

Depression

Depression:

Depression is a very serious disorder. 40 million of adults of USA are in depression. 90-90 % Pakistani people face it. Mostly it is seen in women.

Symptoms of depression

- feelings of sadness and hopelessness,
- the inability to experience pleasure in usual activities,
- changes in sleep patterns and appetite,
- loss of energy,
- Suicidal thoughts.

Mania:

Mania is characterized by the opposite behavior: enthusiasm, anger, rapid thought and speech patterns, extreme self-confidence, and impaired judgment.

Classification of Anti-depressant Drugs:

1- SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs):

- ✓ Citalopram
- ✓ Escitalopram
- ✓ Fluoxetine
- ✓ Fluvoxamine
- ✓ Paroxetine
- ✓ Sertraline

KEY: CEFF PS

2- SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs):

- ✓ Duloxetine
- ✓ Venlafaxine
- ✓ Desvenlafaxine

KEY: DVD

3- ATYPICAL ANTIDEPRESSANTS:

- ✓ Bupropion
- ✓ Nefazodone
- ✓ Trazodone
- ✓ Vilazodone
- ✓ Metrazipine

KEY: BN TV M

4- TRICYCLIC ANTIDEPRESSANTS (TCAs):

- ✓ Amoxapine
- ✓ Doxepin
- ✓ Clomipramine
- ✓ Desipramine
- ✓ Imipramine
- ✓ Trimipramine
- ✓ Maprotiline
- ✓ Amitriptyline
- ✓ Nortriptyline
- ✓ Protriptyline

KEY: AD CDI T-MANP

5- MONOAMINE OXIDASE INHIBITORS (MAOIs):

- ✓ Phenelzine
- ✓ Selegiline

KEY: PS

6- DRUGS USED TO TREAT MANIA and BIPOLAR DISORDER:

- ✓ Valproic acid
- ✓ Lithium
- ✓ Carbamazepine

KEY: VLC

Mechanisms and Properties

Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin in the brain.

This, along with other evidence, led to the biogenic amine theory, which proposes that depression is due to a deficiency of mono- amines, such as norepinephrine and serotonin, at certain key sites in the brain.

A- Selective serotonin reuptake inhibitors (SSRIs):

- The SSRIs block the reuptake of **serotonin**, leading to increased concentrations of the neurotransmitter in the synaptic cleft.
- 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.

Therapeutic Uses of SSRIs:

- SSRI's are used in depression.
- Used in Obsessive compulsive disorder, Post-traumatic stress disorder, generalized anxiety disorder, Social anxiety disorder. Pre-menstrual dysphonic disorder. Drug of choice in obsessive compulsive disorder is Fluvoxamine.
- Used in Bulimia nervosa. Drug of choice is Fluoxetine.
- Orally administered and peak level is approx. 2-8 hours. Food affects its absorption (reduces). Only Sertraline's absorption is increased by food.
- Half-life of SSRI ranges from 16-36 hours.
- Metabolism is cytochrome p-450 dependent.
- Fluoxetine is mostly used clinically. It differs from other members that it has 5 hours of half-life (longer). It is also in sustained release forms. Sustained release is in weekly dosing. Also, its metabolite's half-life (e.g. S-norfluoxetine) is more than 10 days.
- Fluoxetine and paroxetine are potent inhibitors of a CYP450.
- Excretion of SSRI is via Kidney.

Pharmacokinetics:

Well absorbed after oral administration. The majority of SSRIs have plasma half-lives that range between 16 and 36 hours. Metabolism is by cytochrome P450

ADRs:

- **Sleep disorders.** In patients already having sleep disorders, induce sleep. It is the best for fatigued patients.

- 2 % out of 50 **children** become suicidal. Pediatric patients should be observed for worsening depression and suicidal thinking with initiation or dosage change of any antidepressant.
- **Sexual dysfunction:** This may include loss of libido, delayed ejaculation, and anorgasmia. 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.
- **Overdose** may cause seizures, serotonin syndrome (may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), changes in mental status and vital signs)
- **Discontinuation syndrome** (headache, malaise, and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern).

B- Serotonin/Nor-epinephrine reuptake inhibitors:

- Inhibit the reuptake of both serotonin and norepinephrine
- Both SNRIs and the TCAs, with their dual inhibition of serotonin and norepinephrine reuptake, are sometimes effective in relieving pain associated with diabetic peripheral neuropathy, fibromyalgia, and low back pain etc.
- 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 if treatment is abruptly stopped.

Duloxetine:

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.

GI side effects are common with duloxetine, including nausea, dry mouth, and constipation. Insomnia, dizziness, somnolence, sweating, and sexual dysfunction are also seen. Duloxetine may increase blood pressure or heart rate. Duloxetine is a moderate inhibitor of CYP2D6 isoenzymes and may increase concentrations of drugs metabolized by this pathway, such as antipsychotics.

Venlafaxine and desvenlafaxine:

Venlafaxine is a potent inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake. The most common side effects of venlafaxine are nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation. At high doses, there may be an increase in blood pressure and heart rate. The clinical activity and adverse effect profile of desvenlafaxine are similar to that of venlafaxine.

C- Atypical antidepressants:

Atypical antidepressants are a mixed group of agents that have actions at several different sites.

E.g. **Mirtazapine** (enhances serotonin and norepinephrine neurotransmission by serving as an antagonist at presynaptic α_2 receptors)

Bupropion(weak dopamine and norepinephrine reuptake inhibitor)

Nefazodone and **Trazodone** (weak inhibitors of serotonin reuptake)

Bupropion:

Bupropion is a weak dopamine and norepinephrine reuptake inhibitor that is used to alleviate the symptoms of depression. Bupropion is also 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. Bupropion is metabolized by the CYP2B6 pathway. Use of bupropion should be avoided in patients at risk for seizures or those who have eating disorders such as bulimia.

Mirtazapine:

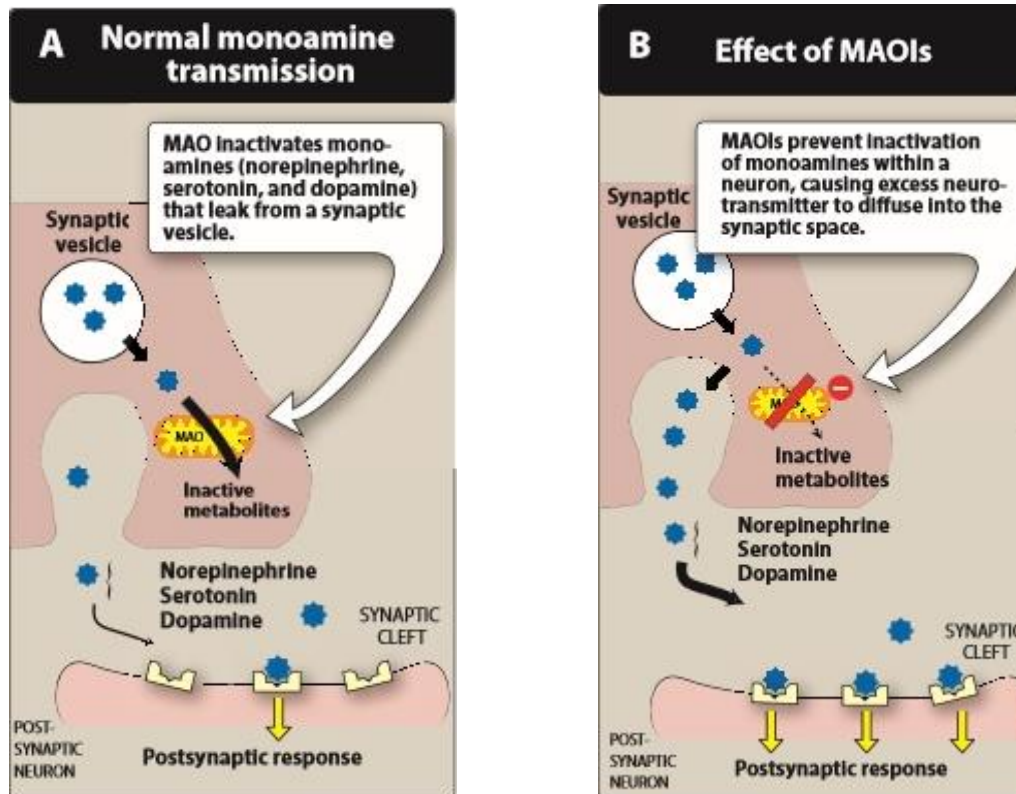
Mirtazapine enhances serotonin and norepinephrine neurotransmission by serving as an antagonist at presynaptic α_2 receptors. It is sedating because of its potent antihistaminic activity, but it does not cause the antimuscarinic side effects of the TCAs, or interfere with sexual function like the SSRIs.

Increased appetite and weight gain frequently occur.

Mirtazapine is markedly sedating, which may be an advantage in depressed patients having difficulty sleeping.

D- Monoamine oxidase Inhibitors (MAOI):

- Depression is due to deficiency of monoamines
- Deficiency of monoamine occurs due to increased reuptake
- Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues.
- MAO functions as a “safety valve” to oxidatively de-amine and inactivate any excess neurotransmitters (for example, norepinephrine, dopamine, and serotonin)
- MAOI 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 not only MAO in the brain but also MAO in the liver and gut that catalyzes oxidative deamination of drugs and potentially toxic substances.
- Show a high incidence of drug–drug and drug–food interactions.



Monoamine oxidase enzyme acts at monoamines, causing its metabolism (break down). So they are not properly released and do not bind properly to post-synaptic receptor. So, for its treatment, MAO-inhibitors may be used like Phenelzine.

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.
- MAOIs are considered last-line agents in many treatment settings.

Pharmacokinetics:

Oral administration, are hepatically metabolized and excreted rapidly in urine.

Adverse effects:

- Severe and often unpredictable side effects, due to drug–food and drug–drug interactions, limit the widespread use of MAOIs.
- Stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures and, possibly, stroke.
- Other possible side effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation.

E- Tricyclic Anti-depressants:

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. It is not known if any of these actions produce the therapeutic benefit of the TCAs.

Actions:

- The 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. 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.

Therapeutic uses:

- Imipramine has been used to control bed-wetting in children older than 6 years of age
- amitriptyline, have been used to help prevent migraine headache and treat chronic pain syndromes
- doxepin, can be used to treat insomnia.

Pharmacokinetics:

Well absorbed upon oral administration. Because of their lipophilic nature, they are widely distributed and readily penetrate into the CNS.

There is variable first-pass metabolism. TCAs have low and inconsistent bioavailability. TCAs are excreted as inactive metabolites via the kidney.

ADRs:

- Blurred vision, xerostomia (dry mouth), urinary retention, sinus tachycardia, constipation, and aggravation of angle-closure glaucoma.
- TCAs also block α -adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia. Imipramine is the most likely, and nortriptyline the least likely, to cause orthostatic hypotension.
- Weight gain is a common adverse effect of the TCAs.
- Sexual dysfunction

F- Mania:

Mania is caused by an over- production of neurotransmitters such as norepinephrine and serotonin.

However, the biogenic amine theory of depression and mania is overly simplistic.

It fails to explain the pharmacological effects of any of the antidepressant and antimania drugs on neurotransmission, which often occur immediately; however, the time course for a therapeutic response occurs over several weeks. The treatment of bipolar disorder has increased in recent years, due to increased recognition of the disorder and also an increase in the number of available medications for the treatment of mania.