PHL 322

ANTIDEPRESSANTS

AND

MODE STABILISING DRUGS

Dr. Mohamed El-Sayed
DEPRESSION
"Depression" is a very common psychiatric disorder that is related to the "mood" (affective disorder).

- Depression is the most common of the affective disorders (Changes in mood associated with depression and/or mania)

- **Disorders of MOOD** rather than disturbance in thought or cognition

- **Clinical depression**: feeling sad for more than two weeks.
Symptoms of Depression

1- Emotional Symptoms:

- Misery and apathy
- Loss of self esteem: feeling of guilt and ugliness
- Indecisiveness and loss of motivation
- Decreased mood
- Loss of energy and interest
- Feelings of hopelessness, helplessness, guilt and anxiety
2- Biological symptoms:

1- Retardation of thought and action

2- Loss of libido

3- Loss of appetite and sleep disturbance

*** DEPRESSION IS THE MOST COMMON CAUSE OF SUICIDE
Symptoms of "mania" are exactly the opposite:

- Excessive enthusiasm
- Self-confidence
- Mental alertness
- Rapid thought and speech
- Hyperactivity
- Irritability
- Impatience
- Aggression
Classification of Depression

A) According to number of symptoms and degree:

1. Mild depression----------self-limiting
2. Moderate depression--------difficulties at home and work
3. Severe depression--------serious, associated with suicidal thoughts
B) According to type

1. **Unipolar depression (major depression):**
   The patient *swings* between "normal mood" and "depression".
   - Repeated episodes of depression
   - Mood returns to normal at the end of episode
   - Common (75 % of cases)
   - Non-familial
   - Associated with stressful life-events
   - Reactive depression

2. **Endogenous depression**
   - Less common (25 % of cases)
   - Familial
   - Unrelated to external stress
3. Bipolar depression (manic-depressive)

The patient swings between "mania" and "depression" (manic-depressive illness).

- It is mainly hereditary and appears in early adult life.
- Alternating depression and mania
- both depression and mania occur
Disorders of Mood (Affective Disorders)

- Depression (unipolar depression)
- Mania
- Manic-depression (bipolar depression)
- Reactive depression (75%)
- Endogenous depression (25%)

What are the possible mechanisms of depression?

- Depression is associated with insufficient central release of NA and 5-HT.
- Led to development of the Biogenic Amine Hypothesis.
Etiology of depression

“The monoamine theory” (proposed in 1965) suggests that depression is due to a deficiency of monoamines at certain sites in the brain, while mania is caused by an overproduction of these neurotransmitters. Therefore, monoamines should be considered as regulators of these adaptive changes that occur in the same time as mood changes. However, recent biochemical studies on depressed patients do not support this theory in its simple form, since it was found that the biochemical effect of antidepressants (i.e. increasing the level of monoamines) appears very rapidly whereas their antidepressant effect takes 2-3 weeks to develop.
The Monoamine Theory of Depression

- Proposed in 1965 and states that DEPRESSION is caused by a functional deficit of Monoamine transmitter at certain sites in the brain, while MANIA results from functional excess.

- The Theory is based on the ability of known antidepressant drugs (TCAs and MAOIs) to facilitate monoaminergic transmission and of drugs as Reserpine to cause depression.
## Pharmacological evidence supporting The Monoamine Theory of Depression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Principal action</th>
<th>Effect in depressed patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>Block NA and 5-HT reuptake</td>
<td>Increase MOOD</td>
</tr>
<tr>
<td>MAO Inhibitors</td>
<td>Increase stores of NA and 5-HT</td>
<td>Increase MOOD</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Inhibits NA and 5-HT storage</td>
<td>Decrease MOOD</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Inhibits NA synthesis</td>
<td>Decrease MOOD</td>
</tr>
<tr>
<td>ECT</td>
<td>Increase CNS response to NA and 5-HT</td>
<td>Increase MOOD</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Increase 5-HT synthesis</td>
<td>Increase MOOD</td>
</tr>
</tbody>
</table>
Monoamine Hypothesis of Depression

NORMAL STATE - NO DEPRESSION

DEPRESSION: CAUSED BY NEUROTRANSMITTER DEFICIENCY
The Need to Modify the Biogenic Amine Hypothesis

- **Iprindole** has no effect on monoamine metabolism or uptake but is an antidepressant.

- **Amphetamine** increases NA release and inhibits NA uptake but is not effective against endogenous depression.

- **Cocaine** inhibits NA & DA uptake but is not antidepressant.

- **Methysergide** is a 5-HT antagonist but does not affect mood in depressed patients.

- **L-Dopa** increases NA synthesis but does not affect mood in depressed patients.

- Poor correlation between the rate of onset of action of antidepressants (rapid) and the rate at which depressed patients improve (slow).
Facilitated vesicular noradrenaline release by amphetamine
Modification of Biogenic Amine Hypothesis

Antidepressant drugs

Increased synaptic concentrations of NA and 5-HT

e.g. down regulation of $\beta_1$- and of $\alpha_2$-adrenoceptors

Adaptive changes in the brain

Relief from depression

ECT

**NB:** $\beta_1$-adrenoceptor antagonists are not antidepressant

---

Antidepressant drugs downregulate $5\text{HT}_{2A}$ receptors (postsynaptic).
- Several post-mortem studies have shown increased $5\text{HT}_2$ binding in cerebrocortical tissue from depressed patients.
- Nefazodone (selective $5\text{HT}_2$ receptor antagonist and weak inhibitor of $5\text{HT}$ neuronal reuptake) has antidepressant activity.
Monoamine Receptor Hypothesis of Depression

Normal functioning

Decrease in neurotransmitters

Receptor upregulation due to lack of neurotransmitters
Gene Expression Hypothesis of Depression
Brain-derived neurotrophic factor (BDNF)
Treatment of Depression

1. Psychological treatment

2. Pharmacological treatment
   70% of depressed patients respond to antidepressants

3. ECT (electroconvulsive therapy)
   for very severe depression, which has not responded to other treatments or for patients who cannot take antidepressants
Antidepressants

- Antidepressants do not act immediately *show clinical effects after 2 weeks* indicating that secondary adaptive changes in the brain are important.

- The most consistent adaptive change seen with antidepressant drugs is the downregulation of beta-, alpa-2 and 5-HT2 receptors. Alpha-1 is not affected.

- Affect only people who are depressed.

- Effect does not increase with increasing doses.

- Antidepressants are not habit-forming.

- Antidepressants differ widely in side effects.
Postulated Neurotransmitter Receptor Hypothesis of Antidepressant Action

Antidepressants introduced
Postulated Adaptive Mechanisms at Gene Expression
Antidepressants

1) **Tricyclics and Tetracyclics (TCAs)**
   - Imipramine
   - Doxepin
   - Desipramine
   - Amoxepine
   - Trimipramine
   - Maprotiline
   - Clomipramine
   - Amitriptyline
   - Nortriptyline
   - Protriptyline

2) **Monoamine Oxidase Inhibitors (MAOIs)**
   - Tranylcypromine
   - Phenelzine
   - Moclobemide

3) **Selective Serotonin Reuptake Inhibitors (SSRIs)**
   - Fluoxetine
   - Fluvoxamine
   - Sertraline
   - Paroxetine
   - Citalopram

4) **Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)**
   - Venlafaxine
   - Duloxetine

5) **Serotonin-2 Antagonist and Reuptake Inhibitors (SARIs)**
   - Nefazodone
   - Trazodone

6) **Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)**
   - Bupropion

7) **Noradrenergic and Specific Serotonergic Antidepressant (NaSSAs)**
   - Mirtazapine

8) **Noradrenalin Specific Reuptake Inhibitor (NRI)**
   - Reboxetine

9) **Serotonin Reuptake Enhancer**
   - Tianeptine
The first tricyclic antidepressant discovered was **Imipramine**, which was discovered accidentally in a search for a new antipsychotic in the late 1950s.

Imipramine hydrochloride is a member of the dibenzazepine group of compounds. It is designated 5-[3-(Dimethylamino)propyl]-10,11-ihydro-5H-dibenz[b,1]azepine Monohydrochloride.

![Imipramine (Tofranil)](image-url)
CASE PRESENTATION

34 years old female resident on the Nile River, Cairo Egypt. She got divorced 4 years ago. Her Teenage children moved to live with father in Alexandria. Her new husband recently jailed for Narcotic trafficking. She found herself alone and took complete bottle of unidentified tablets.

**Physically** She was unconscious, barely breathing, dry skin, mouth and mucous membranes, Decreased bowel sounds as well as uncontrolled muscle hyperactivity.

**Her vital signs** showed HR 140 / min, BP 100 / 52, RR 10 / min, T 41 °C.
TRICYCLIC ANTIDEPRESSANTS (TCAs)

- Imipramine
- Amitriptyline
- Maprotiline

- Trimipramine

- Desipramine
- Nortriptyline
- Trimipramine

- Clomipramine
- Doxepin
MECHANISM OF ACTION of TCAs:

• All tricyclics block reuptake pumps for both 5HT and NE in nerve terminals by competing for binding site of the transport protein.

• Some have more potency for inhibition of 5HT uptake pump
  clomipramine, imipramine, amitryptyline

• Others have more potency for inhibition of NE uptake pump
  nortriptyline, desipramine

Synthesis of amines, storage and release are not directly affected, though some TCA increase transmitter release indirectly by blocking presynaptic alpha-2 adrenoreceptors.
- Relief of biological symptoms results from facilitation of NE-mediated transmission

- Relief of emotional symptoms results from facilitation of 5-HT-mediated transmission

- TCAs (given alone) are contraindicated in manic-depressive illness, because they tend to "switch" the depressed patient to the "manic" phase, therefore, they should be combined with "lithium salts".
PHARMACOKINETICS of TCAs

- **Peak levels:** 2-6 hours post ingestion
  - TCAs are "lipophilic" in nature (3ry amines), therefore they are well absorbed from the GIT and readily cross the blood brain barrier to penetrate the CNS.

- **Elimination:** hepatic oxidation
  - TCAs are metabolized in the liver by demethylation (Imipramine to Desipramine, Amitriptyline to Nortriptyline) and by hydroxylation into metabolites that retain the biological activity of the parent compounds.
PHARMACOKINETICS of TCAs

- TCAs are strongly bound to plasma proteins.

- **Average t1/2:** 24 hours
  Up to 72 hours in overdose

- Large T1/2 and large VD because TCA extensively bound to plasma protein
  (90-95 %)
Side Effects of TCAs

All tricyclics block:
- $\alpha_1$ adrenergic
- H1 histaminergic
- M1 cholonergeric receptor
- Na+ channels
- Potassium channel
Side Effects of TCAs

- Weight gain
- Drowsiness
- Constipation
- Blurred vision
- Dry mouth
- Drowsiness
Side Effects of TCAs
Side effects of TCAs

- Four major toxic syndromes (A, C, S, D)
  
  A = Anticholinergic
  
  C = Cardiovascular
  
  S = Seizures
  
  D = Death
ANTICHLINERGIC EFFECTS

- Sedation, Delirium, coma
- Tachycardia
- Mydriasis
- Dry mucous membranes and skin
- Dry mouth
- Decreased or absent bowel sounds
- Constipation
- Urinary retention
CARDIOVASCULAR EFFECTS

1- Postural Hypotension due to venodilatation
   (alpha-adrenergic blocking action).

2- Cardiac arrhythmias
   (due to increased catecholamine activity as a result of inhibition of monoamine reuptake).

3- ECG findings includes:
   - Sinus Tachycardia
   - Prolongation of PR, QRS, and QT intervals.
   - AV blocks
   - Prolongation of QRS > 100ms
     - Predictor of adverse outcome
     - Indication for treatment
CARDIOVASCULAR EFFECTS

4- Inhibit neuronal catecholamines reuptake

5- Inhibit alpha-adrenergic receptors induces vasodilatation

6- Membrane Depressant (quinidine like) effects cause myocardial depression and cardiac conduction disturbance due to:
   * Sodium channel blockade
   * Potassium channel blockade
SEIZURES

* The muscular hyperactivity from seizures combined with decreased sweating can lead to severe HYPERTHERMIA resulting in Rhabdomyolysis, brain damage, multisystem failure and death.

* Seizures occur as a result of inhibition of reuptake of Norepinephrine and serotonin in the brain.

* TCAs lower the seizure threshold.
Death

Sudden Death Occurs from:

1. Ventricular fibrillation
2. Status Epilepticus
3. Hyperthermia
**Interaction of TCA with other drugs**

- TCA are strongly bound to plasma protein, therefore their effect can be potentiated by drugs that compete for their plasma protein binding site (Aspirin and Phenylbutazone).

- TCAs are metabolized by liver microsomal enzymes, therefore their effect can be reduced by inducers of liver microsomal enzymes (Barbiturates), or potentiated by inhibitors of liver microsomal enzymes (Oral contraceptives, Antipsychotics, and SSRIs).
Contraindications

- TCAs should not be used in patients with Glaucoma or with enlarged prostate because of their atropine-like action.

- TCA should not be given with MAOIs because TCAs (inhibitors of monoamine reuptake) can interact with MAOIs (inhibitors of monoamine degradation) leading to "hypertensive crisis".
DIAGNOSIS of TCAs Overdose

1- Specific levels:

- Therapeutic Plasma concentrations are < 300 ng / ml
- Total concentrations of parent drug plus metabolite (1000 ng / ml or greater) are associated with serious poisoning
2- ECG monitoring

A- Ventricular Tachycardia:
**B- Torsades De Point (TDP):**

* QT prolongation

* Prolonged repolarization leads to ventricular fibrillation and sudden death.

* Occurs due to blockade of K+ channels.

Prolongation of repolarization results in activation of an inward depolarization current (An early after depolarization).
“Twisting (spindle) about the Points” (node)

“Spindle-node” pattern

“Spindle”

“Node” (“point”)
TREATMENT

1- Emergency and supportive measure:

1- Maintain an open airway and assist ventilation
2- Treat coma
3- Treat Seizures
4- Treat Hyperthermia
5- Treat Hypotension
6- Treat Dysrhythmia

Note: Avoid Type Ia antiarrhythmic agents (quinidine, procainamine, disopyramide) and Type IC (ecainide, flecainide, propafenone) because these drugs aggravates cardiotoxicity as they Inhibit fast sodium channels
2- Medications

1- Sodium Bicarbonate (1-2 mEq/kg IV) in patients with:
   - QRS > 100 ms
   - Dysrhythmias
   - Cardiac arrest
   - Hypotension

- Action of Sodium bicarbonate
  1- Maintain arterial PH (7.4-7.5)
  2- Reverses the membrane depressant effect by increasing the extracellular Sodium concentration and by direct effect of PH on the fast sodium channel
2- Anticonvulsants:

- **Benzodiazepines**
  - Lorazepam
  - Midazolam
  - Diazepam

- **Phenobarbital**
  - Seizures refractory to benzodiazepines

3- Anticholinesterase: "physostigmine".
Monoamine Oxidase Inhibitors

- Phenelzine
- Tranylcypromine
- Isocarboxazid
- Moclobemide
- Pargyline
Monoamine Oxidase

- MAO is found in nearly all tissues and is located intracellularly associated with mitochondria.

- Present in nerve terminals that release NA, DA or 5-HT.

- Located on outer surface of mitochondrial membranes.

- Catalyses oxidative deamination of extravesicular NA, DA or 5-HT.

- MAO regulates the free intraneuronal concentration of NA, 5-HT.

- MAO is not involved in the inactivation of released transmitter.
MAO Enzyme

- MAO exists in two forms coded by separate genes
  - **MAO-A**: has substrate preference for 5-HT and is the main target for antidepressant MAOIs
  - **MAO-B**: has substrate preference for phenylethylamine
- Both enzymes act on NA and dopamine
- Mutation in the MAO-A gene causes increased brain accumulation of 5-HT and NA in the brain leading to mental retardation and aggressive behaviour
Monoamine Oxidase Inhibitors (MAOIs)

1- Irreversible and nonselective MAOIs (Classic MAOI)

- Phenelzine
- Tanylcypromine
- Isocarboxazid
- pargyline

- Can not distinguish between the two isoenzymes

- MAO-A and B enzyme activity can not be restored unless new enzyme is synthesized, therefore the effect of MAOIs persists for a period of 2-3 weeks after stopping treatment, where a new (fresh) enzyme has to be synthesized
2- Reversible and selective inhibitors of MAO-A:
   - Moclobemide
     (antidepressant action, Short acting)

3- Selective inhibitor of MAO-B:
   - Deprenyl (neurodegenerative disorder)
   - Selegiline (used in the treatment of Parkinsonism)
MPTP, MAO-B and Parkinsonism

- 1-methyl-4-phenyl-tetrahydropyridine (MPTP) is a protoxin that is converted by MAO-B to N-methyl-4-phenylpyridinium (MPP+).

- MPP+ is selectively taken up by cells in the substantia nigra through an active mechanism normally responsible for dopamine reuptake.

- MPP+ inhibits mitochondrial complex I, thereby inhibiting oxidative phosphorylation. The interaction of MPP+ with complex I probably leads to cell death and thus to striatal dopamine depletion and parkinsonism.

- Recognition of the effects of MPTP suggested that spontaneously occurring Parkinson's disease may result from exposure to an environmental toxin that is similarly selective in its target. However, no such toxin has yet been identified.
MPTP, MAO-B and Parkinsonism

- It also suggested a successful means of producing an experimental model of Parkinson's disease in animals, especially nonhuman primates. This model is assisting in the development of new antiparkinsonism drugs.

- Pretreatment of exposed animals with MAO-B inhibitor such as selegiline prevents the conversion of MPTP to MPP+ and thus protects against the occurrence of parkinsonism.

- This observation has provided one reason to believe that selegiline may retard the progression of Parkinson's disease in humans.
MAOIs

- **Pharmacologicals effects:**

- MAOIs increase the cytoplasmic concentration of monoamines in nerve terminal

- Increases cytoplasmic pool results in spontaneous leakage of monoamines and also an increased release by indirectly acting sympathomimetic amines as amphetamine and Tyramine. These amines work by displacing NA from the vesicles into the nerve terminal cytoplasm from which it may either leak out and produce response or degraded by MAO
Side Effects of MAOIs

1- **Hypotension**: After MAO inhibition, other amines such as dopamine or octapamine are able to accumulate in peripheral sympathetic nerve terminals and displace vesicular NA, thus reducing NA release and sympathetic activity (sympathetic block).

2- **Antimuscarinic effects (atropine-like side-effects)**:
   - Dry mouth
   - Blurred vision
   - Urinary retention

3- **CNS stimulation**:
   - Insomnia
   - Tremors
   - Excitement
   - Convulsions

4- **Weight gain**: associated with increased appetite

5- **Hepatotoxicity**: seems to be caused by the hydrazine moiety of the drug (rare)
Drug interactions of MAOIs

1- Pethidine:

MAOIs interact with the opioid receptor agonist (pethidine) which may cause severe hyperpyrexia, restlessness, coma, hypotension. The mechanism still unclear – but it is likely that an abnormal pethidine metabolite is produced because of inhibition of normal demethylation pathway.
Drug interactions of MAOIs

2- Amphetamine and Ephedrine:
Indirectly acting sympathomimetics can interact with MAOIs causing the liberation of accumulated monoamines in neuronal terminals leading to hypertensive crisis.

3-TCAs (inhibitors of monoamine reuptake) can interact with MAOIs (inhibitors of monoamine degradation) leading to hypertensive crisis.
Drug interactions of MAOIs

4. **Levodopa:**
   precursor of dopamine can interact with **MAOIs** leading to **hypertensive crisis**.

5. **Tyramine:**
   indirectly acting sympathomimetic amine present in many food stuffs, e.g. cheese, yogurt, yeast extracts,..) can interact with **MAOIs** leading to **hypertensive crisis** known as "**cheese reaction**".
Tyramine is normally metabolized by MAO in gut and liver and so little dietary tyramine reaches systemic circulation.

If unmetabolized, tyramine enters sympathetic nerve terminals where it displaces NA from vesicles into cytosol.
• Because MAO in the nerve terminals is inhibited there is a massive ‘non-physiological’ release of NA from sympathetic nerve terminals which can lead to acute hypertensive crises, severe headache and fatal intracranial haemorrhage.

• Patients prescribed an MAOI are warned not to eat or drink certain substances (substances that contain tyramine etc.) e.g. beer, wine, cheese, marmite.

• At least 10 mg tyramine needs to be ingested to produce this reaction.

• The special advantage claimed for the reversible MAOI is that, No cheese reaction occurs with Moclobemide.
Selective 5-HT reuptake inhibitors (SSRIs)

- **Fluoxetine (prozac)**
  20-80 mg/d

- **Fluvoxamine (luvox)**
  50-300 mg/d

- **Paroxetine (paxil)**
  20-50 mg/d

- **Sertraline (zoloft)**
  50-200 mg/d

- **Citalopram**
  Initiate with 10-20 mg/d
Selective Serotonin Reuptake Inhibitors

[Diagram showing serotonin synthesis, reuptake, and inhibition by MAO inhibitors and SSRIs.]
Selective Serotonin Reuptake Inhibitors

Diagram showing the process of serotonin in neurons before and after the use of SSRIs.
Selective Serotonin Reuptake Inhibitors

- The SSRIs are currently the most widely utilized class of antidepressants in clinical practice.

- They act within the brain to increase the amount of the neurotransmitter, serotonin (5-hydroxytryptamine or 5-HT), in the synaptic gap by inhibiting its re-uptake.

- Instead of being discovered by accident, SSRIs were specifically designed while considering the biological causes of depression.

- SSRIs are described as 'selective' because they affect only the reuptake pumps responsible for serotonin, as opposed to earlier antidepressants, which affect other monoamine neurotransmitters as well. Because of this, SSRIs lack some of the side effects of the more general drugs.
Side effects of SSRIs:

- SSRIs are free from the side effects of TCAs (cardiac arrhythmias, antimuscarinic effects, postural hypotension) and are less dangerous in overdose. Therefore, they are the most widely used antidepressants.

- Side effects include: nausea, insomnia, and sexual dysfunction.
Drug interactions of SSRIs

- **SSRIs** are potent inhibitors of liver microsomal enzymes. Therefore they should not be used in combination with **TCAs** because they can inhibit their metabolism increasing their toxicity.

- **SSRIs** should not be used in combination with **MAOIs** because of the risk of life-threatening "serotonin syndrome" (tremors, hyperthermia, cardiovascular collapse and death). Both drugs require a "washout" period of 6 weeks before the administration of the other.
Selective Serotonin Reuptake Inhibitors

- SSRI drugs include many of the popular drugs on the market today

- They include Fluoxetine (Prozac) and Sertraline (Zoloft).
Fluoxetine (Prozac)

- Fluoxetine, also known as Prozac, was initially approved for treatment of depression in Belgium in 1986, and then Eli Lilly's Prozac was approved by the FDA on December 27th 1987 and introduced in the United States at the beginning of 1988.

- Prozac was the first of a new class of drugs, called selective serotonin reuptake inhibitors (SSRIs), to be approved for use in the United States.

- Fluoxetine hydrochloride is an antidepressant for oral administration. It is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents.
The body eliminates Fluoxetine very slowly.

The half-life of fluoxetine after a single dose is 2 days and after multiple dosing 4 days.

The liver then metabolizes fluoxetine into norfluoxetine, a desmethyl metabolite, which is also a serotonin reuptake inhibitor.

Norfluoxetine has an even longer half-life, i.e. 8.6 and 9.3 days for single and repeated dosage respectively.

Because fluoxetine's metabolism involves the P450IID6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the tricyclic antidepressants) may lead to drug interactions.
Sertraline (Zoloft)

- Sertraline HCl is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It is chemically unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant agents.

- The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT).
Sertraline (Zoloft) cont’d

- In vitro studies have shown that sertraline has no significant affinity for adrenergic (alpha1, alpha2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5HT1A, 5HT1B, 5HT2), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs.

- Sertraline does not inhibit monoamine oxidase.

- Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours.
Sertraline Dosage and Side Effects

- Sertraline is manufactured by Pfizer as small green 25 mg tablets, blue 50 mg tablets, or off-yellow 100 mg tablets. It is used in dosages of between 25 mg and a maximum of 200 mg per day.

- It has a number of adverse effects including insomnia, asthenia, gastrointestinal complaints, tremours, confusion, and dizziness; it can induce mania or hypomania in around 0.5% of patients.

- One property of sertraline is that it appears to be also a minor inhibitor of dopamine reuptake.
Selective Serotonin Reuptake Inhibitors

**Pharmacokinetics:**

- absorbed orally
- plasma half-life: 5-24 hours, fluoxetine being longer acting (24-96 hours).

- Paroxetine and fluoxetine are not used in combination with TCA because they may inhibit TCA hepatic metabolism and hence increase TCA toxicity.
Selective Serotonin Reuptake Inhibitors

**Advantages:**

- The Most commonly prescribed antidepressants

- **lacks cardiovascular and anticholinergic side effects** compared to TCA

- In contrast to MAOI, they do not cause ‘cheese’ reaction

- safer (low risk of overdose)

- Acute toxicity is less than that of MAOI or TCA
Selective Serotonin Reuptake Inhibitors

**Toxic Effects:**

- Nausea
- Insomnia
- Decreased libido and Sexual dysfunction

**SEROTONIN SYNDROME:**

In combination with MAOI, SSRIs can result in serotonin syndrome (Tremors, hyperthermia, Muscle rigidity, cardiovascular collapse)
Selective Serotonin Reuptake Inhibitors

Therapeutic uses:

- Depression, obsessive–compulsive disorder, anorexia nervosa, alcoholism, obesity, post–traumatic stress disorder
NE Selective Reuptake Inhibitors (NRIs)

- Reboxetine
- Tomoxetine

- Selective to NE uptake

- May be more effective in noradrenaline deficiency syndrome (e.g., depression associated with fatigue, apathy, cognitive disturbances), or non responders to SSRIs

- Also act at presynaptic $\alpha_2$, postsynaptic $\alpha_1$, $\alpha_2$ and $\beta$ adrenergic receptors (tremor, agitation, blood pressure)

**Advantages**

- lacks antagonistic activity at histamine H1, muscarinic & adrenergic receptors or Na+ pump as with TCA

- Fewer unwanted cardiovascular effects than TCA’s.
Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

- Serotonin norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressant used in the treatment of clinical depression and other affective disorders.
- They act upon two neurotransmitters in the brain that are known to play an important part in mood, namely, serotonin and norepinephrine. This can be contrasted with the more widely-used selective serotonin reuptake inhibitors (SSRIs), which act only on serotonin.
- SNRIs were developed more recently than SSRIs, and there are relatively few of them. Their efficacy as well as their tolerability appears to be somewhat better than the SSRIs, owing to their compound effect.
- These new drugs, because of their specificity for the serotonin and norepinephrine reuptake proteins, lack most of the adverse side effects of tricyclic antidepressants and monoamine oxidase inhibitors.
Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

Venlafaxine

• Combines the action of SSRI and NRI

• Selective 5HT and NE uptake blockers

• But without α1, M1 cholinergic or H receptor blocking properties

• Causes dual action on serotonin and adrenergic systems, thus amplifying these two systems synergistically
Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

- SNRIs are currently some of the newest antidepressant drugs available on the market, and due to this there are only a few selected drugs that have been approved by the FDA for use.

Venlafaxine
Venlafaxine (Effexor)

- Venlafaxine hydrochloride is a prescription antidepressant first introduced by Wyeth in 1993, and marketed under the trade name Effexor®.

- It is used primarily for the treatment of depression, generalized anxiety disorder, and social anxiety disorder in adults. Venlafaxine is the first and most commonly used SNRI.
Venlafaxine (Effexor)

- The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS.

- Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake.

- Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or α1 adrenergic receptors.
**Venlafaxine Dosage and Side Effects**

- Prescribed dosages are typically in the range of 75mg-225mg per day, but higher dosages are sometimes used for the treatment of severe or treatment-resistant depression. Because of its relatively short half-life of 4 hours, Effexor should be administered in divided dosages throughout the day.

- Side effects may include nausea, dizziness, sleepiness, abnormal ejaculation, sweating, dry mouth, gas or stomach pain, abnormal vision, nervousness, insomnia, loss of appetite, constipation, confusion/agitation, tremors, and drowsiness.
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)

- These are a class of antidepressants that are not really categorized as a special group of antidepressants.

- The only antidepressant in this group is **Bupropion**, which is an antidepressant of the aminoketone class, chemically unrelated to tricyclics or SSRIs. It is similar in structure to the stimulant cathinone, and to phenethylamines in general.
Bupropion (Wellbutrin)

- Bupropion was first synthesized by Burroughs Research in 1966, and patented by Burroughs-Wellcome (later Glaxo-Wellcome) in 1974. It was approved by the FDA in 1985 and marketed under the name Wellbutrin as an antidepressant.

- Bupropion is designated as $(\pm)-1-(3$-chlorophenyl)$-2-[(1,1$-\text{dimethylethyl})\text{amino}]$-1$-$propanone$\text{hydrochloride}$. The empirical formula is $\text{C}13\text{H}18\text{ClNO} \cdot \text{HCl}$. 

Bupropion
Bupropion (Wellbutrin)

- Bupropion is a selective catecholamine (norepinephrine and dopamine) reuptake inhibitor. It has only a small effect on serotonin reuptake. It does not inhibit MAO.

- Bupropion is metabolised in the liver. It has at least three active metabolites; hydroxybupropion, threohydrobupropion and erythrohydrobupropion. These active metabolites are further metabolised to inactive metabolites and eliminated through excretion into the urine.

- Partial agonist at 5-HT type IA receptors (decrease 5HT activity) but enhances dopaminergic and noradrenergic activity.
Bupropion and its Metabolites
Wellbutrin pills are available in three forms: immediate release, sustained release (SR) and extended release (XL). Generic forms of immediate and sustained release are available.

<table>
<thead>
<tr>
<th>Name</th>
<th>Dosage</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wellbutrin</td>
<td>75 mg</td>
<td>yellow-gold</td>
</tr>
<tr>
<td>Wellbutrin</td>
<td>100 mg</td>
<td>red</td>
</tr>
<tr>
<td>Wellbutrin SR</td>
<td>100 mg</td>
<td>blue</td>
</tr>
<tr>
<td>Wellbutrin SR</td>
<td>150 mg</td>
<td>purple</td>
</tr>
<tr>
<td>Wellbutrin SR</td>
<td>200 mg</td>
<td>pink</td>
</tr>
<tr>
<td>Zyban SR</td>
<td>150 mg</td>
<td>purple</td>
</tr>
<tr>
<td>Wellbutrin XL</td>
<td>150 mg</td>
<td>white</td>
</tr>
<tr>
<td>Wellbutrin XL</td>
<td>300 mg</td>
<td>white</td>
</tr>
</tbody>
</table>
Bupropion Side Effects

- Common side effects include dry mouth, tremors, anxiety, loss of appetite, agitation, dizziness, headache, excessive sweating, increased risk of seizure, and insomnia. Bupropion causes less insomnia if it is taken just before going to bed.

- Sexual side effects normally accompanying SSRI's do not accompany bupropion. Interestingly, patients commonly report increased libido, perhaps evidence of its dopaminergic properties.
Serotonin-2A Antagonist and Reuptake Inhibitors (SARI)

Trazodone
Nefazodone

- Blocks 5HT uptake selectively but in a less potent manner than tricyclics
- This helps reduces depression
- However, they are powerful 5HT2A antagonists
- But blockade of 5HT2A receptors stimulate 5HT1A receptors, which may help reduce depression
- 5HT2A antagonism also reduces the risk of anxiety, sedation or sexual dysfunction which is normally associated with SSRIs
Noradrenergic and specific Serotonergic Antidepressant (NaSSA)

Mirtazapine

- $\alpha_2$ receptor antagonist
- Increase NE and 5HT levels
- Blocks 5HT2A, 5HT3 and thus reduces side effects of anxiety, and sexual dysfunction
- But by blocking 5HT2C, and H1 receptors cause side effects: sedation, and weight gain
Electroconvulsive Therapy

- Stimulation through electrodes placed on either side of the head with the patient anaesthetized, paralysed with a NMB drug to avoid physical injury and artificially ventilated.
- Response rates 60-80%.
- The most effective treatment for severe suicidal depression.
- **DISADVANTAGES**
  - Confusion
  - Memory loss lasting for days or weeks.
Antimanic agents or mood stabilizers

- **Lithium Carbonate:**
  - Drug of choice for bipolar Depression
  - Decrease release of norepinephrine and dopamine but not serotonin
  - Increase choline uptake and acetylcholine synthesis
  - Decrease second messengers (interfere with IP3 and c-AMP formation)
Proposed Mood Stabilising Mechanism of Action of Lithium Salts

Neurotransmitter → Receptor

Lithium carbonate → X

IP$_3$ formation

Signalling events involving other receptors

Hormone-induced cAMP production (but not thought to be a significant mechanism in brain)
Effect of lithium on the IP3 and DAG second-messenger system.

The schematic diagram shows the synaptic membrane of a neuron. (PIP2, phosphatidylinositol-4,5-bisphosphate; PLC, phospholipase-C; G, coupling protein; EFFECTS, activation of protein kinase C, mobilization of intracellular Ca2+, etc.).

Lithium, by inhibiting the recycling of inositol substrates, may cause depletion of the second-messenger source PIP2 and therefore reduce the release of IP3 and DAG.
Lithium is clinically effective at plasma concentration of 0.5-1 mM. Above 1 mm, it produces a variety of toxic effects, therefore, monitoring of plasma concentration is essential.
After the drug is started, 7-10 day must be elapsed before the antimanic effect is reached.

- Lithium causes depletion of membrane phosphatidylinositol and accumulation of intracellular inositol phosphate.

- Hormone-mediated cAMP production is reduced
Lithium Carbonate

- Rely on their ability to stabilize mood.

- Used prophylactically.

- Narrow therapeutic index (produce kidney damage at doses very close to therapeutic doses).

- May act by inhibiting phosphoinositide signal transduction thereby reducing neurotransmission.
Pharmacology of Lithium Salts

- no effect in normal person
- stabilizes mood in affective disorder
- low therapeutic index
- toxicity: correlated with plasma concentration; fine tremors, ataxia, confusion, delirium, convulsions, cardiac arrhythmias
- treatment should be under normal Na+ intake and normal cardiac and renal function
Therapeutic uses

- Bipolar disorder
- Mania
- Major depression
- Neutropenia (chemotherapy & zidovudine–induced neutropenia)
- SIADH (syndrome of inappropriate secretion of ADH)
Lithium Carbonate

- **Adverse effects**
  - Anorexia, diarrhoea, hypothyroidism, seizures (Convulsion and death if plasma concentration reaches 3-5 Mm).
  - Leukocytosis, nephrotic syndrome and polyuria, impotence.
  - A toxic drug; adverse reactions are dose- and concentration-dependent.
Polydipsia and polyuria are frequent but reversible concomitants of lithium treatment, occurring at therapeutic serum concentrations.

The principal physiologic lesion involved is loss of the ability of the collecting tubule to conserve water under the influence of antidiuretic hormone, resulting in excessive free water clearance.

Patients receiving lithium should avoid dehydration and the associated increased concentration of lithium in urine. Periodic tests of renal concentrating ability should be performed to detect changes.
Edema

- **Edema** is a frequent adverse effect of lithium treatment and may be related to some effect of lithium on sodium retention. Although weight gain may be expected in patients who become edematous, water retention does not account for the weight gain observed in up to 30% of patients taking lithium.
The bradycardia-tachycardia ("sick sinus") syndrome is a definite contraindication to the use of lithium because the ion further depresses the sinus node. T wave flattening is often observed on the ECG but is of questionable significance.
Use During Pregnancy

- Lithium is transferred to nursing infants through breast milk, in which it has a concentration about one-third to one-half that of serum. Lithium toxicity in newborns is manifested by lethargy, cyanosis, poor suck and Moro reflexes, and perhaps hepatomegaly.

- The issue of dysmorphogenesis is not settled. An earlier report suggested an increase in the frequency of cardiac anomalies, especially Ebstein’s anomaly, in lithium babies, but the most recent data suggest that lithium carries a relatively low risk of teratogenic effects.
Drug Interactions

- Renal clearance of lithium is reduced about 25% by thiazide diuretics (hydrochlorothiazide, chlorothiazide) and doses may need to be reduced by a similar amount.

- A similar reduction in lithium clearance has been noted with several of the newer nonsteroidal anti-inflammatory drugs that block synthesis of prostaglandins (Ibuprofen, Indomethacin). This interaction has not been reported for either aspirin or acetaminophen.

- All neuroleptics tested to date, with the possible exception of clozapine and the newer antipsychotics, may produce more severe extrapyramidal syndromes when combined with lithium.
Other Antimanic Agents

1- Valproic acid:
   facilitates GABAergic transmission; preferred over lithium for initial therapy but lithium is still preferred for maintenance treatment

2- Carbamazepine:
   reduces release of neurotransmitters

3- Gabapentin:
   inhibits GABA uptake

4- Lamotrigine
Valproic acid

- Valproic acid has been effective in some patients who have failed to respond to lithium.

- The starting dose is 750 mg/d, increasing rapidly to the 1500–2000 mg range with a recommended maximum dose of 60 mg/kg/d.

- Combinations of valproic acid with other psychotropic medications likely to be used in the management of either phase of bipolar illness are generally well tolerated.

- Many clinicians argue for combining valproic acid and lithium in patients who do not fully respond to either agent alone.
Lamotrigine

- Lamotrigine is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder.

- Lamotrigine also acts as a mood stabilizer. It is the first medication since lithium to be granted approval by the U.S. Food and Drug Administration (FDA) for the maintenance treatment of bipolar type I.

lamotrigine is most effective in the treatment and prophylaxis of bipolar depression
Mechanism of action

One proposed mechanism of action for lamotrigine involves an effect on sodium channels, although this remains to be established in humans. *In vitro* pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (for example glutamate and aspartate).
Pharmacokinetic data

- **Bioavailability**: 98%
- **Protein binding**: 55%
- **Metabolism**: Hepatic
- **Half life**: 24-34 hours
- **Excretion**: Renal
Side effects

- Lamotrigine prescribing information has a **black box warning** about life threatening skin reactions, including **Stevens-Johnson Syndrome** and **Toxic Epidermal Necrolysis**. The manufacturer states that nearly all cases appear in the first 2 to 8 weeks of therapy and if medication is suddenly stopped then resumed at the normal dosage. Patients should seek medical attention for any unexpected skin rash as its presence is an indication of a possible serious or even deadly side effect of the drug.

- Lamotrigine binds to **melanin**-containing tissues such as the iris of the eye. The long-term consequences of this are unknown.