

ANTIDEPRESSANTS

Depression is a mental health disorder characterized by persistently depressed mood or loss of interest in activities causing significant impairment in life. It is caused by a combination of genetic, biological, environmental and psychological factors.

Depression could be

1. Unipolar
 - Reactive
 - Endogenous
2. Bipolar mood disorder or manic depressive illness.

Reactive depression is due to stressful and distressing circumstances in life.

Endogenous depression is major depression and results from a biochemical abnormality in the brain. Deficiency of monoamine (NA, 5HT) activity in the CNS is thought to be responsible for endogenous depression

Symptoms are

- Emotional symptoms - sadness, misery, hopelessness, low self esteem, loss of interest and suicidal thoughts.
- Biological symptoms - fatigue, apathy, loss of libido, loss of appetite, lack of concentration and sleep disturbances. *Bipolar depression* is characterised by alternate mania and depression. It is less common and is associated with a hereditary tendency.

Mania can be considered opposite of depression with elation, over-enthusiasm, over-confidence, often associated with irritation and aggression.

Classification

1. *Tricyclic antidepressants (TCA)*-

Imipramine, desipramine, clomipramine, amitriptyline, nortriptyline, doxepin

2. *Selective serotonin reuptake inhibitors (SSRI)*-

Fluoxetine, fluoxetine, paroxetine, citalopram, sertraline,

3. Monoamine oxidase (MAO) inhibitors -

Phenelzine, tranylcypromine, isocarboxazid, moclobemide.

4. Atypical antidepressants

Trazodone, nefazodone, venlafaxine, bupropion, mianserine, mirtazapine, reboxetine

Tricyclic Antidepressants

Pharmacological Actions

1. CNS In normal subjects, TCA caused dizziness, drowsiness, confusion and difficulty in thinking.

2. CVS Postural hypotension and tachycardia in overdose.

3. ANS TCAs have anticholinergic properties and cause dry mouth, blurred vision, constipation and urinary retention

Adverse Effects

Sedation, postural hypotension, tachycardia, sweating and anticholinergic side effects like dry mouth, constipation, blurred vision and urinary retention are relatively common.

TCA may precipitate convulsions in epileptics; may cause hallucinations and mania in some patients. Many TCAs may also cause weight gain due to increased appetite

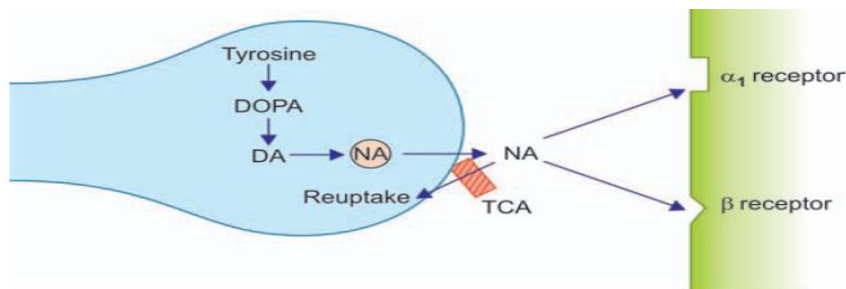


Fig. 29.2: Mechanism of action of tricyclic antidepressants. 80% of noradrenaline released into the synaptic cleft enters into the synaptic neuron by reuptake. This reuptake is blocked by TCA.

Drug Interactions

1. Tricyclics potentiate sympathomimetics– even small amounts of adrenaline used with local anaesthetics can cause serious hypertension.
2. Highly protein bound drugs like phenytoin, aspirin and phenylbutazone displace TCAs from binding sites resulting in toxicity.
3. TCAs potentiate the effects of alcohol and other CNS depressants.

Selective Serotonin Reuptake Inhibitors (SSRI)

Include fluoxetine, fluoxetine, paroxetine, citalopram, and sertraline. Antidepressant actions and efficacy of SSRIs are similar to TCAs.

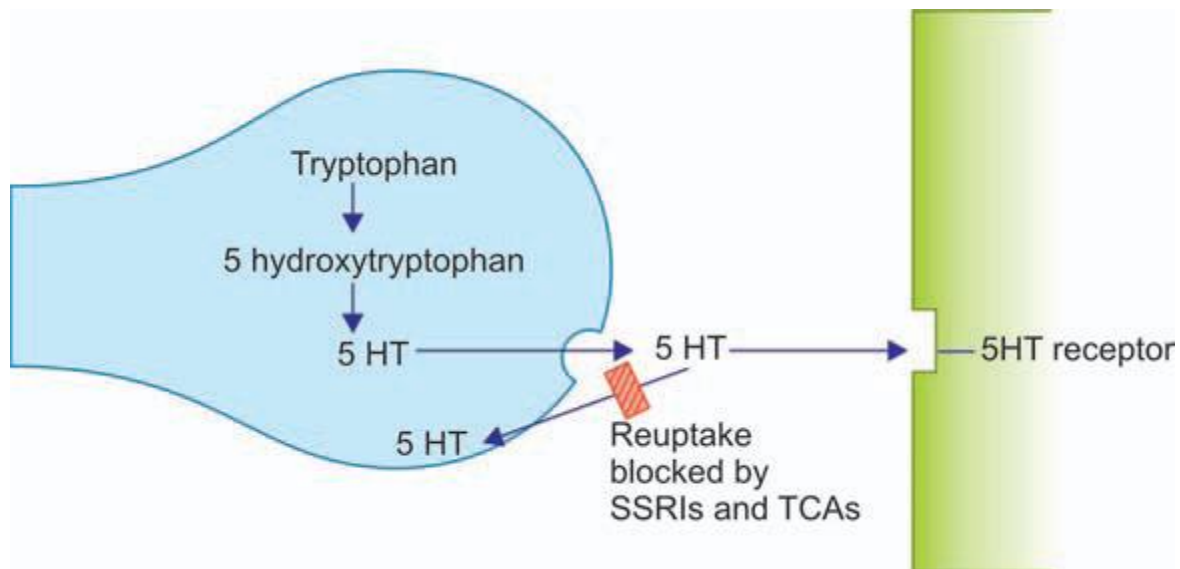
Mechanism of action–SSRIs block the reuptake of serotonin into the serotonergic nerve endings. Hence they enhance serotonin levels in these synapses

Adverse effects to SSRIs include nausea, vomiting, insomnia, anxiety and sexual dysfunction.

Among the SSRIs, fluoxetine is the most commonly used

MAO Inhibitors

Monoamine oxidase (MAO) is an enzyme which metabolizes NA, 5-HT and DA. Drugs which inhibit this enzyme enhance the neuronal levels of NA, DA and 5HT. MAO exists as two isozymes - MAOA and MAOB. MAOA is selective for 5-HT.



Moclobemide is a reversible, competitive, selective MAOA inhibitor. It is short acting and MAO activity recovers within 1-2 days after stopping the drug.

Atypical Antidepressants

Atypical antidepressants include trazodone, bupropion, mianserin, nefazodone and mirtazapine.

Advantages

- Fewer side effects—particularly sedation and anticholinergic effects
- Safer in overdose
- Effective in patients not responding to TCA.

Trazodone is a weak serotonin reuptake inhibitor. It is short acting ($t_{1/2}$ - 6 hr) and lacks anticholinergic activity. It is well tolerated and safe in overdosage. It can cause postural hypotension

Nefazodone blocks serotonin reuptake and is an effective antidepressant. It is well tolerated—causes sedation and mild postural hypotension.

Nefazodone is used in the prophylaxis of recurrent depression.

Venlafaxine is considered by some as atypical antidepressant because it inhibits the reuptake of noradrenaline in addition to 5 HT (Serotonin and noradrenaline reuptake inhibitor - SNRI).

It is thought to be faster acting and may be useful in patients not responding to other antidepressants.

Mirtazapine blocks 5HT₂, 5HT₃ receptors and enhances the release of NA and 5HT. It is faster acting - action

Bupropion is a weak DA reuptake inhibitor and has CNS stimulant effects. It is used in depression with anxiety. Bupropion is also used to help stop smoking (along with nicotine patch).