Depression is the most common of the affective disorders (define as disorders of mood rather than disturbance of thought or cognition). It may range from a very mild condition, bordering on normality, to severe (psychotic) depression accompanied by hallucination and delusions. Worldwide depression is a major cause of disability and premature death. In addition to the significant suicide risk depressed individual are more likely to die from other causes such as heart disease or cancer.

The symptoms of depression include emotional and biological components.

- Emotional symptoms:
  - misery, apathy and pessimism
  - low self-esteem: feelings of guilt, inadequacy and ugliness
  - Indecisiveness, loss of motivation.

- Biological symptoms:
  - retardation of thought and action
  - loss of libido
  - sleep disturbance and loss of appetite

There are two distinct types of depressive syndrome, namely unipolar depression, in which the mood swings are always in the same direction, and bipolar affective disorder, in which depression alternates with mania

**The Monoamine Theory**

The main biochemical theory of depression is the *monoamine hypothesis*, which states that depression is caused by a functional deficit of monoamine transmitters at certain sites in the brain, while mania results from a functional excess. Although the monoamine hypothesis in its simple form is insufficient as an explanation of depression, pharmacological manipulation of monoamine transmission remains the most successful therapeutic approach

**Classification of antidepressant**

1. Tricyclic Antidepressants (Amitriptyline - Amoxapine -- Desipramine - Doxepin - Imipramine - Maprotiline - Nortriptyline - Protriptyline - Trimipramine)
2. Selective Serotonin Reuptake Inhibitors (Fluoxetine , Fluvoxamine, Paroxetine, Sertraline)
3. Serotonin norepinephrine Reuptake Inhibitors (Duloxetine, Venlafaxine)
4. Atypical antidepressants (Nefazodone ,Trazodone,mirtazapine, and bupropion)
5. Monoamine Oxidase Inhibitors (selegiline ,Phenetazine ,Tranylcypromine)
Tricyclic Antidepressants

The tricyclic and polycyclic antidepressants block norepinephrine, and serotonin uptake into the neuron. Prolonged therapy probably leads to alterations in selected central nervous system (CNS) receptors. The important drugs in this group are listed above. All the tricyclic antidepressants (TCAs) have similar therapeutic efficacy, and the choice of drug depends on tolerance of side effects and duration of action. Patients who do not respond to one TCA may benefit from a different drug in this group.

Mode of action

1. Inhibition of neurotransmitter uptake: TCAs inhibit the neuronal reuptake of norepinephrine, and serotonin into presynaptic nerve terminals, at therapeutic dose it does not block dopamine transporters. By blocking the major route of neurotransmitter removal, the TCAs lead to increased concentrations of monoamines in the synaptic cleft, resulting in antidepressant effects.

2. Blocking of receptors: The TCAs also block serotonergic, α-adrenergic, histamine, and muscarinic receptors. It is not known which, if any, of these accounts for the therapeutic benefit.

Actions
TCAs elevate mood, improve mental alertness, increase physical activity, and reduce morbid preoccupation in 50 to 70% of individuals with major depression. The onset of the mood-elevation is slow, requiring 2 weeks or longer. These drugs do not produce CNS stimulation or mood elevation in normal individuals.

Therapeutic uses

1. The tricyclic antidepressants are effective in treating moderate to severe major depression.

2. Some panic disorders also respond to TCAs. Imipramine has been used to control bed-wetting in children (older than 6 years) by causing contraction of the internal sphincter of the bladder.

3. The TCAs particularly amitriptyline have been used to treat migraine headache and chronic pain syndrome (e.g. neuropathic pain) in number of condition for which the cause of pain are unclear.

Pharmacokinetics

The TCAs are well absorbed upon oral administration and because of their lipophilic nature, are widely distributed and readily penetrate into the CNS. As a result of their variable first pass metabolism in the liver, TCAs have low and inconsistent bioavailability. Therefore the patient's response is used to adjust dosage. The
initial treatment period is typically 4 to 8 weeks. The dosage can be gradually reduced unless relapse occurs.

**Adverse effect**

1. Antimuscarinic effects: Blockade of acetylcholine receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, constipation, and aggravation of glaucoma.
2. These agents slow cardiac conduction similarly to quinidine which may precipitate life threatening arrhythmias.
3. Orthostatic hypotension: TCAs block α-adrenergic receptors, causing orthostatic hypotension, dizziness and reflex tachycardia. In clinical practice this is the most serious problem in the elderly.
4. Sedation: Sedation may be prominent, especially during the first several weeks of treatment. And is related to the ability of these drugs to block histamine H receptor.

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**Selective Serotonin-Reuptake Inhibitors**

The selective serotonin-reuptake inhibitors (SSRI) are a group of drugs that specifically inhibit serotonin reuptake. This contrasts with the tricyclic antidepressants that nonselectively inhibit the uptake of norepinephrine, and serotonin, and block muscarinic, H1-histaminic and α-adrenergic receptors.

**Therapeutic uses:**
The primary indication for SSRI is depression, for which they are as effective as the tricyclic antidepressants. These drugs have been used for a variety of other indications, including obsessive-compulsive disorder (the only approved indication for fluvoxamine), panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, bulimia nervosa (the only approved indication for Fluoxetine) and premenstrual syndrome.

**Pharmacokinetics:**
All SSRI are well absorbed after oral administration. Only sertraline undergo significant first pass metabolism. Fluoxetine and norfluoxetine are slowly cleared from the body, with a 1 to 10 day half-life for the parent compound, and 3 to 30 days for the active metabolite. Excretion of SSRI is primarily through the kidney except sertraline and paroxetine which also undergo fecal excretion.

**Adverse effects:**
Although SSRI are considered to have fewer and less severe adverse effects than TCA and MAO inhibitors the SSRI are not without troublesome adverse effects, such as, headach,
sweating, anxiety, and agitation, GIT effects (nausea, vomiting, diarrhoea), weakness and fatigue, sexual dysfunction, change in weight and sleep disturbance.

**Serotonin norepinephrine Reuptake Inhibitors**
*(Duloxetine, Venlafaxine)*

Duloxetine and Venlafaxine are selectively inhibiting the reuptake of Serotonin norepinephrine. These agent termed selective Serotonin norepinephrine Reuptake Inhibitors (SNRIs), may be effective in treating depression in patient in whom the SSRI are ineffective, furthermore depression is often accompanied by chronic pain painful symptoms, such as backache and muscle aches against which SSRI are also relatively ineffective. Both TCA and SNRI sometimes are effective in relieving physical symptom of neuropathic pain. The SNRI unlike TCA have little or no activity on muscarinic, histamine and adrenergic receptors, and thus have fewer adverse effects than TCA.

**Adverse effect**
The most common adverse effect of these agents includes nausea, headache, insomnia, sexual dysfunction, sweating, dizziness and constipation.

**Atypical antidepressant**
Atypical antidepressant are mixed group of agents that have action at several different site.

1. **Bupropion**
   This drug act as weak dopamine and norepinephrine reuptake inhibitor to alleviate the symptoms of depression. Bupropion is unique in that it is assist in decreasing the craving and attenuating the withdrawal symptom of nicotine in tobacco. The side effect of this drug include dry mouth, sweat in, nervousness, tremor, very low incidence of sexual dysfunction, and increase the risk of seizure at high doses.

2. **Mirtazapine**
   This drug enhance serotonin and norepinephrine neurotransmission via mechanism related to it is ability to block presynaptic α2 and 5-HT2 receptors. It is sedative because of its potent antihistaminic activity but it does not cause the antimuscarinic side effects of TCA , or interfere with sexual function as do the SSRI , increase appetite and weight gain frequently occur.

3. **Nefazodone and Trazodone.**
   These agents are serotonin reuptake inhibitor. Their therapeutic benefit appear to be related to their ability to block 5-HT2 receptors.

**MONOAMINE OXIDASE INHIBITORS**
Monoamine oxidase (MAO) is a mitochondrial enzyme found in neural and other tissues, such as the gut and liver. In the neuron, MAO functions as a "safety valve" inactivate any excess neurotransmitter molecules (norepinephrine, dopamine, and serotonin) that may
leak out of synaptic vesicles when the neuron is at rest. The MAO inhibitors may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitter molecules to escape degradation and therefore to both accumulate within the presynaptic neuron and to leak into the synaptic space. This causes activation of norepinephrine and serotonin receptors, and may be responsible for the antidepressant action of these drugs. Use of MAO inhibitors is now limited because of the complicated dietary restrictions.