Drugs used in Depression- Old groups

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Depression

"**Depression**" is a very common psychiatric disorder that is related to the "**mood**" **(affective disorder).**

- **Changes in mood are associated with depression and/or mania.**
- **Disorders of mood rather than disturbance in thought or cognition.**

- **Incidence:** Depression is a chronic and recurrent illness that can affect at least 20% of the population at some period in their lifetime.
- An estimated **35-40 million Americans** living **today** will suffer from major Depressive Illness during their lives.

- **Cost:** **15-35 billions $ / year in USA only.**

Classification of Depression

A) According to severity of symptoms:

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):

- mood swings are always in the same direction (depresion)

2- Bipolar depression (manic-depressive):

- in which depression alternates with mania

3- Other forms of depression:

- Psychotic depression
- Postpartum depression

Symptoms of Depression

Loss of energy and interest

- Diminished ability to enjoy oneself.
- Decreased -- or increased -- sleeping or appetite.
- Difficulty in concentrating; indecisiveness; slowed thinking.
- Exaggerated feelings of sadness, hopelessness, or anxiety.

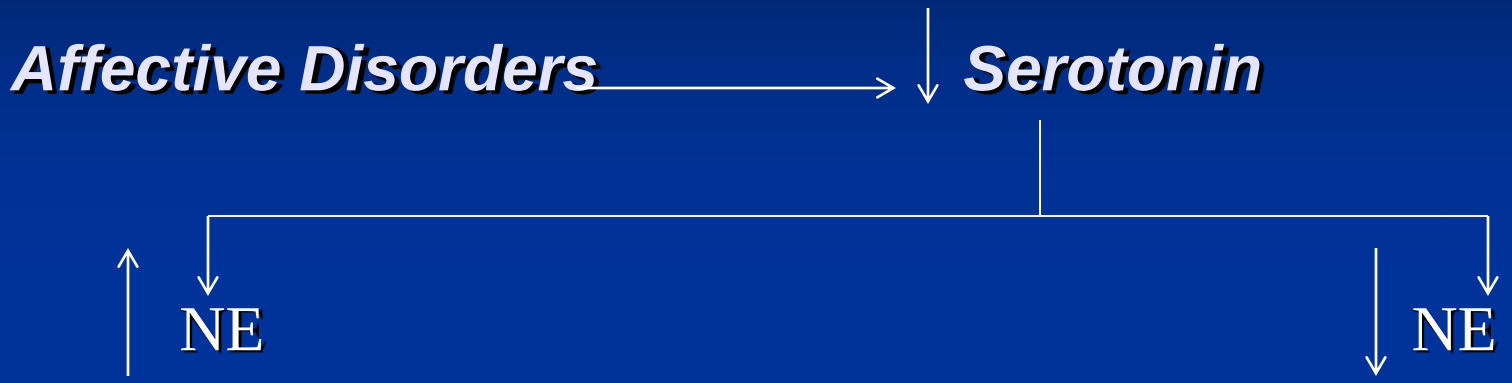
Feelings of worthlessness.

- Recurring thoughts about death and **suicide**.
- If most of these symptoms last for two weeks or more, the person probably has Depressive illness.

Symptoms of Mania

- **decreased need for sleep.**
- **Unwarranted or exaggerated belief in one's own ability.**
- **Extreme irritability.**
- **Rapid, unpredictable emotional changes.**

Biochemical Theory of Affective Disorders.



Rx Drugs that decrease NE

Drugs that increase NE

What is the evidence to support this theory ?

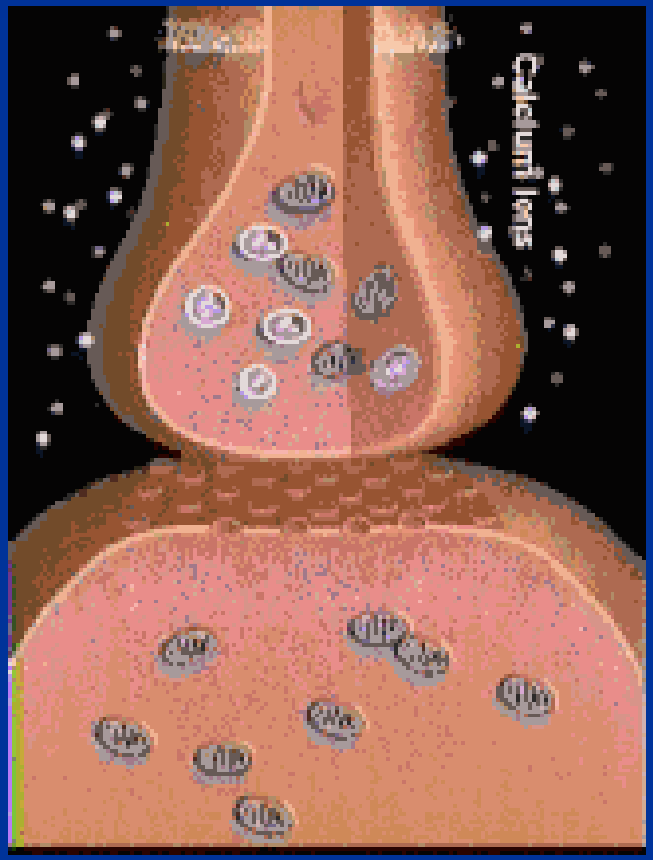
Amphetamine causes mania while reserpine and methyldopa produce depression (these drugs depletes NE and dopamine storage).

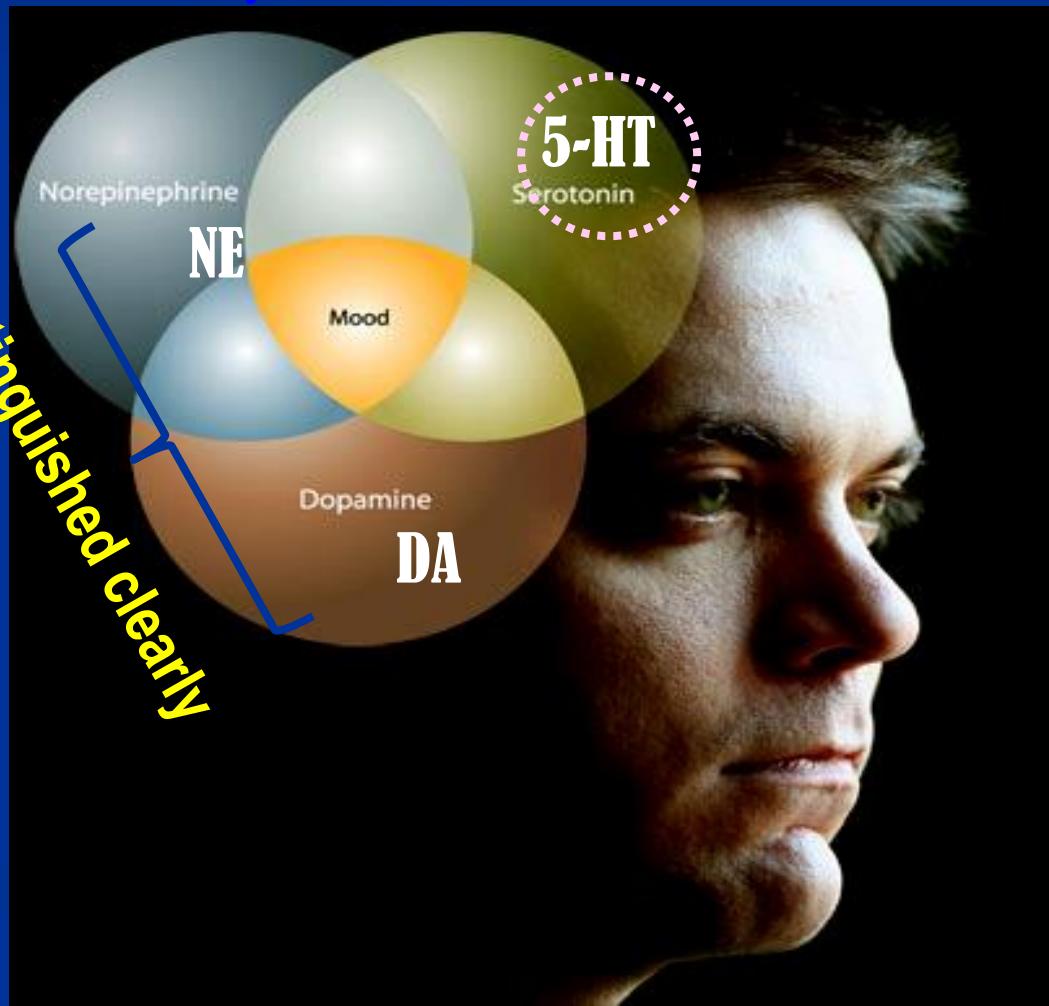
Pathophysiology of depression

Synaptic transmission

Neurotransmitter Imbalances & Dysregulation

➔ creates a state of deficiency in monoamines ???





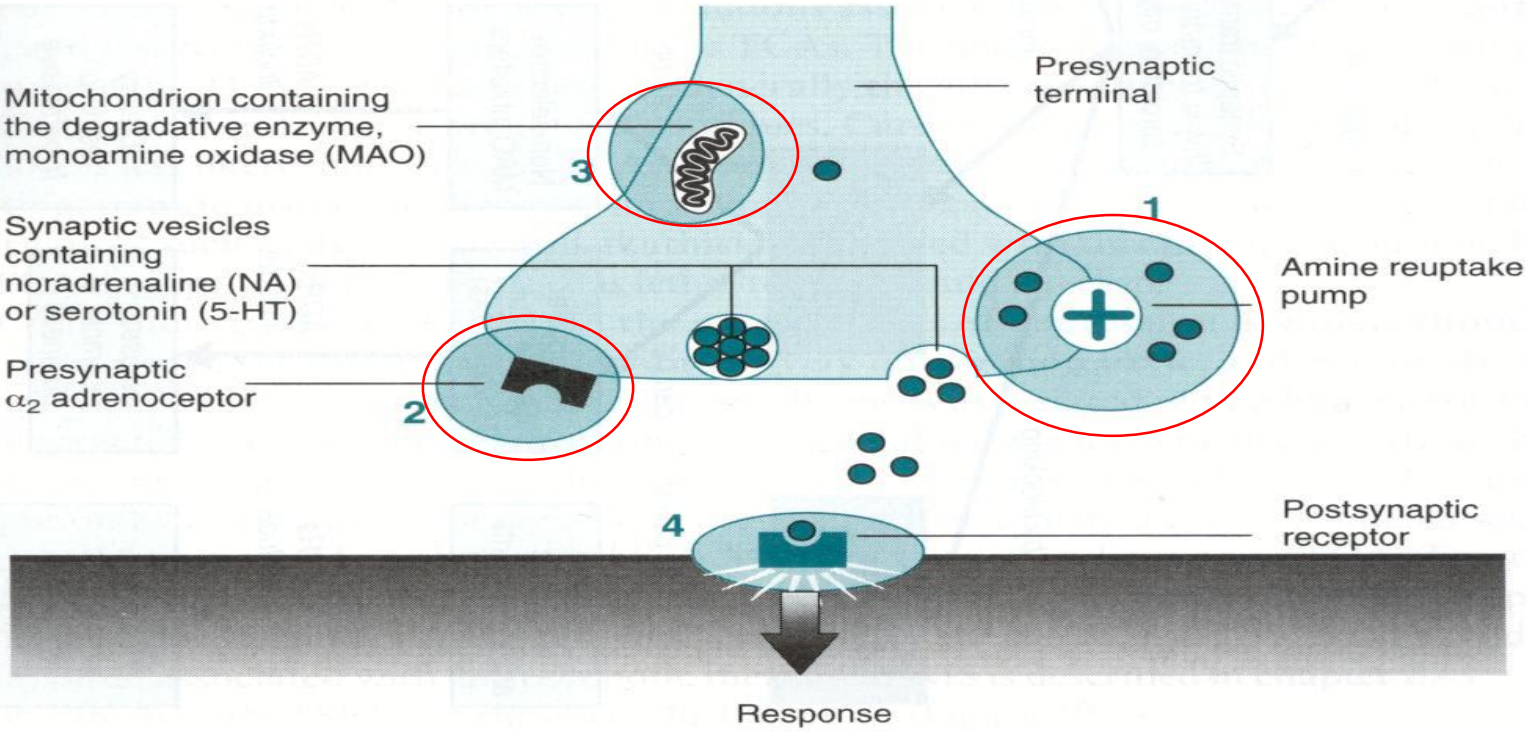
- **5-HT deficiency** may cause the sleep problems, irritability and anxiety associated with depression
- **Decreased level of NE** which regulates mood. alertness, arousal, appetite, reward & drives
- **Dopamine** is important for pleasure,

  Sexual function & psychomotor activity.

What are the features of drugs that should be used for Rx of Depression?

- **Simply to increase the levels of these amines.**

Sites of Action for Antidepressants



1- Monoamine (NE or/ and 5-HT) re-uptake pump inhibitors

2- Blockade of pre-synaptic α_2 receptors

3- Inhibition of MAO enzyme

Classification of antidepressants based on site of action

A) Drugs that block the reuptake of NE and 5-HT (e.g.:Most tricyclics) (old antidepressants)

B) Drugs that Inhibit MonoAminoOxidase (MAOIs, Phenelzine, Tranylcypraine, Moclobemide) (old Antidepressants

C) Drugs that selectively block reuptake of 5-HT (SSRIs) (Fluoxetine; Paroxetine; Sertraline; Citalopram)

D) Drugs that Block Presynaptic α_2-adrenoceptors (e.g.: Mirtazapine, Mianserin).

Antidepressants Available in the Market (Worldwide)

1) Tricyclics (TCAs) and Tetracyclics

Imipramine		Desipramine
Amoxapine	Trimipramine	
Maprotiline	Clomipramine	Amitriptyline
Nortriptyline	Protriptyline	

2) Monoamine Oxidase Inhibitors (MAOIs)

Tranylcypramine	Phenelzine	Moclobemide

3) Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine	Fluvoxamine	Citalopram
Sertraline	Paroxetine	Escitralopram

Classification of Antidepressants

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) Noradrenaline Reuptake Inhibitor (NRI)

Reboxetine

9) Serotonin Reuptake Enhancer

Tianeptine

- Antidepressants do not act immediately (show clinical effects after 3 weeks) indicating that secondary adaptive changes must occur before the benefit is gained

- The most consistent adaptive change seen with antidepressant drugs is the downregulation of beta-, alpa-2 and 5-HT2 receptors. These receptor mediate negative feedback on monoamine release in the brain.

- Desensitization (down-regulation) of β- adrenoceptors (decrease c-AMP) is very important and is related to clinical response.

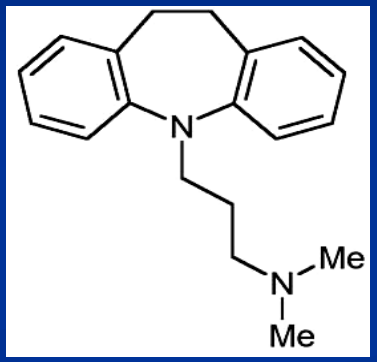
Old antidepressants

TRICYCLIC ANTIDEPRESSANTS (TCAs)

TCAs are the oldest class of antidepressant drugs

They have characteristic three-ring nucleus

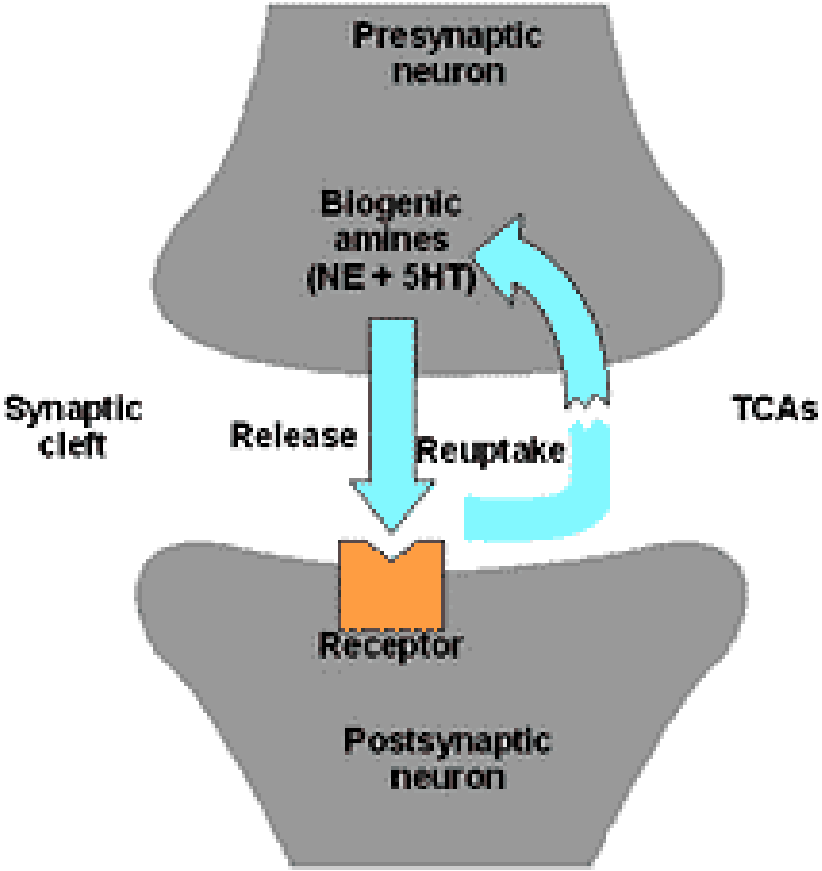
- Imipramine
- Clomipramine
- Nortriptyline
- Desipramine
- Amitriptyline
- Trimipramine



TETRACYCLIC ANTIDEPRESSANTS

- Maprotiline
- Amoxapine

Mechanism of action of tricyclic antidepressants



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
  - So ↑ conc. of NE & serotonin in the synaptic cleft & at the receptor site
- 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

PHARMACOLOGICAL ACTIONS

1- Elevate mood

2- Improve mental alertness

3- Increase physical activity

 # The antidepressant effect may develop after several weeks of continued treatment (2 - 3 weeks)

4- In non-depressed patients →They cause sedation, confusion & motor incoordination

PHARMACOKINETICS of TCAs

- **Peak levels:** 2-6 hours post ingestion

TCAs are "lipophilic" in nature, therefore they are well absorbed from the GIT and readily cross the blood brain barrier to penetrate the CNS.

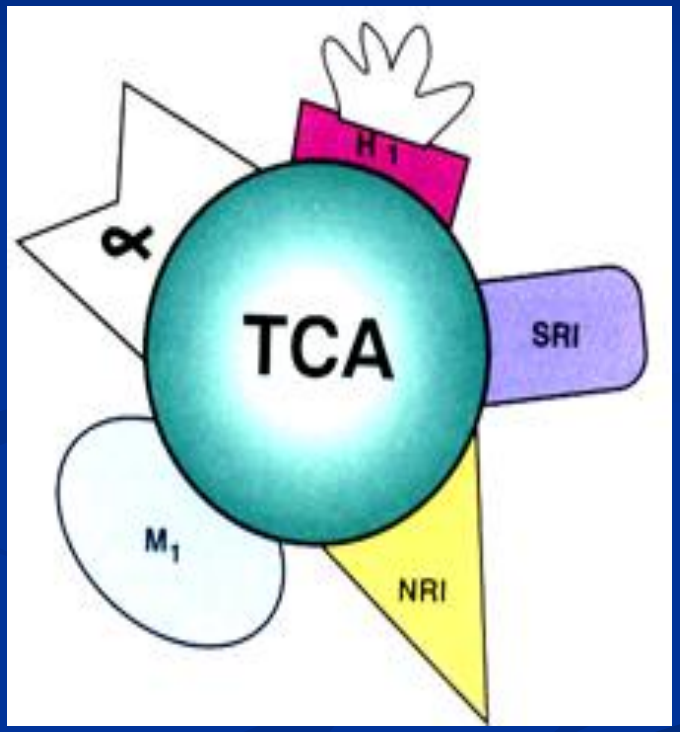
- **Elimination:** hepatic oxidation

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.

Side Effects of TCAs

TCAs block:

- α1 adrenergic receptors
- H1 histamines receptors
- M1 cholinergic receptors
- 5HT2 receptors



Adverse Effects of TCAs

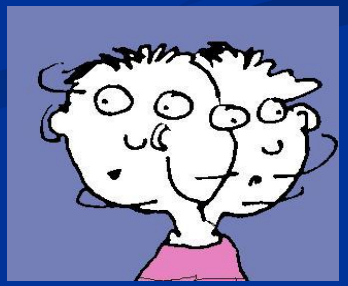
- Anti-cholinergic: Dry mouth (dental problem; xerostomia), blurred vision, constipation & urine retention, aggravation of glaucoma.
- Anti-histaminic: Sedation, confusion.
- Anti-adrenergic ➔ Postural hypotension, arrhythmias, conduction defects.
- Weight gain, sexual dysfunction & impotence
- Lower seizure threshold

TCAs have narrow therapeutic index ➔ toxicity can develop; excitement, delirium , convulsions, respiratory depression, coma, atropine like- effects, cardiac arrhythmias, sudden death

- TADs have a large volume of distribution therefore hemodialysis is not effective for Rx of TCA toxicity also they are bound to plasma proteins.

Therapeutic uses of TCAs

- Endogenous (Major) Depression -- moderate to severe.
- Panic attack /acute episode of anxiety.
- **Imipramine** is used for treatment of **nocturnal enuresis** in children and geriatric patients as it constricts internal urethral sphincter (anti-muscarinic effect).
- Generalized Anxiety Disorder (GAD).
- Obsessive Compulsive Disorder (OCD)
- Attention Deficit Hyperkinetic Disorder (ADHD).
- Chronic neuropathic pains or unexplained body pains.



Interaction of TCAs with other drugs

- TCA are strongly bound to plasma proteins, 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).

- TCAs (inhibitors of monoamine reuptake) should not be given with MAOIs (inhibitors of monoamine degradation) ⇨ "hypertensive crisis".

- Additive to antipsychotics & anti- parkinsonisms ➔ ↑ anti-cholinergic effects.

Contraindications

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

- 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".

- Seizure disorders
- Cardiovascular (IHD and arrythmias)

Monoamine Oxidase Inhibitors

- **Clinical Uses:** Only used for refractory cases and in atypical depression where phobia and anxiety are prominent symptoms.
- Limited use now because;

➔ADR, Food & Drug Interactions

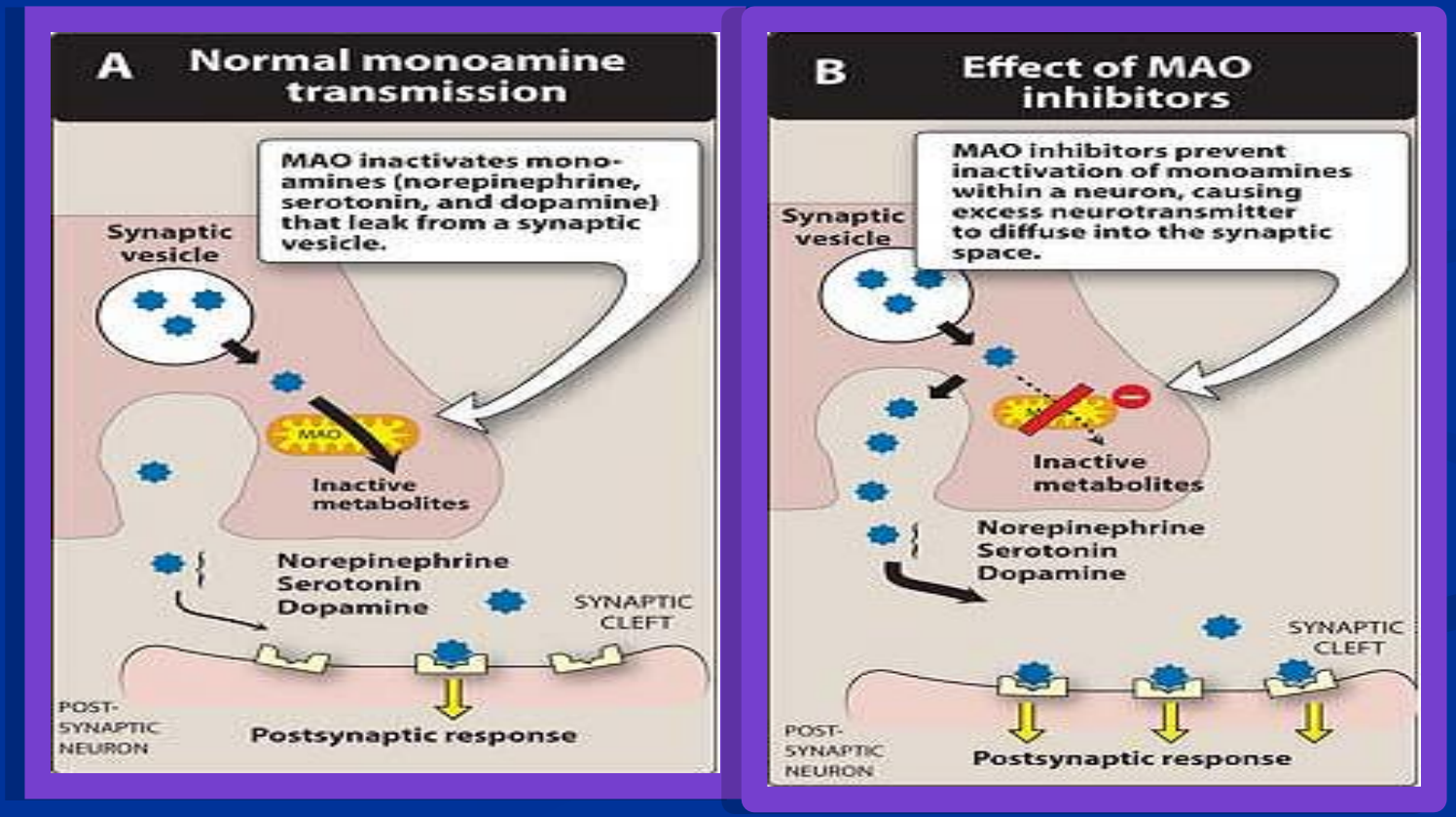
➔ Low antidepressant efficacy

= Low benefit/risk ratio

Monoamine Oxidase

- MAO is a mitochondrial enzyme found in nearly all tissues
  - Two forms of monoamine oxidase exist:
    - MAO-A responsible for NE, 5-HT catabolism. It also metabolizes tyramine of ingested food
    - MAO-B is more selective for dopamine metabolism

Monoamine Oxidase Inhibitors (MAOIs)



Monoamine Oxidase Inhibitors (MAOIs)

1- Non Selective irreversible Inhibitors *(MAO-A & MAO-B)*

- ➔ Phenelzine, long acting
- ➔ Tranylcypromine
- **The effect of irreversible MAOIs persists for a period of 2-3 weeks after stopping treatment, time needed by the body to synthesize new enzyme.**

2- Selective Reversible Inhibitors

- ➔ **Moclobemide,** ***(MAO-A)*** (antidepressant action, Short acting)
- ➔ Selegiline, ***(MAO-B)*** (used in the treatment of Parkinsonism)

MAO inhibitors

	Drug	Sedation	Anticholinergic effects	Hypotension
Non-selective irreversible	Isocarboxazid	+	++	+
	Phenelzine	+	++	+
	Tranylcypromine	-	+	+
Selective reversible	Moclobemide	-	-	-

Side Effects of MAOIs

1-Antimuscarinic effects.
2- Postural hypotension.
3- Sedation, sleep disturbance.
4- Weight gain.
5- Sexual dysfunction mainly with phenelzine.
6- Hepatotoxicity (phenelzine).

MAOIs interaction with tyramine ‘cheese reaction’

- This occurs when **Tyramine** rich foods are taken with MAOIs.
- **Tyramine** in food is normally degraded in the gut by **MAO-A.**
- Tyramine rich foods include Old cheese, Concentrated yeast products, Pickled or smoked fish, Red beans, Red Wine, Chicken liver, Sausages.

- Since the enzyme is inhibited by MAOIs, **tyramine** from ingested food is absorbed, and then taken up into adrenergic neurons where it is converted into **octopamine** - a false transmitter which causes massive release of **NE** and may result in **hypertensive crisis ;** severe hypertension, severe headache and fatal intracranial haemorrhage.

- **The special advantage claimed for Moclobemide is that, No cheese reaction occurs with its use.**

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.

2- Levodopa:

Precursor of dopamine can interact with MAOIs leading to hypertensive crisis.

Drug interactions of MAOIs

3- Amphetamine and Ephedrine:

Indirectly acting sympatho-mimetics can interact with MAOIs causing the liberation of accumulated monoamines in neuronal terminals leading to hypertensive crisis.

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

5- MAOIs & SSRIs ------- Serotonin syndrome (give 1-2 weeks gap before initiating SSRIs).

To be continued…