Chapter 89: Bipolar Disorder

Jordan Haygood; Shannon J. Drayton

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 68, Bipolar Disorder.

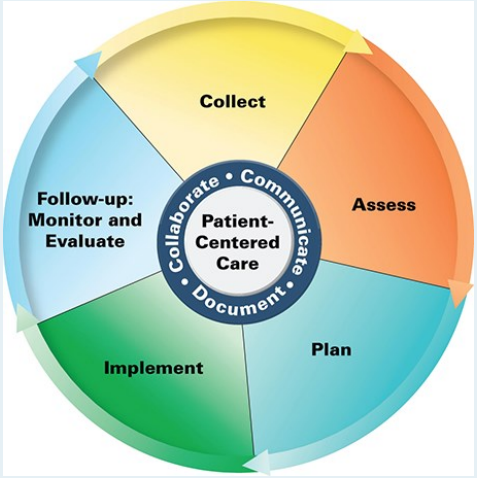
KEY CONCEPTS

KEY CONCEPTS

1. Bipolar disorder is a cyclic mental illness with recurrent mood episodes that occur over a person's lifetime. The symptoms, course, severity, and response to treatment differ among individuals.
2. Bipolar disorder is likely caused by genetic factors, environmental triggers, and the dysregulation of neurotransmitters, neurohormones, and second messenger systems in the brain.
3. Clinicians should obtain a detailed history, including medical history and substance use history, to expedite the diagnosis and treatment of bipolar disorder.
4. Bipolar disorder is a complex psychiatric illness with significant morbidity and mortality. Suicidal thoughts and behaviors are common in individuals with bipolar disorder and need to be managed with medical and therapeutic interventions.
5. The goal of therapy for bipolar disorder should be to improve an individual's functioning by reducing mood episodes. This is accomplished by maximizing adherence to therapy and limiting medication adverse effects.
6. Patients and family members should be educated about bipolar disorder and treatments. Long-term monitoring and adherence to treatment are primary factors in achieving disease stabilization.
7. Lithium, valproate, and second-generation antipsychotics are the mainstays of treatment for different phases of bipolar disorder, acting as primary mood stabilizers. When individuals with bipolar disorder present with an acute mood episode (eg, depressed episode, manic episode or mixed state) despite a primary mood stabilizer, adjunctive medications are considered to target the specific mood state or subtype. These medications can often be tapered once the acute episode has resolved and euthymia is reached. Baseline and follow-up laboratory tests are required for most medications used for bipolar disorder to monitor for adverse effects.
8. Some individuals can be stabilized on one mood stabilizer, but others may require combination therapies or adjunctive agents during an acute mood episode. Adjunctive agents should be tapered and discontinued when the acute mood episode remits and the patient is stabilized, if possible. These agents may include benzodiazepines, additional mood stabilizers, antipsychotics, and/or antidepressants.

PATIENT CARE PROCESS

Patient Care Process for Bipolar Disorder



Collect

- Patient characteristics (eg, age, race, sex, pregnancy status)
- Patient psychiatric, medical, social, and family history
- Current medications and prior medication use
- Current and past sleep habits/patterns

- Objective data
  - Blood pressure, heart rate, height, weight, and body mass index (BMI)
  - Laboratory test (eg, serum electrolytes, serum creatine [SCr], liver function tests [LFTs], thyroid stimulating hormone [TSH], urine drug screen [UDS], pregnancy test)
  - Rating scale scores (eg, Young Mania Rating Scale [YMRS], Hamilton Depression Rating Scale (HDRS or HAM-D), Patient Health Questionnaire 9 [PHQ-9])

Assess

- Presence of hypomania, mania, or depression
- Adherence to medication regimen
- Appropriateness, tolerability, and effectiveness of current medication regimen
- Serum concentration of medication if appropriate (eg, lithium)
- Current medications and/or substances that may contribute to or worsen mania or depression
- Suicidality
- Current sleep patterns
- If no response to current medication regimen, reassess diagnosis

Plan*

- If exhibiting euthymia, continue current regimen if appropriate
- If exhibiting mania symptoms, immediately discontinue antidepressants, optimize regimen, and consider the short-term use of benzodiazepine (see Table 89-4)
- If exhibiting depressive symptoms, optimize regimen and consider adding an antipsychotic (ie, quetiapine, cariprazine, or lurasidone) (see Table 89-4)
- Lifestyle modifications (eg, nutrition, sleep, exercise, stress and substance use reduction)
- Monitor for efficacy and safety of medications (see Table 89-6)
- Treat comorbid psychiatric disease states
- Patient education (eg, purpose of treatment, lifestyle modification, drug therapy)
- Self-monitoring for new mood episodes (eg, daily mood chart) and sleep patterns
- Referrals to other providers when appropriate (eg, psychologist, psychiatrist, primary care)

Implement*

- Provide education to patients and their families regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up visits

Follow-up: Monitor and Evaluate

- Patient's psychiatric status (eg, rating scale) and safety (eg, suicidality)
- Mood episodes: Document symptoms on a daily mood chart including life stressors, type of episode, length of episode, and treatment outcome. Monthly and yearly life charts are valuable for documenting patterns of mood cycles
- Suicidal ideation or attempts: 6% to 7% of patients with bipolar I disorder die by suicide. Suicide attempts are primarily associated with depressive episodes, mixed episodes with severe depression, or presence of psychosis
- Presence of medication-associated adverse effects should be managed rapidly and vigorously to avoid non-adherence (eg, weight gain, sedation)
- Laboratory tests (see Table 89-6)
- Patient adherence to treatment plan using multiple sources of information and presence of residual symptoms (eg, missing doses of medications is a primary reason for non-response and recurrence of episodes)

*_*Collaborate with patient, caregivers, and other healthcare professionals.*_

BEYOND THE BOOK

BEYOND THE BOOK

Introductory Video About Bipolar Disorder: Use the link below to view the video titled, "Mental Illness in Stressful Times—An Asian American Family's Story" on the National Institute of Mental Health website. This 6-minute video provides a glimpse into one family's experience with bipolar disorder. The viewing of this video is intended to stimulate deeper thinking about social implications of bipolar disorder and to provoke an appreciation of the hardships and successes that patients with the disorder may face.

Link to video: https://www.nimh.nih.gov/news/media/2016/mental-illness-in-stressful-times-an-asian-american-familys-story.shtml

INTRODUCTION

1 Bipolar disorder is a common, chronic, and often severe cyclic mood disorder characterized by recurrent fluctuations in mood, energy, and behavior.[1,2] It differs from recurrent major depression, or unipolar depression, in that a manic or hypomanic episode occurs during the course of the illness (see section "Clinical Presentation and Diagnosis").[1] Bipolar disorder is a lifelong illness with a variable course and requires both non-pharmacologic and pharmacologic treatments for mood stabilization.[1,2]

EPIDEMIOLOGY

The lifetime prevalence of bipolar disorder in the United States is 4.4% with 1% of patients meeting criteria for bipolar I, 1.1% for bipolar II, and 2.4% of patients with subthreshold bipolar disorder (ie, cyclothymia, unspecified bipolar disorder).[3] Similar rates of bipolar I disorder are seen in males and females.[4] Symptom onset for depression, mania, or hypomania in bipolar disorder typically occurs in late adolescence or early adulthood, with approximately one-third to two-thirds of patients diagnosed with bipolar disorder experiencing their first episode as a child or adolescent.[2] Depression and mixed presentations may occur more frequently in females.[2,5]

ETIOLOGY AND PATHOPHYSIOLOGY

2 The exact etiology of bipolar disorder is unknown but is thought to be influenced by a complex of developmental, genetic, neurobiologic, and psychological factors.[4,6] Many theories have been proposed regarding the pathophysiology of mood disorders. Family, twin, and adoption studies report an increased lifetime prevalence risk of having mood disorders among first-degree relatives of patients with bipolar disorder.[7] Genetic linkage studies suggest that multiple gene loci, such as Calcium Channel, Cardiac Dihydropyridine-Sensitive, Alpha-1 Subunit (*CACNA1C*), and Ankyrin 3 (*ANK3*), may be involved in the heredity of mood disorders.[6] Additionally, recent studies have uncovered that there may be genetic differences driving the manifestations of the bipolar disorder subtypes.[8] Neuroimaging studies indicate that several anatomic regions, primarily the amygdala within the limbic system and the prefrontal cortex, may contribute to functional abnormalities in patients with bipolar disorder.[9] It is suspected that altered synaptic and circuit functioning account for mood and cognitive changes seen in bipolar disorder, rather than the dysfunction of individual neurotransmitters.[9] Environmental or psychological stressors, immunologic factors, and sleep dysregulation are also associated with bipolar disorder and can negatively influence the course of illness.[4,10,11]

CLINICAL PRESENTATION AND DIAGNOSIS

Bipolar disorder is a cyclic mood disorder where patients sequentially experience different types of episodes with or without a period of normal mood (euthymia) between episodes. Individuals with bipolar disorder can have mood fluctuations that continue for months, or after one episode, they can sometimes go years without the recurrence of any type of mood episode. 1 The essential feature of bipolar spectrum disorders is a history of mania or hypomania that is not caused by any other medical conditions, substances, or psychiatric disorders.[1] The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) of the American Psychiatric Association (APA) details the present understanding of mood disorders.[1] Bipolar disorder is divided into five subtypes based on the identification of specific mood episodes: bipolar I, bipolar II, cyclothymic disorder, other specified bipolar and related disorder, and unspecified bipolar and related disorder.[1] Table 89-1 defines the mood disorders by type of episode. Specifiers (ie, hypomanic or major depressive episode) can be added to bipolar I and II to reflect the most recent mood state. Comorbid conditions associated with bipolar disorder include, but are not limited to, unhealthy substance use, personality disorders, anxiety disorders, eating disorders, and a higher incidence of several medical conditions.[1,2,4]

TABLE 89-1

Mood Disorders Defined by Episodes

Disorder Subtype	Episode(s)[a]
Major depressive disorder, single episode	Major depressive episode
Major depressive disorder, recurrent	Two or more major depressive episodes
Bipolar I disorder[b]	Manic episode ± major depressive or hypomanic episode
Bipolar II disorder[c]	Major depressive episode + hypomanic episode
Persistent depressive disorder (Dysthymia)	Depressed mood most days for at least 2 years (1 year in children and adolescents)
Cyclothymic disorder[d]	Chronic fluctuations between subsyndromal depressive and hypomanic episodes (2 years for adults and 1 year for children and adolescents)
Unspecified bipolar and related disorder	Mood states do not meet full criteria for any specific disorder in the bipolar and related disorders class

[a]The length and severity of a mood episode and the interval between episodes vary from patient to patient. Manic episodes are usually shorter and end more abruptly than major depressive episodes, and even with treatment episodes may last upwards of 3 months and 5 months, respectively. The average length of untreated manic episodes ranges from 4 to 13 months. Episodes can occur regularly (at the same time or season of the year) and often cluster at 12-month intervals. Females have more depressive episodes than manic episodes, whereas males have a more even distribution of episodes.

[b]For bipolar I disorder, 90% of individuals who experience a manic episode later have multiple recurrent major depressive, manic, or hypomanic episodes alternating with a normal mood state.

[c]Approximately 5% to 15% of patients with bipolar II disorder will develop a manic episode over a 5-year period. If a manic episode develops in a patient with bipolar II disorder, the diagnosis is changed to bipolar I disorder.

[d]Patients with cyclothymic disorder have a 15% to 50% risk of later developing a bipolar I or II disorder.

Data from References 1 and 12.

CLINICAL PRESENTATION: Major Depressive Disorder[a]

DSM-5 Criteria[b]

At least 2-week period of either depressed mood or loss of interest or pleasure in normal activities, associated with at least five of the following symptoms:

- Depressed, sad mood in adults, can be irritable mood in children
- Decreased interest and pleasure in normal activities
- Decreased or increased appetite, weight loss or weight gain
- Insomnia or hypersomnia
- Psychomotor retardation or agitation
- Decreased energy or fatigue
- Feelings of excessive guilt or worthlessness
- Impaired concentration or indecisiveness
- Recurrent thoughts of death, suicidal thoughts, or attempts

Mania[a]

DSM-5 Criteria[b]

At least 1-week period of abnormally and persistently elevated mood (eg, expansive or irritable) and energy, associated with at least three of the following symptoms (four if the mood is only irritable)

- Inflated self-esteem (grandiosity)
- Decreased need for sleep
- Increased talking (pressure of speech)
- Racing thoughts (flight of ideas)
- Distractibility (poor attention)
- Increased goal-directed activity (socially, at work, or sexually) or psychomotor agitation
- Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)

Hypomania[a]

DSM-5 Criteria[b]

At least 4 days of abnormally and persistently elevated mood (eg, expansive or irritable) and energy, associated with at least three of the following symptoms listed under Mania above (four if the mood is only irritable):

[a]Impairment in social or occupational functioning; may include need for hospitalization because of potential self-harm, harm to others, or psychotic symptoms.

[b]The disorder is not caused by a medical condition (eg, hypothyroidism) or substance-induced disorder (eg, antidepressant treatment, other medications), or a substance use disorder. Numerous specifiers are available to further characterize episodes (eg, with mixed features, with anxious distress, with rapid cycling, with melancholic features).

Data from Reference 1.

Diagnostic Difficulty

Episodes of mania or depression may be induced or caused by medical illness, medications, or substance intoxication or withdrawal (refer to Table 89-2 for causes of mania[13-21] and Chapter 88, "Depressive Disorders" for causes of depression). The timely diagnosis and treatment of bipolar disorder may be difficult due to frequent episodes of depression, comorbid conditions, and lack of treatment during periods of elevated mood. A complete medical, psychiatric, and medication history; physical examination; and laboratory testing are important tools to rule out any organic causes of mania or depression.[22] An accurate diagnosis is critical as some psychiatric and neurologic disorders present with mania-like or depressive-like symptoms.[2] Bipolar disorder commonly co-occurs with substance use disorders and may be difficult to diagnose in the presence of cocaine use or other illicit substances (eg, psychostimulants, bath salts, synthetic cannabinoids).[2] When making the diagnosis of new-onset bipolar disorder, particularly in an older population, clinicians should be aware of secondary causes of mania and depression that may impact the treatment.[23,24]

TABLE 89-2

Secondary Causes of Mania

Medical conditions that induce mania

- CNS disorders (eg, brain tumor, strokes, head injuries, subdural hematoma, multiple sclerosis, systemic lupus erythematosus, temporal lobe seizures, Huntington's disease)
- Infections (eg, encephalitis, neurosyphilis, sepsis, human immunodeficiency virus)
- Electrolyte or metabolic abnormalities (eg, calcium or sodium fluctuations, hyperglycemia, or hypoglycemia)
- Endocrine or hormonal dysregulation (eg, Addison's disease, Cushing disease, hyperthyroidism or hypothyroidism, menstruation-related, or pregnancy-related or perimenopausal mood disorders)

Medications or drugs that induce mania

- Alcohol intoxication
- Drug withdrawal states (eg, alcohol, α_2-adrenergic agonists, antidepressants, barbiturates, benzodiazepines, opiates)
- Antidepressants (eg, MAOIs, TCAs, 5-HT and/or NE and/or DA reuptake inhibitors, 5-HT antagonists)
- DA-augmenting agents (CNS stimulants: amphetamines, cocaine, sympathomimetics; DA agonists, releasers, and reuptake inhibitors)
- Hallucinogens (eg, LSD, PCP)
- Cannabis intoxication precipitates psychosis, paranoid thoughts, anxiety, and restlessness
- NE-augmenting agents (eg, α_2-adrenergic antagonists, β-agonists, NE reuptake inhibitors)
- Steroids (eg, anabolic, adrenocorticotropic hormone, corticosteroids)
- Thyroid preparations
- Xanthines (eg, caffeine, theophylline)
- Non-prescription weight loss agents and decongestants (eg, ephedra, pseudoephedrine)
- Herbal products (eg, St. John wort)

Somatic therapies that induce mania

- Bright light therapy
- Deep brain stimulation
- Sleep deprivation

CNS, central nervous system; DA, dopamine; 5-HT, serotonin; LSD, lysergic acid diethylamide; MAOI, monoamine oxidase inhibitor; NE, norepinephrine; PCP, phencyclidine; TCA, tricyclic antidepressant.

Data from References 1,4, and 13-21.

Schizoaffective disorder, which is essentially a mix between schizophrenia and bipolar disorder or unipolar depression, also presents similarly to bipolar disorder. Patients with schizoaffective disorder have mood episodes, but a primary distinguishing factor from bipolar disorder is the occurrence of psychosis between mood episodes during periods of euthymic mood.[1,2] Clinicians must rely on the longitudinal history provided by collateral historians who know the patient well to determine if the patient experiences psychosis between mood episodes. It can be difficult for clinicians to obtain a full psychiatric history on individuals presenting with manic or psychotic symptoms, thus making schizoaffective disorder difficult to differentiate from bipolar disorder.[2] Schizoaffective disorder, bipolar type is best treated with antipsychotics with or without a mood stabilizer as maintenance therapy.

Course of Illness

Bipolar disorder is frequently not recognized or treated for many years because of its initial fluctuating course with subsyndromal symptoms of depression, irritability, and hypomania that build up gradually in intensity. Though the overall average age of onset falls within the early 20s, patients typically experience delays averaging 8 years after the index mood episode until appropriate medication initiation.[2,25] This delay confers a risk of poor social functioning, increased hospitalizations, and a greater likelihood of lifetime suicide attempts.[26] Onset of illness in early childhood, as opposed to onset in early adulthood, tends to be associated with longer delay to treatment initiation, increased mood episodes, rapid cycling, and comorbid psychiatric conditions as well as a stronger family history of mood disorders.[27,28] Gender differences may influence the course of illness, tolerability of medication, and response to treatment. Females are more likely to have increased depressive symptoms, older age of onset, better adherence, complex management in pregnancy, and higher association with physical illness such as thyroid abnormalities. In males, there may be increased incidence of mania and substance use/misuse.[29]

The kindling theory is used to explain how bipolar disorder can progress over one's life and why preventive treatment is imperative. Without effective treatment, episodes can become more frequent, severe, and refractory to treatment.[4,10,30,31,44] Usually, there is a period of euthymia between episodes, but approximately 20% to 30% of patients with bipolar I disorder and 15% with bipolar II disorder have no inter-episode period of euthymia because of mood lability, residual subsyndromal mood symptoms, or a direct switch to the opposite polarity.[1]

Rapid cycling is defined as four or more mood episodes per year and is more common in females and has a lifetime prevalence as high as 25% to 43% in all patients with bipolar disorder.[2,32] Frequent and severe episodes of depression are the most common hallmark of rapid cycling. The use of alcohol, stimulants, and antidepressants, as well as sleep deprivation, hypothyroidism, and seasonal changes, can play a role in rapid cycling.[2,32] Seasonal patterns of mania in the summer and depression during the winter have been observed. Patients with rapid cycling have a poorer long-term prognosis and often require combination therapies.[1,2]

Fluctuations in hormones and neurotransmitters during the luteal phase of the menstrual cycle, postpartum period, and perimenopause, starting ~10 years before menopause, can precipitate mood changes and increase mood cycling.[1,2] Evidence supports that females with a history of premenstrual dysphoric disorder (PMDD) diagnosed with bipolar disorder display higher rates of rapid cycling and a greater number of mood episodes.[33] Females with bipolar disorder are at greater risk for relapse into mania or depression during the postpartum period.[2] If a severe mood episode occurs postpartum, there is an increased risk for recurrences during subsequent postpartum periods.[2]

Bipolar disorder is associated with several comorbid psychiatric diagnoses most commonly substance use disorders, anxiety disorders, personality disorders, and impulse control disorders that require careful treatment considerations. Often times, medications utilized to stabilize mood may also be effective in managing comorbidities. Conversely, certain treatment options for comorbidities such as anxiety disorders may further destabilize patients if adequate treatment for mood stability is not first employed. A hierarchical approach should be taken when managing comorbid psychiatric diagnoses.[2]

Alcohol and other substance use or misuse is common among patients with bipolar disorder and can have a significant impact on the age of onset, course of the illness, and response to treatment.[2] Substance use disorders have been reported in 33% to 45% of individuals with bipolar disorder.[34,35] Those with substance use disorders are more likely to have an earlier onset of their illness, mixed states, higher rates of relapse, poorer response to treatment, comorbid personality disorders, increased suicide risk, and more psychiatric hospitalizations.[2] When individuals with bipolar disorder use substances such as alcohol, cannabis, or cocaine during episodes, it can result in further impairment of judgment, poor impulse control, treatment non-adherence, and a worsening of the clinical course. Alcohol and other substance use should be addressed as early as

possible in the individual's clinical course to improve outcomes.[2]

4 For those living with bipolar disorder, approximately one-half of their lifetime is spent with syndromal and subsyndromal symptoms, particularly those with depressive episodes.[2] More than one-half (55%-65%) of patients with bipolar I have some degree of functional disability after the onset of their illness, and approximately 10% to 20% of patients with bipolar disorder have severe impairment in their psychosocial and occupational functioning.[1,22,36] Functional impairment is often more pronounced in patients with depression, a greater number of previous episodes, a longer duration of illness, and lower cognition. In a 1-year longitudinal study in 258 patients with bipolar disorder, two-thirds had four or more mood episodes a year despite comprehensive pharmacologic treatment, and approximately 33.2% of the year was spent being depressed compared with 10.8% of the time in the mania phase.[36]

Compared with the general population, individuals with bipolar disorder have a two-fold higher mortality rate.[37] Suicide attempts occur in one-third to one-half of individuals with bipolar disorder, and approximately 6% to 7% of individuals with bipolar I disorder die by suicide.[2,38] Roughly 43% of patients with bipolar disorder worldwide report suicidal ideation. Many factors are associated with suicide attempts including female sex, depression as a current or more recent episode, previous attempts, and comorbid substance use disorder.[2]

The best predictor for the level of functioning during a person's lifetime is adherence with medication treatment. Medication non-adherence is estimated to occur in 20% to 60% of patients secondary to multiple factors including intolerance of adverse medication effects.[39] Due to failure to recognize the disorder, reluctance to acknowledge it, or poor adherence with treatment, an estimated two-thirds of patients with bipolar disorder do not receive appropriate treatment. Non-adherence with pharmacologic treatment and substance use are major factors in relapse and hospitalizations.[2]

TREATMENT

Desired Outcomes

5 The desired outcome in treating bipolar disorder is to effectively resolve acute manic, hypomanic, and depressive episodes, as well as prevent further episodes, maintain healthy functioning, promote treatment adherence, and minimize medication adverse effects.[2,4] The general principles and goals for the management of bipolar disorder are listed in Table 89-3.

TABLE 89-3

General Principles for the Management of Bipolar Disorder

Goals of treatment

- Eliminate mood episode with complete remission of symptoms (ie, acute treatment)
- Prevent recurrences or relapses of mood episodes (ie, continuation phase treatment)
- Return to baseline psychosocial functioning
- Maximize adherence with therapy
- Minimize adverse effects
- Use medications with the best tolerability and fewest drug interactions
- Minimize polypharmacy when possible
- Treat comorbid substance use and use disorders
- Eliminate alcohol, cannabis, cocaine, amphetamines, and hallucinogens
- Minimize nicotine use and stop caffeine intake at least 8 hours prior to bedtime
- Avoid stressors or substances that precipitate an acute episode

Data from References 2 and 4.

General Approach to Treatment

6 Treatment of bipolar disorder must be individualized because the clinical presentation, severity, and frequency of episodes vary widely among patients. Treatment approach should include both non-pharmacologic and pharmacologic strategies.[2] Patients and family members should be educated about bipolar disorder (eg, symptoms, causes, and course) and treatment options. Long-term adherence to treatment is the most important factor in achieving stabilization of the disorder.

7 The treatment of bipolar disorder can vary depending on the type of episode the patient is experiencing. Once diagnosed with bipolar disorder, patients should remain on a mood stabilizer (eg, lithium, valproate, or a second-generation antipsychotic) for their lifetime. During acute episodes, medications can be added and then tapered once the patient is stabilized and euthymic. For example, when treating a patient for mania with psychotic features, the patient should be on a mood stabilizer and an antipsychotic. If an antipsychotic is the patient's currently prescribed maintenance therapy, the dose should be increased or perhaps the medication should be changed altogether if the patient's mood becomes manic. If treating a patient for a severe depressive episode, a clinician may need to maximize the dose of the mood stabilizer or add another medication (eg, quetiapine) with efficacy in that polarity.

Non-pharmacologic Therapy

The basics of non-pharmacologic approaches should address issues of adequate nutrition, sleep, exercise, and stress reduction.[2] Sleep deprivation, high stress, and dietary deficiencies in essential amino acids, fatty acids, vitamins, and minerals can exacerbate mood episodes and result in worse outcomes.[2,40,41] Psychological interventions are aimed at providing individuals with self-management skills and tools for mood regulation. Adjunctive psychosocial interventions are useful for acute depressive episodes and in maintenance and relapse prevention.[2] Evidence-based approaches include: cognitive behavioral therapy (CBT), interpersonal and social rhythm therapy, group psychoeducation, family-focused therapy, and enhanced relapse prevention/individual psychoeducation.[2] Common features of these approaches are providing education about the condition, identifying prodromal warning signs, and developing coping strategies and crisis plans.[2]

Pharmacologic Therapy

7 Pharmacotherapy is crucial for acute and maintenance treatments of bipolar disorder and includes lithium, valproate, carbamazepine, lamotrigine, first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs), and adjunctive agents such as antidepressants and benzodiazepines. General treatment guidelines for the acute treatment of mood episodes in patients with bipolar I disorder are listed in Table 89-4.[2,22]

TABLE 89-4

Algorithm and Guidelines for the Acute Treatment of Mood Episodes in Patients with Bipolar I Disorder

Acute Manic or Mixed Episode		Acute Depressive Episode	
General Guidelines		**General Guidelines**	
• Assess for secondary causes of mania or mixed states (eg, alcohol or drug use) • Discontinue antidepressants • Taper off stimulants and caffeine if possible • Treat substance use • Encourage good nutrition with regular protein and essential fatty acid intake, exercise, adequate sleep, stress reduction, and psychosocial therapy		• Assess for secondary causes of depression (eg, alcohol or drug use) • Taper off antipsychotics, benzodiazepines, or sedative–hypnotic agents if possible • Treat substance use/misuse • Encourage good nutrition with regular protein and essential fatty acid intake, exercise, adequate sleep, stress reduction, and psychosocial therapy	
Hypomania	**Mania**	**Mild-to-Moderate Depressive Episode**	**Severe Depressive Episode**
• **First**, optimize current mood stabilizer if non-adherence is suspected or initiate mood-stabilizing medication: lithium,[a] valproate,[a] carbamazepine,[a] or SGAs • Consider adding a benzodiazepine (eg, lorazepam or clonazepam) for short-term adjunctive treatment of agitation or insomnia if needed • Oxcarbazepine is an alternative medication treatment option • **Second**, if response is inadequate, consider a two-drug combination: • Lithium[a] **plus** an antiseizure medication or an SGA, or • antiseizure medication **plus** an antiseizure medication or SGA	• **First**, optimize the previously prescribed mood stabilizer or medication regimen if non-adherence suspected or initiate new mood-stabilizing two- or three-drug combinations (lithium,[a] valproate,[a] or SGA) **plus** a benzodiazepine (eg, lorazepam or clonazepam) and/or antipsychotic for short-term adjunctive treatment of agitation or insomnia; lorazepam is recommended for catatonia • Do not combine antipsychotics • Alternative options: carbamazepine[a]; if patient does not respond or tolerate, consider oxcarbazepine • **Second**, if response is inadequate, consider a three-drug combination: • Lithium[a] **plus** an antiseizure medication **plus** an antipsychotic, or • antiseizure medication **plus** an antiseizure medication **plus** an antipsychotic • **Third**, if response is inadequate, consider ECT for mania with psychosis or catatonia[b] or add clozapine for treatment-refractory illness	• **First**, initiate and/or optimize mood-stabilizing medication: lithium,[a] quetiapine, lurasidone • Alternative antiseizure medications: lamotrigine,[c] valproate[a] • Alternative antipsychotics: fluoxetine/olanzapine combination, cariprazine, lumateperone	• **First**, optimize current mood stabilizer if non-adherence is suspected or initiate a new mood-stabilizing medication: lithium,[a] quetiapine, or lurasidone • fluoxetine/olanzapine combination • If psychosis is present, optimize current antipsychotic or initiate in combination with above • Alternative antipsychotics: cariprazine, lumateperone • Do not combine antipsychotics • Alternative antiseizure medications: lamotrigine,[c] valproate[a] • **Second**, if response is inadequate, consider carbamazepine[a] or adding antidepressant[d] • **Third**, if response is inadequate, consider a three-drug combination: • Lithium **plus** lamotrigine[c] **plus** an antidepressant[d] • Lithium **plus** quetiapine **plus** antidepressant[d] • **Fourth**, if response is inadequate, consider ECT for treatment-refractory illness and depression with psychosis or catatonia[b]

ECT, electroconvulsive therapy; SGA, second-generation antipsychotic.

[a]Use standard therapeutic serum concentration ranges if clinically indicated; if partial response or breakthrough episode, adjust dose to achieve higher serum concentrations without causing intolerable adverse effects; lithium, SGAs, and/or lamotrigine are preferred over valproate and carbamazepine for bipolar depression.

[b]ECT is used for severe mania or depression during pregnancy and for mixed episodes; prior to treatment, antiseizure medication, lithium, and benzodiazepines should be tapered off to maximize therapy and minimize adverse effects.

[c]Lamotrigine is not approved for the acute treatment of depression, and the dose must be started low and slowly titrated up to decrease adverse effects if used for maintenance therapy. Lamotrigine may be initiated during acute treatment with plans to transition to this medication for long-term maintenance. A drug interaction and a severe dermatologic rash can occur when lamotrigine is combined with valproate (ie, lamotrigine doses must be halved from standard dosing titration).

[d]Controversy exists concerning the use of antidepressants, and they are often considered third line in treating acute bipolar depression, except in patients with no recent history of severe acute mania or potentially in bipolar II patients.

Data from References 2,22, and 47.

Product information, dosing, and administration of agents used in the treatment of bipolar disorder are found in Table 89-5.

TABLE 89-5

Products, Dosage and Administration, and Clinical Use of Agents Used in the Treatment of Bipolar Disorder

Drug (Brand	Initial Dosing	Usual Dosing; Special Population Dosing	Comments

Name)			
Lithium salts			
Lithium carbonate (Eskalith)[a,b] (Eskalith CR) (Lithobid) Lithium citrate	300 mg twice daily	900-2,400 mg/day in two to four divided doses, preferably with meals Renal impairment: lower doses required with frequent serum monitoring. There is wide variation in the dosage needed to achieve therapeutic response. Trough serum lithium concentration (ie, 0.6-1.2 mEq/L [mmol/L] for maintenance therapy and 0.8-1.2 mEq/L [mmol/L] for acute mood episodes taken 12 hours after the last dose)	Use alone or in combination with other medications (eg, valproate, carbamazepine, antipsychotics) for the acute treatment of mania and for maintenance treatment Lithium citrate discontinued in the US and Canada. Availablility varies by country.
Antiseizure medications			
Divalproex sodium (Depakote)[a] (Depakote ER) Valproic acid[a] (Depakene) Valproate sodium (Depacon)	250-500 mg twice daily A loading dose of divalproex (20-30 mg/kg/day) can be given	750-3,000 mg/day (20-60 mg/kg/day) given once daily or in divided doses Titrate to clinical response Dose adjustment needed with hepatic impairment	Use alone or in combination with other medications (eg, lithium, carbamazepine, antipsychotics) for the acute treatment of mania and for maintenance treatment Use caution when combining with lamotrigine because of potential drug interaction
Lamotrigine (Lamictal)[b]	25 mg daily	50-400 mg/day in divided doses. Dosage should be slowly increased (eg, 25 mg/day for 2 weeks, then 50 mg/day for weeks 3 and 4, and then 50-mg/day increments at weekly intervals up to 200 mg/day) Dose adjustment needed with hepatic impairment	Use alone or in combination with other medications (eg, lithium, carbamazepine) for long-term maintenance treatment for bipolar I disorder
Carbamazepine (Equetro)[a] (Tegretol) (Epitol) (Tegretol-XR) (Carbatrol)	200 mg twice daily	200-1,800 mg/day in two to four divided doses Titrate to clinical response Dose adjustment needed with hepatic impairment	Use alone or in combination with other medications (eg, lithium, valproate, antipsychotics) for the acute and long-term maintenance treatment of mania or mixed episodes for bipolar I disorder. APA guidelines recommend reserving it for patients who were unable to tolerate or who have inadequate response to lithium or valproate Extended-release tablets should be swallowed whole and not be broken or chewed "Carbatrol" capsules can be opened and contents sprinkled over food
Oxcarbazepine (Trileptal)	300 mg twice daily	300-1,200 mg/day in two divided doses Titrate based on clinical response Dose adjustment required with severe renal impairment	Use after patients have failed treatment with carbamazepine or have intolerable adverse medication effects May have fewer adverse effects and be better tolerated than carbamazepine
Second-generation antipsychotics			
Aripiprazole (Abilify)[a,b] (Abilify Asimtufii or Maintena)[b]	10-15 mg daily orally 960 mg every 2 months or 400 mg every month intramuscular	10-30 mg/day once daily orally 960 mg every 2 months or 400 mg every month intramuscular	
Asenapine (Saphris)[b]	5-10 mg twice daily sublingually	5-10 mg twice daily sublingually	
Cariprazine (Vraylar)[a]	1.5 mg daily	3-6 mg daily	
Lumateperone (Caplyta)[c]	42 mg daily	42 mg daily	
Lurasidone (Latuda)[c]	20 mg daily	20-120 mg daily with food	

Olanzapine (Zyprexa)[a,b] (Zyprexa Zydis)	2.5-5 mg twice daily	5-20 mg/day once daily or in divided doses	
Olanzapine and fluoxetine (Symbyax)[c]	6 mg olanzapine and 25 mg fluoxetine daily	6-12 mg olanzapine and 25-50 mg fluoxetine daily	
Quetiapine)Seroquel[a,b]	50 mg twice daily	50-800 mg/day in divided doses or once daily when stabilized	
Risperidone (Risperdal)[a] (Risperdal M-Tab) (Risperdal Consta)[b]	0.5-1 mg twice daily orally 25-50 mg intramuscularly every 2 weeks	0.5-6 mg/day once daily or in divided doses orally 25-50 mg intramuscularly every 2 weeks	
Ziprasidone (Geodon)[a]	40-60 mg twice daily	40-160 mg/day in divided doses	
Benzodiazepines			
Various	Dosage should be slowly adjusted up and down according to response and adverse effects	Use in combination with other medications (eg, antipsychotics, lithium, valproate) for the acute treatment of mania or mixed episodes Use as a short-term adjunctive sedative–hypnotic agent	

[a]FDA-approved for acute mania.

[b]FDA-approved for maintenance.

[c]FDA-approved for acute bipolar depression.

FDA-approved agents may be used as monotherapy in various phases of the illness as noted in table footnotes.

Data from References 42 and 47.

The term *mood stabilizer* is often used to describe the class of medications used for stabilizing the patient's mood and as maintenance therapy for the prevention of mood fluctuations (eg, mania or depression). However, this term may not be accurate, as some medications are more effective for acute mania, some for the depressive episode, and others for the maintenance phase. Table 89-5 provides the US Food and Drug Administration (FDA) approval status for medications used.

Combination therapies (eg, lithium plus valproate or carbamazepine, lithium, or valproate plus an SGA) can provide better acute response and long-term prevention of relapse and recurrence than monotherapy in some patients with bipolar disorder.[48] The majority of patients hospitalized for an acute episode will be initiated on combination therapy, and after acute symptoms resolve, the medication regimen should be simplified as much as possible.

Several guidelines and algorithms have been published regarding bipolar disorder treatment, based on the best available data and expert consensus. The Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) published updated treatment guidelines in 2018.[2] In addition, an international task force of the World Federation of Societies of Biological Psychiatry (WFSBP) has published guidelines for maintenance of mania, depression, and mixed episodes.[49-52]

An example treatment algorithm for acute mood episodes in adult patients with bipolar I disorder is listed in Table 89-4. The selection of treatment for acute mood episodes (eg, mania or depression) and for maintenance treatment should be individualized. Treatment plans should be based on patient-specific characteristics, comorbid psychiatric and medical conditions, consideration of drug interactions, and avoidance of adverse effects.[2]

Lithium

Lithium was first used in 1949 as a treatment for mania and was approved in 1972 in the United States for the treatment of acute mania and for maintenance therapy. Despite numerous investigations into the biologic and clinical properties of lithium, there is no unified theory for its mechanism of action[42]; however, it is thought to modulate neurotransmission at both the neuronal and intracellular levels, and chronic administration may modulate gene expression and have neuroprotective effects.[53] Lithium is a monovalent cation that is rapidly absorbed and widely distributed with no protein binding. It is also not metabolized and is excreted unchanged in the urine and other body fluids.[42]

Efficacy

Lithium is considered a first-line agent for acute mania and maintenance treatment of bipolar I and II disorders.[2] Early placebo-controlled studies with lithium reported up to a 78% response rate in aborting an acute manic or hypomanic episode, but more recent studies suggest a slower onset of action and more moderate effectiveness when compared with other agents.[54,55]

Recent treatment guidelines recommend lithium as a second-line agent for acute bipolar II depression based on conflicting efficacy in clinical studies comparing lithium alone to various alternative treatments or placebo.[2] In placebo-controlled studies in bipolar depression, lithium has been found to have efficacy, but there can be a 6- to 8-week delay for its antidepressant effects.[55] A potential rationale for lithium's reduced efficacy in certain trials may be subtherapeutic serum levels in the lithium treatment arm.[2] Lithium also produces antisuicidal actions in patients with bipolar disorder which has been demonstrated consistently in clinical studies.[56] Relapse can be reduced with the combination of lithium and other medications such as valproate, carbamazepine, lamotrigine, and antipsychotics.[55] Abrupt discontinuation or non-adherence with lithium therapy can increase the risk of relapse.[55]

Adverse Effects

Adverse effects related to lithium use can be divided into three categories: those that occur early in therapy but are generally innocuous and transient, those that are not dose related occurring with long-term treatment, and toxic effects that occur with high serum concentrations.[42]

Initial gastrointestinal (GI) and central nervous system (CNS) adverse effects are often dose related and are worse at peak serum concentrations, approximately 1-2 hours post-dose. GI side effects are often associated with lithium initiation and may include anorexia, nausea, vomiting, abdominal pain, and diarrhea.[57] Standard approaches for minimizing adverse effects include lowering the dose, taking doses with food, using extended-release products, and trying once-daily dosing at bedtime.[57] Diarrhea can sometimes be managed by switching from extended-released tablet formulation to immediate release capsule or liquid formulation.[57] Diarrhea produced by lithium is commonly an osmotic diarrhea, and therefore switching to a formulation that clears the gut quickly can ameliorate symptoms.

A benign fine hand tremor can be evident in many patients while a course hand tremor may be a sign of toxicity.[2,54] Strategies to reduce the fine tremor include standard approaches (eg, switch to long-acting preparation, lower dose if possible) or adding a β-adrenergic antagonist (eg, propranolol 20-120 mg/day).[57]

Polydipsia with polyuria associated with or without nephrogenic diabetes insipidus (DI) can occur in patients treated with lithium. About 20% to 40% of patients will develop nephrogenic DI soon after treatment initiation.[2] Patients who develop uncontrolled nephrogenic DI may experience fluid and electrolyte disturbances.[58] Nephrogenic DI will persist in about 10% to 25% of patients on continued treatment and typically is reversible with discontinuation of lithium.[42] Other nonspecific renal effects may be seen with lithium treatment, including proteinuria, distal renal tubular acidosis, and reduced glomerular filtration rate.[58]

Both overt (8%-19%) and subclinical (23%) hypothyroidism can occur in patients treated with lithium, occurring more frequently in females than males.[54,57] Supplemental exogenous thyroid hormone (ie, levothyroxine) can be added to the patients' regimen. If lithium is discontinued, the need for the exogenous thyroid hormone should be reassessed because hypothyroidism can be reversible.[2]

Lithium can cause a variety of benign and reversible cardiac effects, particularly T-wave depression in up to 16% to 33% of patients, atrioventricular block, and bradycardia.[42,59] If a patient has significant preexisting cardiac disease, consultation with a cardiologist and an electrocardiogram (ECG) is recommended at baseline and during lithium therapy.[25]

Other adverse effects associated with lithium include acne and folliculitis, reversible leukocytosis, and weight gain.[42] Approximately 20% of patients gain greater than 10 kg [22 lbs] which can be related to fluid retention, the consumption of high-calorie beverages as a result of polydipsia, or a decreased metabolic rate because of hypothyroidism.[60]

Toxicity

Lithium is an extremely toxic medication if accidentally or intentionally taken in overdose. Lithium toxicity usually occurs with serum levels greater than 1.5 mEq/L (mmol/L), but older patients may experience toxicity at lower levels.[42] Severe lithium intoxication occurs when concentrations are higher than 2 mEq/L (mmol/L), and there is a worsening in several key adverse medication effects *GI* (eg, vomiting, diarrhea, or incontinence), *coordination* (eg, fine to coarse hand tremor, unstable gait, slurred speech, and muscle twitching), and *cognition* (eg, poor concentration, drowsiness, disorientation, confusion, apathy, and coma).[4,54] There have been several reports of seizures, cardiac dysrhythmias, permanent neurologic impairments with ataxia and memory deficits, and kidney damage with reduced glomerular filtration rate after lithium intoxication.[54]

Situations that predispose patients to lithium toxicity include sodium restriction, dehydration, vomiting, diarrhea, older than 50 years, heart failure, cirrhosis, and drug interactions that decrease lithium clearance. Heavy exercise, sauna baths, hot weather, and fever can promote sodium loss.[61,62] Patients should be cautioned to maintain adequate sodium and fluid intake (2.5-3 qt [~2.5-3 L] per day of fluids) and to avoid the excessive use of alcohol, coffee, tea, cola, and other caffeine-containing beverages.

If lithium toxicity is suspected, the person should go to an emergency room to be monitored, and lithium should be discontinued.[22] Gastric lavage and IV fluids may be needed, and the patient should be monitored for fluid balance, renal/electrolyte status, and neurologic changes. Activated charcoal is not useful in the setting of lithium toxicity due to its electrically charged nature. Serial serum concentrations should be obtained as renal excretion of lithium may reach a ceiling.[57] Intensive care unit measures should be considered in patients experiencing severe symptoms of toxicity including dysrhythmias, obtundation, or complex fluid/electrolyte imbalances. Hemodialysis may be considered in lithium-naïve patients who may be presenting in an acute overdose situation when lithium concentrations equal or exceed 4 mEq/L (mmol/L) regardless of clinical status or in patients previously taking lithium when lithium concentrations are 2.5 mEq/L (mmol/L) or greater and moderate-to-severe neurologic toxicity, or as clinically indicated.[63] If hemodialysis is initiated, it should be continued until the lithium concentration is below 1 mEq/L (mmol/L) with levels being taken 8 hours after the last dialysis to account for lithium redistribution leading to additional increases in serum levels.

Chronic lithium toxicity may be uncommonly associated with interstitial nephritis. Patients exposed to elevated serum levels of lithium and longer-term use may be at risk.[58] Risk of chronic kidney disease is low and mimic that which is seen in the general population.[64]

Drug-Drug Interactions

Thiazide diuretics, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, angiotensin-converting enzyme inhibitors, and salt-restricted diets can elevate lithium levels.[42] Neurotoxicity can occur when lithium is combined with antipsychotics, metronidazole, methyldopa, and phenytoin.[42] Combining lithium with non-dihydropyridine calcium channel blockers is not recommended because of reports of altered lithium levels and neurotoxicity.[42] Analgesics such as acetaminophen or aspirin and loop diuretics are less likely to interfere with lithium clearance. Caffeine and theophylline can enhance the renal elimination of lithium. Because lithium has no effect on hepatic metabolizing enzymes, it has fewer drug-drug interactions compared with carbamazepine, oxcarbazepine, and valproate.

Dosing and Administration

Lithium dosing depends on the patient's age and weight, tolerance to adverse effects, and the acuity of the illness. Lithium therapy is usually initiated with low-to-moderate doses (600 mg/day) for prophylaxis and higher doses (900-1,200 mg/day) for acute mania, using a two-to-three-times daily dosing regimen.[42] The dose should be adjusted based on the steady-state serum concentration and clinical picture of the patient. Immediate-release lithium preparations should be given in two or three divided daily doses, whereas extended-release products can be given once or twice daily. In clinical practice many clinicians dose the immediate-release and extended-release preparations once daily. It is best to initially begin a patient on divided dosing, but once stabilized many patients are able to switch to once-daily dosing without decompensating.[54,65]

Lithium levels should be monitored for efficacy and to guide dosing. In general, lithium serum concentrations should be maintained between 0.6 and 1 mEq/L (mmol/L) for maintenance therapy.[2,55] Lithium levels are considered to be at steady-state at approximately day 5, and serum samples should be drawn 12 hours post dose. When being used acutely, some clinicians may order lithium levels prior to reaching steady-state to more closely monitor the therapy. Once a desired serum concentration has been achieved, levels should be redrawn in 2 weeks. Maintenance lithium serum concentrations are usually measured every 3 months but can be

adjusted to every 6 months for stabilized patients, or more frequently if clinically indicated (eg, patients with frequent mood episodes).[2] Lithium clearance rates increase by 50% to 100% during pregnancy and return to normal postpartum. Thus, lithium levels should be determined monthly during pregnancy and weekly the month before delivery. At delivery, rapid fluid changes can significantly increase lithium levels; thus, a reduction to pre-pregnancy lithium doses and adequate hydration are recommended.[22]

The recommended guidelines for baseline and routine laboratory testing for lithium are listed in Table 89-6. A therapeutic trial for outpatients should last a minimum of 4 to 6 weeks with lithium serum concentrations of 0.6 to 1.2 mEq/L (mmol/L). Antidepressant efficacy may take longer. Acutely manic patients can require serum concentrations of 1 to 1.2 mEq/L (mmol/L), and some need up to 1.5 mEq/L (mmol/L) to achieve a therapeutic response. Although serum concentrations less than 0.6 mEq/L (mmol/L) may be associated with higher rates of relapse, some patients can do well at 0.4 to 0.7 mEq/L (mmol/L).[55] For prevention of relapse in older patients, serum concentrations of 0.4 to 0.6 mEq/L (mmol/L) are recommended because of increased sensitivity to adverse effects with up to 0.8 mEq/L (mmol/L) being beneficial for acute episodes.[2]

TABLE 89-6

Guidelines for Baseline and Routine Laboratory Tests and Monitoring for Patients with Bipolar Disorder Taking Mood Stabilizers

	Baseline: Physical Examination and General Chemistry[a]	Hematologic Tests[b]		Metabolic Tests[c]		Liver Function Tests[d]		Renal Function Tests[e]		Thyroid Function Tests[f]		Serum Electrolytes[g]		Dermatologic[h]		Pharmacogenomic Testing
	Baseline	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline	6-12 months	Baseline
SGAs[i]	X			X	X											
Carbamazepine[j]	X	X	X			X	X	X				X	X	X	X	X
Lamotrigine[k]	X													X	X	
Lithium[l]	X	X	X	X	X			X	X	X	X	X	X	X	X	
Oxcarbazepine[m]	X											X	X			X
Valproate[n]	X	X	X	X	X	X	X							X	X	

SGAs, second-generation antipsychotics.

[a]Screen for substance use and pregnancy.

[b]Complete blood cell count (CBC) with differential and platelets.

[c]Fasting glucose, lipid panel, and weight.

[d]Lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and alkaline phosphatase.

[e]Serum creatinine, blood urea nitrogen, urinalysis, urine osmolality, and specific gravity.

[f]Triiodothyronine, total thyroxine, thyroxine uptake, and thyroid-stimulating hormone.

[g]Serum sodium.

[h]Rashes, hair thinning, and alopecia.

[i]Second-generation antipsychotics: Monitor for increased appetite with weight gain (primarily in patients with initial low or normal body mass index); monitor closely if rapid or significant weight gain occurs during early therapy; cases of hyperlipidemia and diabetes reported.

[j]Carbamazepine: Manufacturer recommends CBC and platelets (and possibly reticulocyte counts and serum iron) at baseline and that subsequent monitoring be individualized by the clinician (eg, CBC, platelet counts, and liver function tests every 2 weeks during the first 2 months of treatment, and then every 3 months if normal). Monitor more closely if patient exhibits hematologic or hepatic abnormalities or if the patient is receiving a myelotoxic drug; discontinue if platelets are <100,000/mm^3 (100 × 10^9/L), if white blood cell (WBC) count is <3,000/mm^3 (3 × 10^9/L), or if there is evidence of bone marrow suppression or liver dysfunction. Serum electrolyte levels should be monitored in older patients or those at risk for hyponatremia. Carbamazepine interferes with some pregnancy tests.

[k]Lamotrigine: If renal or hepatic impairment, monitor closely and adjust dosage according to manufacturer's guidelines. Serious dermatologic reactions have occurred within 2 to 8 weeks of initiating treatment and are more likely to occur in patients receiving concomitant valproate, with rapid dosage escalation, or using doses exceeding the recommended titration schedule.

[l]Lithium: Obtain baseline electrocardiogram for patients older than 40 years or if preexisting cardiac disease (benign, reversible T-wave depression can occur). Renal function tests should be obtained every 2 to 3 months during the first 6 months, and then every 6 to 12 months; if impaired renal function, monitor 24-hour urine volume and creatinine every 3 months; if urine volume>3 L/day, monitor urinalysis, osmolality, and specific gravity every 3 months. Thyroid function tests should be obtained once or twice during the first 6 months, and then every 6 to 12 months; monitor for signs and symptoms of hypothyroidism; if supplemental thyroid therapy is required, monitor thyroid function tests and adjust thyroid dose every 1 to 2 months until thyroid function indices are within normal range, and then monitor every 3 to 6 months.

[m]Oxcarbazepine: Hyponatremia (serum sodium concentrations <125 mEq/L [mmol/L]) has been reported and occurs more frequently during the first 3 months of therapy; serum sodium concentrations should be monitored in patients receiving drugs that lower serum sodium concentrations (eg, diuretics or drugs that cause inappropriate antidiuretic hormone secretion) or in patients with symptoms of hyponatremia (eg, confusion, headache, lethargy, malaise). Hypersensitivity reactions have occurred in approximately 25% to 30% of patients with a history of carbamazepine hypersensitivity and require immediate discontinuation.

[n]Valproate: Weight gain reported in patients with low or normal body mass index. Monitor platelets and liver function during first 3 to 6 months if evidence of increased bruising or bleeding. Monitor closely if patients exhibit hematologic or hepatic abnormalities or in patients receiving drugs that affect coagulation, such as aspirin or warfarin; discontinue if platelets are <100,000/mm^3 (100 × 10^9/L) or if prolonged bleeding time. Pancreatitis, hyperammonemic encephalopathy, polycystic ovary syndrome, increased testosterone, and menstrual irregularities have been reported; not recommended during first trimester of pregnancy due to risk of neural tube defects.

Data from References 42-47,66 and 67.

Antiseizure Medications

Antiseizure medications are widely prescribed for the treatment of bipolar disorder with varying degrees of evidence. The valproic acid derivative, divalproex sodium was marketed in 1995 and is FDA-approved only for the treatment of acute manic or mixed episodes. However, it is commonly used in clinical practice as maintenance monotherapy for bipolar disorder. Limited data support its use in acute bipolar depression.[2] Carbamazepine is commonly used for both acute and maintenance therapy with the only formulation approved in the United States for bipolar disorder being extended-release carbamazepine, although other

formulations can be used. Some data support the use of oxcarbazepine, a 10-keto analog of carbamazepine, in the treatment of bipolar disorder. However, it is not approved for the treatment of bipolar disorder in the United States. Valproate, carbamazepine, and oxcarbazepine all have a wide range of neurologic, GI, electrolyte, and hematologic adverse effects that require regular assessment and routine blood work.[43,45,46] Lamotrigine is FDA-approved for the maintenance treatment of bipolar I disorder. This medication is most effective in the prevention of relapse of depression.[2]

Sodium Valproate and Valproic Acid

Valproate has antimigraine, mood-stabilizing, and antiaggressive effects.[45] In 1995, the enteric-coated formulation divalproex sodium was approved for the acute treatment of mania. Data have shown valproate to be more effective than placebo for acute mania and perhaps as effective as lithium and olanzapine.[68] In addition, valproate can potentially be more effective than lithium in certain subtypes of bipolar disorder (eg, multiple prior episodes, mixed features, comorbid substance use disorder).[2] Valproate reduces or prevents recurrent manic, depressive, and mixed episodes.[2]

Giving lithium, carbamazepine, antipsychotics, or benzodiazepines with valproate can augment its antimanic effects. The addition of valproate to lithium can have synergistic effects in patients who are treatment-refractory and have specifiers of rapid cycling or mixed features, and the combination has demonstrated efficacy in maintenance therapy for bipolar I disorder. Combinations of valproate and carbamazepine can have synergistic effects, but the potential drug interactions make serum level monitoring of both agents essential.[2] Adding adjunctive SGAs to valproate can be effective for breakthrough mania if there is incomplete or partial response to monotherapy, or for quicker time to treatment response. Clozapine, olanzapine, and quetiapine can increase the risk of sedation and weight gain when combined with valproate. The combination of valproate and lamotrigine can be effective, but valproate reduces the clearance of lamotrigine leading to increased risk of serious rashes, ataxia, tremor, sedation, and fatigue.[45]

Adverse Effects

The most frequent dose-related adverse effects with valproate are GI complaints (eg, anorexia, nausea, indigestion, vomiting, mild diarrhea, and flatulence), fine hand tremors, and sedation.[45] The GI complaints are usually transient, but they can be minimized by giving the medication with food, using lower initial doses with gradual increases, or switching to divalproex sodium extended-release tablets.[2] Dose reduction or the addition of a β-blocker can alleviate tremors, and giving the total daily dose at bedtime can minimize daytime sedation.[22]

Other adverse effects of valproate include ataxia, lethargy, alopecia, changes in the texture or color of hair, pruritus, prolonged bleeding because of inhibition of platelet aggregation, transient increases in liver enzymes, and hyperammonemia.[45] Increased appetite and propensity for significant weight gain is associated with long-term therapy, and should be considered prior to combining with agents that also cause weight gain (eg, SGAs). Thrombocytopenia can occur at higher doses, and patients should be monitored for bleeding and bruising. Lowering the valproate dose can restore platelet counts to normal levels.[22] Fatal necrotizing hepatitis is a rare idiosyncratic, non–dose-related adverse effect that has occurred in children with epilepsy receiving multiple antiseizure drugs.[45] A life-threatening hemorrhagic pancreatitis has been reported in both children and adults.[45] An in-depth discussion of adverse effects can be found in Chapter 75, “Epilepsy.”

Drug-Drug Interactions

A summary of drug-drug interactions for valproate can be found in Chapter 75.

Dosing and Administration

For healthy inpatient adults with acute mania, the initial starting dosage of valproate is typically 20 mg/kg/day in divided doses over 12 hours.[45] The daily dose is adjusted by 250 to 500 mg every 1 to 3 days based on clinical response and tolerability. Maximum recommended dosing is 60 mg/kg/day (see Table 89-5).[45] For outpatients experiencing hypomania or euthymia, or for older patients, the initial starting dose is generally lower (5-10 mg/kg/day in divided doses) and gradually titrated to avoid adverse effects. Once an optimal dose has been achieved, the total daily dose can be continued in two divided doses or given once at bedtime if tolerated.[45] Extended-release divalproex can be administered once daily, but bioavailability can be 15% lower than that of immediate- and delayed-release products, thus requiring slightly higher doses.[45,69] In clinical practice, patients with bipolar disorder who are stable can be switched between formulations without having to change the dose. This is not the case for patients with seizure disorders.

Recommended baseline and routine laboratory tests for patients taking valproate are listed in Table 89-6. Although therapeutic serum concentrations of valproic acid have not been established in bipolar disorder, most clinicians use the antiseizure therapeutic serum range of 50 to 125 mcg/mL (mg/L; 347-866 µmol/L) taken 12 hours after the last dose.[2,45] Levels greater than 94.1 mcg/mL (mg/L; 652 µmol/L) have been found to have greater efficacy for bipolar mania.[70] Patients with cyclothymia or mild bipolar II disorder can have a therapeutic response to lower doses and serum levels, whereas some patients with a more severe form of bipolar disorder can require up to 150 mcg/mL (mg/L; 1,040 µmol/L). Serum valproic acid levels are most useful when assessing for adherence and toxicity.[2]

Carbamazepine

Carbamazepine, an iminostilbene derivative, is structurally related to tricyclic antidepressants (TCAs).[46] It is not a first-line agent for bipolar disorder and is generally reserved for use after treatment failure with lithium or divalproex sodium due to its drug interactions and other safety concerns.[2] Data supporting the use of carbamazepine for bipolar depression are lacking and are not strong for the routine use of carbamazepine in maintenance treatment.[2] Patients with a history of head trauma, anxiety, or a substance use disorder may respond to treatment with carbamazepine. The combination of carbamazepine with lithium, valproate, or antipsychotics is often used for treatment-resistant patients experiencing a manic episode.[2]

Adverse Effects

A summary of adverse effects for carbamazepine can be found in Chapter 75. Acute overdoses are potentially lethal, and serum levels above 15 mcg/mL (mg/L; 63 µmol/L) are associated with ataxia, choreiform movements, diplopia, nystagmus, cardiac conduction changes, seizures, and coma.[22] Gastric decontamination, hemoperfusion, ECG monitoring, and symptomatic treatment are recommended for the management of carbamazepine toxicity.[22,71] New information is quickly evolving in the area of pharmacogenomics that may help clinicians individualize treatment for patients with bipolar disorder. Pharmacogenetic testing is available to determine if patients are poor or rapid metabolizers of cytochrome P450 2D6 and 2C19, as well as other important pharmacogenomic variants, thus predicting an individual’s potential to respond to particular therapies as well as help to tailor dosing regimens in an effort to reduce adverse effects. The use of commercially available testing panels is controversial; however, the Clinical Pharmacogenomic Implementation Consortium (CPIC), funded by the National Institutes of Health, has resources to guide clinicians in the use of this information (http://cpicpgx.org/). For carbamazepine in particular, a boxed warning is located in the FDA package insert recommending genetic testing for the human leukocyte antigen (HLA) allele, HLA-B 1502, in patients of Asian ancestry to help detect a higher risk of Stevens–Johnson syndrome and toxic epidermal necrolysis.[46] Similar considerations should be made for patients prior to prescribing oxcarbazepine based on manufacturer’s labeling.[43]

Drug-Drug Interactions

There are numerous drug-drug interactions that clinicians must consider when prescribing carbamazepine as it significantly induces the hepatic cytochrome P450 isoenzyme 3A4 and to a lesser degree 1A2, 2C9/10, and 2D6, thus increasing the metabolism of many medications (eg, quetiapine, lurasidone).[46] Individuals taking oral contraceptives who receive carbamazepine should be counseled to use alternatives such as intrauterine devices or depot medroxyprogesterone acetate in addition to barrier methods of birth control.[72]

Carbamazepine is metabolized to an active 10,11-epoxide metabolite; thus, medications that inhibit 3A4 isoenzymes can result in carbamazepine toxicity (eg, valproate, diltiazem, fluconazole, ketoconazole, nefazodone,

verapamil).[46] Combining clozapine and carbamazepine is not recommended because of decreased clozapine concentrations and the possibility of bone marrow suppression with both agents.[46]

Dosing and Administration

During an acute manic episode in most hospitalized patients, carbamazepine can be started at 400 to 600 mg/day in divided doses with meals and increased by 200 mg/day every 2 to 4 days up to a usual range of 1,200 to 1,600 mg/day.[46] In outpatients, the initial dose of carbamazepine should be lower, and in all patients, the dose should be titrated gradually until response is achieved or there is evidence of toxicity. Conversely, some patients may require up to 1,600 to 1,800 mg/day.[46] Many patients are able to tolerate once-daily dosing of carbamazepine once their mood episode has stabilized. During the first month of therapy, serum concentrations of carbamazepine may be affected due to autoinduction of the cytochrome P450 3A4 isoenzyme.[46]

Carbamazepine serum levels are usually obtained every 1 to 2 weeks during the first 2 months and then every 6 to 12 months during maintenance therapy.[2,46] Trough serum levels should be drawn 10 to 12 hours after the dose at least 2 to 5 days after a dosage change.[46] Although there is no correlation between carbamazepine serum concentrations and degree of mania or depressive symptom response, most clinicians attempt to maintain levels between 6 and 10 mcg/mL (mg/L; 25 and 42 µmol/L). However, some treatment-resistant patients can require serum concentrations of 12 to 14 mcg/mL (mg/L; 51-59 µmol/L). Recommended baseline and routine laboratory tests for carbamazepine are listed in Table 89-6.

Oxcarbazepine

There are currently less data supporting the use of oxcarbazepine than carbamazepine in the treatment of bipolar disorder. Guidelines typically recommend oxcarbazepine as a third-line treatment option for bipolar mania, and it is not recommended for the treatment of bipolar depression.[2]

Adverse Effects

Severe and sometimes life-threatening dermatologic reactions (eg, Stevens–Johnson syndrome) have been reported; therefore, oxcarbazepine should be discontinued at the first sign of a skin reaction.[43] Risk of this adverse effect may be greater in patients with specific genetic markers similar to carbamazepine. Other adverse effects may include impaired cognitive or psychomotor performance, somnolence or fatigue, and coordination difficulties.[43] Incidence of hyponatremia with oxcarbazepine is greater than that seen with carbamazepine, ranging from 0.14% to 73.3% versus 4.8% to 31.3%, respectively, in clinical studies depending on study design and serum sodium cut offs.[74] An in-depth discussion of adverse effects can be found in Chapter 75, “Epilepsy.”

Drug-Drug Interactions

Oxcarbazepine, a cytochrome P450 2C19 enzyme inhibitor and a 3A4/5 enzyme inducer, has the potential for causing drug interactions.[43] It induces the metabolism of oral contraceptives; thus, alternative contraceptive measures are required.[72] Additional drug interactions can be found in Chapter 75.

Dosing and Administration

Initial dosing usually follows that of epilepsy at 150 to 300 mg twice daily, with daily doses being increased by 300 to 600 mg every 3 to 6 days up to 1,200 mg/day in divided doses (with or without food).[43]

Lamotrigine

Lamotrigine is effective for the maintenance treatment of bipolar I disorder in adult patients.[2,22] Doses of 200 mg/day are more effective than lower doses, and there are no advantages to using 400 mg/day.[75] Lamotrigine has mood-stabilizing effects; it may have augmenting properties when combined with lithium or valproate and have low rates of switching patients to mania.[2] There are case reports of possible lamotrigine-induced mania when added to lithium, carbamazepine, and valproate.[76] In each of these cases, the patients had depressive mood symptoms or rapid mood changes requiring additional therapy.[76] Although lamotrigine is not effective for acute mania when compared with standard mood stabilizers, it may be beneficial as maintenance therapy of treatment-resistant bipolar I and II disorders.[2] It may also be effective for acute bipolar depression[2,77] and is most effective for the prevention of bipolar depression; therefore, clinically, it is often used in the treatment of patients with bipolar II.

Adverse Effects

Common adverse effects include headache, nausea, dizziness, ataxia, diplopia, drowsiness, tremor, rash, and pruritus.[44] Approximately 10% of individuals treated with lamotrigine will develop a non-serious rash.[2] Although most rashes are self-limiting and resolve with continued treatment, some progress to life-threatening conditions such as Stevens–Johnson syndrome. The incidence of rash is greatest with co-administration of valproate, with higher than recommended initial doses, and with rapid dose escalation.[2,44] Patients should be warned about the rash and the need for discontinuing lamotrigine and seeking medical attention if the rash is diffuse, involves mucosal membranes, and is accompanied by a fever or sore throat. For an in-depth discussion of the adverse effects of lamotrigine, see Chapter 75.

Drug-Drug Interactions

Valproate decreases the clearance of lamotrigine (ie, more than doubles the half-life), and lamotrigine must be administered at a reduced dosage of approximately half the standard dose.[44] For an in-depth discussion of drug-drug interactions with lamotrigine, see Chapter 75.

Dosing and Administration

For the maintenance treatment of bipolar disorder, the usual dosage range of lamotrigine is 50 to 300 mg/day. The target dose is generally 200 mg/day (100 mg/day in combination with valproate and 400 mg/day in combination with carbamazepine).[44] For patients not taking medications that affect lamotrigine clearance, the dose is 25 mg/day for the first 2 weeks of therapy, 50 mg/day for weeks 3 and 4, 100 mg/day for week 5, and 200 mg/day for week 6 and beyond.[44] Patients who stop lamotrigine therapy for more than a few days should be restarted on a low dose and titrated every 2 weeks back to their maintenance dose.[44]

Antipsychotics

FGAs and SGAs such as aripiprazole, asenapine, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone are effective as monotherapy or adjunctive therapy in the treatment of acute mania.[2] Controlled studies in acute mania with lithium or valproate plus an antipsychotic suggest greater efficacy with combination therapies compared to these agents alone.[2,22] The FGAs (eg, chlorpromazine and haloperidol) are effective in acute mania, particularly those with psychosis and psychomotor agitation,[2,22] while the SGAs have demonstrated similar efficacy for the treatment of acute mania associated with agitation, aggression, and psychosis.[2]

Treating acute bipolar depression is challenging, and some antipsychotics may play a useful role. Multiple large randomized controlled trials support the use of quetiapine and lurasidone as a monotherapy and adjunctive treatment options for bipolar depression.[2] Data also support the use of combined fluoxetine/olanzapine in treating bipolar depression.[2] Newer SGAs, cariprazine and lumateperone, have also gained FDA approval for bipolar depression (monotherapy for bipolar I, monotherapy or adjunct for bipolar I and bipolar II, respectively).

Oral aripiprazole, oral olanzapine, and sublingual asenapine are effective and FDA approved as monotherapy options for maintenance treatment in bipolar disorder.[2,47] Additionally, long-acting injectable SGAs, risperidone long-acting and aripiprazole extended release are also FDA approved for maintenance treatment. Long-acting injectable FGAs haloperidol decanoate and fluphenazine decanoate can have a place in maintenance treatment of bipolar disorder for patients who are non-adherent or treatment-resistant.[2] Clozapine adjunct and monotherapy has acute and long-term mood-stabilizing effects in refractory bipolar disorder but requires regular white blood cell monitoring for agranulocytosis.[2] The long-term safety of antipsychotics as monotherapy or as adjunctive therapy for bipolar maintenance treatment should be evaluated with ongoing assessment of utility.[2] Refer to Table 89-5 for antipsychotic specific indications. Metabolic syndrome is comorbid in 20%-65% of patients with bipolar disorder; therefore, the risks versus benefits must be weighed due to the long-term metabolic and endocrine adverse effects (eg, weight gain, type 2 diabetes, hyperlipidemia, hyperprolactinemia) in addition to tardive dyskinesia that antipsychotics may cause.[2,78]

Adverse Effects

A summary of adverse effects for antipsychotics can be found in Chapter 87, "Schizophrenia."

Drug-Drug Interactions

A summary of drug interactions with antipsychotics can be found in Chapter 87.

Dosing and Administration

For acute mania, higher initial doses of antipsychotics may be required (eg, olanzapine 20 mg/day in hospitalized patients). Once the acute mania is controlled (usually within 7-28 days), the antipsychotic can be gradually tapered and discontinued, and the patient maintained on the mood stabilizer monotherapy as appropriate.

Monitoring

7 Recommendations for baseline and routine laboratory testing for patients receiving antipsychotics are found in Table 89-6.

Alternative Medication Treatments

8 Some patients can be stabilized on one mood stabilizer, but others may require combination therapies or adjunctive agents during an acute mood episode. If possible, adjunctive agents should be tapered and discontinued when the acute mood episode remits and the patient is stabilized.

Benzodiazepines

Benzodiazepines such as clonazepam and lorazepam may be used as an alternative to or in combination with antipsychotics when patients are experiencing acute mania, agitation, anxiety, panic, and insomnia, or cannot take mood stabilizers (eg, during the first trimester of pregnancy).[2] Risk versus benefit should be carefully weighed in patients with a history of substance use disorders and/or acute risk for suicide.[2] Lorazepam is available for intramuscular injection and is useful in the acute management of agitation. Benzodiazepines cause minimal adverse effects compared with antipsychotics, and at higher doses, rapidly reduce symptoms in patients experiencing agitation. They can cause CNS depression, sedation, cognitive and motor impairment, dependence, and withdrawal reactions. When no longer required, benzodiazepines should be gradually tapered and discontinued to avoid withdrawal symptoms.

Antidepressants

For many years, antidepressants were recommended as adjunctive therapy for acute bipolar depression. Data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) suggest that adjunctive antidepressants may be no better than placebo for acute bipolar depression when combined with mood stabilizers.[79] A meta-analysis of six trials identified a small treatment effect on clinician-rated depressive symptoms when antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and bupropion were added to lithium, antiseizure drugs, or SGAs.[2,80] The concern of mood switching (ie, rapidly switching from depression to mania or hypomania) with the use of antidepressants is valid, although not common. Data show that the rate of mood switch with dual-acting agents (eg, TCAs or venlafaxine) is higher, and thus, these agents should be used with caution.[81] Additionally, the type of bipolar disorder may play a role in increased risk of mood switching, in that patients with bipolar I may carry a greater risk.[81] Controversy exists concerning the use of antidepressants, and many clinicians and treatment guidelines consider them to be second or third line in treating acute bipolar depression and should be avoided or used with extreme caution in patients with a history of antidepressant-induced mania/hypomania, mixed features, or recent rapid cycling.[2] Generally before initiating therapy with an antidepressant, it is important to ensure that the patient is on a therapeutic dosage or serum level of a primary mood stabilizer (eg, lithium, antiseizure medications, or antipsychotics).[2] Patients who have a history of mania after a depressive episode should be treated cautiously with antidepressants.[22] For more information, see Chapter 88 for comparisons among antidepressants.

Special Populations

The approach for treating bipolar disorder in special populations can vary among clinicians. Patients with comorbid medical conditions or concomitant substance use, those older than 65 or younger than 18 years, and pregnant individuals can require different treatment approaches.

Bipolar Disorder in Pregnancy

Comprehensive management during pregnancy is important to decrease the risk of birth defects, perinatal complications and mortality, preterm birth, low birth weight, low Apgar scores, and adverse neurodevelopmental effects.[2,82] Pharmacotherapy during pregnancy is complicated, and the risk-to-benefit ratio must be weighed. Clinicians should always use the lowest effective dose of any medication during pregnancy. Monotherapy should also be considered in order to decrease the risk to the pregnant individual and child. Contraception and pre-conception counseling should be a part of the patient education plan for individuals of child-bearing age diagnosed with bipolar disorder, who are able to become pregnant.[2] Education should include information regarding the risk of medications for the fetus, the impact of pregnancy on bipolar illness and vice versa. Additionally, consideration into contraceptive methods should take into account that antiseizure drugs such as carbamazepine and lamotrigine may have pharmacokinetic interactions with oral contraceptives.[2]

When lithium is given during the first trimester, the prevalence of Ebstein's anomaly is estimated between 1 and 10:1,000 and the risk of neural tube defects is 13:1,000.[82] Though newer data may suggest that the absolute risk of cardiac abnormalities may be small, lithium use is generally not recommended in the first trimester of pregnancy unless the benefit outweighs the risk.[2,83,84] Lithium freely crosses the placenta and is found in equal concentrations in the fetal and pregnant person's blood.[42] When lithium is used during pregnancy, it should be tapered down to the lowest effective dose necessary to decrease the risk of relapse. Lithium can cause perinatal complications in the infant such as hypotonia, jaundice, cyanosis, and lethargy.[82] Dose adjustments and close monitoring of serum levels will be needed due to changes in glomerular filtration rates and renal perfusion rates during pregnancy and immediately after delivery.[57,82] Milk concentrations of lithium range from 30% to 50% of the parent's serum concentration, and serum concentrations in the nursing infant are 10% to 50% of the adult's; thus, nursing is usually discouraged.[42,57]

Neural tube defects cause the most concern for clinicians treating pregnant patients during their first trimester. Data from the North American Antiepileptic Drug Pregnancy Registry show the risk of neural tube defects is about 0.12% for non-exposed babies.[85] Carbamazepine's risk of neural tube defects is estimated to be 3%.[85] Carbamazepine is excreted in breast milk with a milk-to-plasma ratio of ~0.4.[46] Craniofacial abnormalities,

developmental delays, microcephaly, and other abnormalities are also of concern when using antiseizure drugs. For pregnant patients treated with lamotrigine, the risk of neural tube defects is estimated to be 2%, but data for lamotrigine are limited compared with those for some older antiseizure drugs.[85] If the pregnant individual requires lamotrigine while nursing, infants should be monitored as infant concentrations can reflect 18% to 50% of the parent's serum concentration.[86,87] Valproate is usually not recommended during the first trimester of pregnancy because the risk of neural tube defects is estimated to be 4%.[85] Australian registry data in patients with epilepsy show dose-related teratogenicity with doses greater than 1,100 mg/day of valproate.[88] Additionally, data from the North American Antiepileptic Drug Pregnancy Registry showed that the median daily dose for first trimester exposure in babies born without malformations was 750 mg.[85] Fetal valproate syndrome is characterized by abnormalities such as facial clefts, cardiac and limb defects, and abnormal facial features.[86] The risks versus benefits of using valproate during pregnancy must be discussed with the patient.[2] Administration of folate can reduce the risk of neural tube defects. Individuals of childbearing age, able to become pregnant receiving valproate and those currently pregnant should receive folic acid supplementation; however, there is not a consensus on the recommended folic acid dose to use. Valproate is excreted into human milk in low concentrations and is considered to be compatible with nursing.[45] One case report of thrombocytopenia and anemia from valproate exposure has been reported in a nursing infant.[45] If the nursing parent receives valproate, the infant should have identical laboratory monitoring.

Caution should be used when prescribing antipsychotics during pregnancy. FGAs have been prescribed for many years in pregnancy and data show little teratogenic risk, but the data are not without question.[89] Data on the SGAs are limited, and clinicians should consider the potential risk of gestational diabetes.89 Extrapyramidal symptoms, neonatal withdrawal, and sedation should also be considered when using both FGAs and SGAs during the third trimester of pregnancy.[89] There is still a paucity of human data with antipsychotics, and therefore, risk-to-benefit ratio must be weighed.

Child and Adolescent Bipolar Disorder

Approximately one-third to two-thirds of patients diagnosed with bipolar disorder experience their first episode as a child or adolescent; however, there are few controlled studies in this population.[2] Little is known about the long-term efficacy and safety of specific agents or combination therapies in this population.[90] Lithium is the only medication approved as a mood stabilizer for children and adolescents and its efficacy in pediatric manic or mixed states has been documented in one double-blind placebo-controlled trial as well as an open-label trial.[90] Age restrictions vary by formulation, with immediate-release lithium being approved in children age 7 years and older for acute manic or mixed episodes and maintenance treatment, and extended-release being approved in children aged 12 years and older for acute manic and mixed episodes.[42] Valproate and carbamazepine are utilized in pediatric patients based on experience in adults.[2,90]

Aripiprazole and risperidone are FDA-approved for bipolar mania or mixed states in patients aged 10 to 17 years.[90] Quetiapine and quetiapine XR are approved as monotherapy or adjunct to lithium or divalproex in patients aged 10 to 17 years during a manic or mixed episode, but did not show efficacy in two double-blind, placebo-controlled studies in children and adolescents with bipolar depression.[2,90] Olanzapine is approved for use in patients with manic or mixed episodes aged 13 to 17 years as well as for monotherapy maintenance treatment in this subset of patients.[67] Ziprasidone has supporting data for its use in pediatric acute mania but does not have FDA approval.[6] Lurasidone's approval includes monotherapy treatment of bipolar depression in children 10 years of age and older.[91] Long-term data are still needed and recommendations on the treatment of pediatric bipolar depression and maintenance treatment are lacking due to insufficient data.[2] Additionally, children and adolescents treated with SGAs are more susceptible to metabolic effects of these medications, requiring close attention to diet and physical exercise.[2]

Bipolar Disorder Management in Individuals with Comorbidities

Patients with bipolar illness are more likely to have medical comorbidities than the general population complicating the management of bipolar disorder in older adults who average three to four medical comorbidities (eg, hypertension, diabetes).[2] Older adults may be more susceptible to mood stabilizer and antipsychotic adverse effects. Anticholinergic burden of medications should be considered when prescribing.[2] Specific for lithium and aging, reductions in renal clearance may significantly increase the elimination half-life in older patients requiring more frequent renal monitoring.[42] The elimination of valproate has been reported to also decrease with age and has been associated with motor side effects and metabolic effects in older patients.[2,45] The efficacy and tolerability of lithium and divalproex sodium for acute manic, hypomanic, or mixed episodes in patients age 60 years and older have been studied in one randomized double-blind trial.[92] Both medications were efficacious at serum concentrations between 0.8 and 0.99 mEq/L (mmol/L) for lithium and 80 to 99 mcg/mL (mg/L; 555-686 µmol/L) for divalproex, though greater reduction in manic symptoms was seen with lithium at the expense of tremor.[92]

EVALUATION OF THERAPEUTIC OUTCOMES

The establishment and maintenance of a therapeutic alliance between the patient and clinician is essential in monitoring a patient's psychiatric status and safety; enhancing treatment adherence; promoting good nutrition, sleep, and exercise; identifying stressors; recognizing new mood episodes; and minimizing adverse reactions and drug interactions.[2] Patients who have a partial response or non-response to established bipolar therapies should be reassessed for an accurate diagnosis, concomitant medical or psychiatric conditions, adherence with treatment (including serum levels if appropriate), and medications or substances that exacerbate mood symptoms. Non-adherence to medication treatment, delusional symptoms, alcohol or substance use, rapid cycling, or mixed states are often associated with poorer treatment outcomes.

CONCLUSION

The diagnosis and treatment of bipolar disorder can be complicated. Once an accurate diagnosis is made, clinicians must collaborate with patients and follow the patient-centered model to select the best treatment regimen. Clinicians must educate patients to be diligent in self-monitoring of their disease and the reporting of medications adverse effects. Adherence with medications is a key component in treatment. Clinicians must realize that there are various options for treating each phase of bipolar disorder and selection of the correct medication is essential to achieve optimal patient outcomes.

ABBREVIATIONS

5-HT	serotonin
ANK3	Ankyrin 3
APA	American Psychiatric Association
BMI	body mass index
CACNA1C	Calcium Voltage-Gated Channel Subunit Alpha1 C
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBC	complete blood count
CBT	cognitive behavioral therapy
CNS	central nervous system
CPIC	Clinical Pharmacogenomic Implementation Consortium
DA	dopamine
DI	diabetes insipidus
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ECG	electrocardiogram
ECT	electroconvulsive therapy
FDA	Food and Drug Administration
FGAs	first-generation antipsychotics
GI	gastrointestinal
HAM-D or HDRS	Hamilton Depression Rating Scale
HLA	human leukocyte antigen
ISBD	International Society for Bipolar Disorders
LFTs	liver function tests
LSD	lysergic acid diethylamide
MAOI	monoamine oxidase inhibitor
NE	norepinephrine
PCP	phencyclidine
PHQ-9	Patient Health Questionnaire 9
PMDD	premenstrual dysphoric disorder
Scr	serum creatinine
SGAs	second-generation antipsychotics
SSRI	selective serotonin reuptake inhibitor
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
TCA	tricyclic antidepressant
TSH	thyroid stimulating hormone
UDS	urine drug screen
WFSBP	World Federation of Societies of Biological Psychiatry
YMRS	Young Mania Rating Scale

REFERENCES

1. American Psychiatric Association. Available at: http://dsm.psychiatryonline.org/book.aspx?bookid=556. DSM-5 Task Force Diagnostic and Statistical Manual of Mental Disorders DSM-5: American Psychiatric Association; 2013. http://dsmpsychiatryonlineorg/book.aspx?bookid=556.

2. Yatham LN, Kennedy SH, Parikh SV. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 2018;20(2):97–170. Epub 2018/03/15. doi: 10.1111/bdi.12609. PubMed PMID: 29536616; PubMed Central PMCID: PMCPMC5947163.

3. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry* 2011;68(3):241–51. Epub 2011/03/09. doi: 10.1001/archgenpsychiatry.2011.12. PubMed PMID: 21383262; PubMed Central PMCID: PMCPMC3486639.

4. Carvalho AF, Firth J, Vieta E. Bipolar disorder. *N Engl J Med.* 2020;383(1):58–66. Epub 2020/07/02. doi: 10.1056/NEJMra1906193. PubMed PMID: 32609982.

5. Sole E, Garriga M, Valenti M, et al. Mixed features in bipolar disorder. *CNS Spectr.* 2017;22(2):134–40. Epub 2016/12/30. doi: 10.1017/S1092852916000869. PubMed PMID: 28031070.

6. Harrison PJ, Geddes JR, Tunbridge EM. The emerging neurobiology of bipolar disorder. *Trends Neurosci.* 2018;41(1):18–30. Epub 2017/11/25. doi: 10.1016/j.tins.2017.10.006. PubMed PMID: 29169634; PubMed Central PMCID: PMCPMC5755726.

7. Craddock N, Sklar P. Genetics of bipolar disorder. *Lancet*. 2013;381(9878):1654–62. Epub 2013/05/15. doi: 10.1016/s0140-6736(13)60855-7. PubMed PMID: 23663951.

9. Acuff HE, Versace A, Bertocci MA, et al. Association of neuroimaging measures of emotion processing and regulation neural circuitries with symptoms of bipolar disorder in offspring at risk for bipolar disorder. *JAMA Psychiatry* 2018;75(12):1241–51. Epub 2018/09/08. doi: 10.1001/jamapsychiatry.2018.2318. PubMed PMID: 30193355; PubMed Central PMCID: PMCPMC6528787.

8. Charney AW, Ruderfer DM, Stahl EA, et al. Evidence for genetic heterogeneity between clinical subtypes of bipolar disorder. *Transl Psychiatry* 2017;7(1):e993. Epub 2017/01/11. doi: 10.1038/tp.2016.242. PubMed PMID: 28072414; PubMed Central PMCID: PMCPMC5545718.

10. Aldinger F, Schulze TG. Environmental factors, life events, and trauma in the course of bipolar disorder. *Psychiatry Clin Neurosci.* 2017;71(1):6–17. Epub 2016/08/09. doi: 10.1111/pcn.12433. PubMed PMID: 27500795; PubMed Central PMCID: PMCPMC7167807.

11. Takaesu Y. Circadian rhythm in bipolar disorder: a review of the literature. *Psychiatry Clin Neurosci.* 2018;72(9):673–82. Epub 2018/06/06. doi: 10.1111/pcn.12688. PubMed PMID: 29869403.

12. Tondo L, Vazquez GH, Baldessarini RJ. Depression and mania in bipolar disorder. *Curr Neuropharmacol.* 2017;15(3):353–8. Epub 2017/05/16. doi: 10.2174/1570159X14666160606210811. PubMed PMID: 28503106; PubMed Central PMCID: PMCPMC5405618.

13. Ceide ME, Rosenberg PB. Brief manic episode after rituximab treatment of limbic encephalitis. *J Neuropsychiatry Clin Neurosci.* 2011;23(4):E8. Epub 2012/01/11. doi: 10.1176/jnp.23.4.jnpe8. PubMed PMID: 22231352.

14. Dias RS, Lafer B, Russo C, et al. Longitudinal follow-up of bipolar disorder in women with premenstrual exacerbation: findings from STEP-BD. *Am J Psychiatry* 2011;168(4):386–94. Epub 2011/02/18. doi: 10.1176/appi.ajp.2010.09121816. PubMed PMID: 21324951.

15. Goldsmith M, Singh M, Chang K. Antidepressants and psychostimulants in pediatric populations: is there an association with mania? *Paediatr Drugs*. 2011;13(4):225–43. Epub 2011/06/23. doi: 10.2165/11591660-000000000-00000. PubMed PMID: 21692547; PubMed Central PMCID: PMCPMC3394932.

16. Habek M, Brinar M, Brinar VV, et al. Psychiatric manifestations of multiple sclerosis and acute disseminated encephalomyelitis. *Clin Neurol Neurosurg.* 2006;108(3):290–4. Epub 2005/12/21. doi: 10.1016/j.clineuro.2005.11.024. PubMed PMID: 16364539.

17. Navinés R, Castellví P, Solà R, et al. Peginterferon- and ribavirin-induced bipolar episode successfully treated with lamotrigine without discontinuation of antiviral therapy. *Gen Hosp Psychiatry* 2008;30(4):387–9. Epub 2008/07/01. doi: 10.1016/j.genhosppsych.2007.12.010. PubMed PMID: 18585548.

18. Plante DT, Winkelman JW. Sleep disturbance in bipolar disorder: therapeutic implications. *Am J Psychiatry* 2008;165(7):830–43. Epub 2008/05/17. doi: 10.1176/appi.ajp.2008.08010077. PubMed PMID: 18483132.

19. Santos CO, Caeiro L, Ferro JM, et al. Mania and stroke: a systematic review. *Cerebrovasc Dis.* 2011;32(1):11–21. Epub 2011/05/18. doi: 10.1159/000327032. PubMed PMID: 21576938.

20. Spiegel DR, Weller AL, Pennell K, et al. The successful treatment of mania due to acquired immunodeficiency syndrome using ziprasidone: a case series. *J Neuropsychiatry Clin Neurosci.* 2010;22(1):111–4. Epub 2010/02/18. doi: 10.1176/jnp.2010.22.1.111. PubMed PMID: 20160218.

21. Valenti M, Pacchiarotti I, Bonnin CM, et al. Risk factors for antidepressant-related switch to mania. *J Clin Psychiatry* 2012;73(2):e271–6. Epub 2012/03/10. doi: 10.4088/JCP.11m07166. PubMed PMID: 22401488.

22. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002;159(4 Suppl):1–50. Epub 2002/04/18. PubMed PMID: 11958165.

23. Brooks JO, 3rd, Hoblyn JC. Secondary mania in older adults. *Am J Psychiatry* 2005;162(11):2033–8. Epub 2005/11/03. doi: 10.1176/appi.ajp.162.11.2033. PubMed PMID: 16263839.

24. Sami M, Khan H, Nilforooshan R. Late onset mania as an organic syndrome: a review of case reports in the literature. *J Affect Disord.* 2015;188:226–31. Epub 2015/09/15. doi: 10.1016/j.jad.2015.08.027. PubMed PMID: 26368947.

25. National Collaborating Centre for Mental Health (UK). Bipolar Disorder: The NICE Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care (Updated 2020). 2014. (number 40)

26. Conus P, Macneil C, McGorry PD. Public health significance of bipolar disorder: implications for early intervention and prevention. *Bipolar Disord.* 2014;16(5):548–56. Epub 2013/10/17. doi: 10.1111/bdi.12137. PubMed PMID: 24127825.

27. Frías Á, Palma C, Farriols N. Comorbidity in pediatric bipolar disorder: prevalence, clinical impact, etiology and treatment. *J Affect Disord.* 2015;174:378–89. Epub 2014/12/30. doi: 10.1016/j.jad.2014.12.008. PubMed PMID: 25545605.

28. Joslyn C, Hawes DJ, Hunt C, et al. Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review. *Bipolar Disord.* 2016;18(5):389–403. Epub 2016/08/18. doi: 10.1111/bdi.12419. PubMed PMID: 27530107.

29. Vega P, Barbeito S, Ruiz de Azúa S, et al. Bipolar disorder differences between genders: special considerations for women. *Women's Health (Lond)*. 2011;7(6):663–74; quiz 75-6. Epub 2011/11/02. doi: 10.2217/whe.11.71. PubMed PMID: 22040208.

30. Kemner SM, Mesman E, Nolen WA, et al. The role of life events and psychological factors in the onset of first and recurrent mood episodes in bipolar offspring: results from the Dutch Bipolar Offspring Study. *Psychol Med.* 2015;45(12):2571–81. Epub 2015/04/14. doi: 10.1017/s0033291715000495. PubMed PMID: 25865058.

31. Kemner SM, van Haren NE, Bootsman F, et al. The influence of life events on first and recurrent admissions in bipolar disorder. *Int J Bipolar Disord.* 2015;3:6. Epub 2015/02/27. doi: 10.1186/s40345-015-0022-4. PubMed PMID: 25717427; PubMed Central PMCID: PMCPMC4339321.

32. Carvalho AF, Dimellis D, Gonda X, et al. Rapid cycling in bipolar disorder: a systematic review. *J Clin Psychiatry* 2014;75(6):e578–86. Epub 2014/07/09. doi: 10.4088/JCP.13r08905. PubMed PMID: 25004199.

33. Slyepchenko A, Frey BN, Lafer B, et al. Increased illness burden in women with comorbid bipolar and premenstrual dysphoric disorder: data from 1 099 women from STEP-BD study. *Acta Psychiatr Scand.* 2017;136(5):473–82. Epub 2017/08/29. doi: 10.1111/acps.12797. PubMed PMID: 28846801; PubMed Central PMCID: PMCPMC5630503.

34. Hunt GE, Malhi GS, Cleary M, et al. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990-2015: systematic review and meta-analysis. *J Affect Disord.* 2016;206:331–49. Epub 2016/10/25. doi: 10.1016/j.jad.2016.07.011. PubMed PMID: 27476137.

35. Hunt GE, Malhi GS, Cleary M, et al. Comorbidity of bipolar and substance use disorders in national surveys of general populations, 1990-2015: systematic review and meta-analysis. *J Affect Disord.* 2016;206:321–30. Epub 2016/10/25. doi: 10.1016/j.jad.2016.06.051. PubMed PMID: 27426694.

36. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. *J Clin Psychiatry* 2003;64(6):680–90; quiz 738-9. Epub 2003/06/26. doi: 10.4088/jcp.v64n0610. PubMed PMID: 12823083.

37. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry* 2015;72(4):334–41. Epub 2015/02/12. doi: 10.1001/jamapsychiatry.2014.2502. PubMed PMID: 25671328; PubMed Central PMCID: PMCPMC4461039.

38. Miller JN, Black DW. Bipolar disorder and suicide: a review. *Curr Psychiatry Rep.* 2020;22(2):6. Epub 2020/01/20. doi: 10.1007/s11920-020-1130-0. PubMed PMID: 31955273.

39. Jawad I, Watson S, Haddad PM, et al. Medication nonadherence in bipolar disorder: a narrative review. *Ther Adv Psychopharmacol.* 2018;8(12):349–63. Epub 2018/12/14. doi: 10.1177/2045125318804364. PubMed PMID: 30524703; PubMed Central PMCID: PMCPMC6278745.

40. Beyer JL, Payne ME. Nutrition and bipolar depression. *Psychiatr Clin North Am.* 2016;39(1):75–86. Epub 2016/02/16. doi: 10.1016/j.psc.2015.10.003. PubMed PMID: 26876319.

41. Bauer IE, Galvez JF, Hamilton JE, et al. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. *J Psychiatr Res.* 2016;74:1–7. Epub 2016/01/03. doi: 10.1016/j.jpsychires.2015.12.006. PubMed PMID: 26724541; PubMed Central PMCID: PMCPMC4744495.

42. Lexicomp Online. Lithium. Hudson, OH: Lexi-Comp, Inc.

43. Lexicomp Online. Oxcarbazepine. Hudson, OH: Lexi-Comp, Inc.

44. Lexicomp Online. Lamotrigine. Hudson, OH: Lexi-Comp, Inc.

45. Lexicomp Online. Valproic acid and derivatives. Hudson, OH: Lexi-Comp, Inc.

46. Lexicomp Online. Carbamazepine. Hudson, OH: Lexi-Comp, Inc.

47. Lexicomp Online. Lexi-Drugs. Hudson, OH: Lexi-Comp, Inc.

48. Buoli M, Serati M, Altamura AC. Is the combination of a mood stabilizer plus an antipsychotic more effective than mono-therapies in long-term treatment of bipolar disorder? A systematic review. *J Affect Disord.* 2014;152-154:12–8. Epub 2013/09/18. doi: 10.1016/j.jad.2013.08.024. PubMed PMID: 24041717.

49. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long-term treatment of mixed states in bipolar disorder. *World J Biol Psychiatry* 2018;19(1):2–58. Epub 2017/11/04. doi: 10.1080/15622975.2017.1384850. PubMed PMID: 29098925.

50. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *World J Biol Psychiatry* 2009;10(2):85–116. Epub 2009/04/07. doi: 10.1080/15622970902823202. PubMed PMID: 19347775.

51. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry* 2010;11(2):81–109. Epub 2010/02/13. doi: 10.3109/15622970903555881. PubMed PMID: 20148751.

52. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *World J Biol Psychiatry* 2013;14(3):154–219. Epub 2013/03/14. doi: 10.3109/15622975.2013.770551. PubMed PMID: 23480132.

53. Malhi GS, Tanious M, Das P, et al. Potential mechanisms of action of lithium in bipolar disorder. *Current Understanding* 2013;27(2):135–53. Epub 2013/02/02. doi: 10.1007/s40263-013-0039-0. PubMed PMID: 23371914 CNS Drugs.

54. Won E, Kim YK. An oldie but goodie: lithium in the treatment of bipolar disorder through neuroprotective and neurotrophic mechanisms. *Int J Mol Sci.* 2017;18(12). Epub 2017/12/14. doi: 10.3390/ijms18122679. PubMed PMID: 29232923; PubMed Central PMCID: PMCPMC5751281.

55. Curran G, Ravindran A. Lithium for bipolar disorder: a review of the recent literature. *Expert Rev Neurother.* 2014;14(9):1079–98. Epub 2014/08/19. doi: 10.1586/14737175.2014.947965. PubMed PMID: 25130062.

56. Smith KA, Cipriani A. Lithium and suicide in mood disorders: updated meta-review of the scientific literature. *Bipolar Disord.* 2017;19(7):575–86. Epub 2017/09/13. doi: 10.1111/bdi.12543. PubMed PMID: 28895269.

57. Grandjean EM, Aubry JM. Lithium: updated human knowledge using an evidence-based approach: part III: clinical safety. *CNS Drugs*. 2009;23(5):397–418. Epub 2009/05/21. doi: 10.2165/00023210-200923050-00004. PubMed PMID: 19453201.

58. Gong R, Wang P, Dworkin L. What we need to know about the effect of lithium on the kidney. *Am J Physiol Renal Physiol.* 2016;311(6):F1168–F71. Epub 2016/04/29. doi: 10.1152/ajprenal.00145.2016. PubMed PMID: 27122541; PubMed Central PMCID: PMCPMC5210210.

59. Mehta N, Vannozzi R. Lithium-induced electrocardiographic changes: a complete review. *Clin Cardiol.* 2017;40(12):1363–7. Epub 2017/12/17. doi: 10.1002/clc.22822. PubMed PMID: 29247520; PubMed Central PMCID: PMCPMC6490621.

60. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. *Int J Bipolar Disord.* 2016;4(1):27. Epub 2016/12/03. doi: 10.1186/s40345-016-0068-y. PubMed PMID: 27900734; PubMed Central PMCID: PMCPMC5164879.

61. Heath LJ, Billups SJ, Gaughan KM, et al. Risk factors for utilization of acute care services for lithium toxicity. *Psychiatr Serv.* 2018;69(6):671–6. Epub 2018/04/03. doi: 10.1176/appi.ps.201700346. PubMed PMID: 29606078.

62. Hedya S, Avula A, Swoboda H. *Lithium Toxicity*. Treasure Island, FL: StatPearls Publishing.; 2021.

63. Baird-Gunning J, Lea-Henry T, Hoegberg LCG, et al. Lithium poisoning. *J Intensive Care Med.* 2017;32(4):249–63. Epub 2016/08/16. doi: 10.1177/0885066616651582. PubMed PMID: 27516079.

64. Bendz H, Schon S, Attman PO, et al. Renal failure occurs in chronic lithium treatment but is uncommon. *Kidney Int.* 2010;77(3):219–24. Epub 2009/11/27. doi: 10.1038/ki.2009.433. PubMed PMID: 19940841.

65. Malhi GS, Tanious M. Optimal frequency of lithium administration in the treatment of bipolar disorder: clinical and dosing considerations. *CNS Drugs*. 2011;25(4):289–98. Epub 2011/03/24. doi: 10.2165/11586970-000000000-00000. PubMed PMID: 21425882.

66. American Diabetes A, American Psychiatric A, American Association of Clinical E. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry* 2004;65(2):267–72. Epub 2004/03/09. doi: 10.4088/jcp.v65n0219. PubMed PMID: 15003083.

67. Lexicomp Online. Olanzapine. Hudson, OH: Lexi-Comp, Inc.

68. Jochim J, Rifkin-Zybutz RP, Geddes J, et al. Valproate for acute mania. *Cochrane Database Syst Rev.* 2019;10:CD004052. Epub 2019/10/18. doi: 10.1002/14651858.CD004052.pub2. PubMed PMID: 31621892; PubMed Central PMCID: PMCPMC6953329.

69. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder. *Am J Psychiatry* 1994;151(12 Suppl):1–36. Epub 1994/12/01. doi: 10.1176/ajp.151.12.1. PubMed PMID: 7977902.

70. Allen MH, Hirschfeld RM, Wozniak PJ, et al. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. *Am J Psychiatry* 2006;163(2):272–5. Epub 2006/02/02. doi: 10.1176/appi.ajp.163.2.272. PubMed PMID: 16449481.

71. Al Khalili Y, Sekhon S, Jain S. Carbamazepine Toxicity. 2021. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.

72. Tepper NK CK, Cox S, Whiteman MK, et al., US Medical Eligibility Criteria for Contraceptive Use; US Medical Eligibility Criteria for Contraceptive Use. 2016; http://dx.doi.org/10.15585/mmwr.rr6503a1 65:1104.

73. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disord.* 2014;16(4):409–31. Epub 2014/12/18. doi: 10.1684/epd.2014.0714. PubMed PMID: 25515681.

74. Lu X, Wang X. Hyponatremia induced by antiepileptic drugs in patients with epilepsy. *Expert Opin Drug Saf.* 2017;16(1):77–87. Epub 2016/10/16. doi: 10.1080/14740338.2017.1248399. PubMed PMID: 27737595.

75. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 2003;64(9):1013–24. Epub 2003/11/25. doi: 10.4088/jcp.v64n0906. PubMed PMID: 14628976.

76. Raskin S, Teitelbaum A, Zislin J, et al. Adjunctive lamotrigine as a possible mania inducer in bipolar patients. *Am J Psychiatry* 2006;163(1):159–60. Epub 2006/01/05. doi: 10.1176/appi.ajp.163.1.159-a. PubMed PMID: 16390907.

77. Calabrese JR, Huffman RF, White RL, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord.* 2008;10(2):323–33. Epub 2008/02/15. doi: 10.1111/j.1399-5618.2007.00500.x. PubMed PMID: 18271912.

78. de Almeida KM, Moreira CL, Lafer B. Metabolic syndrome and bipolar disorder: what should psychiatrists know? *CNS Neurosci Ther.* 2012;18(2):160–6. Epub 2011/11/11. doi: 10.1111/j.1755-5949.2011.00240.x. PubMed PMID: 22070636; PubMed Central PMCID: PMCPMC6493593.

79. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med.* 2007;356(17):1711–22. Epub 2007/03/30. doi: 10.1056/NEJMoa064135. PubMed PMID: 17392295.

80. McGirr A, Vöhringer PA, Ghaemi SN, et al. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. *The Lancet Psychiatry* 2016;3(12):1138–46. 10.1016/s2215-0366(16)30264-4.

81. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry* 2013;170(11):1249–62. Epub 2013/09/14. doi: 10.1176/appi.ajp.2013.13020185. PubMed PMID: 24030475; PubMed Central PMCID: PMCPMC4091043.

82. Gentile S. Lithium in pregnancy: the need to treat, the duty to ensure safety. *Expert Opin Drug Saf.* 2012;11(3):425–37. Epub 2012/03/10. doi: 10.1517/14740338.2012.670419. PubMed PMID: 22400907.

83. Patorno E, Huybrechts KF, Bateman BT, et al. Lithium use in pregnancy and the risk of cardiac malformations. *N Engl J Med.* 2017;376(23):2245–54. Epub 2017/06/08. doi: 10.1056/NEJMoa1612222. PubMed PMID: 28591541; PubMed Central PMCID: PMCPMC5667676.

84. Fornaro M, Maritan E, Ferranti R, et al. Lithium exposure during pregnancy and the postpartum period: a systematic review and meta-analysis of safety and efficacy outcomes. *Am J Psychiatry* 2020;177(1):76–92. Epub 2019/10/19. doi: 10.1176/appi.ajp.2019.19030228. PubMed PMID: 31623458.

85. Hernández-Díaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 2012;78(21):1692–9. Epub 2012/05/04. doi: 10.1212/WNL.0b013e3182574f39. PubMed PMID: 22551726.

86. Khan SJ, Fersh ME, Ernst C, et al. Bipolar disorder in pregnancy and postpartum: principles of management. *Curr Psychiatry Rep.* 2016;18(2):13. Epub 2016/01/20. doi: 10.1007/s11920-015-0658-x. PubMed PMID: 26781551.

87. LactMed. Lamotrigine. Bethesda, MD: National Library of Medicine; 2006.

88. Vajda FJ, Hitchcock A, Graham J, et al. The Australian Register of Antiepileptic Drugs in Pregnancy: the first 1002 pregnancies. *Aust N Z J Obstet Gynaecol.* 2007;47(6):468–74. Epub 2007/11/10. doi: 10.1111/j.1479-828X.2007.00781.x. PubMed PMID: 17991111.

89. Galbally M, Snellen M, Power J. Antipsychotic drugs in pregnancy: a review of their maternal and fetal effects. *Ther Adv Drug Saf.* 2014;5(2):100–9. Epub 2014/08/02. doi: 10.1177/2042098614522682. PubMed PMID: 25083265; PubMed Central PMCID: PMCPMC4110873.

90. Stepanova E, Findling RL. Psychopharmacology of bipolar disorders in children and adolescents. *Pediatr Clin North Am.* 2017;64(6):1209–22. Epub 2017/11/28. doi: 10.1016/j.pcl.2017.08.002. PubMed PMID: 29173781.

91. Lexicomp Online. Lurasidone. Hudson, OH: Lexi-Comp, Inc.

92. Young RC, Mulsant BH, Sajatovic M, et al. GERI-BD: A randomized double-blind controlled trial of lithium and divalproex in the treatment of mania in older patients with bipolar disorder. *Am J Psychiatry* 2017;174(11):1086–93. Epub 2017/11/02. doi: 10.1176/appi.ajp.2017.15050657. PubMed PMID: 29088928; PubMed Central PMCID: PMCPMC6214451.

SELF-ASSESSMENT QUESTIONS

1. The preferred treatment option for a 20-year-old patient with bipolar disorder who has severe liver disease is:
   A. Valproic acid
   B. Lithium
   C. Carbamazepine
   D. Oxcarbazepine
2. During the lag time for onset of action of lithium, an appropriate adjunctive medication for acute mania might include a medication from which of the following classes?
   A. Antihistamines
   B. Benzodiazepines
   C. Beta-blockers
   D. Antidepressants
3. Lamotrigine should be used for which phase of bipolar disorder?
   A. Acute mania
   B. Acute depression
   C. Maintenance
   D. Rapid cycling
4. If lamotrigine is initiated in a patient receiving valproic acid (VPA), the starting dose of lamotrigine should be:
   A. Lower than if started in a patient not receiving VPA
   B. Higher than if started in a patient not receiving VPA
   C. The same as in a patient not receiving VPA
   D. Lamotrigine is contraindicated in patients receiving VPA
5. Which of the following laboratory tests is needed prior to initiating therapy with valproic acid?
   A. Potassium level
   B. Liver function test
   C. Thyroid function test
   D. Magnesium level
6. Which adverse effect is more frequently associated with oxcarbazepine than carbamazepine?
   A. Ataxia
   B. Nausea and vomiting

C. Stevens–Johnson syndrome

D. Hyponatremia

7. All of the following are symptoms of acute mania *except*:

A. Grandiosity

B. Racing thoughts

C. Decreased appetite

D. Pressured speech

8. Antidepressants may be considered when treating a patient with bipolar disorder who is currently:

A. Depressed, with a history of treatment-resistant depression

B. Not depressed, but has a history of severe depression before each manic episode

C. Hypomanic, but has a history of severe depression

D. Manic, but has a history of severe depression after a manic episode

9. A diagnosis of bipolar I disorder comes only after a patient has a:

A. Manic episode

B. Hypomanic episode

C. Depressed episode

D. Both A and B

10. Antipsychotics could be used in a patient displaying which of the following symptoms?

A. Mania with psychotic features

B. Mania without psychotic features

C. Depression with psychotic features

D. All of the above.

11. A first-line treatment option in a patient with bipolar disorder current episode manic is:

A. Lithium

B. Carbamazepine

C. Lamotrigine

D. Oxcarbazepine

12. Which of the following medication lists would be appropriate for a patient who is currently experiencing a manic episode?

A. Lamotrigine, lorazepam, olanzapine

B. Carbamazepine, fluoxetine, olanzapine

C. Haloperidol, lorazepam, fluoxetine

D. Valproic Acid, lorazepam, olanzapine

13. Which medication has an FDA indication for the treatment of bipolar depression?

A. Olanzapine

B. Quetiapine

C. Risperidone

D. Ziprasidone

14. Which medication has an FDA indication for maintenance therapy in bipolar disorder?

A. Olanzapine

B. Quetiapine

C. Risperidone

D. Ziprasidone

15. Which of the following laboratory tests is needed prior to initiating lithium therapy?

A. Potassium level

B. Platelet count

C. Thyroid function test

D. Magnesium level

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Lithium is cleared renally so this would be the best option for this patient. The other medications listed are all hepatically metabolized. See "Lithium" section and Table 89-6.
2. **B.** Benzodiazepines are effective in helping treat and resolve symptoms of mania. Antidepressants would potentially make mania worse. Beta-blockers and antihistamines are not used in treating mania. See "Alternative Medication Treatments" section.
3. **C.** Lamotrigine has the best data to support its use in the maintenance phase of the illness. It is not helpful in mania and does not have data to support its use in rapid cycling. There is controversial data for its use in acute depression. See "Antiseizure Medications" section.
4. **A.** It is recommended to decrease the dose of lamotrigine by 50% when used in combination with valproic acid. See "Lamotrigine" section and Table 89-5.
5. **B.** It is important to make sure patients being initiated on valproic acid have good liver function since this medication is cleared by the liver. Thyroid function is not needed, nor are magnesium or potassium levels. See "Valproate Sidium and Valproic Acid" section and Table 89-6.
6. **D.** Clinically significant hyponatremia and SIADH may develop during use with oxcarbazepine. See "Oxcarbazepine" section and Table 89-5.
7. **C.** A change in appetite is not a symptom of mania. See "Clinical Presentation and Diagnosis" section and Table 89-1.
8. **A.** Antidepressants should not be used in patients with a recent history of mania. If antidepressants are used they should only be used while the patient is depressed. When used without depression present it increases the risk of a switch to mania. See "Alternative Medication Treatments" section.
9. **A.** Mania and hypomania are what indicate bipolar disorder. See "Clinical Presentation and Diagnosis" section and Table 89-1.
10. **D.** Antipsychotics can be used to resolve mania with and without psychotic features. Antipsychotics are also used to treat the psychosis associated with severe depression. See "Antipsychotics" section.
11. **A.** Lithium is a first-line treatment option for mania. Carbamazepine and Oxcarbazepine are 3rd line options. Lamotrigine is not effective in treating mania. See "Pharmacologic Therapy" section and Table 89-4.
12. **D.** Valproic Acid, lorazepam, and olanzapine would be appropriate for treating mania. Lamotrigine is not effective. Fluoxetine should not be used as it could make the mania worse. See "Pharmacologic Therapy" section and Table 89-4.
13. **B.** Quetiapine is FDA-approved as monotherapy for the treatment of bipolar depression. See "Antipsychotics" section.
14. **A.** Olanzapine is approved by the FDA for monotherapy maintenance treatment. Risperidone Long Acting injection is also approved, but not oral therapy. See "Antipsychotics" Section.
15. **C.** Hypothyroidism can occur in patients taking lithium; therefore, it is important to have baseline values prior to initiation of therapy. See "Lithium" section and Table 89-6.