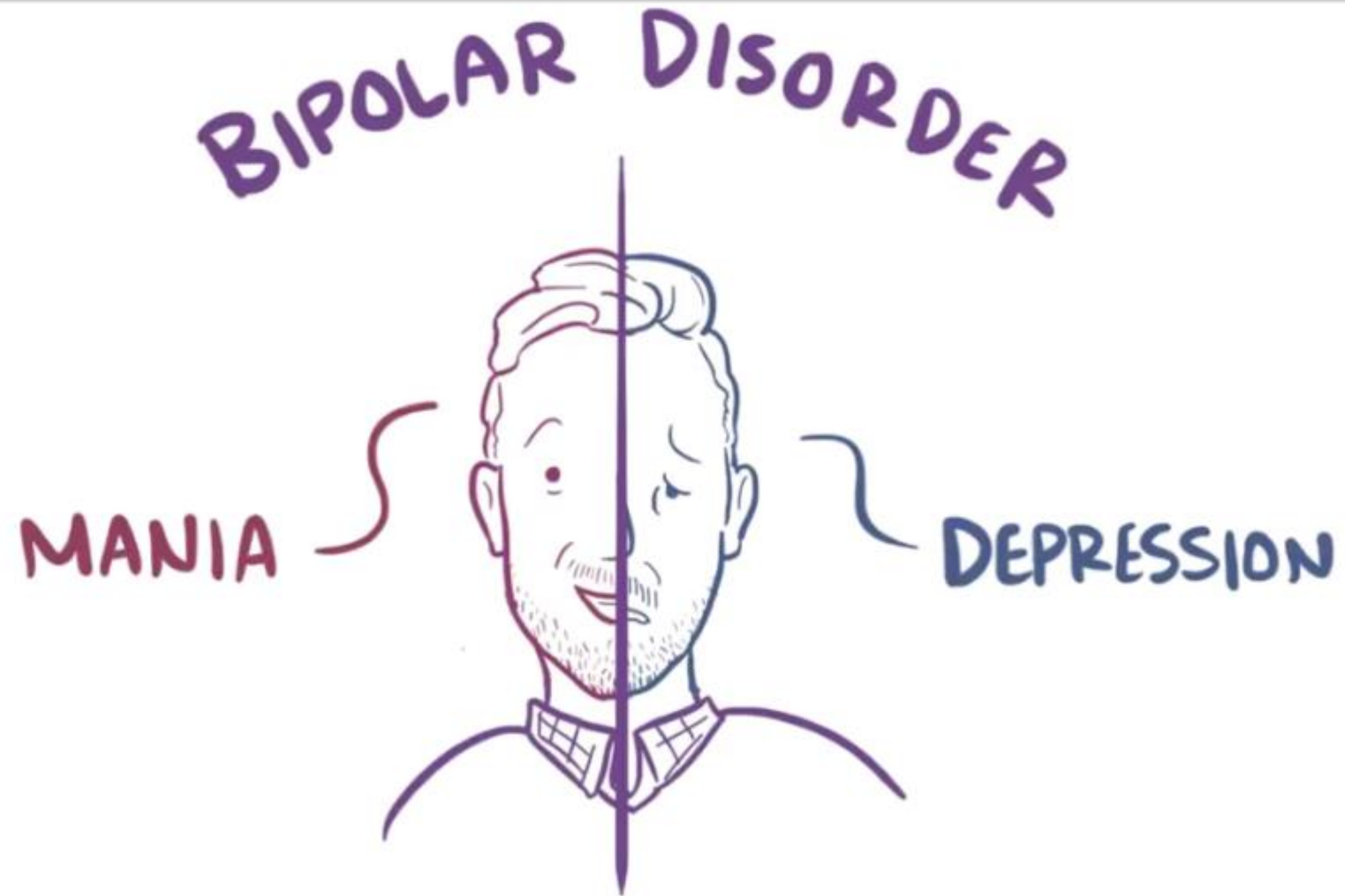


Bipolar Disorder



Learning objectives

Upon completion of the chapter, the student will be able to:

1. Explain the *pathophysiologic mechanisms* underlying bipolar disorder.
2. Recognize the symptoms of a manic episode and depressive episode in patients with bipolar disorder.
3. Identify common comorbidities of bipolar disorder.
4. Recognize the criteria for bipolar disorder as well as its subtypes.
5. Recommend individualized drug therapy for acute treatment and relapse prevention based on patient specific data.
6. Recommend monitoring methods for assessment of therapeutic and adverse effects of drugs used in the treatment of bipolar disorder.

Introduction

*Bipolar disorder: is psychiatric disorder characterized by **one or more episodes of mania** or **hypomania**, with a history of **one or more major depressive episodes**.*

- *It is chronic, with relapses and remissions.*
- *Mood episodes can be **manic**, **depressed**, or **mixed**. **separated by periods of long stability** or **cycle rapidly**. They occur **with or without psychosis**.*
- *Early diagnosis and treatment are essential to **prevent complications** and **maximize response** to treatment.*

Epidemiology and etiology

- *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.*
- *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.*
- *Patients with bipolar disorder have higher rates of suicidal thoughts attempts than the general population.*
- *Etiology: The precise etiology is unknown.*
- *Genetic and Enviromental may play role in the etiology (first-degree relatives are 10x to)*

Pathophysiology

Neurochemical hypothesis:

- One hypothesis is that bipolar disorder is caused by an imbalance of cholinergic and catecholaminergic activity. Dysregulation of this relationship could cause mood disturbance.
- Another hypothesis propose that bipolar disorder may be related to inositol disturbance.
- Brain-derived neurotrophic factor (BDNF) may play a role in bipolar disorder. Serum BDNF is low in mania and improves with treatment.

Clinical Presentation And Diagnosis

Patients presenting with depressive or elevated mood features and a history of unusual mood swings should be assessed for bipolar disorder.

Bipolar disorder is categorized into four subtypes:


- bipolar I (periods of major depressive disorder, manic);*
- bipolar II (periods of major depression and hypomania),*
- cyclothymic disorder (periods of hypomanic episodes and depressive episodes that do not meet all criteria for diagnosis of a major depressive episode), and*
- other specified and unspecified bipolar and related disorders).*

Evaluation and Diagnosis of Mood Episodes

Diagnosis episode	Impairment of functioning or need for hospitalization ^a	DSM-5 criteria ^b
Major depressive	Yes	<p>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:</p> <ul style="list-style-type: none">• 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
Manic	Yes	<p>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):</p> <ul style="list-style-type: none">• 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)

↓
mood for 2wk
W 5 sym.

↑
mood for 1wks
W3 sym.

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):
	 <i>mood for 4d</i> <i>W 3sym.</i>	<ul style="list-style-type: none"> • 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	<i>MDD W mani</i> <i>Qd ≥ W</i>	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

FOI, flight of ideas.

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- The defining feature of bipolar disorder is one or more manic or hypomanic episodes in addition to depressive episodes that are not caused by a medical condition, substance abuse, or other psychiatric disorder.
 - Initial and subsequent episodes are mostly depressive symptoms.
 - 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.

Differential Dx

- *Bipolar 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.*
- *Schizophrenia and bipolar disorder share certain symptoms, including psychosis in some patients.*

Cyclothymic Disorder

Cyclothymic disorder: is a *chronic mood disturbance* lasting at least 2 years 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*.

Suicide:

- Patients with bipolar disorder *have high risk of suicide*
- About one-third of individuals with bipolar *disorder report a previous attempt*.

Comorbid Psychiatric and Medical Conditions

Psychiatric comorbidities include:

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

TREATMENT

Desired Outcomes:

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

Nonpharmacologic Therapy

- ***Cognitive-behavioral therapy (CBT)** : is a type of psychotherapy*
- ***Electroconvulsive 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.*

General Approach to Treatment:

- *Not all patients with bipolar disorder 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.*
- *Antipsychotic drugs may be used as monotherapy or adjunctively with mood-stabilizing drugs.*
- *early and accurate treatment is essential to maximizing response.*
- *Treatment is often lifelong*

Pharmacologic Therapy

- The primary treatment modality for manic episodes is mood stabilizing agents or antipsychotic drugs, *often in combination*.
- Mood-stabilizing drugs include: *lithium, divalproex, carbamazepine(2nd), and lamotrigine*.
- 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*.

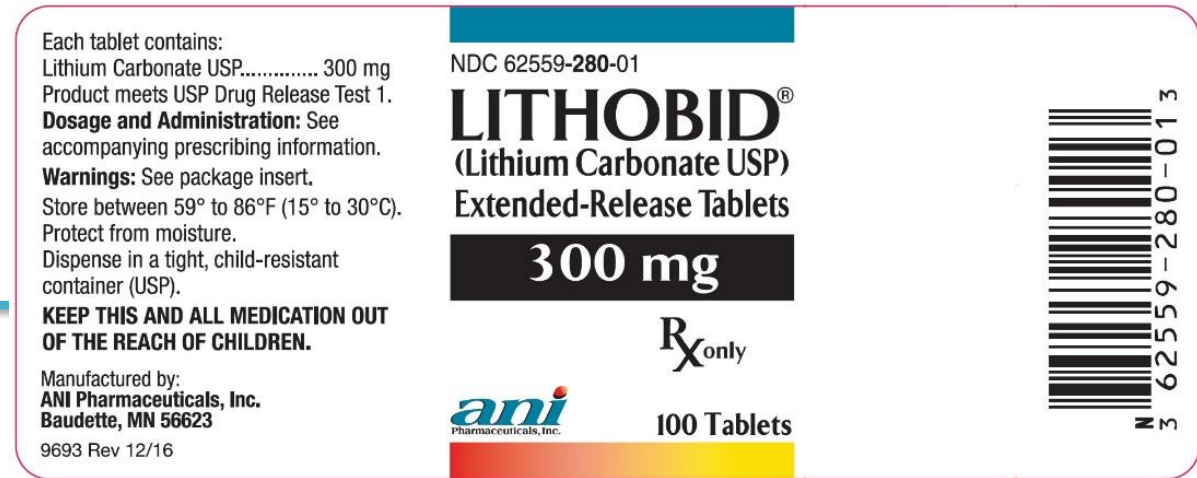
Pharmacologic Therapy

- *The primary treatment for depressive episodes in bipolar disorder is mood-stabilizing agents or certain antipsychotics .*
- *Among antipsychotic drugs, quetiapine or lurasidone as monotherapy, or adjunctive to lithium or divalproex, and olanzapine in combination with fluoxetine are approved.*
- *Antidepressants can be used but along with a mood stabilizer to reduce risk of a mood switch to mania.*
- *The primary treatment for relapse prevention is mood-stabilizing agents, often combined with antipsychotic drugs. Aripiprazole, olanzapine, and quetiapine are approved for maintenance therapy.*

Mood-Stabilizing Drugs

- *The optimal mood-stabilizing drug is effective in treatment of :*
 - *acute mania*
 - *acute bipolar depression*
 - *prevention of manic relapse*
 - *prevention bipolar depression relapse.*
- *Lithium and divalproex are first-choice drugs for the classic presentation of bipolar disorder.*

Lithium: *first approved mood-stabilizing drug.*



- *Lithium and Lamotrigine is preferred over valproate for bipolar depression. However, valproate is preferred over lithium for mixed episodes and rapid cycling.*
- *Lithium is usually initiated at a dosage of 600 to 900 mg/day.*
- *The dosage is titrated to achieve a serum lithium concentration of 0.6 to 1.2 mEq/L(trough conc.).*
- *S/E: GIT, tremor, and polyuria, acneiform rash, alopecia, worsening of psoriasis, weight gain, impaired glucose regulation, hypothyroidism, ECG change.*

Management of lithium complications

Tremor is present in up to 50% of patients (low-dose β -blockers, such as **propranolol 20 to 60 mg/day**).

- **Polyuria and polydipsia** occur in up to 60% of patients. when urine volume **exceeds 3 L/day** is termed **lithium-induced nephrogenic diabetes insipidus** (It can be treated with **hydrochlorothiazide** or **amiloride**; lithium should be reduced by 33%-50% if HCTZ used).
- **Lithium-induced hypothyroidism** is not usually an indication to discontinue the drug (**levothyroxine** can be supplemented).

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- **Acute lithium toxicity**, which occurs at serum concentrations over 2 mEq/L. Symptoms include: severe vomiting and diarrhea, deterioration in motor coordination, (coarse tremor, ataxia, and dysarthria, and impaired cognition), seizures, cardiac arrhythmias, coma, and kidney damage.
 - (Treatment of **Acute lithium toxicity** includes discontinuation of lithium, IV fluids to correct fluid and electrolyte imbalance, and osmotic diuresis or hemodialysis.
 - Drug Interactions: involve **thiazide diuretics, NSAID, and ACEi.. They increase lithium concentration.**
 - **ACEI/ARBs with lithium** combination can abruptly increase serum lithium with the potential for acute toxicity; therefore it is strongly discouraged).

Divalproex :

- *It is FDA approved for treatment of the **manic phase of bipolar disorder**.*
- *It has utility in bipolar disorder with:*
 - *rapid cycling,*
 - *mixed mood features, and*
 - *substance abuse comorbidity.*
- ***Divalproex** can be used as **monotherapy** or in **combination with lithium** or an **antipsychotic**.*
- ***Divalproex** is initiated at 500 to 1000 mg/ day.*

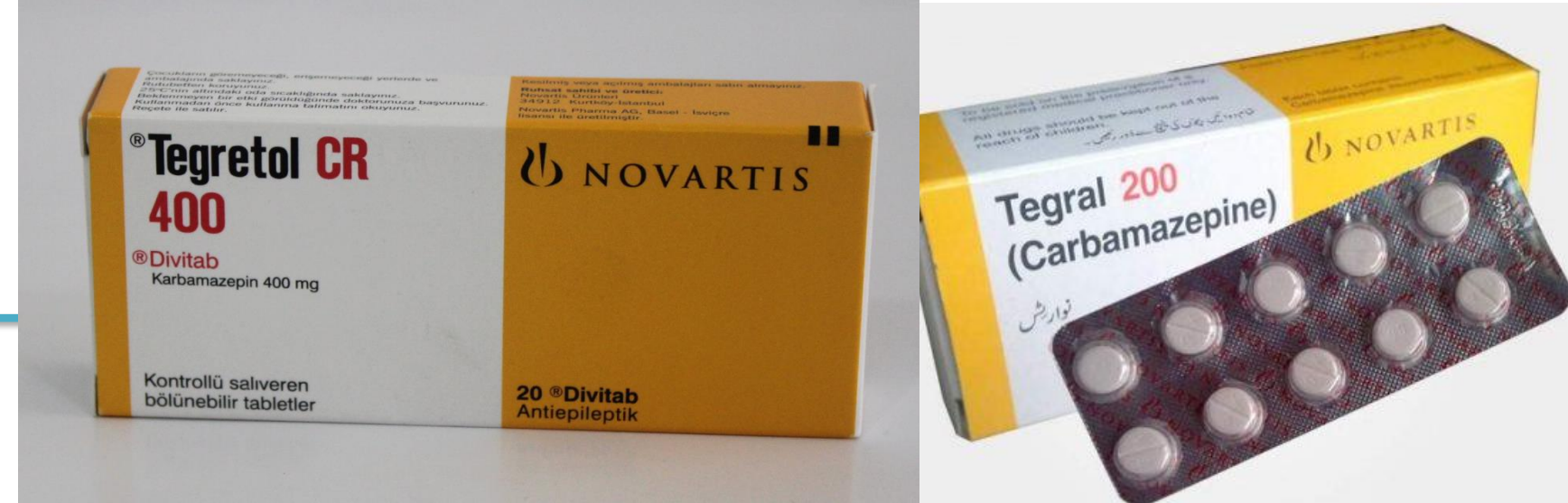


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- *The most often referenced desired VPA **serum concentration is 50 to 125 mcg/mL** (trough concentration).*

*S/E: **GI**, **tremor**, and **drowsiness**. **Weight gain(50%)**, **alopecia**, **Thrombocytopenia** (DC if $\text{plt} < 100 \times 10^3/\text{mm}^3$)*

- *Hair loss can be minimized by supplementation with a **vitamin containing selenium and zinc**.*
 - ***low-dose β -blocker** may alleviate tremor.*
- *Drug interaction : The interaction between divalproex and lamotrigine is significant.*
 - *lamotrigine dosage should be **reduced by 50% to decrease the risk of rash***

Carbamazepine:



- 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.
- Carbamazepine is initiated at 400 to 600 mg/day.
- The suggested therapeutic serum concentration is 4 to 12 mcg/mL.
- Adverse Effects. The most common adverse effects are drowsiness, dizziness, ataxia, lethargy, and confusion.
- Drug Interactions: (anticonvulsants, antipsychotics, some antidepressants, oral contraceptives, macrolide, azole antifungal).

-
- *Carbamazepine should not be given concurrently with clozapine why ?*
 - *Oxcarbazepine: is an **analogue of carbamazepine**. An advantage over carbamazepine is **less likely to cause hematologic abnormalities**. Additionally, **drug interactions are less significant**.*

Lamotrigine:

- Lamotrigine is effective for **maintenance treatment** of bipolar disorder.
- It is **more effective** for **depression relapse prevention** than for **mania relapse prevention**.
- 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**.





- *The greatest significance adverse effect of lamotrigine is a **maculopapular rash**, occurring in up to 10% of patients.*
- *The risk of rash is greater with **a rapid dosage titration** and when given concurrently with **divalproex** or other **metabolic enzyme inhibitors**.*
- *Drug interaction : **Divalproex** slows the rate of elimination of lamotrigine by about half, necessitating dosage reduction. Conversely, **carbamazepine** increases the rate of lamotrigine metabolism.*
- *In contrast to other mood-stabilizing drugs such as lithium and divalproex, lamotrigine **does not** significantly influence **body weight**.*

Antipsychotic Drugs

- SGA drugs, are approved for the treatment of *bipolar mania* or *mixed mood episodes* as *monotherapy* or in *combination* with mood stabilizers.
- Aripiprazole, olanzapine, and quetiapine are approved for *maintenance therapy* for *prevention of manic relapse*.
- The combination of *olanzapine and fluoxetine* is approved for treatment of *acute bipolar depression*.



-
- *SGAs are equivalent or superior in efficacy to lithium and divalproex for treatment of acute mania.*
 - *SGAs are less likely than FGAs to cause neurologic side effects (EPS).*
 - *SGAs are more likely to cause metabolic side effects, such as weight gain, glucose dysregulation, and dyslipidemia (olanzapine is the most likely one).*
 - *Aripiprazole, lurasidone, and ziprasidone are least associated with effects on weight, glucose, and lipids.*

Antidepressants

- Treatment of depressive episodes in patients with bipolar disorder presents a particular **challenge** because of risk of a drug induced mood switch to mania.
- **antidepressants should be combined with a mood stabilizer** to reduce risk of **mood switch**.
- Tricyclic antidepressants are thought to carry greater risk of mood switch (mania).

Special Populations:

Pediatrics:

- **evidence supports** use of **mood stabilizers and SGAs** in **children and adolescents** with bipolar disorder.
- **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.

Special Populations

Geriatrics:

Geriatrics need slow titration and close monitoring

Pregnancy and Postpartum:

- Lithium administration during the first trimester is associated with Ebstein anomaly, (a downward displacement of the tricuspid valve to the right ventricle) . The absolute risk is small, around 0.1%.
- Valproic acid and carbamazepine are human teratogens. Neural tube defects such as spina bifida occur in up to 9% of infants exposed during the first trimester during 3rd and 4th week.
- Carbamazepine can cause fetal vitamin K deficiency. Vitamin K is important for facial growth and for clotting factors.

Table 39-6

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