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Diagnosis and Treatment of Bipolar Disorder
A Review

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IMPORTANCE Bipolar disorder affects approximately 8 million adults in the US and approximately 40 million individuals worldwide.

OBSERVATIONS Bipolar disorder is characterized by recurrent episodes of depression and mania or hypomania. Bipolar depressive episodes are similar to major depressive episodes. Manic and hypomanic episodes are characterized by a distinct change in mood and behavior during discrete time periods. The age of onset is usually between 15 and 25 years, and depression is the most frequent initial presentation. Approximately 75% of symptomatic time consists of depressive episodes or symptoms. Early diagnosis and treatment are associated with a more favorable prognosis. Diagnosis and optimal treatment are often delayed by a mean of approximately 9 years following an initial depressive episode. Long-term treatment consists of mood stabilizers, such as lithium, valproate, and lamotrigine. Antipsychotic agents, such as quetiapine, aripiprazole, asenapine, lurasidone, and cariprazine, are recommended, but some are associated with weight gain. Antidepressants are not recommended as monotherapy. More than 50% of patients with bipolar disorder are not adherent to treatment. Life expectancy is reduced by approximately 12 to 14 years in people with bipolar disorder, with a 1.6-fold to 2-fold increase in cardiovascular mortality occurring a mean of 17 years earlier compared with the general population. Prevalence rates of metabolic syndrome (37%), obesity (21%), cigarette smoking (45%), and type 2 diabetes (14%) are higher among people with bipolar disorder, contributing to the risk of early mortality. The annual suicide rate is approximately 0.9% among individuals with bipolar disorder, compared with 0.014% in the general population. Approximately 15% to 20% of people with bipolar disorder die by suicide.

CONCLUSIONS AND RELEVANCE Bipolar disorder affects approximately 8 million adults in the US. First-line therapy includes mood stabilizers, such as lithium, anticonvulsants, such as valproate and lamotrigine, and atypical antipsychotic drugs, such as quetiapine, aripiprazole, asenapine, lurasidone, and cariprazine.

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Bipolar disorder is characterized by alternating episodes of depression and either mania (bipolar I) or hypomania (bipolar II). Manic and hypomanic episodes are characterized by discrete periods of elevated or irritable mood, increased energy, and heightened activity that represent a noticeable change from previous behavior. Bipolar I is defined by manic symptoms severe enough to require inpatient treatment, while bipolar II involves milder hypomanic episodes not sufficiently severe to require hospitalization but still capable of affecting relationships, finances, and physical health. The term *bipolar disorder* in this article refers to both types I and II unless otherwise specified.

The global prevalence of bipolar disorder is approximately 2%.[1] Data from the latest World Mental Health surveys between 2001 and 2022 involving 156 331 respondents across 29 countries reported a lifetime prevalence of 2.5% (95% CI, 2.4%-2.7%) in men and 2.3% (95% CI, 2.1%-2.4%) in women.[2] The probability of first onset peaked at approximately 15 years of age and the median age of onset of bipolar disorder was approximately 20 years.[2] Data from a meta-analysis of 276 221 people reported a global prevalence of 1.06% (95% CI, 0.81%-1.31%) for bipolar I and 1.57% (95% CI, 1.15%-1.99%) for bipolar II.[3] The prevalence of bipolar disorder I and II in the US is estimated to be 4.4%.[4] Bipolar II and other bipolar-spectrum disorders, including cyclothymic disorder, characterized by chronic alternating periods of hypomanic and depressive symptoms that last for at least 2 years and do not meet the criteria for full hypomanic or major depressive episodes, and subthreshold bipolar symptoms—mood fluctuations that resemble bipolar disorder but do not meet the criteria for specific episodes—are more prevalent in females, while bipolar I is equally prevalent in males and females.[5]

Onset of bipolar disorder typically occurs during adolescence or early adulthood.[6] Early recognition and optimal treatment of bipolar disorder are important because treatment response is greater in the early stages.[6] However, the time between a first depressive

Box 1. Bipolar Disorder Criteria From *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision*

Bipolar I disorder
Criteria met for at least 1 manic episode, which might have been preceded or followed by a hypomanic episode or major depressive disorder; depressive episodes or psychosis do not have to be present for a diagnosis.

Bipolar II disorder
Criteria met for at least 1 current or past hypomanic episode and a major depressive episode.

Cyclothymic disorder
Hypomanic symptoms that do not meet the criteria for hypomania and depressive symptoms that do not meet the criteria for major depressive episodes in numerous periods (at least half of the time) for at least 2 years (1 year in those <18 years); criteria for major depressive, manic, or hypomanic episodes never met.

Other specified bipolar disorder
Bipolar-spectrum phenomena that do not satisfy the criteria for bipolar I disorder, bipolar II disorder, or cyclothymic disorder (ie, short-duration or low severity of hypomanic episodes, hypomanic episodes without a previous major depressive episode).

Unspecified bipolar and related disorder
Symptoms in the bipolar spectrum that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, but do not meet the full criteria for any of the disorders in the bipolar and related disorders diagnostic class.

Box 2. Differential Diagnoses and Characteristics Associated With Bipolar Disorder in the Context of Depression

Depressive symptoms in major depressive disorder and bipolar depression
Depressive symptoms are similar between major depressive disorder and bipolar depression and include persistent sad or irritable mood, loss of interest or pleasure in nearly all activities, significant changes in appetite or weight, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, and recurrent thoughts of death or suicide.

Differential diagnosis
Previous manic or hypomanic symptoms define the diagnosis of bipolar disorder and should be investigated in all patients with depression.

Asking patients (and their families) about previous periods when they felt excessively energized with high levels of activity, decreased need for sleep, increased sexuality, and elevated or irritable mood is essential for diagnosis.

Clinical characteristics associated with bipolar depression
Abrupt onset and offset of symptoms

Mixed manic and depressive features

Atypical symptoms (increased appetite, hypersomnia)

Psychotic symptoms or catatonia

Other factors associated with bipolar depression
Family history of bipolar disorder

Childhood maltreatment

Early age of onset of depression

Recurrent or severe illness

Treatment-resistant depression

episode and a clinical diagnosis of bipolar disorder is approximately 9 years.[7] This review summarizes current evidence regarding the diagnosis and treatment of bipolar disorder.

Methods

We conducted a systematic search of the PubMed and Google Scholar databases for English-language studies of bipolar disorder in adults published between January 1, 2003, and July 1, 2023. References of selected articles were manually searched to further identify relevant studies. We preferentially included randomized clinical trials (RCTs), systematic reviews, meta-analyses, and clinical practice guidelines relevant to a general medical readership. Of 460 identified articles, 82 were included, consisting of 26 epidemiological studies, 25 meta-analyses or systematic reviews, 11 reviews, 9 RCTs, and 11 clinical practice guidelines.

Clinical Presentation and Diagnosis

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* criteria for bipolar disorder require the presence of at least 1 episode of mania or hypomania (**Box 1**).[8] Mania is characterized by an elevated, expansive, or irritable mood lasting at least 1 week, with significant consequences that often require hospitalization (bipolar I). Symptoms of mania include mood elevation, grandiosity, impulsivity, risk-taking behavior, restlessness, racing thoughts, reduced need for sleep, increased productivity, inflated self-confidence, impaired judgment, irritability, and agitation. Hypomania, which, along with a previous depressive episode, defines bipolar II, is a milder form of mania requiring at least 4 consecutive days of elevated or irritable mood and increased energy and goal-directed behavior.

Although hypomanic or manic episodes are the defining feature of bipolar disorder, patients typically seek treatment during depressive episodes, and depression is usually the initial presentation.[6] Depressive symptoms are similar between bipolar depression and major depressive disorder. However, some clinical characteristics may suggest bipolar disorder in the context of depression (**Box 2** and **Box 3**). To establish a diagnosis of bipolar disorder, clinicians should ask about previous periods of increased energy and elevated or irritable mood in all patients presenting with depression. Obtaining information from family members is important because hypomanic and manic symptoms may be more obvious to people who are familiar with the patient's usual behavior.

Comorbid psychiatric illness is common in bipolar (**Table 1**). Approximately 65% of individuals with bipolar disorder have one or more concomitant psychiatric disorder, particularly anxiety disorders (approximately 71%), substance use (approximately 56%), personality disorders (approximately 36%), and attention-deficit hyperactivity disorder (approximately 10%-20%).[9] Women with bipolar disorder have higher rates of anxiety and eating disorders

Box 3. Commonly Asked Questions About Bipolar Disorder

1. What are first-line treatment options for bipolar disorder?

First-line treatments for bipolar disorder include mood stabilizers (such as lithium, lamotrigine, and valproate) and atypical antipsychotics, such as quetiapine, aripiprazole, asenapine, or lurasidone, combined with psychotherapy. The choice of treatment depends on the phase of the illness, adverse effects of medications, and individual patient factors, such as the presence of medical and psychiatric comorbidities.

2. How can major depressive disorder be distinguished from bipolar disorder?

A prior history of mania or hypomania is the defining feature separating bipolar disorder from depression. There are less clear differences in the depressive presentation of the 2 disorders, including the presence of atypical depressive symptoms such as hypersomnia and hyperphagia, psychotic features, and psychomotor retardation in bipolar depression. A history of hypomania or mania is necessary for diagnosis of bipolar disorder.

3. What are the most common differential diagnoses with bipolar disorder?

Personality disorders such as borderline personality disorder presenting with affective dysregulation are common differential diagnoses, as is major depressive disorder. Substance abuse and attention deficit disorder are also part of the differential diagnosis.

than men.[5] Men with bipolar disorder are more likely to have simultaneous substance use disorders and alcohol misuse than women.[5]

Episodes with mixed features, in which hypomanic/manic and depressive symptoms co-occur, are associated with increased risk of suicide and require careful assessment and monitoring for suicidal ideation.[10,11] The **Figure** illustrates the heterogeneity in frequency and duration of mood patterns in bipolar disorder.

Medical Comorbidities and Premature Mortality

Bipolar disorder is associated with a higher prevalence of medical conditions and premature mortality.[12] Suicide risk is significantly increased in bipolar disorder. Annual suicide attempt rates range from 0.4% to 1.4%, approximately 30 to 60 times higher than the general population's mean (SD) rate of 0.014% (0.007%) per year.[13] Approximately 34% of individuals with bipolar disorder attempt suicide and 15% to 20% of people with bipolar disorder die by suicide.[14] Demographic factors such as male sex, living alone, divorced status, unemployment, White race, and age younger than 35 years or older than 75 years are associated with higher rates of completed suicide.[15]

Patients with bipolar disorder have a significantly higher rate of mortality due to cardiovascular disease, with a standardized mortality ratio of 1.73 (95% CI, 1.54-1.94), compared with the general population.[16] A population-based study including 19 955 patients with bipolar disorder in Denmark reported higher rates of ischemic heart disease (4.7% vs 4.4%; hazard ratio [HR],1.17 [95% CI, 1.09-1.25), diabetes (5.6% vs 4.4%; HR, 1.33 [95% CI, 1.24-1.41]), dementia (3.0% vs 1.8%; HR, 2.30 [95% CI, 2.11-2.50]), hypertension (18.2% vs 16.6%; HR, 1.22 [95% CI, 1.17-1.27]), hypercholesterolemia, and hyperlipidemia (14% vs 13.3%; HR, 1.18 [95% CI, 1.14-1.23]) compared with the general population.[17]

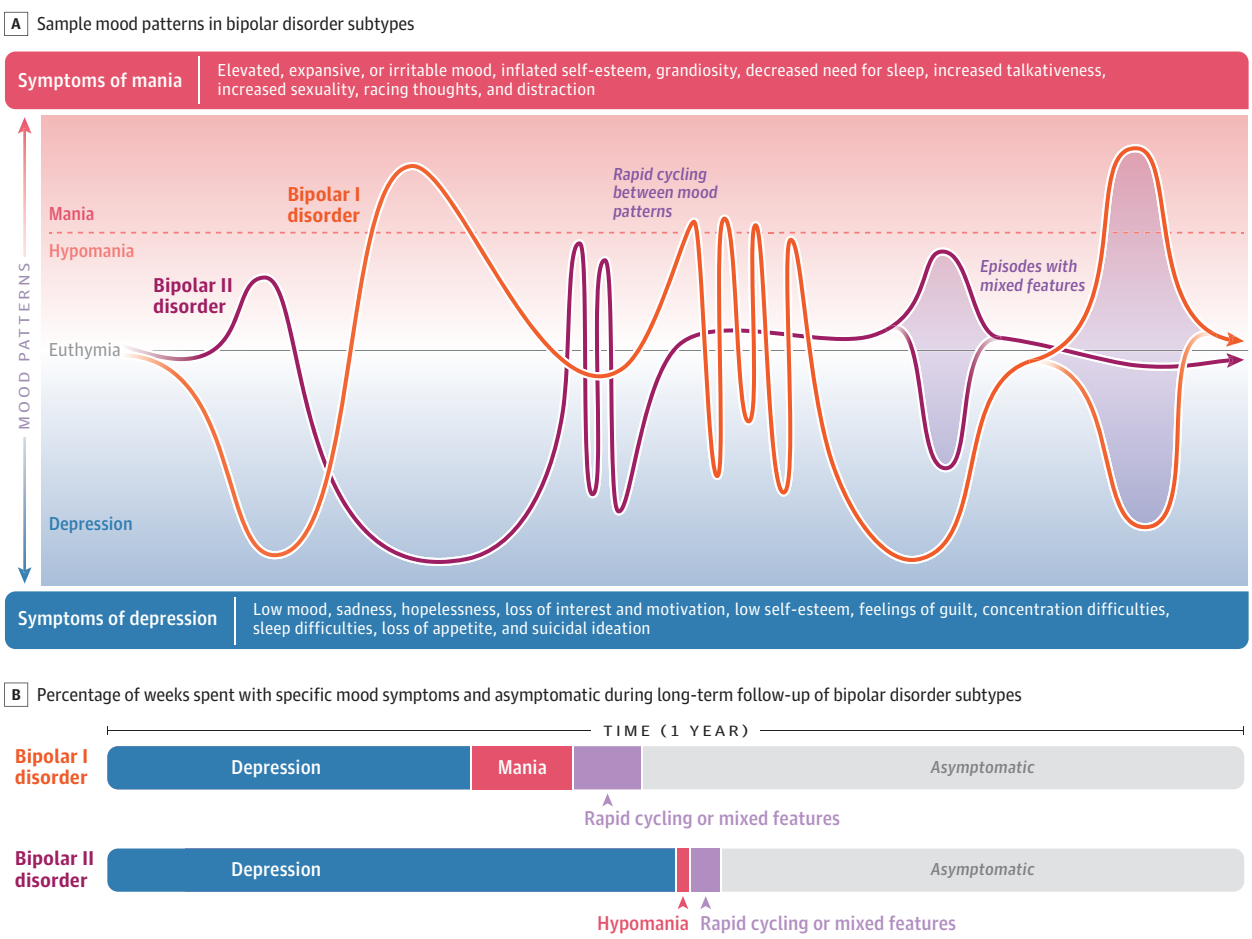
Table 1. Differential Diagnosis and Psychiatric Comorbidities in Bipolar Disorder

Differential diagnosis	Symptoms associated with bipolar disorder and other psychiatric disorders	Features specific to bipolar disorder
Anxiety disorders	Restlessness, irritability, racing thoughts, sleep disturbances	Anxiety is often present in patients with bipolar disorder and is more often associated with female sex and rapid transition between depressive and manic states. Differential diagnostic considerations include (1) intensity and duration of symptoms (more severe in bipolar disorder, longer in anxiety), (2) that sleep disturbances in anxiety are related to difficulty falling or staying asleep and mania is related to decreased need for sleep (sleeps for a few hours and feels energized or rested), and (3) anxiety tends to revolve around specific worries or concerns, while patients experiencing mania can shift rapidly from one topic to another.
Attention-deficit/ hyperactivity disorder (ADHD)	Agitation, racing thoughts, impulsivity, distractibility	Hypomanic symptoms represent a clear break in previous function and are classically phasic, with periods of well-being or depression; ADHD symptoms are not episodic and do not represent a clear change in previous behavior.
Personality disorders	Exaggerated emotional reactivity, affective dysregulation, sudden changes in mood	Mood symptoms in personality disorders tend to be enduring, with an unclear start, and are frequently reactive to psychosocial circumstances; reactivity to abandonment, rapidity, and transient nature of mood symptoms and identity disturbances also suggest a personality disorder.
Psychotic disorders	Delusions, hallucinations	The presence of manic symptoms preceding the psychotic episode (eg, increase in energy and goal directed activities, decreased need for sleep) suggests a diagnosis of bipolar disorder; psychotic symptoms can occur in manic and depressive episodes and are usually (but not exclusively) congruent with current mood.
Acute intoxication	Agitation, irritability, racing thoughts, distractibility, perceptual disturbances	Drugs such as cocaine, amphetamines, hallucinogens, and corticosteroids might mimic or trigger manic symptoms. If symptoms persist after the drug is discontinued, a diagnosis of bipolar disorder can be made. Clinical characteristics associated with drug induced mania include rapid onset of symptoms after starting a new medication or drug, symptoms more consistent with the effects of a particular drug (eg, visual disturbances with psychedelic drugs), absence of previous mood episodes, and no family history of bipolar disorder.

The link between bipolar disorder and cardiovascular disease may be influenced by potentially modifiable factors, such as antipsychotic treatment, substance/alcohol use, poor diet, low levels of physical activity, and smoking. Approximately 45% of people with bipolar disorder smoke tobacco, which was approximately 3.5 times higher (95% CI, 3.39-3.54) than the general population in a 2015 study of 41 710 people.[18]

Lifestyle interventions have shown promise in reducing cardiovascular risk in serious mental illnesses, including bipolar disorder. An RCT including 269 individuals (mean age, 49 years) compared

Figure. Mood Patterns in Bipolar Disorder



an 18-month cardiovascular disease risk reduction intervention that assisted participants with smoking cessation and provided individually tailored behavioral counseling and care coordination with a control group who received group physical activity classes and dietary recommendations. Smoking rates declined significantly in the intervention group from 49.2% to 35% at 18 months, which was a 21% relative reduction in smoking prevalence compared with the control group (from 53.3% to 48.9% at 18 months). The mean baseline Framingham Risk Score decreased from 11.5% to 9.9% in the intervention group and increased from 12.3% to 12.7% in the control group after 18 months, representing a 12.7% (95% CI, 2.5%-22.9%) relative reduction in 10-year cardiovascular disease risk.[19]

Collaborative care is essential for cardiovascular risk management in patients with bipolar disorder and involves systematic monitoring of cardiovascular risk factors and evidence-based management of concurrent medical conditions.[20] These should include aiding smoking cessation and promoting physical activity and diet quality.[21]

Pharmacological Treatment

Pharmacological therapy is the mainstay of treatment and should be tailored to the individual's clinical presentation (depression or hypomania/mania).[22] The primary goal is to reduce the intensity of the current mood episode and limit the number and severity of future episodes.

Mood stabilizers, including lithium, valproate, and lamotrigine, along with atypical antipsychotic drugs, such as quetiapine, aripiprazole, and cariprazine, are recommended as pharmacological therapies for acute and long-term management of bipolar disorder in most clinical practice guidelines (**Table 2**).[21,23-25,27-30] Treatment for bipolar I and bipolar II is similar. However, few studies investigate specific subtypes of bipolar disorder and few RCTs have focused on treatment for bipolar II disorder. Although antidepressants are not recommended for long-term treatment, they might be considered in combination with mood stabilizers or antipsychotics, especially for bipolar II. Therapy should be selected according to an individual's symptoms, the presence of comorbidities, prior treatment response, adverse effect profiles, cost of medication, and personal preferences.[22,26]

Acute Treatment of Manic/Hypomanic Episodes

Manic episodes involve impaired judgment, which often results in high-risk behaviors with the potential to adversely affect relationships, employment, and finances. Acute treatment aims to restore patients' behavior and decision-making to their typical judgment and functioning.

Table 2. Pharmacological Treatments of Bipolar Disorder

Drug class	Use in bipolar disorder	Absolute rates; odds ratio for response to treatment vs placebo (95% CI)[a]	Adverse events	Monitoring schedule[b]
Mood stabilizers				
Lithium[23-25]	Acute mania	1.45 (1.27-1.65)	Tremor (14%)	Serum levels: every 3-6 mo Urea and creatinine: every 3-6 mo Thyrotropin calcium and weight: at 6 mo then annually
	Acute depression	38.1% vs 34.7%; 1.16 (0.79-1.71)[c]	Sedation (10%) Weight gain (3%) Hypothyroidism (14%) Hyperparathyroidism Chronic kidney disease (1%)	
	Maintenance[d]	24.5% vs 50.5%; 2.17 (1.33-3.57)		
Anticonvulsants				
Carbamazepine[24]	Acute mania	1.90 (1.41-2.57)	Sedation Nausea Teratogenicity (3%-6%)	Serum levels: as clinically indicated (every 6 mo for carbamazepine) Weight, complete blood cell count, liver function, electrolytes, urea, and creatinine: every 3 mo for the first year then annually Inquiry of menstrual changes every 3 mo for the first year (risk of teratogenicity)
Lamotrigine[23,25]	Acute depression	44% vs 35%; 1.51 (1.21-1 .87)	Rash (5%-10%) Stevens-Johnson syndrome (0.02%)	
	Maintenance	38.4% vs 46.6%; 1.52 (1.03-2.22)		
Valproate[23-25]	Acute mania	1.42 (1.19-1.71)	Alopecia Sedation Weight gain Tremor Elevation in liver function tests Teratogenicity (6%)	
	Acute depression	59.7% vs 35%; 2.8 (1.26-6.18)		
	Maintenance	24% vs 39%; 2.04 (1.19-3.45)		
Antipsychotics				
Aripiprazole[24,25]	Acute mania	1.53 (1.33-1.76)	Akathisia	Weight: monthly for the first 3 mo then every 3 mo for the duration of treatment Blood pressure and fasting glucose: every 3 mo for the first year then annually Fasting lipid profile: at 3 mo then annually
	Maintenance	26.5% vs 51%; 2.63 (1.75-3.85)		
Asenapin[24,25]	Acute mania	1.28 (1.05-1.56)	Extrapyramidal symptoms Weight gain	
	Maintenance	8.7% vs 33.3%; 5.26 (2.6-11.1)		
Cariprazine[23,24]	Acute mania	1.56 (1.26-1.92)	Akathisia	
	Acute depression	44.5% vs 35%; 1.51 (1.18-1 .93)		
Haloperidol[24]	Acute mania	1.64 (1.43-1.88)	Extrapyramidal symptoms Akathisia	
Lumateperone[23]	Acute depression	42.4% vs 35%; 1.39 (1.05-1 .83)	Sedation Nausea	
Lurasidone[23]	Acute depression	48.5% vs 35%; 1.77 (1.4-2.24)	Sedation Nausea Weight gain (5%)	
Olanzapine[23-25]	Acute mania	1.59 (1.40-1.80)	Sedation Weight gain (28%)	
	Acute depression	44.3% vs 35%; 1.50 (1.15-1.96)		
	Maintenance	23.9% vs 56.4%; 3.85 (2.70-5.56)		
Paliperidone[24]	Acute mania	1.34 (1.10-1.76)	Extrapyramidal symptoms Akathisia	
Quetiapine[23-25]	Acute mania	1.55 (1.31-1.83)	Sedation Weight gain (18%)	
	Acute depression	49% vs 35%; 1.81 (1.53-2.16)		
	Maintenance	21.5% vs 50%; 2.78 (1.64-4.76)		
Risperidone[24]	Acute mania	1.69 (1.41-2.02)	Extrapyramidal symptoms in higher doses Weight gain Hyperprolactinemia Akathisia	
Risperidone LAI[25]	Maintenance	39% vs 56.4%; 2.44 (1.67-3.57)	Extrapyramidal symptoms in higher doses Weight gain Hyperprolactinemia Akathisia	
Ziprazidone[24]	Acute mania	1.35 (1.06-1.72)	QT interval prolongation	

[a] Response defined as a 50% reduction in study scale. Odds ratio refers to recent network meta-analytic data of pharmacological treatment of acute mania,[24] acute depression,[23] and maintenance treatment.[25]

[b] Monitoring schedule derived from the study by Ng et al.[26]

[c] Not statistically significant at $P > .05$.

[d] Odds ratio for maintenance expressed as 1/odds ratio for relapse to any mood episode.

Similar principles used to assess and manage mania are applied to hypomania, and treatment options are the same. Treatment involves discontinuing agents that may exacerbate or prolong symptoms, such as antidepressants and stimulants, and initiating appropriate pharmacotherapy.[27] Guidelines recommend mood-stabilizing agents, such as lithium and valproate, and atypical antipsychotic agents, such as quetiapine, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine, alone or in combination as first-line treatments for acute hypomania/mania (Box 3).[27]

However, treatment acceptance and adherence are often affected by diminished insight during manic episodes.[31] For safety reasons, inpatient care is often recommended in mania, and involuntary admission may be necessary when appropriate treatment cannot be provided otherwise. Involuntary admission is appropriate when impaired judgment adversely affects the capacity to consent. Patients who are aggressive or with psychosis are more likely to need involuntary admission during manic episodes.[32]

Combination therapy with a mood stabilizer, such as lithium or valproate, associated with an antipsychotic medication, such as risperidone, quetiapine, asenapine, or aripiprazole, is frequently necessary and should be considered based on factors including previous treatment response, severity of mania, and tolerability concerns.[21,27] Benzodiazepines and typical antipsychotics (such as haloperidol) may be prescribed for acute management of agitation, but are not recommended for long-term use.[27]

Acute Treatment of Bipolar Depressive Episodes

Five antipsychotic drugs or drug combinations have been approved by the US Food and Drug Administration for acute bipolar depression: olanzapine/fluoxetine combination, quetiapine, lurasidone, cariprazine, and lumateperone (Table 2). Clinical guidelines also recommend lithium and lamotrigine for acute bipolar depression, although these are considered second-line agents for acute depression in bipolar II.[27]

Atypical antipsychotics have demonstrated efficacy in bipolar depression but often lead to weight gain, even with short-term use.[33] A network meta-analysis of 101 RCTs that included 20 081 participants treated for 2 to 16 weeks reported that, compared with placebo, the following treatments were associated with significantly better response rates, defined as a 50% reduction in depressive scores: olanzapine plus fluoxetine (56.7% response rate), quetiapine (49% response rate), lurasidone (48.5% response rate), cariprazine (44.5% response rate), lamotrigine (44.4% response rate), olanzapine (44.3% response rate), and lumateperone (42.4% response rate). Other drugs, such as lithium (38.1% response rate), aripiprazole (35.2% response rate), and paroxetine (42.1% response rate), were not associated with significantly better response rates than placebo (34.7% response rate). Other antidepressants, such as fluoxetine, esketamine, and venlafaxine, presented higher response rates than placebo but were classified as having very low level of evidence.[23]

In this meta-analysis, 30.3% of people who received olanzapine plus fluoxetine and 28.4% of people who received olanzapine alone had weight gain of 7% or more, compared to 1.1% with placebo. Rates of weight gain of 7% or more were 5.4% for lurasidone, 3.9% for quetiapine, 3.1% for cariprazine, 0.8% for lumateperone,[23] and 0.4% for lamotrigine.[33]

Lamotrigine is not approved by the US Food and Drug Administration for acute bipolar depression but is recommended as first-line therapy for acute depression in bipolar I and second-line therapy in bipolar II.[27] Lamotrigine is well-tolerated, has minimal effect on weight, and is associated with higher treatment response rates in monotherapy for acute depression compared with placebo.[34] In a meta-analysis of 5 trials with duration of 7 to 10 weeks that included 1072 participants with acute bipolar depression, compared with placebo, lamotrigine was associated with a significantly greater response, defined as a 50% reduction in study scale (46.6% vs 38%; relative risk, 1.22 [95% CI, 1.06-1.41]; number needed to treat = 13).[35]

In 2 randomized clinical trials, when used in combination with lithium for 8 weeks in 124 individuals with bipolar depression and when used as adjunctive therapy to quetiapine for 12 weeks in 202 patients with bipolar depression, lamotrigine improved depressive scores in both trials and a higher percentage of patients responded to lamotrigine compared with adjunctive placebo (51.6% vs 31.7% for lithium adjunct; 31% vs 16% for quetiapine adjunct).[36,37] In RCTs for acute bipolar depression, the extended dose-titration phase of lamotrigine, which requires 6 weeks of weekly incremental doses to mitigate the risk of rash (5%-10%), weakened effectiveness in short-duration trials.[27] The favorable tolerability of lamotrigine in the short and long term and its efficacy in preventing depressive episodes make it a first-line therapy for acute bipolar depression.[27]

Antidepressant therapy for acute bipolar depression remains controversial.[38] Clinical guidelines do not recommend monotherapy with antidepressants for bipolar depression, especially in people with bipolar I, due to concerns that antidepressant drugs may induce manic and hypomanic episodes and promote more frequent switches between depression and hypomanic/manic states.[39] Antidepressants should be avoided in patients with manic symptoms and in patients with frequent switches between mood states. Agitation or irritability may indicate the presence of mixed features (co-occurrence of depressive and hypomanic symptoms), in which case antidepressant drugs are also not indicated and should be discontinued.[39]

Antidepressants are considered adjunctive therapeutic options in patients in whom bipolar depression is resistant to treatment with mood stabilizers and antipsychotics. However, antidepressants have limited evidence of efficacy. Two meta-analyses found that adjunctive antidepressants for acute bipolar depression, combined with a mood stabilizer or antipsychotic medication, were associated with a small statistically significant improvement in depressive symptoms compared with placebo, but the effect size was not clinically meaningful (mean difference in depressive symptoms score change, −0.13 [95% CI, −0.24 to −0.02]; small effect). Both studies found no significant improvement in response rates, defined as a 50% improvement in depressive scores compared with adjunctive placebo (approximately 48% vs 43%).[40,41] During a 52-week extension period, there was a significant increase in rates of mania or hypomania in patients taking adjunctive antidepressants compared with placebo (17% vs 10%; odds ratio [OR], 1.77 [95% CI, 1.02-3.09]).[41]

In an RCT of 209 patients with bipolar I who were in remission, treatment with escitalopram or bupropion together with mood stabilizers or antipsychotics for 52 weeks did not prevent relapse of depression or mania (31% vs 46%; HR, 0.68 [95% CI, 0.43-1.10]) compared with a control group treated with adjunctive antidepressants

for 8 weeks before receiving placebo.[42] Antidepressants are generally not recommended for long-term management of bipolar disorder. However, few randomized clinical trials consider bipolar disorder subtypes, and guidelines have little evidence to provide clinical recommendations for bipolar II, for which antidepressant use may be more effective.

Electroconvulsive therapy (ECT) is reserved for patients with bipolar depression that is refractory to medication, and is considered the most effective treatment for severe and treatment-resistant depression, including bipolar depression. Other indications for ECT include the need for rapid treatment response, such as in patients with suicidal ideation, patients with severe disease, and pregnant persons or older patients with low tolerability to medication. In a meta-analysis that included 567 patients with bipolar depression, ECT was associated with a 77.1% response rate in people with bipolar depression and a 52.3% rate of remission.[43] In a Swedish national register study that included 1251 patients with bipolar depression, 80.2% of patients had significant improvement with ECT, defined as a score on the Improvement component of the Clinical Global Impressions Scale of 1 ("very much improved") or 2 ("much improved"). However, the observational study design was a significant limitation and causal inferences must not be made.[44] Adverse effects of ECT are usually transient and include short-term memory loss (approximately 41%), headache (48%), nausea (23%), and muscle pain (15%).[45]

Maintenance Treatment

Most patients require lifelong treatment to reduce relapse rates and improve functioning and quality of life. The standard approach requires a mood stabilizer, such as lithium, valproate, or lamotrigine, either alone or in combination with atypical antipsychotic agents such as quetiapine, aripiprazole, asenapine, or lurasidone.[27,28,46] For bipolar II, first-line options for long-term therapy include quetiapine, lithium, and lamotrigine.[27] Long-term use of antidepressants in the maintenance phase of bipolar disorder is usually not recommended, but may be considered, mainly in bipolar II, together with a mood stabilizer or antipsychotic drug.[21,27,39] Treatments that are effective in the acute phase are typically continued in the maintenance phase.[22]

Lithium, prescribed alone or in combination with other medications, remains first-line treatment for mood stabilization and long-term treatment of bipolar disorder in most guidelines.[27,28,46] Lithium prevents both manic and depressive episodes.[47] Despite its efficacy, lithium use has decreased in the past 2 decades, partially due to the marketing of antipsychotic agents and concerns about lithium tolerability and potential adverse effects, including in kidney and thyroid/parathyroid function.[48]

In a meta-analysis of 1402 patients, lithium was associated with increased rates of hypothyroidism, compared with placebo or alternate medications (13.9% vs 1.7% over a mean of 70.1 months; OR, 5.78 [95% CI, 2.00-16.67]). Lithium was also associated with increased levels of parathyroid hormone (7.32 pg/L [95% CI, 3.42-11.23]) and blood calcium (0.09 mmol/L [95% CI, 0.02-0.17]) compared with controls. The rate of primary hyperparathyroidism was higher in lithium users (10%) compared with the general population (0.1%).[49] Hypothyroidism can be easily treated with thyroid hormone replacement, and there is little evidence that stopping lithium leads to a recovery in thyroid function.[49]

Long-term use of lithium impairs kidney function and reduces glomerular filtration rates.[50] In a study of 312 patients with bipolar disorder treated with lithium for a mean (range) of 18 (8-48) years, long-term lithium treatment was associated with a 30%-greater decline in glomerular filtration rate compared with aging alone.[51] In lithium users, glomerular filtration decreased by 0.71% per age year and 0.92% per treatment year, compared with a 0.64% age-related decline in the general population. Lithium treatment required at least 6 to 10 years to be associated with significant decreases in kidney function, and 30 years of lithium exposure was required for users to develop stage 3 chronic kidney disease (18.1% of users). Risk factors for chronic kidney disease included longer treatment, higher serum levels of lithium, older age, and medical comorbidities.[51]

The incidence of stage 3 chronic kidney disease was 0.012 cases per exposed patient-year in a study of 1012 individuals treated with lithium for a mean (SD) duration of 9.2 (8.4) years, a rate 1.3 times higher than the general population (0.093 per person-year). The incidence of stage 4 kidney disease was low (0.0004 per patient-year).[52]

There are no treatments for kidney dysfunction related to lithium use. A proposed preventive strategy in people receiving lithium long-term is to aim for lower serum levels (0.4-0.6 mEq/L), because higher concentrations of lithium are a risk factor for chronic kidney disease.[26,53] Lithium may be effective for the prevention of relapses at doses lower than previously recommended, and clinical response should guide decisions about dose increases to standard therapeutic levels (0.6-1.2 mEq/L).[53,54]

In patients with bipolar disorder, compared with other classes of medication, lithium is associated with significantly lower suicide rates (0.4% vs 1.8%; OR, 0.26 [95% CI, 0.09-0.77]), all-cause mortality (1.3% vs 2.8%; OR, 0.42 [95% CI, 0.21-0.87]), rates of dementia (3.04% vs 6.85%; OR, 0.51 [95% CI, 0.36-0.72]), incidence of osteoporosis (incidence rate per 1000 person-years: 5.98 [95% CI, 5.23-6.83] vs 9.07 [95% CI, 8.52-9.66]; hazard rate ratio, 0.62 [95% CI, 0.53-0.72]), and cancer (incidence rate ratio, 0.94 [95% CI, 0.72-1.22] vs 1.24 [95% CI, 1.05-1.46]).[55-58]

Anticonvulsant mood stabilizers such as valproate and lamotrigine are also recommended for maintenance treatment of bipolar disorder.[27,28] Carbamazepine is a second-line treatment.[59] Valproate and carbamazepine should be avoided in people of childbearing age because of the risk of congenital malformation (approximately 6% for valproate and 3%-6% for carbamazepine) and neurodevelopmental delay or low IQ in offspring of pregnant people taking these drugs.[60,61] People of childbearing age using valproate or carbamazepine should be instructed about these risks and contraceptive strategies must be implemented. Lamotrigine might be a safer option, with a risk of malformation estimated at 2% to 3%, but not much data are available.[62,63]

In a meta-analysis of 706 people, lamotrigine was associated with few adverse effects and reduced relapse rates of mania and depression compared with placebo (risk ratio, 0.81 [95% CI, 0.70-0.93]; number needed to treat, 8.3 [95% CI, 5-25]) over 53 weeks of maintenance treatment in clinically stable patients with bipolar disorder (absolute rates not provided).[64]

Atypical antipsychotic agents, such as quetiapine, aripiprazole, and cariprazine, are also recommended for long-term treatment of bipolar disorder.[21,27,28] These drugs reduce rates of mania,

but their effects on depression are not uniform. Antidepressant effects are best established for the combination of olanzapine/fluoxetine and for quetiapine, lurasidone, and cariprazine as single or adjunctive agents.[47] The long-term use of antipsychotic medication in bipolar disorder requires careful evaluation due to the increased cardiovascular and metabolic risks associated with these drugs, especially during long-term treatment.

In a 5-year longitudinal study involving 49 293 individuals diagnosed with bipolar disorder, exposure to antipsychotic medication was associated with a dose-related increase in overall mortality (HRs of 1.13 [95% CI, 1.21-1.42] for low exposure [defined as half of the daily dose recommended for maintenance], 1.69 [95% CI, 1.51-1.90] for moderate exposure [defined as more than half and less than 1.5 times the daily dose], and 2.08 [95% CI, 1.69-2.57] for high exposure [defined as more than 1.5 times the daily recommended dose]) compared with patients with bipolar disorder not exposed to antipsychotic medications. Additionally, antipsychotic medication use was associated with a dose-related increase in cardiovascular mortality, with the highest risk in the high-exposure group (HR, 2.08 [95% CI, 1.69-2.57]).[65]

Treatment of bipolar disorder often involves combinations of multiple drugs, such as a mood stabilizer, an antipsychotic medication, and/or an antidepressant.[20] Complex treatment regimens increase nonadherence to medication, a common problem in bipolar disorder, affecting approximately 60% of patients.[66] Adverse effects of drugs, misunderstandings about the need for continuous treatment even when patients are well, and the complexity of multiple medication regimes contribute to nonadherence to medication. Clinicians should provide psychoeducation to address potential nonadherence factors and, whenever possible, simplify treatment schedules. Long-acting injectable antipsychotics, such as risperidone or aripiprazole, are appropriate for patients with poor adherence to oral medications or those with inadequate responses to oral treatment.[67]

Psychotherapy

Guidelines for optimal management of bipolar disorder emphasize combined psychopharmacological and psychosocial treatment.[27] Psychoeducation involves providing individuals with information about bipolar disorder, the importance of medication adherence, how to recognize early signs of mood episodes, how to develop strategies for managing symptoms, and potential adverse effects of medications.[68] RCTs of psychoeducation (delivered in individual, group, and family formats) have documented lower relapse rates, longer time to recurrence, reduced manic and depressive symptoms, lower hospitalization rates, and increased treatment adherence compared with nonstructured interventions without psychoeducation.[69,70]

A meta-analysis of 19 RCTs that included 1384 patients with bipolar disorder reported that adjunctive cognitive behavioral therapy, which identifies and helps patients challenge negative thinking patterns and behaviors, was associated with fewer depressive symptoms (effect size Hedges g = −0.494 [95% CI, −0.963 to −0.026]), fewer relapses (pooled OR, 0.506 [95% CI, 0.278-0.921]), and improved social-occupational functioning (Hedges g = 0.457 [95% CI, 0.106-0.809]) compared with usual treatment.[71]

Family-focused treatments are effective for depressive symptoms, number of relapses, time to relapse, hospitalization risk, and medication adherence.[72] Interpersonal and social rhythm therapy focuses on stabilizing circadian rhythms, improving medication adherence, and reducing interpersonal stress, but evidence of efficacy is still limited.[73] Dialectical behavior therapy integrates cognitive behavioral techniques with mindfulness strategies to target emotional dysregulation, suicidality, and self-harm behaviors and might reduce depressive symptoms and suicidal ideation in people with bipolar disorder.[74] Internet adaptations of face-to-face therapies and mindfulness and recovery-focused approaches might be effective, but evidence from RCTs for patients with bipolar disorder is still limited.[75,76]

Clinical Course and Prognosis

The prognosis of bipolar disorder varies, and greater disease duration and more episodes of depression, mania, and hypomania are associated with higher rates of recurrence and greater impairment in mental and physical health and cognitive function.[77,78]

The presence of severe manic episodes, potential psychotic features, and a propensity for cycling between manic and depressive episodes contribute to higher functional impairment and a higher risk of hospitalization in patients with bipolar I. Bipolar II is characterized by a higher frequency and duration of depressive episodes that significantly affect daily functioning and quality of life.

Prospective studies reported that patients with both types of bipolar disorder experience symptoms approximately half of all days. Individuals with bipolar I experience symptoms for approximately 47.3% of weeks each year and experience major depressive symptoms for approximately 31.9% of weeks per year. Compared with patients with bipolar II, those with bipolar I experience manic symptoms more frequently (8.9% vs 1.3% of weeks per year). People with bipolar I also experience more frequent switches between depression and mania (6 changes in symptom status per year) and a higher prevalence of episodes with mixed features when symptoms of depression and hypomania co-occur (6% vs 2.5% of weeks), compared with bipolar II. In contrast, individuals with bipolar II experience symptoms more often, approximately 53.9% of weeks, with major depressive symptoms predominating (50.3% of weeks) over the course of disease. Subsyndromal and minor depressive symptoms are nearly 3 times more common than major depressive and manic symptoms in both subtypes of bipolar disorder and significantly increase the chance of relapse.[79-82]

Limitations

This review has several limitations. First, the review did not formally and systematically evaluate the quality of the included evidence. Second, relevant references may have been missed. Third, the review is limited by the quality of available evidence.

Conclusions

Bipolar disorder affects approximately 8 million adults in the US. First-line therapy for bipolar disorder includes mood stabilizers, such as lithium, and anticonvulsants, such as valproate and lamotrigine, as well as atypical antipsychotic drugs, such as quetiapine, aripiprazole, asenapine, or lurasidone.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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