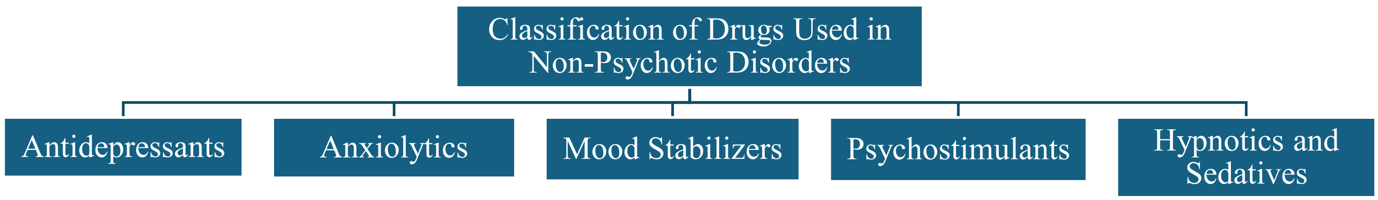
Drugs Used in Non-Psychotic Disorders

Part-01: ANTIDEPRASSANTS

Written By
Md Rasel Mahamud
PHARMACIST
B. Pharm (Professional)

Non-psychotic disorders are mental health conditions in which the patient usually maintains contact with reality. These disorders mainly include anxiety disorders, depressive disorders, obsessive-compulsive disorder (OCD), trauma-related disorders, somatic symptom disorders, sleep disorders, and stress-related conditions. Medicines used in these disorders mainly act by changing neurotransmitter activity in the brain, especially serotonin, norepinephrine, dopamine, gamma-aminobutyric acid (GABA), glutamate, histamine, and melatonin pathways.

Classification of Drugs Used in Non-Psychotic Disorders:



ANTIDEPRESSANTS

Antidepressants are a group of medicines primarily used to treat depressive disorders, but they are also effective in several other mental and physical health conditions such as anxiety disorders, obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), eating disorders, chronic pain syndromes, and some sleep disorders. These medications work mainly by balancing certain neurotransmitters—chemical messengers in the brain—especially serotonin, norepinephrine, and dopamine, which influence mood, emotions, motivation, sleep, and concentration.

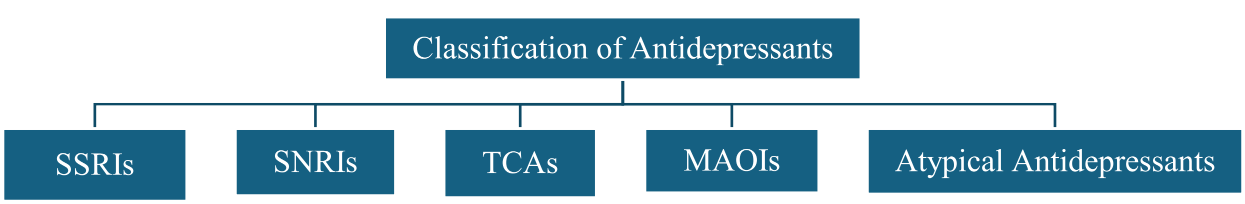
Depression is associated with disturbances in brain chemistry, stress responses, and emotional regulation. Antidepressants help improve communication between nerve cells and gradually restore emotional balance. Unlike painkillers or sedatives, antidepressants usually do not produce immediate effects. Most require several weeks before noticeable improvement occurs because the brain needs time to adapt to the changes in neurotransmitter activity.

The brain contains billions of neurons that communicate through neurotransmitters. In many depressive illnesses, the levels or functioning of neurotransmitters such as serotonin and norepinephrine become altered. Antidepressants increase the availability or activity of these chemicals in the brain.

The major neurotransmitters involved include:

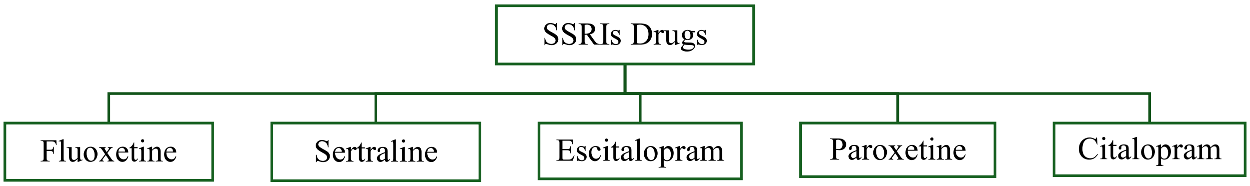
- **Serotonin:** Regulates mood, appetite, sleep, and anxiety.
- **Norepinephrine:** Influences alertness, energy, and concentration.
- **Dopamine:** Associated with motivation, pleasure, and reward.

Different classes of antidepressants target these neurotransmitters in different ways.

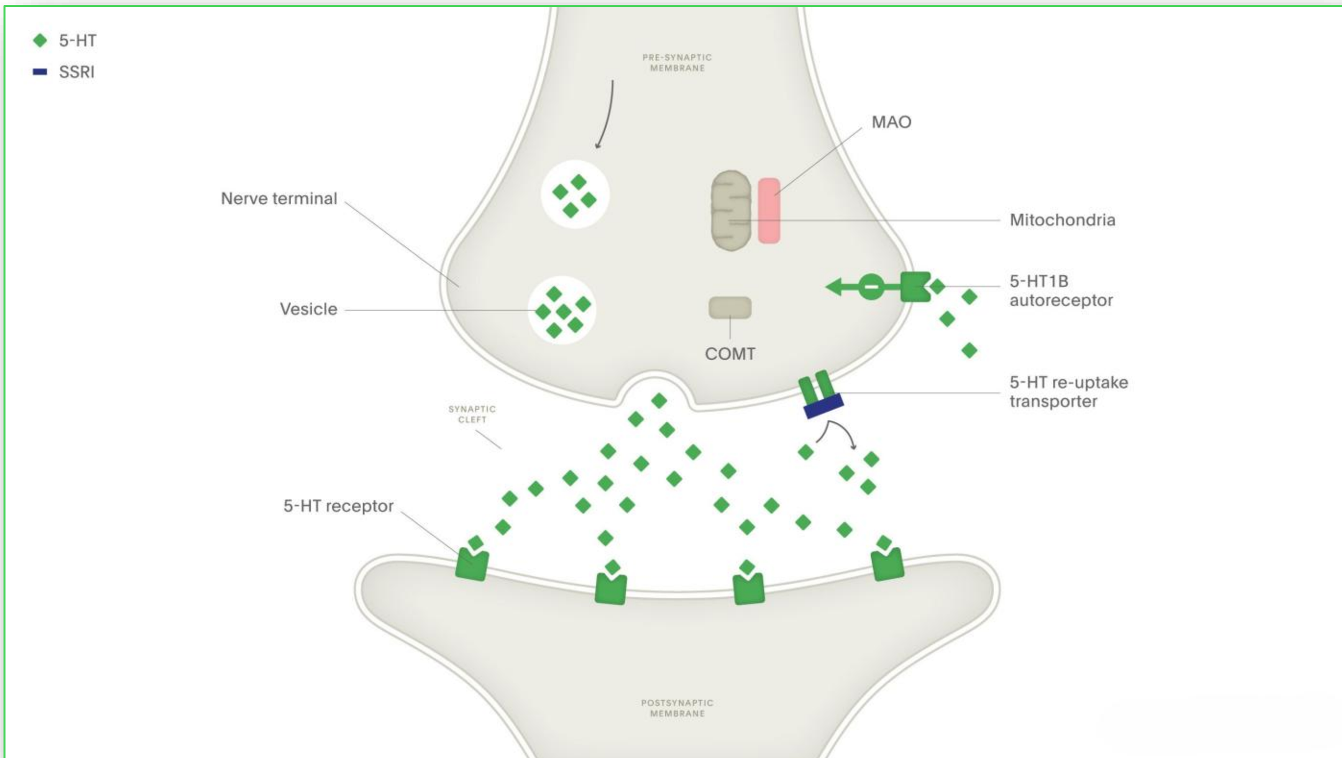


Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are the most commonly prescribed antidepressants because they are generally safer and better tolerated than older drugs. They work by blocking the reuptake of serotonin, increasing its level in the brain.



Mechanism of Action of SSRIs:



Selective Serotonin Reuptake Inhibitors (SSRIs) are a group of antidepressant medications that primarily act by increasing the availability of serotonin in the brain. Serotonin, also known as 5-hydroxytryptamine (5-HT), is an important neurotransmitter involved in regulating mood, emotions, sleep, appetite, anxiety, memory, and overall psychological stability. Under normal physiological conditions, serotonin is released from the presynaptic neuron into the synaptic cleft, where it binds to serotonin receptors located on the postsynaptic neuron and transmits nerve impulses. After this signaling process is completed, most of the serotonin is reabsorbed back into the presynaptic neuron through a specialized protein called the serotonin transporter (SERT). This reuptake mechanism rapidly removes serotonin from the synaptic cleft and limits the duration of its action.

The primary mechanism of SSRIs is the selective inhibition of this serotonin transporter. These drugs bind to the SERT protein on the presynaptic membrane and block the reuptake of serotonin into the neuron. As a result, serotonin accumulates in the synaptic cleft and remains available for a longer period of time to stimulate postsynaptic serotonin receptors. This prolonged serotonergic activity enhances neurotransmission in brain pathways that regulate mood and anxiety.

$$\text{SSRIs} \rightarrow \text{SERTs Inhibition} \rightarrow \uparrow \text{Synaptic Serotonin.}$$

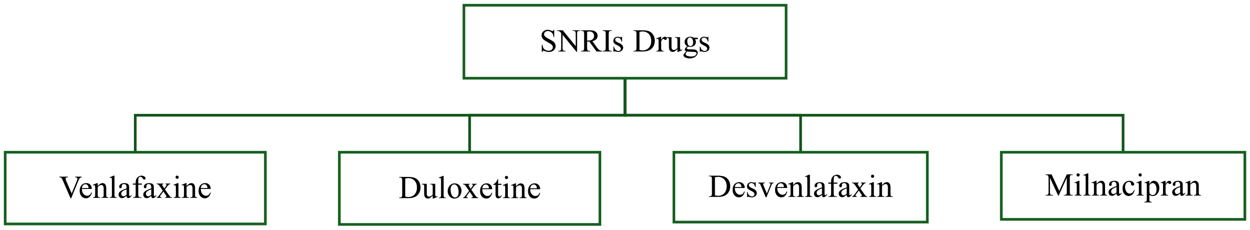
Although SSRIs increase serotonin levels rapidly after administration, the clinical antidepressant effect usually takes several weeks to appear. This delay occurs because the brain initially responds to increased serotonin through activation of presynaptic inhibitory auto receptors, particularly the 5-HT1A auto receptors. These auto receptors function as a feedback mechanism and temporarily reduce the firing rate of serotonin neurons and serotonin release. Over time, however, continued exposure to SSRIs causes these auto receptors to become desensitized and less responsive. Once this desensitization occurs, serotonergic neurons resume more normal firing activity, resulting in a sustained increase in serotonin transmission throughout important emotional and cognitive pathways of the brain.

SSRIs also produce long-term adaptive changes in neural circuits. Chronic enhancement of serotonin signaling influences receptor sensitivity, gene expression, and intracellular signaling pathways. Research suggests that SSRIs may increase levels of brain-derived neurotrophic factor (BDNF), a protein involved in neuronal survival, synaptic plasticity, and neurogenesis. These neuroplastic changes are believed to help restore the function of brain regions affected by chronic stress and depression, particularly the hippocampus, amygdala, and prefrontal cortex. Through these mechanisms, SSRIs gradually improve emotional regulation, reduce anxiety and fear responses, and alleviate depressive symptoms.
The term “selective” is used because these medications mainly affect serotonin reuptake and have relatively little action on other neurotransmitters such as norepinephrine, dopamine, or acetylcholine. This selectivity contributes to their comparatively safer side-effect profile when compared with older antidepressants such as tricyclic antidepressants (TCAs). Common SSRIs include Fluoxetine, Sertraline, Escitalopram, Paroxetine, and Citalopram.

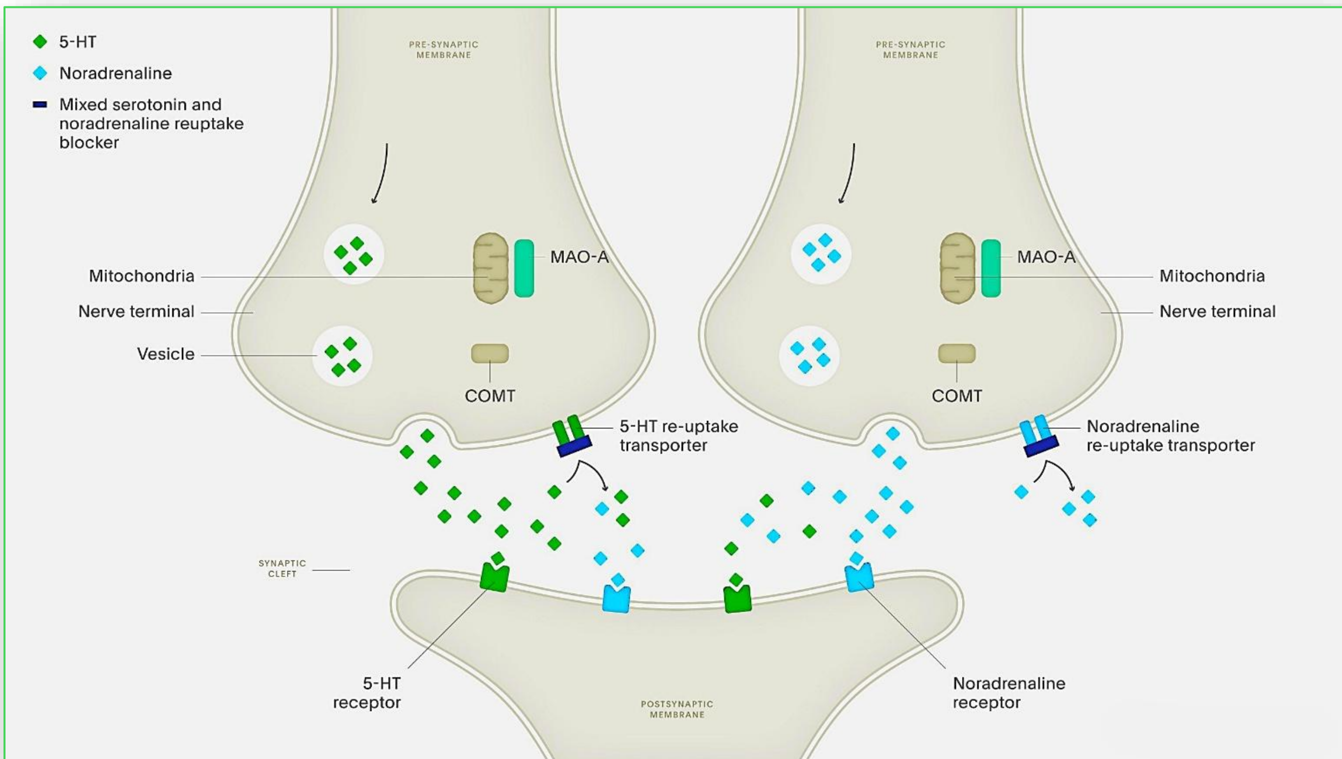
In addition to their antidepressant effects, SSRIs are widely used in the treatment of anxiety disorders, obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder, and post-traumatic stress disorder (PTSD). Their therapeutic action arises not simply from increasing serotonin levels, but from the gradual adaptive changes they produce in neurotransmission, receptor regulation, and neural connectivity within the brain.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs) are a class of antidepressant medications primarily used to treat major depressive disorder, anxiety disorders, neuropathic pain, fibromyalgia, and some panic-related conditions.



Mechanism of Action:



Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs) are a group of antidepressant medications that act primarily by increasing the concentration and activity of two major neurotransmitters in the central nervous system: serotonin (5-hydroxytryptamine or 5-HT) and norepinephrine (NE). These neurotransmitters are critically involved in the regulation of mood, emotional behavior, motivation, attention, sleep, stress response, and pain perception. Common SNRI drugs include Venlafaxine, Duloxetine, Desvenlafaxine, and Milnacipran. Their therapeutic action is based on altering neurotransmission within important brain circuits associated with depression and anxiety.

Under normal physiological conditions, neurons communicate with one another through chemical messengers called neurotransmitters. When an electrical impulse reaches the terminal of a presynaptic neuron, serotonin and norepinephrine are released into the synaptic cleft, the microscopic space between two neurons. These neurotransmitters then bind to specific receptors on the postsynaptic neuron and transmit signals that influence mood, cognition, and behavior. After the signal transmission is completed, most of the released neurotransmitters are transported back into the presynaptic neuron through specialized transporter proteins known as the serotonin transporter (SERT) and norepinephrine transporter (NET). This reuptake process normally terminates neurotransmitter activity and recycles the chemicals for future use.

In depressive and anxiety disorders, the functional activity of serotonergic and noradrenergic systems is often reduced or dysregulated. Lower neurotransmitter availability may impair communication between neurons in mood-regulating areas of the brain such as the prefrontal cortex, hippocampus, amygdala, and limbic system. SNRIs exert their pharmacological effect by inhibiting both SERT and NET transporters.

By blocking these transporters, SNRIs prevent serotonin and norepinephrine from being reabsorbed into the presynaptic neuron. As a result, higher concentrations of these neurotransmitters remain in the synaptic cleft for a longer period of time. This prolonged presence increases the likelihood of neurotransmitters binding to postsynaptic receptors, thereby enhancing neuronal signaling and strengthening neurotransmission within mood-regulating neural pathways.

The increased serotonin activity produced by SNRIs contributes significantly to their antidepressant and anxiolytic effects. Serotonin plays an essential role in emotional stability, feelings of well-being, appetite regulation, sleep, and control of anxiety and fear responses. Enhanced serotonergic transmission improves depressive symptoms such as sadness, hopelessness, emotional emptiness, irritability, and loss of interest in activities. It also helps regulate excessive fear and anxiety by modulating neuronal activity in the amygdala and other limbic structures involved in emotional processing. Improved serotonin function may additionally normalize sleep disturbances and appetite changes commonly associated with depressive disorders.

At the same time, increased norepinephrine activity contributes to improved alertness, energy, motivation, concentration, and psychomotor activity. Norepinephrine is strongly associated with the body’s arousal and stress-response systems. Many depressed individuals experience fatigue, poor concentration, slowed thinking, and reduced motivation, partly due to diminished noradrenergic activity. By increasing norepinephrine availability, SNRIs enhance signaling in pathways involved in attention and executive functioning, leading to improvements in mental focus, cognitive performance, and physical energy.

An important feature of SNRIs is their role in pain modulation. Norepinephrine and serotonin participate in descending inhibitory pain pathways that originate in the brainstem and project to the spinal cord. These pathways suppress the transmission of pain signals ascending from peripheral nerves. By enhancing serotonergic and noradrenergic activity, SNRIs strengthen these inhibitory pathways and reduce pain perception.

This mechanism explains why some SNRIs, especially Duloxetine and Milnacipran, are useful not only for depression and anxiety but also for conditions such as diabetic neuropathy, fibromyalgia, chronic musculoskeletal pain, and chronic back pain.

Although SNRIs increase neurotransmitter levels rapidly after administration, clinical improvement does not occur immediately. Most patients require several weeks before experiencing significant symptom relief. This delay occurs because the long-term therapeutic effects depend not only on increased neurotransmitter concentration but also on adaptive changes within neural circuits. Initially, increased serotonin and norepinephrine stimulate autoreceptors located on presynaptic neurons, which temporarily reduce neurotransmitter release. With continued treatment, these autoreceptors gradually become desensitized, allowing greater neurotransmitter release and more effective synaptic signaling.

Long-term SNRI therapy also produces changes in gene expression and neuronal plasticity. Chronic depression and stress are associated with structural and functional changes in the brain, including reduced neuronal connectivity and decreased activity in the hippocampus and prefrontal cortex. SNRIs may reverse some of these abnormalities by increasing the expression of brain-derived neurotrophic factor (BDNF), a protein involved in neuronal growth, survival, and synaptic plasticity.

Enhanced neuroplasticity improves communication between brain regions involved in emotional regulation, cognition, and stress adaptation. Over time, these structural and functional changes contribute to stabilization of mood and reduction of anxiety symptoms.

Some SNRIs exhibit dose-dependent pharmacological actions. For example, Venlafaxine primarily inhibits serotonin reuptake at lower doses, while norepinephrine reuptake inhibition becomes more prominent at higher doses. This dose-related difference may influence both therapeutic outcomes and adverse effects.

The adverse effects of SNRIs are closely related to their mechanism of action. Increased serotonin activity may cause nausea, headache, gastrointestinal disturbances, insomnia, or sexual dysfunction, while increased norepinephrine activity may produce sweating, tremor, increased heart rate, agitation, or elevated blood pressure. In rare cases, excessive serotonergic activity may lead to serotonin syndrome, a potentially life-threatening condition characterized by fever, muscle rigidity, autonomic instability, and altered mental status.

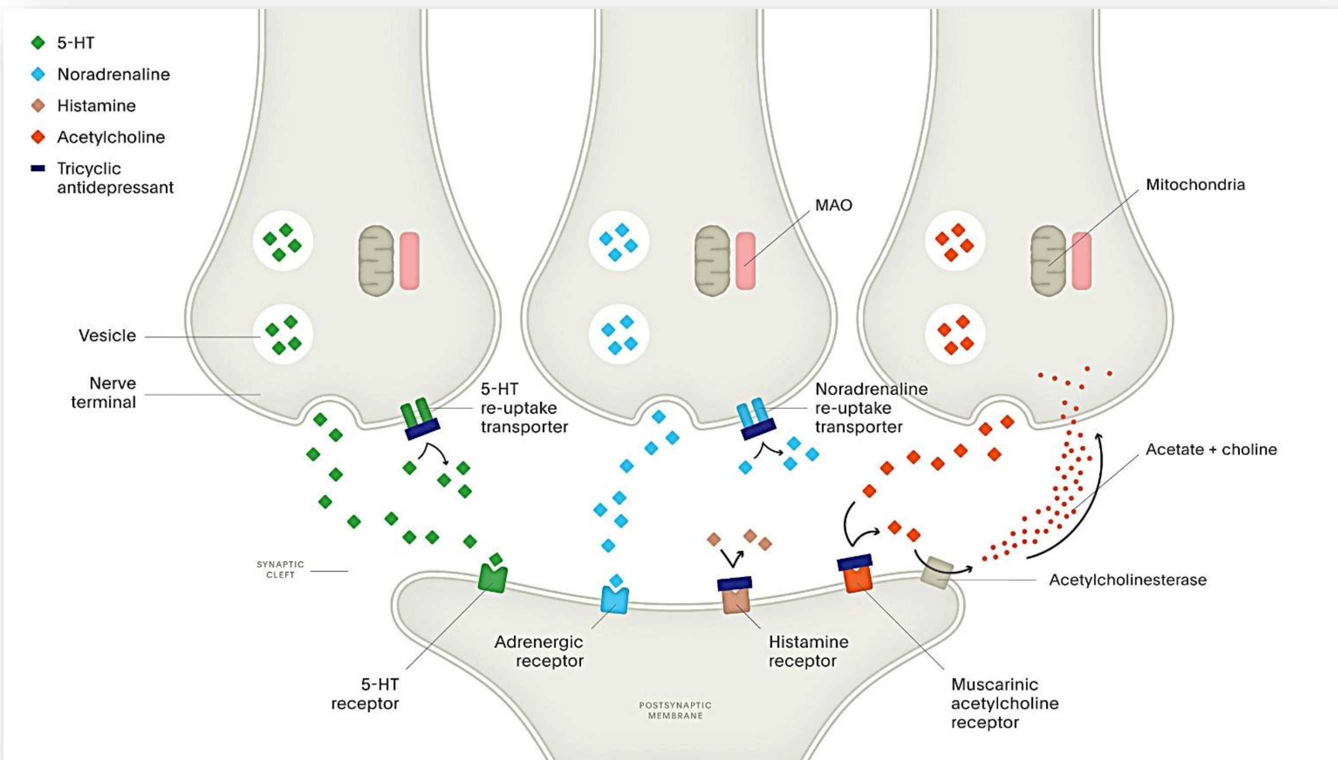
Tricyclic Antidepressants (TCAs)

These medicines were among the earliest effective antidepressants and are used in conditions such as major depressive disorder, anxiety disorders, neuropathic pain, migraine prevention, and obsessive-compulsive disorder.
The term “tricyclic” comes from their chemical structure, which contains three interconnected rings.

TCAs Drugs

- Amitriptyline
- Imipramine
- Nortryptiline
- Clomipramine

Mechanism of Action:



Tricyclic antidepressants (TCAs) are a class of antidepressant medications that exert their therapeutic effects primarily by increasing the concentration of important neurotransmitters in the brain, especially serotonin and norepinephrine. Common examples include Amitriptyline, Imipramine, Nortriptyline, and Clomipramine. These drugs are called “tricyclic” because their chemical structure contains three interconnected rings. TCAs were among the first highly effective antidepressants developed and are still used in the treatment of major depressive disorder, anxiety disorders, neuropathic pain, migraine prevention, and certain sleep disturbances.

The main mechanism of action of TCAs involves inhibition of the reuptake of serotonin (5-hydroxytryptamine or 5-HT) and norepinephrine (NE) at the presynaptic nerve terminal. Under normal physiological conditions, neurons release neurotransmitters into the synaptic cleft, where they bind to receptors on the postsynaptic neuron and transmit nerve signals. After this transmission, the neurotransmitters are normally taken back into the presynaptic neuron through transporter proteins, mainly the serotonin transporter (SERT) and norepinephrine transporter (NET). This reuptake process terminates neurotransmitter activity and helps regulate neurotransmission. TCAs block these transporter proteins, thereby preventing the reabsorption of serotonin and norepinephrine into the presynaptic neuron.

As a result of transporter inhibition, serotonin and norepinephrine remain in the synaptic cleft for a longer period and continue stimulating postsynaptic receptors. Increased serotonin activity contributes to improvement in mood, emotional stability, anxiety reduction, sleep regulation, and appetite control. Increased norepinephrine activity improves alertness, concentration, motivation, energy, and psychomotor activity. The combined enhancement of these neurotransmitter systems gradually alleviates depressive symptoms and restores emotional balance.

Although TCAs elevate neurotransmitter levels relatively quickly, the clinical antidepressant effect usually requires several weeks to become fully evident. This delay occurs because long-term therapeutic improvement depends not only on increased neurotransmitter concentration but also on adaptive changes within the brain. Chronic administration of TCAs causes desensitization and downregulation of certain adrenergic and serotonergic receptors, alters intracellular signaling pathways, and promotes neuroplasticity. These neuroadaptive changes improve neuronal communication and are believed to play a major role in sustained antidepressant effects.

In addition to blocking serotonin and norepinephrine reuptake, TCAs interact with several other receptor systems, making them pharmacologically nonselective. They block muscarinic cholinergic receptors, producing anticholinergic effects such as dry mouth, blurred vision, constipation, urinary retention, and tachycardia. They also block histamine H1 receptors, which leads to sedation, drowsiness, increased appetite, and weight gain. Furthermore, blockade of alpha-1 adrenergic receptors causes vasodilation and orthostatic hypotension, leading to dizziness or fainting when standing suddenly. These additional receptor-blocking actions explain many of the side effects commonly associated with TCAs.

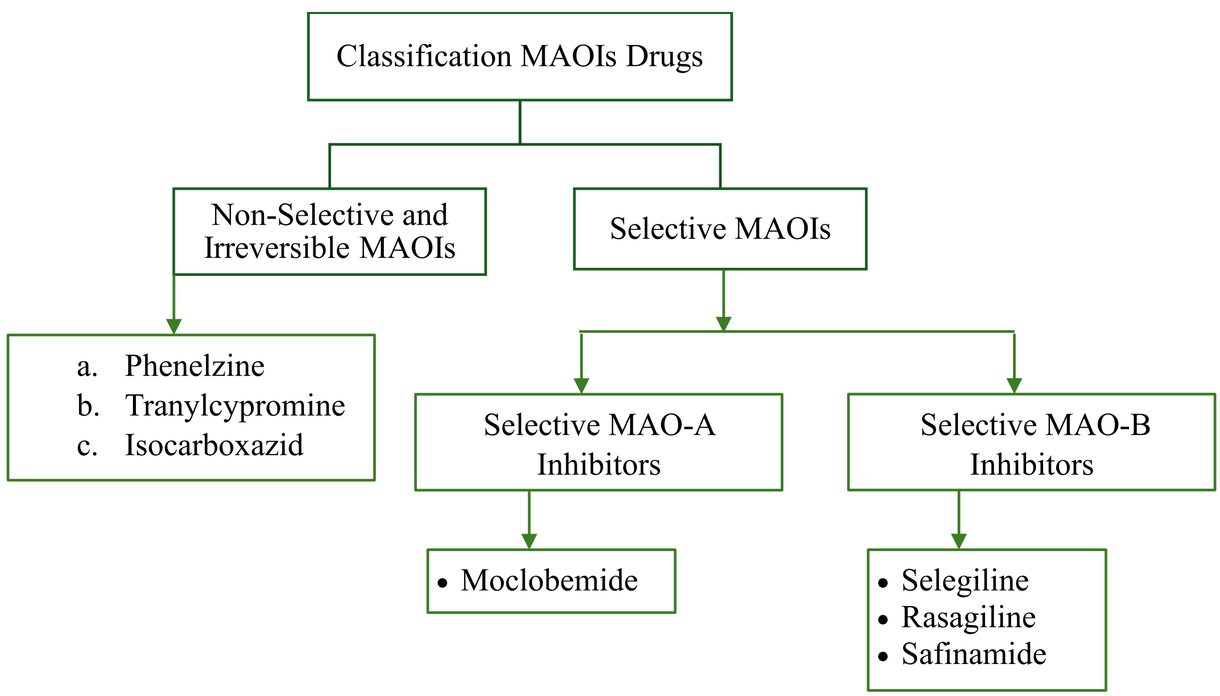
TCAs also have important effects on pain modulation pathways. Serotonin and norepinephrine are involved in descending inhibitory pain pathways within the spinal cord. By increasing the availability of these neurotransmitters, TCAs reduce pain signal transmission and are therefore useful in chronic neuropathic pain conditions such as diabetic neuropathy, post-herpetic neuralgia, and fibromyalgia. Some TCAs additionally block cardiac sodium channels, which can slow cardiac conduction and cause arrhythmias, especially in overdose situations, making these drugs potentially cardiotoxic at high doses.

Monoamine Oxidase Inhibitors (MAOIs)

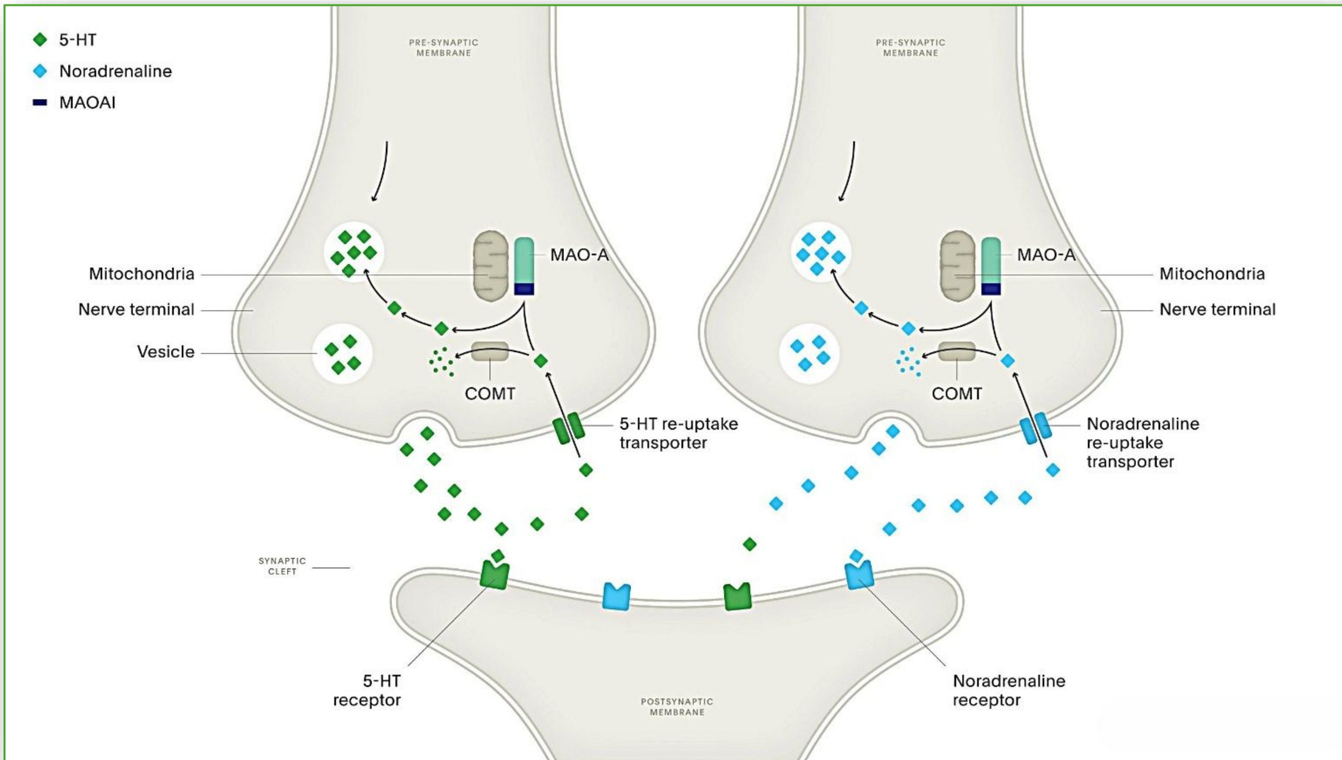
Monoamine Oxidase inhibitors (MAOIs) are a class of antidepressant drugs that produce their therapeutic effect by inhibiting the activity of the enzyme monoamine oxidase, an enzyme responsible for the metabolic breakdown of important monoamine neurotransmitters in the body and brain. These neurotransmitters mainly include Serotonin, Norepinephrine, and Dopamine. Under normal physiological conditions, monoamine oxidase enzymes are located on the outer membrane of mitochondria within nerve terminals, liver cells, and gastrointestinal tissues, where they continuously degrade excess neurotransmitters after synaptic transmission. This enzymatic degradation maintains normal neurotransmitter balance within the nervous system. MAOIs interfere with this normal process by blocking the action of monoamine oxidase, thereby preventing the breakdown of monoamine neurotransmitters and increasing their concentration within presynaptic nerve terminals and synaptic clefts.

The fundamental mechanism can be represented as:

$$\text{Monoamine neurotransmitters} \xrightarrow{\text{MAO}} \text{Inactive metabolites}$$



Mechanism of Action:



After administration of an MAOI, the drug enters the bloodstream and crosses the blood-brain barrier to reach neuronal tissue. There, it binds to monoamine oxidase enzymes and inhibits their activity. As a result, neurotransmitters such as serotonin, norepinephrine, and dopamine are no longer metabolized at their normal rate and begin to accumulate within the presynaptic neuron. During nerve impulse transmission, larger quantities of these neurotransmitters are released into the synaptic cleft, leading to prolonged and enhanced stimulation of postsynaptic receptors. Increased serotonergic neurotransmission improves mood, emotional stability, and anxiety symptoms; increased norepinephrine activity enhances alertness, energy, and concentration; and increased dopamine transmission contributes to improved motivation, pleasure, and psychomotor activity. Because depressive disorders are believed to be associated with reduced monoaminergic neurotransmission, increasing the availability of these neurotransmitters helps alleviate symptoms of depression and certain anxiety disorders.

The overall pharmacological process may be summarized as:

$$\text{MAOIs} \rightarrow \downarrow \text{MAO activity} \rightarrow \uparrow \text{Serotonin, Norepinephrine, Dopamine.}$$

Monoamine oxidase exists in two major isoenzyme forms, MAO-A and MAO-B, each having different substrate preferences and physiological roles. MAO-A primarily metabolizes serotonin, norepinephrine, and tyramine, whereas MAO-B mainly metabolizes dopamine and phenethylamine. MAO-A is especially important in mood regulation and emotional function, while MAO-B is more involved in motor control and neurological activity. Some MAOIs inhibit both forms of the enzyme, whereas others selectively inhibit one subtype.

The roles of the two enzyme forms can be expressed as:

MAO-A→ Serotonin, Norepinephrine, Tyramine.

MAO-B→ Dopamine, Phenethylamine.

Classical MAOIs such as Phenelzine and Tranylcypromine bind irreversibly to monoamine oxidase enzymes. In irreversible inhibition, the enzyme becomes permanently inactivated, and restoration of enzyme activity requires synthesis of new monoamine oxidase molecules, which may take several days or weeks. Consequently, the pharmacological effects of these drugs may persist even after the medication is discontinued. In contrast, reversible MAOIs such as Moclobemide temporarily inhibit the enzyme and dissociate more easily, producing a shorter duration of enzyme inhibition and generally fewer adverse dietary interactions.

An important consequence of MAO inhibition is its effect on tyramine metabolism. Tyramine is a naturally occurring monoamine found in aged cheese, fermented foods, smoked meat, wine, and certain processed foods. Under normal conditions, tyramine is rapidly degraded by MAO-A in the gastrointestinal tract and liver. However, when MAO-A is inhibited, tyramine escapes metabolism and enters systemic circulation in large amounts. Excess tyramine stimulates massive release of norepinephrine from sympathetic nerve endings, producing severe vasoconstriction and sudden elevation of blood pressure known as hypertensive crisis. This dangerous reaction may present with severe headache, palpitations, chest pain, neck stiffness, and risk of intracranial hemorrhage or stroke.

This interaction can be summarized as:

↑ Tyramine→↑ Norepinephrine Release→ Hypertensive Crisis.

MAOIs are therefore used cautiously in clinical practice and are usually reserved for patients with atypical depression, treatment-resistant depression, panic disorder, or social anxiety disorder who do not respond adequately to other antidepressants. Selective MAO-B inhibitors such as Selegiline are also useful in the management of Parkinson's Disease because inhibition of MAO-B decreases dopamine breakdown in the brain and thereby improves dopaminergic neurotransmission and motor function. Overall, the therapeutic action of MAOIs results from enhancement of monoamine neurotransmission through inhibition of enzymatic degradation of serotonin, norepinephrine, and dopamine, ultimately leading to improved mood, emotional stability, and neurological function.

Atypical Antidepressants

Atypical antidepressants are a heterogeneous group of drugs used in the treatment of depressive disorders that do not conform to the classical pharmacological categories such as SSRIs, TCAs, or MAOIs. Their term "atypical" reflects not a single unified mechanism, but rather a variety of distinct and often multimodal actions on different neurotransmitter systems. Despite their differences, the central therapeutic principle remains the same: they restore the functional balance of key monoamine neurotransmitters—mainly serotonin (5-HT), norepinephrine (NE), and dopamine (DA), which are critically involved in regulating mood, motivation, cognition, sleep, and emotional stability.

At the neurochemical level, depression is associated with reduced monoaminergic transmission in specific brain circuits, particularly within the limbic system and prefrontal cortex. Atypical antidepressants counteract this dysfunction through diverse mechanisms such as inhibition of neurotransmitter reuptake, modulation of presynaptic autoreceptors, antagonism or partial agonism of specific serotonin receptor subtypes, and in some cases regulation of circadian rhythm-related receptors. These actions not only increase synaptic concentrations of neurotransmitters but also fine-tune receptor activity to produce a more balanced and tolerable antidepressant effect.

One important representative is ***bupropion***, which primarily acts as a norepinephrine–dopamine reuptake inhibitor (NDRI). By blocking the dopamine transporter (DAT) and norepinephrine transporter (NET), bupropion increases the synaptic availability of these catecholamines, particularly in the mesolimbic and mesocortical pathways. This enhancement of dopaminergic transmission improves motivation, reward perception, and energy levels, while increased norepinephrine contributes to improved alertness and concentration. Unlike serotonergic antidepressants, it has minimal action on serotonin, which explains its lower incidence of sexual dysfunction and sedation.

Another important atypical antidepressant is ***mirtazapine***, which functions as a noradrenergic and specific serotonergic antidepressant (NaSSA). Its primary mechanism involves blockade of presynaptic α2-adrenergic autoreceptors and heteroreceptors. Normally, these receptors inhibit the release of norepinephrine and serotonin; therefore, their inhibition leads to enhanced release of both neurotransmitters. In addition, mirtazapine blocks 5-HT2 and 5-HT3 receptors, thereby redirecting serotonergic transmission toward the 5-HT1A pathway, which is more closely associated with antidepressant and anxiolytic effects. Its strong antihistaminic (H1 receptor) activity contributes significantly to sedation and increased appetite, making it particularly useful in patients with insomnia and weight loss.

Trazodone, another atypical antidepressant, acts as a serotonin antagonist and reuptake inhibitor (SARI). It weakly inhibits serotonin reuptake while strongly antagonizing 5-HT2A and 5-HT2C receptors. This dual action increases overall serotonergic tone while reducing the adverse effects associated with excessive 5-HT2 stimulation, such as anxiety and sexual dysfunction. Additionally, its blockade of histamine H1 and α1-adrenergic receptors contributes to sedative and hypotensive effects, which is why it is frequently used in depression accompanied by insomnia.

Some atypical agents such as ***vilazodone and vortioxetine*** exhibit multimodal serotonergic activity. Vilazodone combines selective serotonin reuptake inhibition with partial agonism at 5-HT1A receptors, enhancing serotonergic neurotransmission while simultaneously reducing anxiety and potentially improving onset of antidepressant response. Vortioxetine extends this concept further by acting not only as a serotonin reuptake inhibitor but also as a modulator of multiple serotonin receptor subtypes, including agonism at 5-HT1A and antagonism at 5-HT3, 5-HT7, and others. This broad receptor profile contributes to both mood improvement and cognitive enhancement, particularly in areas such as memory and executive function.

Agomelatine represents a distinctly different mechanism among atypical antidepressants. Instead of primarily targeting monoamine reuptake, it acts as an agonist at melatonin MT1 and MT2 receptors and as an antagonist at 5-HT2C receptors. Through melatonin receptor stimulation, it helps resynchronize disrupted circadian rhythms, improving sleep quality and normalization of sleep–wake cycles. Its 5-HT2C antagonism indirectly increases dopamine and norepinephrine release in the frontal cortex, thereby improving mood, motivation, and daytime functioning.