Pharmacology II, 4th Stage

Lippincott's Illustrated Reviews, 6th ed.

Unit III: Drugs Affecting the Central Nervous System

10- Antidepressants

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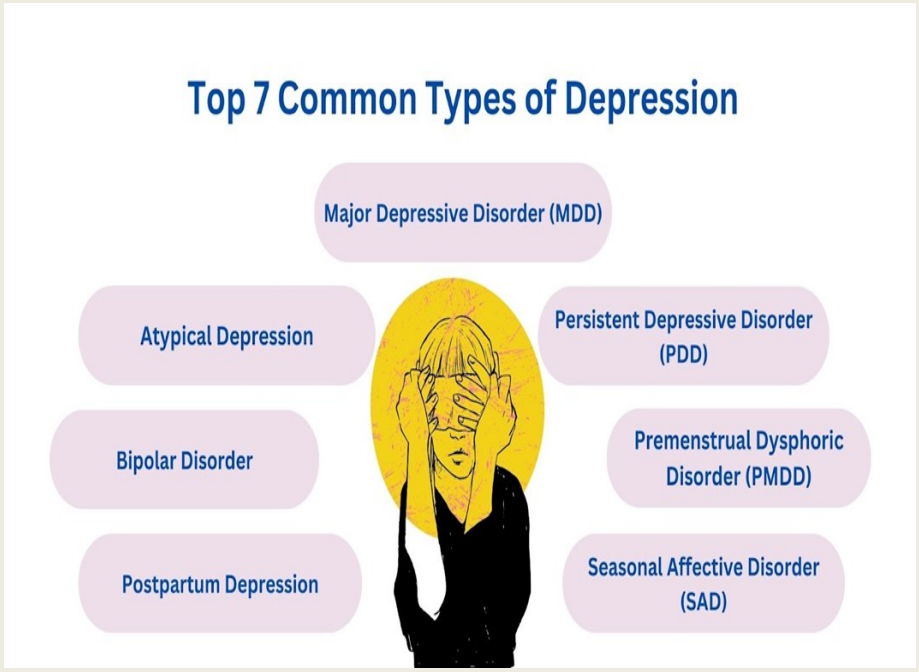
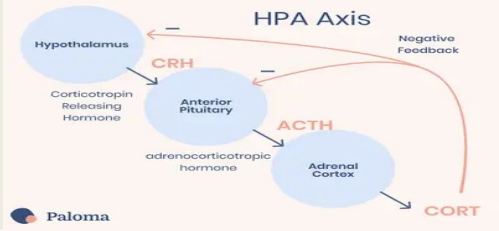
Definitions

- Depression, a global epidemic according to WHO, globally more than 264 million people of all ages suffer from depression.
- More women are affected by depression than men.
- The symptoms of depression are feelings of sadness and hopelessness, as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts.
- Depression and Major Depressive Disorder (MDD) are two terms that are often used interchangeably. However, they are not the same thing.



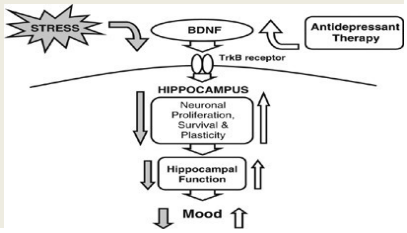
Possible Underling Mechanisms for Depression

- There is a genetic predisposition in major depression that runs in families.
- Monoamine hypothesis: there is a deficit in the concentration of the brain monoamines (norepinephrine, dopamine, and/or serotonin) resulting in depression (that are synthesized mainly in response to brain derived neurotrophic factors (BDNF)).
- The hypothalamic-pituitary-adrenal system (HPA) plays an essential role in an individual's ability to cope with stress (cortisol reduces BDNF).

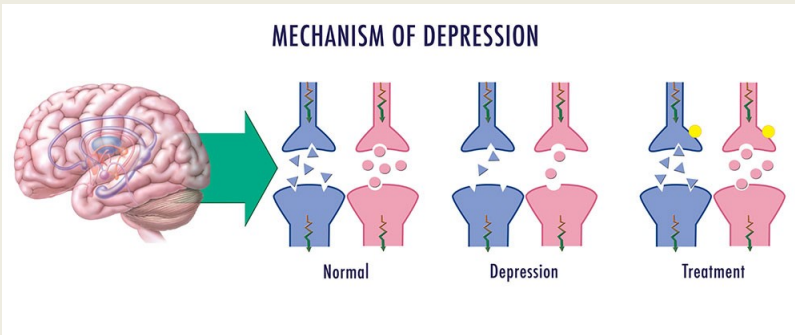


Mechanism of antidepressants action

- Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of NE and/or (5-HT) in the brain, in accordance with the biogenic amine theory. Conversely, the theory proposes that mania is caused by an overproduction of these neurotransmitters.
- Although the pharmacological effects of antidepressant and antimania drugs on neurotransmission, often occur immediately; but the time course for a therapeutic response occurs over several weeks. A truth that the monoamine theory didn't attribute. Until the role of BDNF was accomplished.



- The main subcortical limbic brain regions implicated in depression are the amygdala, hippocampus, and the dorsomedial thalamus. Both structural and functional abnormalities in these areas have been found in depression.



SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)
- *Citalopram* CELEXA
- *Escitalopram* LEXAPRO
- *Fluoxetine* PROZAC
- *Fluvoxamine* LUVOX CR
- *Paroxetine* PAXIL
- *Sertraline* ZOLOFT

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)
- *Desvenlafaxine* PRISTIQ
- *Duloxetine* CYMBALTA
- *Levomilnacipran* FETZIMA
- *Venlafaxine* EFFEXOR

ATYPICAL ANTIDEPRESSANTS
- *Bupropion* WELLBUTRIN, ZYBAN
- *Mirtazapine* REMERON
- *Nefazodone*
- *Trazodone* DESYREL
- *Vilazodone* VIIBRYD
- *Vortioxetine* BRINTELLIX

TRICYCLIC ANTIDEPRESSANTS (TCAs)
- *Amitriptyline*
- *Amoxapine*
- *Clomipramine* ANAFRANIL
- *Desipramine* NORPRAMIN
- *Doxepin* SINEQUAN
- *Imipramine* TOFRANIL
- *Maprotiline* LUDIOMIL
- *Nortriptyline* PAMELOR
- *Protriptyline* VIVACTIL
- *Trimipramine* SURMONTIL

MONOAMINE OXIDASE INHIBITORS (MAOIs)
- *Isocarboxazid* MARPLAN
- *Phenelzine* NARDIL
- *Selegiline* EMSAM
- *Tranylcypromine* PARNATE

Figure 10.1
Summary of antidepressants.

DRUG	UPTAKE INHIBITION	
	Nor-epinephrine	Serotonin
Selective serotonin reuptake inhibitor		
Fluoxetine	0	++++
Selective serotonin/ norepinephrine reuptake inhibitors		
Venlafaxine	++*	++++
Duloxetine	++++	++++
Tricyclic antidepressants		
Imipramine	++++	+++
Nortriptyline	++++	++

Figure 10.2
Relative receptor specificity of some antidepressant drugs. **Venlafaxine* inhibits norepinephrine reuptake only at high doses. ++++ = very strong affinity +++ = strong affinity ++ = moderate affinity + = weak affinity 0 = little or no affinit .

I. Selective serotonin reuptake inhibitors (SSRIs)

- These drugs have 300- to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter.
- Moreover, the SSRIs have little blocking activity at muscarinic, α-adrenergic, and histaminic H1 receptors. Therefore, common side effects associated with TCAs, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are not commonly seen with the SSRIs.
- Because they have different adverse effects and are relatively safe even in overdose, the SSRIs have largely replaced TCAs and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression.
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Table 1. FDA-Approved SSRIs

Generic	Trade Name	Approved Uses
Citalopram	Celexa	Depression
Escitalopram	Lexapro	Depression, generalized anxiety
Fluoxetine	Prozac	Depression, OCD, bulimia, panic disorder
	Sarafem	PMDD
Fluvoxamine	Luvox	OCD
Paroxetine	Paxil	Depression, OCD, generalized anxiety, panic disorder, social anxiety, PTSD
Sertraline	Zoloft	Depression, OCD, panic disorder, social anxiety, PTSD, PMDD
Vilazodone	Viibryd	Depression

OCD: obsessive-compulsive disorder; PMDD: premenstrual dysphoric disorder; PTSD: posttraumatic stress disorder; SSRI: selective serotonin reuptake inhibitor.

- A. Actions Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more. Patients who do not respond to one antidepressant may respond to another, and approximately 80% or more will respond to at least one antidepressant drug.
- B. Therapeutic uses depression, OCD, panic disorder, generalized anxiety disorder, PTDD, social anxiety disorder, premenstrual dysphoric disorder, and bulimia nervosa (fluxetine).
- C. Pharmacokinetics Fluoxetine differs from the other members of the class by having a much longer half-life (50 hours), and the half life of its active metabolite S-norfluxetine is quite long, averaging 10 days. It is available as a sustained-release preparation allowing once-weekly dosing.
- Fluoxetine and paroxetine are potent inhibitors of a CYP450 isoenzyme (CYP2D6) responsible for the elimination of TCAs, antipsychotic drugs, and some antiarrhythmic and β-adrenergic antagonist drugs.
- Dosages of the SSRIs should be reduced in patients with hepatic impairment.

- D. Adverse effects :

1. Sleep disturbances: These drugs may produce insomnia or somnelence. Paroxetine and fluoxamine are generally more sedating than activating, and they may be useful in patients who have difficulty sleeping. Conversely, patients who are fatigued or complaining of excessive somnolence may benefit from one of the more activating SSRIs, such as fluxetine or sertraline.

2. Sexual dysfunction: Sexual dysfunction, which may include loss of libido, delayed ejaculation, and anorgasmia, is common with the SSRIs. One option for managing SSRI-induced sexual dysfunction is to change the antidepressant to one with fewer sexual side effects, such as bupropion or mirtazapine. Alternatively, the dose of the drug may be reduced.

- 3. Use in children and teenagers: Antidepressants should be used cautiously in children and teenagers, because about 1 out of 50 children report suicidal ideation as a result of SSRI treatment. Pediatric patients should be observed for worsening depression and suicidal thinking with initiation or dosage change of any antidepressant.
- Fluoxetine, sertraline, and fluoxamine are approved for use in children to treat obsessive–compulsive disorder, and fluxetine and escitalopram are approved to treat childhood depression.

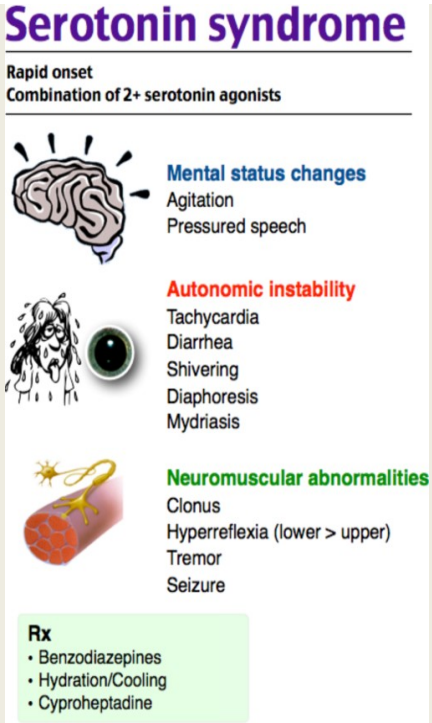
- 4. Overdose:

Seizure, serotonin syndrom.

- 5. Discontinuation syndrome:

All of the SSRIs have the potential to cause a discontinuation syndrome after their abrupt withdrawal, particularly the agents with shorter half-lives and inactive metabolites. Fluoxetine has the lowest risk of causing an SSRI discontinuation syndrome (its longer half-life , active Metabolite).

Possible signs and symptoms of SSRI discontinuation syndrome include headache, malaise, and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern.



II. Serotonin- Norepinephrine Reuptake Inhibitors (SNRIs)

- Venlafaxine, desvenlafaxine, levomilnacipran, and duloxetine inhibit the reuptake of both serotonin and norepinephrine .
- These may be effective in :

1. treating depression in patients in whom SSRIs are ineffective.
2. The chronic painful symptoms, such as backache and muscle aches, that accompanies depression against which SSRIs are also relatively ineffective .
3. Both SNRIs and the TCAs, with their dual inhibition of both 5- HT and NE reuptake, are sometimes effective in relieving pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, and low back pain.

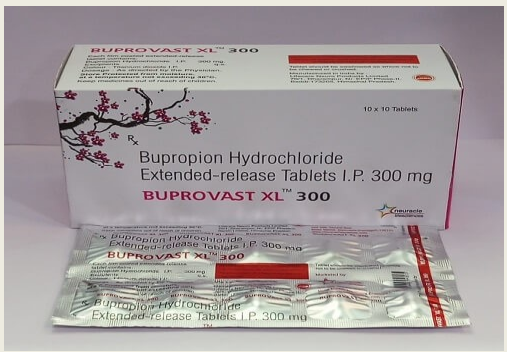
- The SNRIs, unlike the TCAs, have little activity at α-adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the TCAs. The SNRIs may precipitate a discontinuation syndrome.

- A. Venlafaxine and desvenlafaxine Venlafaxine is a potent inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake. Venlafaxine has minimal inhibition of the CYP450 isoenzymes and is a substrate of the CYP2D6 isoenzyme. Desvenlafaxine is the active, demethylated metabolite of venlafaxine.
- B. Duloxetine inhibits serotonin and norepinephrine reuptake at all doses. It is extensively metabolized in the liver to inactive metabolites and should be avoided in patients with liver dysfunction. Duloxetine is a moderate inhibitor of CYP2D6 isoenzymes and may increase concentrations of drugs metabolized by this pathway, such as antipsychotics.
- C. Levomilnacipran It is primarily metabolized by CYP3A4, and, thus, activity may be altered by inducers or inhibitors of this enzyme system.

III. ATYPICAL ANTIDEPRESSANTS

- The atypical antidepressants are a mixed group of agents that have actions at several different sites. This group includes bupropion , mirtazapin , nefazodone , trazodone , vilazodone , and vortioxetine.
- A. Bupropion (SDNRI):
- Is a weak dopamine and norepinephrine reuptake inhibitor that is used to alleviate the symptoms of depression.
- Useful for decreasing cravings and attenuating withdrawal symptoms of nicotine in patients trying to quit smoking.
- Side effects may include dry mouth, sweating, nervousness, tremor, and a dose dependent increased risk for seizures.
- It has a very low incidence of sexual dysfunction.

- Use of bupropion should be avoided in patients at risk for seizures or those who have eating disorders such as bulimia.

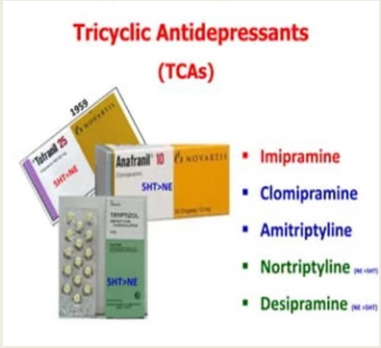


- B. Mirtazapine serving as an antagonist at presynaptic α2 receptors, antagonism at 5-HT2 receptors, potent antihistaminic activity (sedating),, but it does not cause the antimuscarinic side effects of the TCAs, or interfere with sexual function like the SSRIs. Increased appetite and weight gain frequently occur .
- C. Nefazodone and trazodone These are weak inhibitors of serotonin reuptake, their therapeutic benefit appears to be related to their ability to block postsynaptic 5-HT2a receptors, both agents are sedating (H1 -blocking activity). Trazodone is commonly used off-label for the management of insomnia, but is associated with (priapism), and nefazodone has been associated with (a risk for hepatotoxicity).
- Both agents also have mild to moderate α1 receptor antagonism, contributing to orthostasis and dizziness.

- D. Vilazodone is a serotonin reuptake inhibitor and a 5-HT1a partial agonist. Although the extent to which the 5-HT1a receptor activity contributes to its therapeutic effects is unknown, this possible mechanism of action renders it unique from that of the SSRIs. The adverse effect profile of vilazodone is similar to the SSRIs, including a risk for discontinuation syndrome if abruptly stopped.
- E. Vortioxetine utilizes a combination of serotonin reuptake inhibition, 5-HT1a agonism, and 5-HT3 and 5-HT7 antagonism as its suggested mechanisms of action to treat depression.
- The common adverse effects include nausea, vomiting, and constipation, which may be expected due to its serotonergic mechanisms.

VI. Tricyclic Antidepressants

- The TCAs block norepinephrine and serotonin reuptake into the presynaptic neuron and, thus, if discovered today, might have been referred to as SNRIs, except for their differences in adverse effects relative to this newer class of antidepressants.
- Maprotiline and amoxapine are related "tetracyclic" antidepressant agents and are commonly included in the general class of TCAs. Patients who do not respond to one TCA may benefit from a different drug in this group.

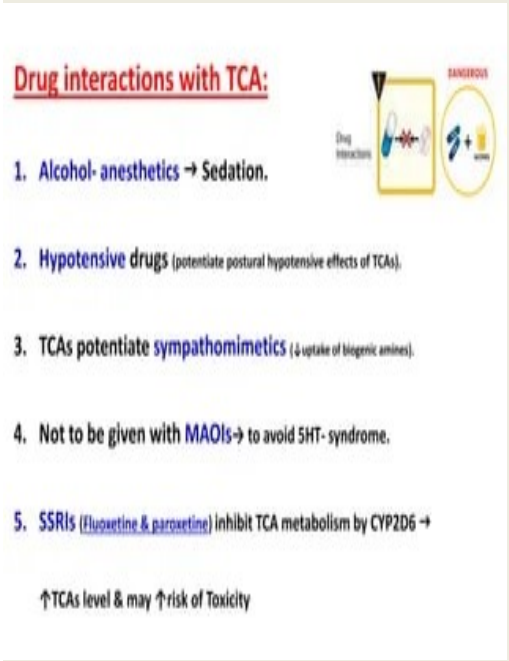


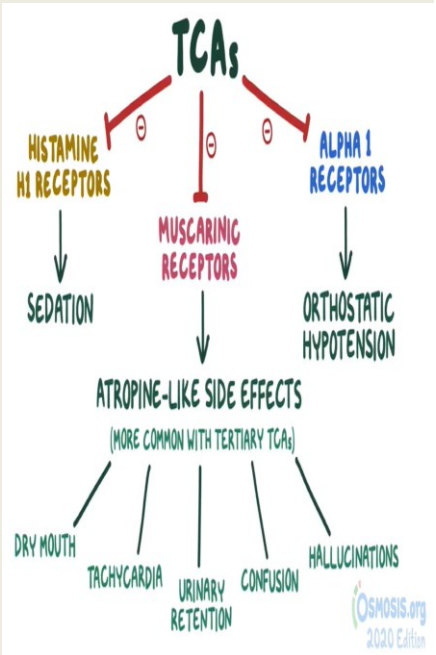
- A. Mechanism of action
- 1. Inhibition of neurotransmitter reuptake: TCAs and amoxapine are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. Maprotiline and desipramine are relatively selective inhibitors of norepinephrine reuptake.
- 2. Blocking of receptors: TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors. Actions at these receptors are likely responsible for many of their adverse effects. Amoxapine also blocks 5-HT2 and dopamine D2 receptors.
- B. Actions: The onset of the mood elevation is slow, requiring 2 weeks or longer . Patient response can be used to adjust dosage. After a therapeutic response, the dosage can be gradually reduced to improve tolerability, unless relapse occurs.

- Physical and psychological dependence have been rarely reported. This necessitates slow withdrawal to minimize discontinuation syndromes and cholinergic rebound effects.

C. Therapeutic uses

1. The TCAs are effective in treating moderate to severe depression, and panic disorder .
2. Imipramine has been used to control bed-wetting in children older than 6 years of age; however, it has largely been replaced by desmopressin and nonpharmacologic treatments (enuresis alarms).
3. The TCAs, particularly amitriptyline, have been used to help prevent migraine headache and treat chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of pain is unclear.
4. Low doses of TCAs, especially doxepin, can be used to treat insomnia.





VI. MONOAMINE OXIDASE INHIBITORS

- Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver. In the neuron, MAO functions as a "safety valve" to oxidatively deaminate and inactivate any excess neurotransmitters (for example, norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest.
- The MAOIs may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitters to escape degradation and, therefore, to accumulate within the presynaptic neuron and leak into the synaptic space.
- The four MAOIs currently available for treatment of depression include phenelzine, tranylcypromine , isocarboxazid, and selegiline.
- Use of MAOIs is limited due to the complicated dietary restrictions required while taking these agents.

- A. Mechanism of action Most MAOIs, such as phenelzine, form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into the synaptic space . These drugs inhibit also MAO in the liver and gut that catalyzes oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods. The MAOIs, therefore, show a high incidence of drug–drug and drug–food interactions.
- Selegiline administered as the transdermal patch may produce less inhibition of gut and hepatic MAO at low doses because it avoids first-pas metabolism.
- B. Actions Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs, SNRIs, and TCAs, is delayed several weeks. Selegiline and tranylcypromine have an amphetamine-like stimulant effect that may produce agitation or insomnia.

C. Therapeutic uses The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs and SSRIs or who experience strong anxiety.
A special subcategory of depression, called atypical depression, may respond preferentially to MAOIs.
Because of their risk for drug– drug and drug–food interactions, the MAOIs are considered last-line agents in many treatment settings

- E. Adverse effects Severe and often unpredictable side effects, due to drug–food and drug–drug interactions, limit the widespread use of MAOIs. For example, tyramine, which is contained in foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish, and red wines, is normally inactivated by MAO in the gut.
- Individuals receiving a MAOI are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in a hypertensive crisis, with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures.

- and, possibly, stroke. Patients must, therefore, be educated to avoid tyramine-containing foods. Phentolamine and prazosin are helpful in the management of tyramine-induced hypertension.
- Other possible side effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation. Due to the risk of serotonin syndrome, the use of MAOIs with other antidepressants is contraindicated.
- For example, SSRIs should not be coadministered with MAOIs. Both SSRIs and MAOIs require a washout period of at least 2 weeks before the other type is administered, with the exception of fluxetine, which should be discontinued at least 6 weeks before a MAOI is initiated.

Mania

- Mania is characterized by the opposite behavior to that of depression: enthusiasm, anger, rapid thought and speech patterns, extreme self-confidenc , and impaired judgment.
- Treatment of Mania and Bipolar Disorder:
- A. Lithium salts are used acutely and prophylactically for managing bipolar patients. The mode of action is unknown. The therapeutic index of lithium is extremely low, and lithium salts can be toxic. Common adverse effects may include headache, dry mouth, polydipsia, polyuria, polyphagia, GI distress (give lithium with food), fine hand tremor, dizziness, fatigue, dermatologic reactions, and sedation. Higher plasma levels may indicate toxicity and include ataxia, slurred speech, coarse tremors, confusion, and convulsions.
- Thyroid function may be decreased and should be monitored. lithium is renally eliminated, and though caution should be used when dosing this drug in renally impaired patients, it may be the best choice in patients with hepatic impairment.

- B. Other drugs
- Several antiepileptic drugs, including carbamazepine, valproic acid, and lamotrigine, have been approved as mood stabilizers for bipolar disorder.
- Other agents that may improve manic symptoms include the older (chlorpromazine and haloperidol) and newer antipsychotics.
- The atypical antipsychotics risperidone, olanzapine, ziprasidone, aripiprazole, asenapine, and quetiapine are also used for the management of mania.
- Quetiapine, lurasidone, and the combination of olanzapine and fluxetine have been approved for bipolar depression.