BIPOLAR DISORDER

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Introduction

- Bipolar disorder is a common, chronic, and often severe cyclic mood disorder characterized by recurrent fluctuations in mood, energy, and behavior.
- It differs from recurrent major depression in that a manic or hypomanic episode occurs during the course of the illness.
- Bipolar disorder is a lifelong illness and requires both non pharmacologic and pharmacologic treatments for mood stabilization.

Epidemiology

- Bipolar disorders are categorized into:
  - Bipolar I disorder,
  - Bipolar II disorder, and
  - Other specified and unspecified bipolar and related disorders.

Epidemiology(1)

- Bipolar I disorder is characterized by one or more manic or mixed mood episodes.
- Bipolar II disorder is characterized by one or more major depressive episodes and at least one hypomanic episode.
- Hypomania is an abnormally and persistently elevated, expansive, or irritable mood but not of sufficient severity to cause significant impairment and does not require hospitalization.

Epidemiology(2)

- The lifetime prevalence of bipolar I disorder is estimated at 0.6%.
- The lifetime prevalence of bipolar II disorder is about 0.4%.
- When including the entire spectrum of bipolar disorders, the prevalence is approximately 3%.
- Bipolar I disorder affects men and women equally.
- Bipolar II is more common in women. Rapid cycling and mixed mood episodes occur more in women.

Epidemiology(3)

- The most common comorbid conditions are anxiety, substance abuse, and impulse control disorders.
- Medical comorbidities are common.
- The mean age of onset is 20 years, although onset may occur in early childhood to the mid-40s.
- If onset occurs after age 60, it is probably due to medical causes.

Epidemiology

- An early onset is associated with greater comorbidities, more mood episodes, a greater proportion of days depressed, and greater lifetime risk of suicide attempts compared with later onset.
- Substance abuse and anxiety disorders are more common in patients with early onset.
- Patients with bipolar disorder have higher rates of suicidal thoughts, attempts, and completed suicides than the general population.

ETIOLOGY AND PATHOPHYSIOLOGY

- **Etiology :**
- The precise etiology is unknown.
- Thought to be genetically based.
- Studies report an increased lifetime prevalence risk of having mood disorders among first-degree relatives of patients with BPD.

Medications/drugs that induce mania

- Alcohol intoxication
- Antidepressants (MAOIs, TCAs, 5-HT and/or NE and/or DA reuptake inhibitors, 5-HT antagonists)
- Marijuana intoxication precipitates psychosis, paranoid thoughts, anxiety, and restlessness
- Steroids (anabolic, adrenocorti cotropic 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
  - ✓ Sleep deprivation

ETIOLOGY AND PATHOPHYSIOLOGY

- **PATHOPHYSIOLOGY**:
- The pathophysiology remains incompletely understood
- Lithium, valproate, and carbamazepine all have similar effects on neuronal growth, supporting a hypothesis that BPD may be related to inositol disturbance.
- Brain-derived neurotrophic factor (BDNF) may play a role in BPD.
- Serum BDNF is low in mania and improves with RX.

Clinical presentation and diagnosis

- **Diagnosis of Bipolar Disorder.**
- Patients presenting with:
- Depressive or elevated mood features and
- A history of abnormal or unusual mood swings should be assessed for bipolar disorder.

Clinical presentation and diagnosis

- Initial and subsequent episodes are mostly depressive.
- Studies show bipolar I patients spend about 32% of weeks with depressive symptoms compared with 9% of weeks with manic or hypomanic symptoms.
- Patients with bipolar II disorder spend 50% of weeks symptomatic for depression and only 1% with hypomania.
- Thus , BPD is often misdiagnosed or under diagnosed.

Clinical presentation and diagnosis

- **Bipolar I disorder**

- The diagnosis of bipolar I disorder requires at least one episode of mania for at least 1 week with:
  - A persistently elevated, expansive, or irritable mood with related symptoms of decreased need for sleep, excessive energy, racing thoughts, a propensity to be involved in high-risk activities, and excessive talkativeness.

Clinical presentation and diagnosis

- **Bipolar I disorder …**

- Bipolar I depression can be misdiagnosed as major depressive disorder (MDD); therefore, it is essential to rule out past episodes of hypomania or mania.
- If bipolar depression is mistaken for MDD and the patient is treated with antidepressants, it can precipitate a manic episode or induce rapid cycling.

Clinical presentation and diagnosis

- **Bipolar II Disorder**
- The distinguishing feature of bipolar II disorder is a current or past hypomanic episode and a current or past major depressive episode.
- Irritability and anger are common.
- There cannot have been a prior full-manic episode

Clinical presentation and diagnosis

- **Cyclothymic Disorder**
- Cyclothymic disorder is a chronic mood disturbance lasting at least 2 years (1 year in children and adolescents) and characterized by:
- mood swings that include periods of hypomanic symptoms that do not meet the criteria for a hypomanic episode and depressive symptoms that do not meet the criteria for a major depressive episode.

Clinical presentation and diagnosis

- **Cyclothymic Disorder**
- Hypomanic symptoms include inflated self-esteem or grandiosity (non delusional), decreased need for sleep, pressured speech, flight of ideas (FOI), distractibility, and increased involvement in goal-directed activities, not causing severe impairment or requiring hospitalization.
- Psychotic features are not present

Clinical presentation and diagnosis

Diagnosis episode	Impairment of functioning or need for hospitalization[a]	*DSM-5* criteria[b]
Major depressive	Yes	Greater than or equal to 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 appetite, weight loss • Insomnia or hypersomnia • Psychomotor retardation or agitation • Decreased energy or fatigue • Feelings of guilt or worthlessness • Impaired concentration and decision making • Suicidal thoughts or attempts

Clinical presentation and diagnosis

Diagnosis episode	Impairment of functioning or need for hospitalization[a]	*DSM-5* criteria[b]
Manic	Yes	Greater than or equal to 1-week period of abnormal and persistently elevated mood (expansive or irritable), associated with at least three of the following symptoms (four if the mood is only irritable): • Inflated self-esteem (grandiosity) • Racing thoughts (FOI) • Distractible (poor attention) • Increased activity (either socially, at work, or sexually) or increased motor activity or 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)

Clinical presentation and diagnosis

Diagnosis episode	Impairment of functioning or need for hospitalization[a]	*DSM-5* criteria[b]
Hypomanic	No	At least 4 days of abnormal and persistently elevated mood (expansive or irritable); 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 (FOI) • Increased activity (either socially, at work, or sexually) or increased motor activity or 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)
Mixed	Yes	Criteria for both a major depressive episode and manic episode (except for duration) occur nearly every day for at least a 1-week period
Rapid cycling	Yes	At least four mood episodes (depressive, manic, mixed, or hypomanic) in 12 months

Suicide

- Patients with bipolar disorder have high risk of suicide.
- Factors that increase risk are:
  - early age at onset,
  - high number of depressive episodes,
  - comorbid alcohol abuse,
  - personal history of antidepressant-induced mania, and family history of suicidal behavior.

Differential Diagnosis

- Schizophrenia and bipolar disorder share certain symptoms, including psychosis in some patients.
- The prominence of mood symptoms and the history of mood episodes distinguish bipolar disorder and schizophrenia.
- In addition, psychosis of schizophrenia occurs in the absence of prominent mood symptoms.

Differential Diagnosis

- Schizoaffective disorder may also be considered when developing a differential diagnosis.
- Schizoaffective disorder is characterized by a period of illness during which there is a major depressive episode or a manic episode, concurrent with symptoms that meet criterion A for schizophrenia.

Differential Diagnosis

- Personality disorders are inflexible and maladaptive patterns of behavior that deviate markedly from expectations of society beginning in adolescence or early adulthood.
- Personality disorders and bipolar disorder may be comorbid, and patients with personality disorders may have mood symptoms.

Comorbid Psychiatric and Medical Conditions

- Lifetime prevalence rates of comorbidity with bipolar disorder are as high as 58%.
- Comorbidities, especially substance abuse, make establishing a diagnosis more difficult and complicate treatment.
- Comorbidities also place the patient at risk for a poorer outcome, high rates of suicidality, onset of depression, and higher costs of treatment.

Comorbid Psychiatric and Medical Conditions

Psychiatric comorbidities include:

- Personality disorders
- Alcohol and substance abuse or dependence
- Anxiety disorders
- Panic disorder, Social phobia
- Eating disorders
- Attention-deficit/hyperactivity disorder
- Obsessive-compulsive disorder

Comorbid Psychiatric and Medical Conditions(2)

- Medical comorbidities include:
  - Migraine
  - Multiple sclerosis
  - Cushing syndrome
  - Brain tumor
  - Head trauma

TREATMENT

- Goals of treatment are to:
  - reduce symptoms,
  - Induce remission,
  - prevent relapse,
  - improve patient functioning, and minimize adverse effects of drug therapy.

General Approach to Treatment

- Although it is a goal of treatment, not all patients achieve remission.
- The mainstay of drug therapy has been mood-stabilizing drugs
- But research based on multiple treatments indicates antipsychotic drugs, both first-generation (FGAs) and second generation (SGAs), may be more effective for acute mania.

General Approach to Treatment

- Antipsychotic drugs may be used as **monotherapy** or adjunctively with mood-stabilizing drugs.
- A person entering treatment for a first mood episode in bipolar disorder must have a complete assessment and careful diagnosis to rule out nonpsychiatric causes.
- Treatment is often lifelong.
- Comorbid conditions should also be addressed

Nonpharmacologic Therapy

- Interpersonal, or group psychotherapy with a qualified therapist or clinician assists individuals with bipolar disorder to improve functional outcomes and may help:
  - Treat or prevent mood episodes,
  - Establish a daily routine and sleep schedule, and
  - Improve interpersonal relationships.

Nonpharmacologic Therapy

- Cognitive-behavioral therapy (CBT) is a type of psychotherapy that stresses the importance of recognizing patterns of cognition (thought) and how thoughts influence subsequent feelings and behaviors.
- Other people, situations, and events external to the individual are not seen as the sources of thoughts .
- With CBT, patients are taught self-management skills to change negative thoughts even if external circumstances do not change.

Nonpharmacologic Therapy

- ECT is the application of electrical impulses to the brain for the treatment of severe depression, mixed states, psychotic depression, and treatment refractory mania.
- It also may be used in pregnant women who cannot take carbamazepine, lithium, or divalproex.
- Education about self-management through sleep hygiene, nutrition, exercise, stress reduction, and abstinence from alcohol or drugs is critical to success.

Pharmacologic Therapy

- The **primary treatment modality** for manic episodes is mood stabilizing agents or antipsychotic drugs, often in combination.
- Mood-stabilizing drugs are first-line treatments and include lithium, divalproex, carbamazepine, and lamotrigine.

Pharmacologic Therapy

- The SGAs, including risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, lurasidone, and asenapine, are approved for treatment of acute mania.
- Lithium, lamotrigine, aripiprazole, olanzapine, and quetiapine are approved **for maintenance therapy.**

Pharmacologic Therapy

- Quetiapine's maintenance therapy indication in bipolar I disorder is adjunctive with lithium or divalproex.
- Drugs used with less research support and without FDA approval include topiramate and oxcarbazepine.
- Benzodiazepines are used adjunctively for mania.

Pharmacologic Therapy

- The primary treatment for depressive episodes in BPD is mood-stabilizing agents or certain antipsychotics.
- Among antipsychotic drugs, quetiapine as monotherapy, lurasidone as monotherapy or adjunctive to lithium or divalproex, and olanzapine in combination with fluoxetine are approved.
- Antidepressants can be used with a mood stabilizer to reduce risk of a mood switch to mania and after the patient has failed to respond adequately to mood-stabilizing therapy.

Pharmacologic Therapy

- Evidence of efficacy of antidepressant drugs in bipolar depression is considered controversial.
- **Combinations of two mood-stabilizing drugs or a mood-stabilizing drug and either an antipsychotic or antidepressant** drug are common, especially in **acute mood episodes**.
- The primary treatment for relapse prevention is mood-stabilizing agents, often combined with antipsychotic drugs.

Lithium

- Lithium, the first approved mood-stabilizing drug, remains a first-line agent and
- sets the standard for efficacy against which other drugs are measured.
- It is antimanic, prevents relapse, and has modest efficacy for acute bipolar depression.
- One of the oldest drugs used for psychiatric illness, research continues to support its use.

Lithium

- In most studies, lithium's efficacy is equivalent to that of anticonvulsant mood stabilizers and SGAs.
- It is most effective for patients with:
  - few previous episodes,
  - symptom-free interepisode remission, and
  - a family history of bipolar disorder with good response to lithium.

Lithium

- Patients with rapid cycling are less responsive to lithium than to other mood-stabilizing drugs such as divalproex.
- Additionally, its efficacy for bipolar depression is less robust than for mania.
- It may also be less effective in mixed mood episodes (symptoms of mania and depression occurring simultaneously).

Lithium

- Evidence shows lithium's effect on suicidal behavior is superior to that of other mood-stabilizing drugs.
- Lithium reduces the risk of deliberate self-harm or suicide by 70%

Lithium

- **Mechanism of Action**
- Lithium's mechanism of action is not well understood and is multimodal.
- Possibilities include altered ion transport, effects on neurotransmitter signaling, blocking adenyl cyclase, effects on inositol, neuroprotection or increased BDNF, and inhibition of second messenger systems.

Lithium

- **Dosing and Monitoring :**Lithium is usually initiated at a dosage of 600 to 900 mg/day.
- Although it is commonly given in a divided dosage, once-daily dosing is recommended, especially with sustained-release formulations.
- Once-daily dosing can improve adherence and reduce renal side effects.

Lithium

- Lithium has a narrow therapeutic index.
- Lithium requires regular serum concentration monitoring as a guide to titration and to minimize adverse effects.
- At least weekly monitoring is recommended until stabilized; then the frequency can be decreased.

Lithium

- Well-maintained patients who tolerate lithium without difficulty can be monitored by serum concentration as infrequently as twice yearly.
- The dosage is titrated to achieve a serum lithium concentration of 0.6 to 1.4 mEq/L (mmol/L).
- Higher serum concentrations are required to treat an acute episode than to prevent relapse.

Lithium

- Serum lithium > 0.8 mEq/L (mmol/L) may be more effective at preventing relapse than lower serum concentrations.
- The suggested therapeutic serum concentration range is based on a 12-hour post dose sample collection, usually a morning trough in patients taking more than one dose per day.
- At least 2 weeks at a suggested therapeutic serum concentration is required for an adequate trial.
- It is common for lithium to be combined with other mood stabilizers or antipsychotics to achieve more complete remission.

Lithium

- **Adverse Effects**
- The most common adverse effects are GI upset, tremor, and polyuria, which are dose related.
- Nausea, dyspepsia, and diarrhea are minimized by coadministration with food, use of the sustained-release formulation, and giving smaller doses more frequently to reduce the amount of drug in the GI tract.

Lithium

- Tremor is present in up to 50% of patients.
- Low-dose β-blockers, such as propranolol 20 to 60 mg/day, reduces tremor.
- Lithium impairs the kidney's ability to concentrate urine because of its inhibitory effect on vasopressin.
- This causes an increase in urine volume and frequency of urination and an increase in thirst.
- Polyuria and polydipsia occur in up to 70% of patients.

Lithium

- A severe form of polyuria, when urine volume exceeds 3 L/day is termed lithium-induced nephrogenic diabetes insipidus.
- It can be treated with hydrochlorothiazide or amiloride.
- If the former is used, the lithium dosage should be reduced by 33% to 50% to account for the drug–drug interaction that increases serum lithium and causes toxicity.

Lithium

- Long-term lithium has been associated with structural kidney changes, such as glomerular sclerosis or tubular atrophy.
- Once-daily dosing of lithium is less likely to cause renal adverse effects than divided-daily dosing.

Lithium

- Lithium is concentrated in the thyroid gland and can impair thyroid hormone synthesis.
- Although goiter is uncommon, as many as 30% of patients develop at least transiently elevated thyroid-stimulating hormone.
- Lithium-induced hypothyroidism is not usually an indication to discontinue the drug.
- Patients can be supplemented with levothyroxine.

Lithium

- Other common adverse effects include poor concentration, acneiform rash, alopecia, worsening of psoriasis, weight gain, metallic taste, impaired glucose regulation, and benign leukocytosis.
- Lithium causes a flattening of the T wave of the electrocardiogram (ECG), but, not clinically significant.
- Less commonly, it can cause or worsen arrhythmias.

Lithium

- Acute lithium toxicity, which occurs at serum concentrations over 2 mEq/L (mmol/L), can be severe and life threatening, necessitating emergency treatment.
- Symptoms include severe vomiting and diarrhea, deterioration in motor coordination, including coarse tremor, ataxia, and dysarthria, and impaired cognition.
- In its most severe form, seizures, cardiac arrhythmias, coma, and kidney damage are reported.
- Treatment includes discontinuation of lithium, IV fluids to correct fluid and electrolyte imbalance, and osmotic diuresis or hemodialysis.

Lithium

- In case of overdose, gastric lavage is indicated.
- Clinical symptoms continue after the serum concentration is lowered because clearance from the central nervous system (CNS) is slower than from serum.
- Factors predisposing to lithium toxicity include fluid and sodium loss from hot weather or exercise or drug interactions that increase serum lithium

Lithium

- **Drug Interactions**
- Common and significant drug interactions involve thiazide diuretics, NSAIDS , and ACEinhs
- If a diuretic must be used with lithium and a thiazide is not required, loop diuretics such as furosemide are less likely to increase lithium retention.
- The ACE inhibitors and ARB can abruptly increase serum lithium with the potential of acute toxicity,
- This combination is strongly discouraged.

Divalproex Sodium and Valproic Acid

- Divalproex sodium: Is composed of sodium valproate and valproic acid.
- The delayed release and extended-release formulations are converted in the intestine into valproic acid (VPA), which is systemically absorbed.
- It is FDA approved for treatment of the manic phase of bipolar disorder.
- It is equal in efficacy to lithium and some other drugs for bipolar mania.

Divalproex Sodium and Valproic Acid

- It has utility in bipolar disorder with rapid cycling, mixed mood features, and substance abuse comorbidity.
- Although not FDA approved for relapse prevention, studies support its use, and it is widely prescribed for maintenance therapy.
- Divalproex can be used as monotherapy or in combination with lithium or an antipsychotic

Divalproex Sodium and Valproic Acid

- Mechanism of Action.
  - The mechanism is not well understood.
  - It is known to affect ion transport and enhance activity of γ-aminobutyric acid (GABA).
  - Similar to lithium, it has possible neuroprotective effects through enhancement of BDNF.

Divalproex Sodium and Valproic Acid

- Dosing and Monitoring.
- Divalproex is initiated at 500 to 1000 mg/ day, but studies indicate a therapeutic serum VPA concentration can be reached more quickly through a loading dose approach of 20 to 30 mg/kg/day.
- Using this approach, patients may respond with a significant reduction in symptoms within the first few days of treatment.
- The dosage is then titrated according to response, tolerability, and serum concentration.

Divalproex Sodium and Valproic Acid

- The most often referenced desired VPA serum concentration is 50 to 125 mcg/mL (347–866 μmoles/L), but it is not unusual for patients to require more than 100 mcg/mL (693 μmoles/L) for optimal efficacy.
- Some patients require high milligram dosages in order to reach a desired serum concentration.
- The suggested serum concentration range is based on trough values.
- Serum concentration monitoring is recommended at least every 2 weeks until stabilized, then less frequently.

Divalproex Sodium and Valproic Acid

- The extended-release formulation can be taken once daily.
- If the extended-release formulation is administered at night, a morning blood sampling is a peak, not a trough.
- The drug should be given in the morning so that blood sampling the following morning would be a trough value and more easily interpreted if the typical blood sampling time is in the morning.

Divalproex Sodium and Valproic Acid

- The systemic bioavailability of extended-release divalproex is about 15% less than that of the delayed-release formulation.
- Patients who have difficulty swallowing large tablets can use the sprinkle formulation.
- The immediate-release formulation, either capsules or syrup, is given three or four times per day.

Divalproex Sodium and Valproic Acid

- Adverse Effects.
- The most common adverse effects are GI (loss of appetite, nausea, dyspepsia, diarrhea), tremor, and drowsiness.
- GI distress can be reduced by coadministration with food.
- The delayed-release and extended-release formulations are less likely to cause gastric distress than immediate-release valproic acid.

Divalproex Sodium and Valproic Acid

- Dosage reduction can reduce all of the common side effects.
- As with lithium, a low-dose β-blocker may alleviate tremor.
- Weight gain is common, occurring in up to 50% of patients.

Divalproex Sodium and Valproic Acid

- Other less common adverse effects include alopecia or a change in hair color or texture.
- Hair loss can be minimized by supplementation with a vitamin containing selenium and zinc.
- Polycystic ovarian syndrome associated with increased androgen production is reported.

Divalproex Sodium and Valproic Acid

- Thrombocytopenia is common, and the platelet count should be monitored periodically.
- It is a dose related adverse effect and usually asymptomatic, but the drug is usually stopped if the platelet count is less than 100 × 103/mm3 (100 × 109/L).
- More rare are hepatic toxicity and pancreatitis, which are not always dose related.

Divalproex Sodium and Valproic Acid

- Severe GI symptoms of hepatic or pancreatic toxicity include vomiting, pain, and loss of appetite.
- When these occur, the patient should be evaluated for possible hepatitis or pancreatitis.
- Divalproex has a wide therapeutic index.
- Acute toxicity for high dosages or over dosage is not life threatening

Divalproex Sodium and Valproic Acid

- Drug Interactions.
- It is a weak inhibitor of some drug metabolizing liver enzymes and can affect metabolism of other drugs.
- These include other anticonvulsants and antidepressants. The interaction between divalproex and lamotrigine is significant.
- The risk of a dangerous rash caused by lamotrigine is increased when given concurrently with divalproex.

Divalproex Sodium and Valproic Acid

- When lamotrigine is added to divalproex, the initial lamotrigine dosage should be one-half the typical starting dosage, and lamotrigine should be titrated more slowly than usual.
- When divalproex is added to lamotrigine, the lamotrigine dosage should be reduced by 50%.
- Conversely, the metabolism of divalproex can be increased by enzyme-inducing drugs such as carbamazepine and phenytoin

Carbamazepine

- Only the extended-release formulation is FDA approved for treatment of bipolar disorder.
- it is less desirable as a first-line agent because of safety and drug interactions.
- It is reserved for patients who fail to respond to lithium or for patients with rapid cycling or mixed bipolar disorder.
- Carbamazepine can be used as monotherapy or in combination with lithium or an antipsychotic drug.

Carbamazepine

- *Mechanism of Action.*
- The mechanism of action of carbamazepine is not well understood.
- It blocks ion channels and inhibits sustained repetitive neuronal excitation, but whether this explains its efficacy as a mood stabilizer is not known.

Carbamazepine

- Dosing and Monitoring.
- Carbamazepine is initiated at 400 to 600 mg/day.
- The sustained-release formulation can be given in two divided doses.
- The suggested therapeutic serum concentration is 4 to 12 mcg/mL (17-51 µmol/L).

Carbamazepine

- As with divalproex, some patients require high dosages to achieve a desired serum concentration and therapeutic effect.
- The dosage can be increased by 200 to 400 mg/day as often as every 2 to 4 days.
- Serum concentration monitoring is suggested at least every 2 weeks until stabilized

Carbamazepine

- *Adverse Effects.* The most common adverse effects are drowsiness, dizziness, ataxia, lethargy, and confusion.
- At mildly toxic levels, it causes diplopia and dysarthria.
- These can be minimized through dosage adjustments, use of sustained-release formulations, and giving more of the drug late in the day.
- GI upset is common.

Carbamazepine

- Carbamazepine has an antidiuretic effect similar to the syndrome of inappropriate antidiuretic hormone secretion and can cause hyponatremia.
- Mild elevations in liver enzymes can occur, but hepatitis is less common.
- Mild, dose-related leukopenia is not unusual and not an indication for discontinuation.
- More serious blood count abnormalities such *as aplastic anemia and agranulocytosis are rare but life threatening*.

Carbamazepine

- *Drug Interactions.* Carbamazepine induces hepatic metabolism of many drugs
- Carbamazepine is an autoinducer (ie, it induces its own metabolism).
- Conversely, the metabolism of carbamazepine can be slowed by enzyme inhibiting drugs.
- Carbamazepine should not be given concurrently with clozapine because of the additive risk of agranulocytosis

Lamotrigine

- Is effective for maintenance treatment of bipolar disorder.
- It is more effective for depression relapse prevention than for mania relapse prevention.
- Its primary limitation as an acute treatment is the time required for titration to an effective dosage.
- In addition to maintenance monotherapy, it is sometimes used in combination with lithium or divalproex, although combination with divalproex increases the risk of rash, and lamotrigine dosage adjustment is required.

Lamotrigine

- *Dosing and Monitoring.*
- Lamotrigine is initiated at 25 mg/day for 1 to 2 weeks, then increased in a dose-doubling manner every 1 to 2 weeks to a target of 200 to 400 mg/day.
- If lamotrigine is added to divalproex, the starting dosage is 25 mg every other day with a slower titration to reduce risk of rash.

Lamotrigine

- If divalproex is added to lamotrigine, the lamotrigine dosage should be reduced by 50% for the same reason.
- If lamotrigine therapy is interrupted for more than a few days, it should be restarted at the initial dosage and retitrated.
- Serum concentration monitoring is not recommended

Lamotrigine

- Adverse Effects.
- The adverse effect of greatest significance is a maculopapular rash, occurring in up to 10% of patients.
- The risk of rash is greater with a rapid dosage titration
- Other side effects include dizziness, drowsiness, headache, blurred vision,and nausea.
- Unlike lithium and divalproex, lamotrigine does not significantly influence body weight

Lamotrigine

- Divalproex slows the rate of elimination of lamotrigine by about half, necessitating dosage reduction.
- Conversely, carbamazepine increases the rate of lamotrigine metabolism.
- Upward adjustment in dosage may be needed

Antipsychotic Drugs

- First-generation antipsychotics have long been used in the treatment of acute mania.
- SGA drugs, including aripiprazole, asenapine, olanzapine, quetiapine,risperidone, and ziprasidone, are approved for the treatment of bipolar mania or mixed mood episodes as monotherapy or in combination with mood stabilizers.
- The combination of olanzapine and fluoxetine is approved for treatment of acute bipolar depression..

Antipsychotic Drugs

- Quetiapine is approved as monotherapy for acute bipolar depression and as adjunctive therapy with lithium or divalproex for prevention of bipolar depression relapse.
- Lurasidone is approved as monotherapy and as adjunctive therapy with lithium or divalproex for acute bipolar depression.

Antipsychotic Drugs

- In comparative studies, SGAs are equivalent or superior in efficacy to lithium and divalproex for treatment of acute mania.
- Treatment guidelines include antipsychotic drugs as first-line therapy.
- The combination of mood stabilizers and antipsychotics is more likely to achieve remission than monotherapy.
- Quetiapine data in relapse prevention of both manic and bipolar depression episodes favored combination therapy over mood-stabilizer monotherapy

Antipsychotic Drugs

- Higher dosages are often required to treat an acute episode.
- The recommended dosage of aripiprazole for bipolar disorder is 20 to 30 mg/day, somewhat higher than the average dosage used in schizophrenia.
- The recommended dosage for quetiapine in treatment of acute bipolar depression is 300 mg/ day, less than the 600 mg/day recommended in acute mania.

Antipsychotic Drugs

- SGAs are less likely than FGAs to cause neurologic side effects, especially movement abnormalities.
- SGAs are more likely to cause metabolic side effects, such as weight gain, glucose dysregulation, and dyslipidemia.
- Among SGAs approved for treatment of bipolar disorder, olanzapine is most likely to cause metabolic side effects.
- Asenapine, lurasidone, quetiapine, and risperidone cause less metabolic effects than olanzapine.

Antidepressants

- Treatment of depressive episodes presents a particular challenge.
- The FDA requires the product label of all antidepressants to contain about the potential risk of inducing a mood switch.
- Most research shows no advantage for adjunctive antidepressant use
- Treatment guidelines and current FDA approvals indicate lithium and quetiapine as first-line therapy.

Antidepressants

- The approval of lurasidone for acute bipolar depression is recent, thus it is not widely included in first-line recommendations.
- When usual treatment fails, evidence supports use of antidepressants.

Antidepressants

- Guidelines agree that when antidepressants are used, they should be combined with a mood stabilizer to reduce risk of mood switch.
- The question of which antidepressant drugs are less likely to cause a mood switch is not resolved, but tricyclic antidepressants are thought to carry greater risk.
- A comparison of venlafaxine, sertraline, and bupropion as adjunctive therapy to a mood stabilizer showed venlafaxine with highest risk of a mood switch to mania or hypomania and bupropion with the least.

Special Populations

- **Pediatrics**
- Children and adolescents are sensitive to medication side effects, including metabolic side effects of SGAs.
- With these cautions, evidence supports use of mood stabilizers and SGAs in children and adolescents with bipolar disorder.

Pediatrics

- Lithium is FDA approved for treatment of bipolar disorder in children and adolescents as young as age 12.
- Aripiprazole, olanzapine, quetiapine, and risperidone are FDA approved in children and adolescents as young as age 10.
- Initial dosages in the pediatric population are lower than in adults.

Pediatrics

- Dosages are titrated carefully according to response and tolerability.
- Children and adolescents are especially likely to experience weight gain from SGAs.
- Cognitive toxicity, manifested as confusion, memory or concentration impairment, or impaired learning, is difficult to detect and is a consideration in the pediatric population

Pediatrics

- For comorbid bipolar disorder and attention-deficit/ hyperactivity disorder when stimulant therapy is indicated, treatment of mania is recommended before starting the stimulant to avoid exacerbation of mood symptoms

Geriatrics

- As physiologic systems change with aging, elimination of drugs is slowed.
- Examples are slowed renal elimination of lithium and slowed hepatic metabolism of carbamazepine and valproic acid.
- As a result, dosages required for therapeutic effect are lower in geriatric patients.

Geriatrics

- Pharmacokinetic interactions include metabolic enzyme induction or inhibition and protein binding displacement interactions (eg, divalproex and warfarin).
- Pharmacodynamic interactions include additive sedation and cognitive toxicity, which increases risk of falls and other impairments

Pregnancy and Postpartum

- Lithium is readily transferred via breast milk.
- Breastfeeding is not advised for patients taking lithium.
- Lamotrigine may be associated with an increased risk of oral clefts.
- Valproic acid and carbamazepine are human teratogens.

Pregnancy and Postpartum

- Neural tube defects occur in up to 9% of infants exposed during the first trimester.
- As such, women with unplanned pregnancies may not know they are pregnant until after the risk of exposure has occurred.
- Carbamazepine can cause fetal vitamin K deficiency.

Guidelines for Baseline and Routine Laboratory Tests and Monitoring for Agents Used in the Treatment of Bipolar Disorder

	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	3–6 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

OUTCOME EVALUATION

- **Assessment of Therapeutic Effects**
- some clinicians use symptom rating scales such as the Young Mania Rating Scale (YMRS) for mania.
- The YMRS is composed of 11 items based on a patient's perception over the preceding 48 hours.
- Adjunctive information is obtained from clinical observations.
- The scale takes about 15 to 30 minutes to administer

OUTCOME EVALUATION

- **Assessment of Adverse Effects**
- Adverse effects cause more nonadherence than any other factor.
- Monitor patients regularly for adverse effects and health status, especially because mood stabilizers and antipsychotics commonly cause metabolic side effects such as weight gain.

OUTCOME EVALUATION

- **Assessment of Adverse Effects**
- Repeat laboratory tests for renal and thyroid function for patients taking lithium and hematology and liver function for patients taking carbamazepine or divalproex.
- Annual measurement of serum lipase is advisable for patients taking divalproex

Patient Education

- Discuss the nature and chronic course of bipolar disorder and risks of repeated relapses.
- Help patients understand treatment is not a cure but that many patients enjoy symptom-free or nearly symptom-free function.
- long-term recovery is dependent on adherence to pharmacologic and nonpharmacologic treatment.

Patient Education

- Explain the purpose of medication, common side effects to expect, and how to respond to side effects.
- Provide the patient and family with written information about indications, benefits, and side effects.
- Discuss less frequent but more dangerous side effects of drugs, and give written instructions on seeking medical attention immediately should they occur.