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Chapter 67: Bipolar Disorder

INTRODUCTION

- *Bipolar disorder* is a common, lifelong, often severe cyclic mood disorder characterized by recurrent fluctuations in mood, energy, and behavior. The mania or hypomania is not substance-related or caused by other medical or psychiatric disorders.

PATHOPHYSIOLOGY

- **Table 67-1** lists medical conditions, medications, and treatments that may induce mania.
- Bipolar disorder is influenced by developmental, genetic, neurobiological, and psychological factors. Multiple gene loci are likely involved in the heredity of mood disorders.

TABLE 67-1

Secondary Causes of Mania

Medical conditions that induce mania

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

Medications or drugs that induce mania

- Alcohol intoxication
- Drug withdrawal states (alcohol, α_2-adrenergic agonists, antidepressants, barbiturates, benzodiazepines, opiates)
- Antidepressants (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 (LSD, PCP)
- Marijuana intoxication precipitates psychosis, paranoid thoughts, anxiety, and restlessness
- NE-augmenting agents (α_2-adrenergic antagonists, β-agonists, NE reuptake inhibitors)
- Steroids (anabolic, adrenocorticotropic hormone, corticosteroids)
- Thyroid preparations
- Xanthines (caffeine, theophylline)
- Nonprescription weight loss agents and decongestants (ephedra, pseudoephedrine)
- Herbal products (St. John's 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.

CLINICAL PRESENTATION

- Different types of episodes may occur sequentially with or without a period of normal mood (euthymia) between them. There can be mood fluctuations that continue for months or after one episode, and there can be years without recurrence of any type of mood episode.

DIAGNOSIS

- The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition classifies bipolar disorders into five subtypes:

  (1) Bipolar I disorder: At least one manic episode, which may have been preceded by and may be followed by hypomanic or major depressive episode(s).

  (2) Bipolar II disorder: At least one hypomanic episode and a current or past major depressive episode.

  (3) Cyclothymic disorder: Chronic fluctuations between subsyndromal depressive and hypomanic episodes.

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(4) Other specified bipolar and related disorder.

(5) Unspecified bipolar and related disorder.

- See **Table 67-2** for diagnostic criteria for major depressive episode, manic episode, and hypomanic episode.
- A medical, psychiatric, and medication history; physical examination; and laboratory testing are necessary to rule out organic causes of mania or depression.
- Delusions, hallucinations, and suicide attempts are more common in bipolar depression than in unipolar depression.
- Acute mania usually begins abruptly, and symptoms increase over several days. Bizarre behavior, hallucinations, and paranoid or grandiose delusions may occur. There is marked impairment in functioning. Manic episodes may be precipitated by stressors, sleep deprivation, antidepressants, central nervous system (CNS) stimulants, or bright light.
- In hypomanic episodes, there is no marked impairment in social or occupational functioning, no delusions, and no hallucinations. Some patients may be more productive than usual, but 5%–15% of patients may rapidly switch to a manic episode.

TABLE 67-2

Evaluation and Diagnosis of Mood Episodes

Diagnosis Episode	Impairment of Functioning or Need for Hospitalization[a]	*DSM-5* Criteria[b]
Major depressive	Yes	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 (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
Manic	Yes	At least 1-week period of abnormally and persistently elevated mood (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)
Hypomanic	No	At least 4 days of abnormally and persistently elevated mood (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)

[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, medications, drugs of abuse). Numerous specifiers are available to further characterize episodes (eg, with mixed features, with anxious distress, with rapid cycling, with melancholic features).

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- Childhood onset is associated with more mood episodes, rapid cycling, and comorbid psychiatric conditions.
- Rapid cyclers, 20% of patients with bipolar disorder, have four or more episodes per year (major depressive, manic, or hypomanic). Rapid cycling is associated with frequent and severe episodes of depression and a poorer long-term prognosis.
- Women are more likely to have depressive symptoms, older age of onset, better adherence, and thyroid abnormalities. Men may have more manic episodes and substance use.
- Suicide attempts occur in up to 50% of patients with bipolar disorder, and ~10%–19% of individuals with bipolar I disorder commit suicide. Patients with bipolar II disorder may have a higher rate of suicide attempts than bipolar I patients.

TREATMENT

- Goals of Treatment: (1) Eliminate mood episode with complete remission of symptoms (ie, acute treatment); (2) prevent recurrences or relapses of mood episodes (ie, continuation phase treatment); (3) return to baseline psychosocial functioning; (4) maximize adherence with therapy; (5) minimize adverse effects; (6) use medications with the best tolerability and fewest drug interactions; (7) minimize polypharmacy when possible; (8) treat comorbid substance use and abuse; (9) eliminate alcohol, marijuana, cocaine, amphetamines, and hallucinogens; (10) minimize nicotine use and stop caffeine intake at least 8 hours prior to bedtime; and (11) avoid stressors or substances that precipitate an acute episode.

General Approach

- **Table 67-3** shows an algorithmic approach to treating acute episodes including refractory episodes in adults.
- Treatment must be individualized because the clinical presentation, severity, and frequency of episodes vary widely among patients. Adherence to treatment is the most important factor in achieving goals.
- During acute episodes, medications can be added and then tapered once the patient is stabilized and euthymic.
- Patients with bipolar disorder should remain on a mood stabilizer (eg, lithium, valproate, or a second-generation antipsychotic [SGA]) lifelong.

TABLE 67-3

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

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<table>
<tr><th colspan="2">Acute Manic or Mixed Episode</th><th colspan="2">Acute Depressive Episode</th></tr>
<tr><td colspan="2">General Guidelines</td><td colspan="2">General Guidelines</td></tr>
<tr><td colspan="2">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 abuse
Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy</td><td colspan="2">Assess for secondary causes of depression (eg, alcohol or drug use)
Taper off antipsychotics, benzodiazepines, or sedative–hypnotic agents if possible
Treat substance abuse
Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy</td></tr>
<tr><th>Hypomania</th><th>Mania</th><th>Mild-to-Moderate Depressive Episode</th><th>Severe Depressive Episode</th></tr>
<tr><td>First, optimize current mood stabilizer if noncompliance is suspected OR initiate mood-stabilizing medication: lithium[a], valproate[a], carbamazepine[a], or SGAs
Consider adding a benzodiazepine (lorazepam or clonazepam) for short-term adjunctive treatment of agitation or insomnia if needed
Alternative medication treatment options: oxcarbazepine</td><td>First, optimize previously prescribed mood stabilizer or medication regimen if noncompliance suspected OR initiate new mood-stabilizing two- or three-drug combinations (lithium[a], valproate[a], or SGA) plus a benzodiazepine (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 medication treatment options: carbamazepine[a]; if patient does not respond or tolerate, consider oxcarbazepine</td><td>First, initiate and/or optimize mood-stabilizing medication: lithium[a], quetiapine, lurasidone
Alternative anticonvulsants: lamotrigine[c], valproate[a]; antipsychotics: fluoxetine/olanzapine combination</td><td>First, optimize current mood stabilizer if noncompliance is suspected OR initiate a new mood-stabilizing medication: lithium[a] or quetiapine or lurasidone
Alternative fluoxetine/olanzapine combination
If psychosis is present, initiate an antipsychotic in combination with above
Do not combine antipsychotics
Alternative anticonvulsants: lamotrigine[c], valproate[a]</td></tr>
<tr><td>Second, if response is inadequate, consider a two-drug combination:
Lithium[a] plus an anticonvulsant or an SGA
Anticonvulsant plus an anticonvulsant or SGA</td><td>Second, if response is inadequate, consider a three-drug combination:
Lithium[a] plus an anticonvulsant plus an antipsychotic
Anticonvulsant plus an anticonvulsant plus an antipsychotic
Third, if response is inadequate, consider ECT for mania with psychosis or catatonia[b], or add clozapine for treatment-refractory illness</td><td></td><td>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]</td></tr>
</table>

[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; valproate is preferred over lithium for mixed episodes and rapid cycling; lithium and/or lamotrigine is preferred over valproate for bipolar depression.

[b]ECT is used for severe mania or depression during pregnancy and for mixed episodes; prior to treatment, anticonvulsants, 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 of bipolar I disorder. 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).

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[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.

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

Nonpharmacologic Therapy

- Patients and family members should be educated about bipolar disorder (eg, symptoms, causes, and course) and treatment options.
- Nonpharmacologic approaches should address adequate nutrition, sleep, exercise, and stress reduction.
- Psychological interventions include cognitive behavioral therapy (CBT), interpersonal and social rhythm therapy, group psychoeducation, family focused therapy, and enhanced relapse prevention/individual psychoeducation.

Pharmacologic Therapy

- See **Table 67-4** for product and dosing information on medications for bipolar disorder.
- **Lithium, divalproex sodium (valproate), extended-release carbamazepine, aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone**, and **ziprasidone** are currently approved by the U.S. Food and Drug administration (FDA) for treatment of acute mania. Lithium, aripiprazole, olanzapine, intramuscular (IM) risperidone, and lamotrigine are approved for maintenance treatment.
- **Quetiapine** and **lurasidone** are the only FDA-approved monotherapy antipsychotics for bipolar depression.
- Combination therapies (see **Table 67-3**) can provide better acute response and long-term prevention of relapse and recurrence than monotherapy in some bipolar patients.
- Sources of useful guidelines include the Canadian Network for Mood and Anxiety Treatments (CANMAT), International Society for Bipolar Disorders (ISBD), and International Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP).

TABLE 67-4

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

Drug (Brand Name)	Initial Dosing	Usual Dosing; Special Population Dosing	Comments
Lithium salts			
Lithium carbonate (Eskalith[a,b]) (Eskalith CR) (Lithobid) Lithium citrate (Cibalith-S[a,b])	300 mg twice daily	900–2400 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 and 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 acute treatment of mania and for maintenance treatment
Anticonvulsants			
Divalproex sodium (Depakote[a]) (Depakote ER) Valproic acid[a] (Depakene) Valproate sodium (Depacon)	250–500 mg twice daily Loading dose of divalproex (20–30 mg/kg/day) can be given	750–3000 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 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. Increase dosage slowly (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

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Carbamazepine (Equetro[a]) (Tegretol) (Epitol) (Tegretol-XR) (Carbatrol)	200 mg twice daily	200–1800 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 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 Carbitrol capsules can be opened and contents sprinkled over food
Oxcarbazepine (Trileptal)	300 mg twice daily	300–1200 mg/day in two divided doses Titrate dosage based on clinical response Dose adjustment required with severe renal impairment	Use after patients have failed treatment with carbamazepine or have intolerable side effects May have fewer adverse effects and be better tolerated than carbamazepine
Atypical antipsychotics			
Aripiprazole (Abilify[a,b]) (Abilify Maintena[b])	10–15 mg daily	10–30 mg/day once daily	
Asenapine (Saphris[a])	5–10 mg twice daily sublingually	5–10 mg twice daily sublingually	
Cariprazine (Vraylar[a])	1.5 mg daily	3–6 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	0.5–6 mg/day once daily or in divided doses	
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	Use in combination with other medications (eg, antipsychotics, lithium, valproate) for acute treatment of mania or mixed episodes	

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	according to response and adverse effects	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 the table footnotes.

Lithium

- Lithium is a first-line agent for acute mania, acute bipolar depression, and maintenance treatment of bipolar I and II disorders.
- Lithium is rapidly absorbed, neither protein bound nor metabolized, and excreted unchanged in the urine and other body fluids.
- It may require 6–8 weeks to show antidepressant efficacy. It produces a prophylactic response in up to two-thirds of patients and reduces suicide risk.
- Abrupt discontinuation or noncompliance with lithium therapy can increase the risk of relapse.
- Initial GI and CNS side effects are often dose related and are worse at peak serum concentrations (1–2 hours postdose). Lowering the dose, taking doses with food, using extended-release products, and once-daily dosing at bedtime may help. Diarrhea can sometimes be improved by switching to a liquid formulation.
- A benign fine hand tremor occurs in many patients whereas a coarse hand tremor may be a sign of toxicity. The fine tremor may be treated by switching to a long-acting preparation, lowering the dose, or adding propranolol, 20–120 mg/day.
- Polydipsia with polyuria with or without nephrogenic diabetes insipidus (DI) can occur. About 30%–50% of patients develop nephrogenic DI soon after initiating lithium, and it persists in about 10%–25% of patients. It is typically reversible with discontinuation of lithium. Nocturia is common and is managed by changing to once-daily dosing at bedtime.
- Lithium reduces the kidneys' ability to concentrate urine and may cause a nephrogenic DI with low urine-specific gravity and low osmolality polyuria (urine volume >3 L/day). This may be treated with loop or thiazide diuretics. If a thiazide diuretic is used, lithium doses should be decreased by 50% and lithium and potassium levels monitored. Amiloride has weaker natriuretic effects and seems to have little effect on lithium clearance.
- Hypothyroidism can occur in lithium-treated patients (more common in women) and does not require discontinuation of lithium. Exogenous thyroid hormone (ie, levothyroxine) can be added to the regimen. If lithium is discontinued, the need for the levothyroxine should be reassessed because hypothyroidism can be reversible.
- Lithium may cause cardiac effects including T-wave flattening or inversion (up to 30% of patients), atrioventricular block, and bradycardia. In patients with significant cardiac disease, an ECG and consultation with a cardiologist are recommended at baseline and periodically during therapy.
- Other late-appearing lithium side effects are benign reversible leukocytosis, acne, folliculitis, and weight gain.
- Lithium toxicity can occur with serum levels greater than 1.5 mEq/L (mmol/L), but older persons may have toxic symptoms at lower levels. Severe toxic symptoms (eg, vomiting, diarrhea, incontinence, incoordination, impaired cognition, arrhythmias, seizures, permanent neurologic impairment, and kidney damage) may occur with serum concentrations above 2 mEq/L (mmol/L).

  ✔ Factors predisposing to lithium toxicity include sodium restriction, dehydration, vomiting, diarrhea, age greater than 50 years, heart failure, cirrhosis, drug interactions that decrease lithium clearance, heavy exercise, sauna baths, hot weather, and fever. Tell patients to maintain adequate sodium and fluid intake and to avoid excessive use of alcohol and caffeine-containing beverages.

  ✔ If lithium toxicity is suspected, discontinue lithium and send the patient immediately to the emergency department.

  ✔ Consider intermittent hemodialysis in these situations:

  - In lithium-naive patients, when lithium serum concentrations are at least 4 mEq/L (mmol/L).
  - In patients previously taking lithium, when lithium serum concentrations are 2.5 mEq/L (mmol/L) or greater and moderate-to-severe neurologic toxicity is present or as clinically indicated.
  - Continue hemodialysis until serum lithium concentration is below 1 mEq/L (mmol/L) when drawn 8 hours after the last dialysis.

  ✔ Thiazide diuretics, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and salt-restricted diets can elevate lithium levels. Neurotoxicity can occur when lithium is combined with antipsychotics, methyldopa, metronidazole, phenytoin, and verapamil. Combining lithium with calcium channel blockers is not recommended because of reports of neurotoxicity. Acetaminophen or aspirin and loop diuretics are less likely to interfere with lithium clearance. Caffeine and theophylline can enhance renal elimination of lithium.
- Lithium is usually initiated with 600 mg/day for prophylaxis and 900–1200 mg/day for acute mania. Give immediate-release preparations two or three times daily and extended-release products once or twice daily. After patients are stabilized, many patients can switch to once-daily dosing.
- In general, lithium serum concentrations should be maintained between 0.6 and 1.0 mEq/L (mmol/L). Lithium levels are considered to be at steady state after approximately 5 days with samples drawn 12 hours postdose. Initially, check serum lithium concentrations once or twice weekly. After a desired serum concentration is achieved, check levels in 2 weeks, and when stable, check

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them every 3–6 months.

- Lithium clearance increases by 50%–100% during pregnancy. Monitor serum levels monthly during pregnancy and weekly the month before delivery. At delivery, reduce dose to prepregnancy levels and maintain hydration.
- A reasonable therapeutic trial in outpatients is at least 4–6 weeks with lithium serum concentrations of 0.6–1.2 mEq/L (mmol/L). Although serum concentrations less than 0.6 mEq/L (mmol/L) may be associated with higher relapse rates, some patients can do well at 0.4–0.7 mEq/L (mmol/L). Acutely manic patients can require serum concentrations of 1–1.2 mEq/L (mmol/L), and some need up to 1.5 mEq/L (mmol/L). For bipolar prophylaxis in older patients, serum concentrations of 0.4–0.6 mEq/L (mmol/L) are recommended.

Anticonvulsants

- For more in-depth information on the side effects, pharmacokinetics, and drug interactions of anticonvulsants, refers to Chapter 54.

Valproate Sodium and Valproic Acid

- **Divalproex sodium** (sodium valproate), FDA-approved for acute manic or mixed episodes, is the most prescribed mood stabilizer in the United States. It is as effective as lithium and olanzapine for pure mania, and it can be more effective than lithium for rapid cycling, mixed states, and bipolar disorder with substance abuse. It reduces the frequency of (or prevents) recurrent manic, depressive, and mixed episodes.
- Lithium, carbamazepine, antipsychotics, or benzodiazepines can augment the antimanic effects of valproate. Valproate can be added to lithium to achieve synergistic effects in patients who are treatment refractory and are rapid cyclers or have mixed features, and the combination is effective as maintenance therapy of bipolar I disorder. The potential for drug interactions necessitate blood level monitoring of both agents. SGAs can be added to valproate for breakthrough mania, but they can increase the risk of sedation and weight gain. Combining valproate with lamotrigine increases the risk of rashes, ataxia, tremor, sedation, and fatigue.
- The most frequent dose-related side effects of valproate are GI complaints, fine tremor, and sedation. Giving it with food, reducing the initial dose and making gradual increases, or switching to the extended-release formulation can help alleviate the GI complaints. Reducing the dose or adding a β-blocker may alleviate tremors. Giving the total dose at bedtime can minimize daytime sedation. Other side effects are ataxia, lethargy, alopecia, pruritus, prolonged bleeding, transient increases in liver enzymes, weight gain, and hyperammonemia. Thrombocytopenia can occur at higher doses; lowering the valproate dose may normalize platelet counts. Fatal necrotizing hepatitis is rare and idiosyncratic, occurring in children on multiple anticonvulsants. Life-threatening pancreatitis has been reported.
- For healthy inpatient adults with acute mania, the initial starting dose of valproate is typically 20 mg/kg/day given in divided doses over 12 hours. The daily dose is adjusted by 250–500 mg every 1–3 days based on response and tolerability. The maximum dose is 60 mg/kg/day (see **Table 67-4**).
  - ✔ For outpatients who are hypomanic or euthymic, or for older patients, the initial dose is generally lower (5–10 mg/kg/day in divided doses) and gradually titrated to avoid side effects.
  - ✔ After establishing the optimal dose, the dose can be given twice daily or at bedtime if tolerated.
  - ✔ Extended-release divalproex can be given once daily, but bioavailability can be 15% lower than that of immediate release products.
- Most clinicians seek a serum concentration range of 50–125 mcg/mL (347–866 µmol/L) measured 12 hours after the last dose. Patients with cyclothymia or bipolar II disorder respond at lower blood levels, while patients with more severe forms may require up to 150 mcg/mL (1040 µmol/L). Serum levels are most useful when assessing for adherence or toxicity.

Carbamazepine

- Because of drug interactions, c**arbamazepine** is usually reserved for use after treatment failure with lithium or divalproex sodium.
- It has acute antimanic effects, but its long-term effectiveness is less clear. It may be less effective than lithium for maintenance therapy and for bipolar depression.
- The combination of carbamazepine with lithium, valproate, and antipsychotics is often used for manic episodes in treatment-resistant patients.
- Adverse effects of carbamazepine are summarized in Chapter 54.
- Carbamazepine induces the hepatic metabolism of antidepressants, anticonvulsants, antipsychotics, and many other medications. Women taking oral contraceptives who receive carbamazepine should be counseled to use a nonhormonal method of contraception.
- Certain medications that inhibit CYP3A4 (eg, cimetidine, diltiazem, erythromycin, fluoxetine, fluvoxamine, itraconazole, ketoconazole, nefazodone, and verapamil) added to carbamazepine therapy may cause carbamazepine toxicity. When carbamazepine is combined with valproate, reduce the carbamazepine dose, as its free levels can be increased. Do not combine clozapine and carbamazepine because of possible additive bone marrow suppression.
- For inpatients in an acute manic episode, doses can be started at 400–600 mg/day in divided doses with meals and increased by 200 mg/day every 2–4 days up to 10–15 mg/kg/day. Outpatients should be started at lower doses and titrated upward more slowly to avoid side effects. Many patients tolerate once-daily dosing after stabilization.
- During the first month of therapy, serum concentrations may decrease because of autoinduction of cytochrome P450 3A4 enzymes, requiring a dose increase.
- Carbamazepine serum levels are usually obtained every 1 or 2 weeks during the first 2 months, then every 3–6 months during maintenance. Serum samples are drawn 10–12 hours postdose and at least 4–7 days after dosage initiation or change. Most clinicians attempt to maintain levels between 6–10 mcg/mL (25–42 µmol/L), but some patients may require 12–14 mcg/mL (51–59 µmol/L).
- Use of carbamazepine in patients of Asian ancestry requires genetic testing for human leukocyte antigen (HLA) allele, HLA-B 1502, to help detect a higher risk of Stevens–Johnson syndrome and toxic epidermal necrolysis.

Oxcarbazepine

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- **Oxcarbazepine** is not FDA-approved for treatment of bipolar disorder in the United States. Guidelines typically recommend it as a third-line option for mania, a third- or fourth-line option for maintenance treatment, and it is not recommended for treatment of bipolar depression.
- Initial dosing is usually 150–300 mg twice daily, which can be increased by 300–600 mg every 3–6 days up to 1200 mg/day in divided doses (with or without food).
- Discontinue oxcarbazepine at the first sign of a skin reaction, as severe dermatologic reactions have been reported (eg, Stevens–Johnson syndrome). Other adverse effects may include impaired cognitive or psychomotor performance, somnolence, fatigue, incoordination, and hyponatremia. Severe hyponatremia is more common with oxcarbazepine than with carbamazepine.
- Oxcarbazepine is a CYP 2C19 inhibitor and a 3A3/4 inducer. It induces the metabolism of oral contraceptives, necessitating use of alternative contraception measures. Oxcarbazepine does not autoinduce its own metabolism.

Lamotrigine

- **Lamotrigine** has both antidepressant and mood-stabilizing effects. It may have augmenting properties when combined with lithium or valproate. It has a low rate of switching patients to mania. Although it is less effective for acute mania compared with lithium and valproate, it may be beneficial for the maintenance therapy of treatment-resistant bipolar I and II disorders. It seems most effective for prevention of bipolar depression.
- Common adverse effects include headache, nausea, dizziness, ataxia, diplopia, drowsiness, tremor, maculopapular rash, and pruritus. Although most rashes resolve with continued therapy, some progress to life-threatening Stevens–Johnson syndrome. Discontinue lamotrigine if the rash is diffuse, involves mucous membranes, and is accompanied by fever or sore throat. The incidence of rash is greatest with concomitant administration of valproate, rapid dose escalation of lamotrigine, and higher than recommended lamotrigine initial doses.
- In patients taking valproate, dose lamotrigine at about one-half the standard doses, and titrate upward more slowly than usual.
- For maintenance treatment of bipolar disorder, the usual dosage range of lamotrigine is 50–300 mg/day. The target dose is generally 200 mg/day (100 mg/day when combined with valproate and 400 mg/day when combined with carbamazepine). For patients not taking medications that affect lamotrigine's clearance, the dose is 25 mg/day for the first 2 weeks, then 50 mg/day for weeks 3 and 4, 100 mg/day for the next week, then 200 mg/day. Patients who stop dosing for more than a few days should restart the dose escalation schedule.

Antipsychotics

- First-generation (eg, fluphenazine, haloperidol) and second-generation (eg, aripiprazole, asenapine, clozapine, lurasidone, quetiapine, risperidone, ziprasidone) antipsychotics are effective as monotherapy or as add-on therapy for acute mania. Long-term antipsychotics can be needed for some patients, but the risks versus benefits must be weighed in view of long-term side effects (eg, obesity, type 2 diabetes, hyperlipidemia, hyperprolactinemia, and tardive dyskinesia).
- Both first- and second-generation antipsychotics are effective in ~70% of patients with acute mania associated with agitation, aggression, and psychosis.
- Clinical trials support the use of **quetiapine** and **lurasidone** as monotherapy and adjunctive treatment for bipolar depression. Data also support use of combined fluoxetine/olanzapine for bipolar depression.
- Oral aripiprazole, olanzapine, and long-acting risperidone are effective monotherapy options for maintenance treatment in bipolar disorder. First-generation depotantipsychotics (eg, haloperidol decanoate, fluphenazine decanoate) can be useful for maintenance treatment in patients who are noncompliant or treatment-resistant.
- Controlled studies in acute mania suggest that lithium or valproate plus an antipsychotic is more effective than any of these agents alone.
- **Clozapine** monotherapy has acute and long-term mood stabilizing effects in refractory bipolar disorder but requires regular white blood cell monitoring for agranulocytosis.
- Higher initial antipsychotic doses (eg, olanzapine 20 mg/day) may be required for acute mania. After mania is controlled (usually 7–28 days), the antipsychotic can be gradually tapered and discontinued, and the patient maintained on mood stabilizer monotherapy.
- For more information on the side effects, pharmacokinetics, and drug interactions of specific antipsychotics, refer to Chapter 70.

Alternative Medications

- High-potency benzodiazepines (eg, clonazepam and lorazepam) are common alternatives (or adjuncts) to antipsychotics for acute mania, agitation, anxiety, panic, and insomnia, or in patients who cannot take mood stabilizers. IM lorazepam may be used for acute agitation. When no longer required, benzodiazepines should be gradually tapered and discontinued to avoid withdrawal symptoms. A relative contraindication for long-term use is a history of drug or alcohol abuse or dependency.
- Many clinicians consider adjunctive antidepressants third-line for acute bipolar depression, except in those with no history of severe and/or recent mania or potentially in bipolar II patients. The rate of mood switching from depression to mania with tricyclic antidepressants and venlafaxine is higher than the rate associated with use of selective serotonin reuptake inhibitors. Before initiating an antidepressant, be sure the patient has a therapeutic dose or blood level of a primary mood stabilizer. Be cautious in using antidepressants in those with a history of mania after a depressive episode, and those with frequent cycling. Generally, the antidepressant should be withdrawn 2–6 months after remission.

Special Populations

- The occurrence of Epstein anomaly in infants exposed to lithium during the first trimester is estimated to be between 1 and 10.78:1000, and the risk of neural tube defects is 13.4:1000.
- When lithium is used during pregnancy, use the lowest effective dose to prevent relapse, thus lessening the risk of "floppy" infant syndrome, hypothyroidism, and nontoxic goiter in the infant. Monitor closely and adjust dose as appropriate.
- Breastfeeding is usually discouraged for women taking lithium.
- When valproate, carbamazepine, and lamotrigine are taken during the first trimester, the risk of neural tube defects is ~4%, ~3%, and ~2%, respectively. Administration of folic acid can reduce

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the risk of neural tube defects.

- Women taking valproate may breastfeed, but mother and infant should have identical laboratory monitoring.
- First-generation antipsychotics seem to have little teratogenic risk when used during pregnancy. Data on the SGAs are more limited. Risk to benefit ratio must be considered before using antipsychotics during pregnancy.
- Lithium, valproic acid, and carbamazepine are used in pediatric bipolar disorder, but data are limited. Aripiprazole and risperidone are FDA-approved for bipolar mania in adolescents 13–17 years. Quetiapine is approved as monotherapy or adjunctive therapy to lithium or divalproex in manic patients aged 10–17 years. Olanzapine is approved for manic or mixed episodes in patients aged 13–17 years.
- Lithium is FDA-approved as a mood stabilizer for children older than 12 years.
- A guideline for treatment of children and adolescents with bipolar disorder is *Practice Parameters for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder.*
- The elimination half-life of lithium and valproate increases with age. Older patients can have many medical comorbidities and increased sensitivity to side effects of mood stabilizers and antipsychotics.

EVALUATION OF THERAPEUTIC OUTCOMES

- Mood episodes: Document symptoms on a daily mood chart (document life stressors, type of episode, length of episode, and treatment outcome); monthly and yearly life charts are valuable for documenting patterns of mood cycles.
- See **Table 67-5** for guidelines for laboratory monitoring of patients on mood stabilizers.
- Assess medication adherence; missing medication doses is a primary reason for nonresponse and recurrence of episodes.
- Ask patients about adverse effects, especially sedation and weight gain; manage side effects rapidly and vigorously to avoid nonadherence.
- Be aware of suicidal ideation or attempts. Suicide completion rates with bipolar I disorder are 10%–15%; suicide attempts are primarily associated with depressive episodes, mixed episodes with severe depression, or presence of psychosis.
- Assess patients with partial treatment response or nonresponse for accurate diagnosis, concomitant medical or psychiatric conditions, medication adherence, and use of medications or substances that exacerbate mood symptoms.
- Involve patients and family members in treatment to monitor target symptom response and side effects and to enhance adherence and reduce stressors. Standardized rating scales may be useful in monitoring for response.

TABLE 67-5

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]	
	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
SGAs[i]	X			X	X										
Carbamazepine[j]	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		
Valproate[n]	X	X	X	X	X	X	X							X	X

[a]Screen for drug abuse and serum pregnancy.

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

[c]Fasting glucose, serum lipids, and weight.

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[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]jCarbamazepine: 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 <3000/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 the elderly 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 2–8 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 2–3 months during the first 6 months, and then every 6–12 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 6–12 months; monitor for signs and symptoms of hypothyroidism; if supplemental thyroid therapy is required, monitor thyroid function tests and adjust thyroid dose every 1–2 months until thyroid function indices are within normal range, and then monitor every 3–6 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, and malaise). Hypersensitivity reactions have occurred in approximately 25%–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 3–6 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/mm3/L (<100 × 109/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.

SGAs, second-generation antipsychotics.

See Chapter 86, Bipolar Disorder, authored by Shannon J. Drayton and Christopher S. Fields, for a more detailed discussion of this topic.

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