periodic psychiatric consultation or use of telehealth and integrated behavioral health services, if available, may be useful if regular follow-up visits with a psychiatrist are not possible.[151,152]

CONCLUSION

BP-I and BP-II are common, potentially disabling, and, in some cases, life-threatening conditions. Bipolar disorders present many challenges to busy clinicians, beginning with accurate diagnosis. Adequate management of bipolar disorders requires pharmacotherapy and psychosocial interventions that are targeted to the specific phase of bipolar illness. Mood symptoms and functioning must be continually reevaluated and, when necessary, the plan of care must be adjusted when treating patients with bipolar disorders over the longer term.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **bid** = twice daily; **BP-I/BP-II** = bipolar I/II disorder; **IM** = intramuscular; **tid** = 3 times daily

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