Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 8

ANTIDEPRESSANTS

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DEFINITION OF DEPRESSION

- **Depression** (also called *major depressive disorder or clinical depression*) is a **common** but **serious** mood disorder.
- It causes **severe symptoms** that affect how you **feel**, **think**, and **handle** daily activities, such as sleeping, eating, or working.
- To be **diagnosed** with depression, the symptoms must be **present** for at least **two weeks**.

CLINICAL PRESENTATION OF DEPRESSION

The **symptoms** of **depression** are:

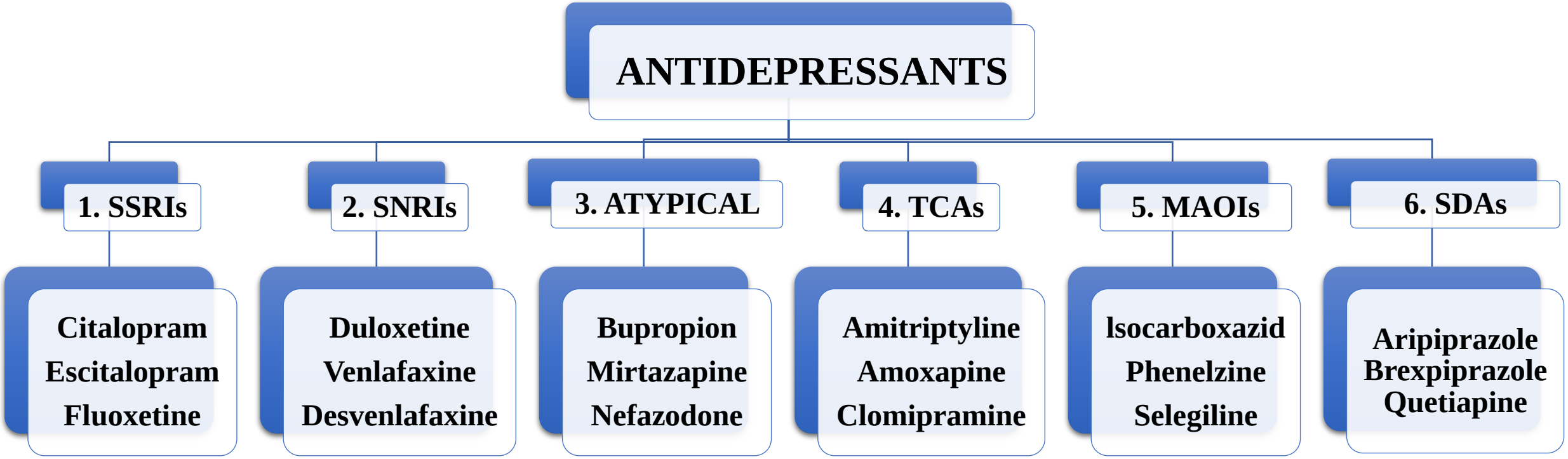
- Feelings of sadness and hopelessness
- Inability to experience pleasure in usual activities
- Changes in sleep patterns and appetite
- Loss of energy
- Suicidal thoughts

THE AMINE HYPOTHESIS OF MOOD

The amine hypothesis of mood postulates that **brain amines**, particularly **norepinephrine** (NE) and **serotonin** (5-HT), are neurotransmitters in pathways that function in the expression of **mood**.

According to the hypothesis, a **functional decrease** in the activity of such **amines** is thought to result in **depression**; a functional increase in activity results in mood elevation.

ANTIDEPRESSANT DRUGS

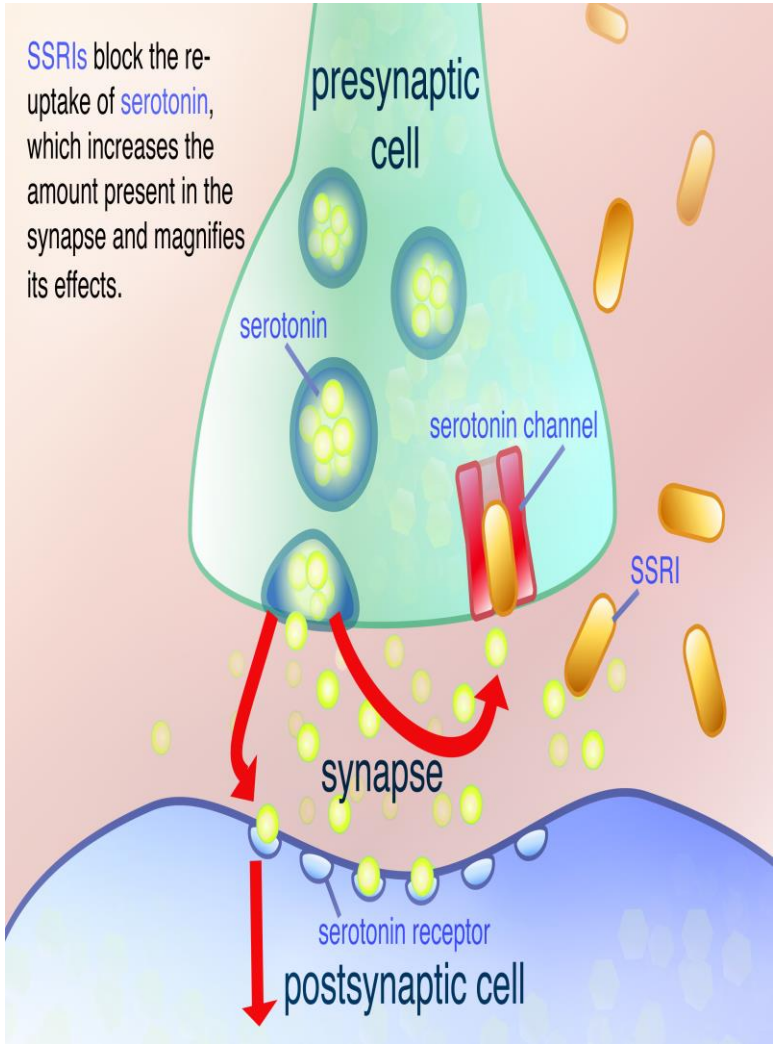


1. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

They specifically **inhibit serotonin reuptake,** having 300-3000 fold **greater selectivity** for the **serotonin** transporter, as compared to the **norepinephrine** transporter.

They are **relatively safe** even in overdose, and largely **replaced TCAs and MAOIs** as the drugs of choice in treating depression.

The SSRIs include **fluoxetine** (the prototypic drug), **citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline**.



1. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

A. Actions

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.

1. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

B. Pharmacokinetics

- **Peak** levels are seen in approximately **2-8** hours on average.
- **Food** has little effect on absorption (except with **sertraline**, for which food increases its absorption).
- **Fluoxetine** differs from the other members of the class by having a much **longer half-life** (50 hours), and the half-life of its **active metabolite** 5-norfluoxetine is quite long, averaging **10 days**.
- **Fluoxetine** and **paroxetine** are potent **inhibitors** of a CYP450 isoenzyme (CYP2D6).

1. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

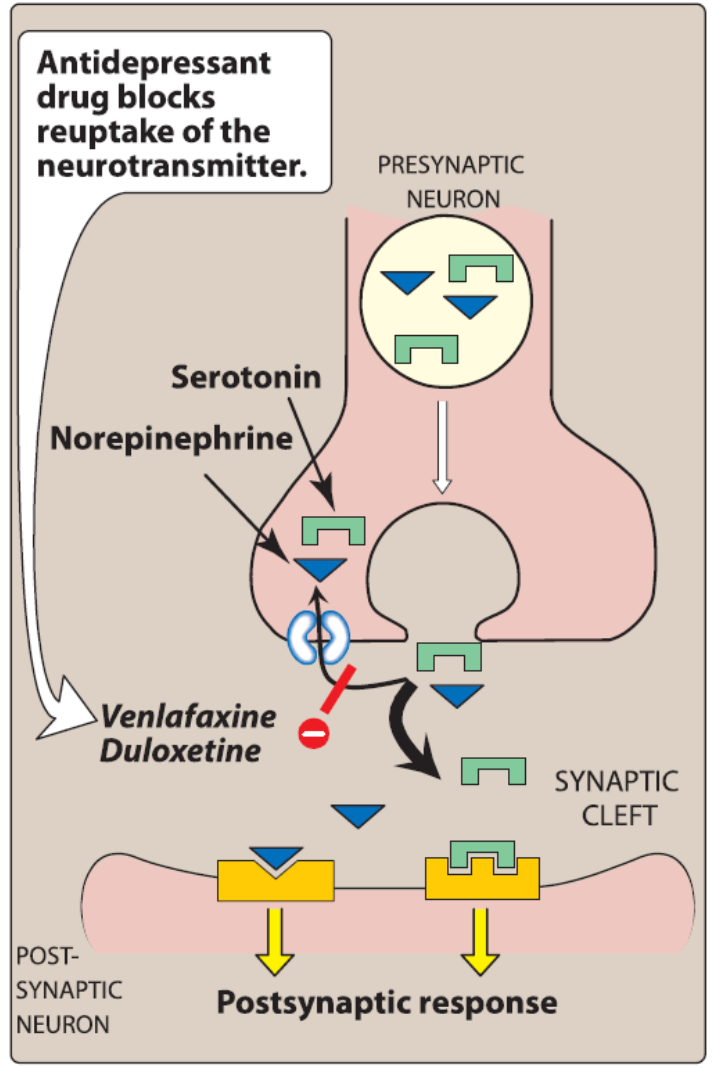
C. Adverse effects

SSRIs are considered to have **fewer** such as headache, sweating, anxiety, agitation, and hyponatremia.

Weakness and fatigue, sexual dysfunction, changes in weight, sleep disturbances , and potential for drug-drug interactions.

2. SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

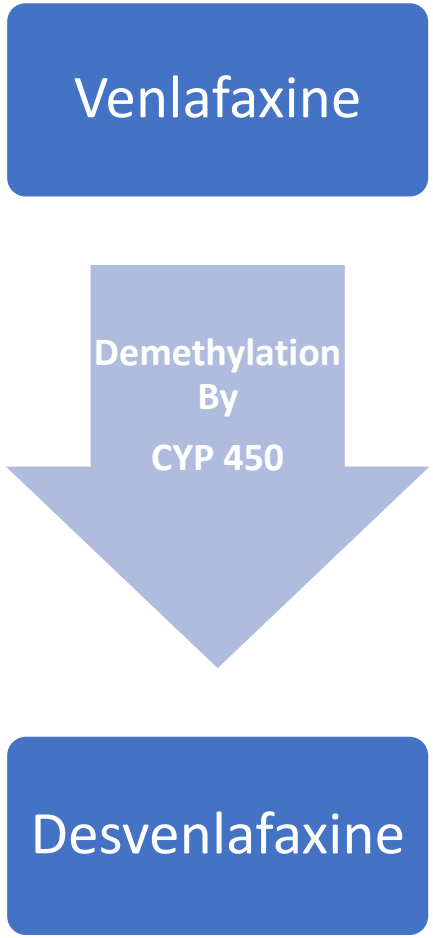
- These drugs **inhibit the reuptake** of **both** serotonin and norepinephrine and, thus, are termed SNRIs.
- Examples of SNRIs are **Venlafaxine**, **desvenlafaxine**, and **duloxetine**
- Depression is often accompanied by **chronic pain**, such as backache, muscle aches, and diabetic neuropathy for which SSRIs are relatively ineffective.
- **Both** the SNRIs and the TCAs may be **effective** in relieving such pain.
- The SNRIs have **fewer** receptor-mediated **adverse effects** than TCAs.



2. SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

A. Venlafaxine and desvenlafaxine

- Venlafaxine is an **inhibitor** of **serotonin** reuptake and, at **medium** to **higher** doses, is an **inhibitor** of **norepinephrine** reuptake.
- **Desvenlafaxine** is the **active**, **demethylated** metabolite of venlafaxine.
- The most **common side effects** of venlafaxine are <u>nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation</u>.
- At **high doses**, there may be an **increase in blood pressure and heart rate**.??



2. SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

B. Duloxetine

- It **inhibits** serotonin and norepinephrine reuptake at **all doses**.
- **GIT 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.

3. ATYPICAL ANTIDEPRESSANTS

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

This group includes:

1. Bupropion
2. Mirtazapine
3. Nefazodone
4. Trazodone
5. Vilazodone
6. Vortioxetine

3. ATYPICAL ANTIDEPRESSANTS

A. Bupropion

- Bupropion is a **weak dopamine and norepinephrine reuptake inhibitor** that is used to alleviate the symptoms of **depression**.
- **Side effects** may include dry mouth, sweating, nervousness, tremor, and a dose-dependent increased risk for seizures.
- Bupropion should be **avoided** in patients at risk for **seizures** or those who have eating disorders such as **bulimia**.

3. ATYPICAL ANTIDEPRESSANTS

C. Nefazodone and trazodone

- These drugs are weak **inhibitors** of serotonin **reuptake** and are also antagonists at the postsynaptic 5-HT2a **receptor**.
- **Both** agents are **sedating**, probably because of their potent histamine **H1-blocking** activity.
- **Trazodone** is commonly used **off-label** for the management of **insomnia**.
- **Trazodone** has been associated with **priapism**, and **nefazodone** has been associated with a risk for **hepatotoxicity**.
- **Both** agents also have mild-to-moderate **α1 receptor antagonism**, contributing to orthostasis and dizziness.

4. TRICYCLIC ANTIDEPRESSANTS

The TCAs **inhibit norepinephrine and serotonin reuptake** into the presynaptic neuron, the TCAs include:

- **The tertiary amines:** imipramine (the prototype drug), amitriptyline, clomipramine, doxepin, and trimipramine
- **The secondary amines:** desipramine, nortriptyline, and protriptyline.

Maprotiline and amoxapine are related to "**tetracyclic**" antidepressant agents and are commonly included in the general class of TCAs.

4. TRICYCLIC ANTIDEPRESSANTS

A. Mechanism of action

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** making them more likely responsible for many of their **adverse effects**.
- **Amoxapine** also blocks **5-HT2** and dopamine **D2 receptors**.

4. TRICYCLIC ANTIDEPRESSANTS

B. Therapeutic uses

- The TCAs are effective in treating **moderate to severe depression**.
- Some patients with **panic disorder** also respond to TCAs.
- **Imipramine** is used as an alternative to desmopressin in the treatment of **bed-wetting** in children.
- The TCAs, particularly **amitriptyline**, have been used to help prevent **migraine headache** and treat **chronic pain syndromes** (for example, neuropathic pain).
- **Low doses** of TCAs, especially **doxepin**, can be used to treat **insomnia**.

4. TRICYCLIC ANTIDEPRESSANTS

C. Adverse effects

Blockade of muscarinic receptors leads to blurred vision, xerostomia, urinary retention, sinus tachycardia, and constipation.

The TCAs also **block α-adrenergic receptors**, causing orthostatic hypotension, dizziness, and reflex tachycardia.

Sedation is related to the ability of these drugs to **block histamine H1 receptors**.

Weight gain is a common adverse effect of TCAs. While, Sexual dysfunction occurs in a minority of patients, and the incidence is **lower than** that associated with **SSRIs**.

5. MONOAMINE OXIDASE INHIBITORS

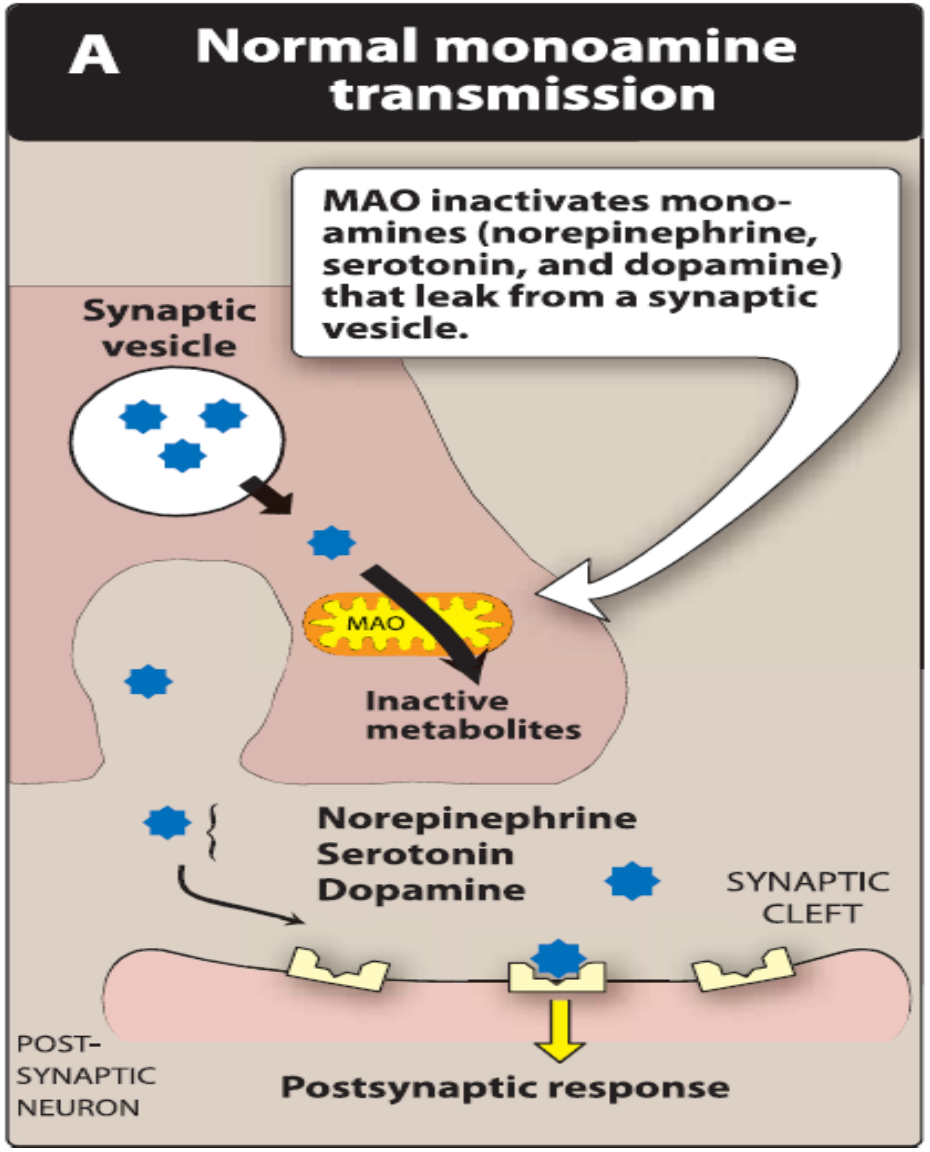
In the neuron, **MAO** functions as a "**safety valve**" to oxidatively deaminate and inactivate any **excess neurotransmitters** (for example, norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest.

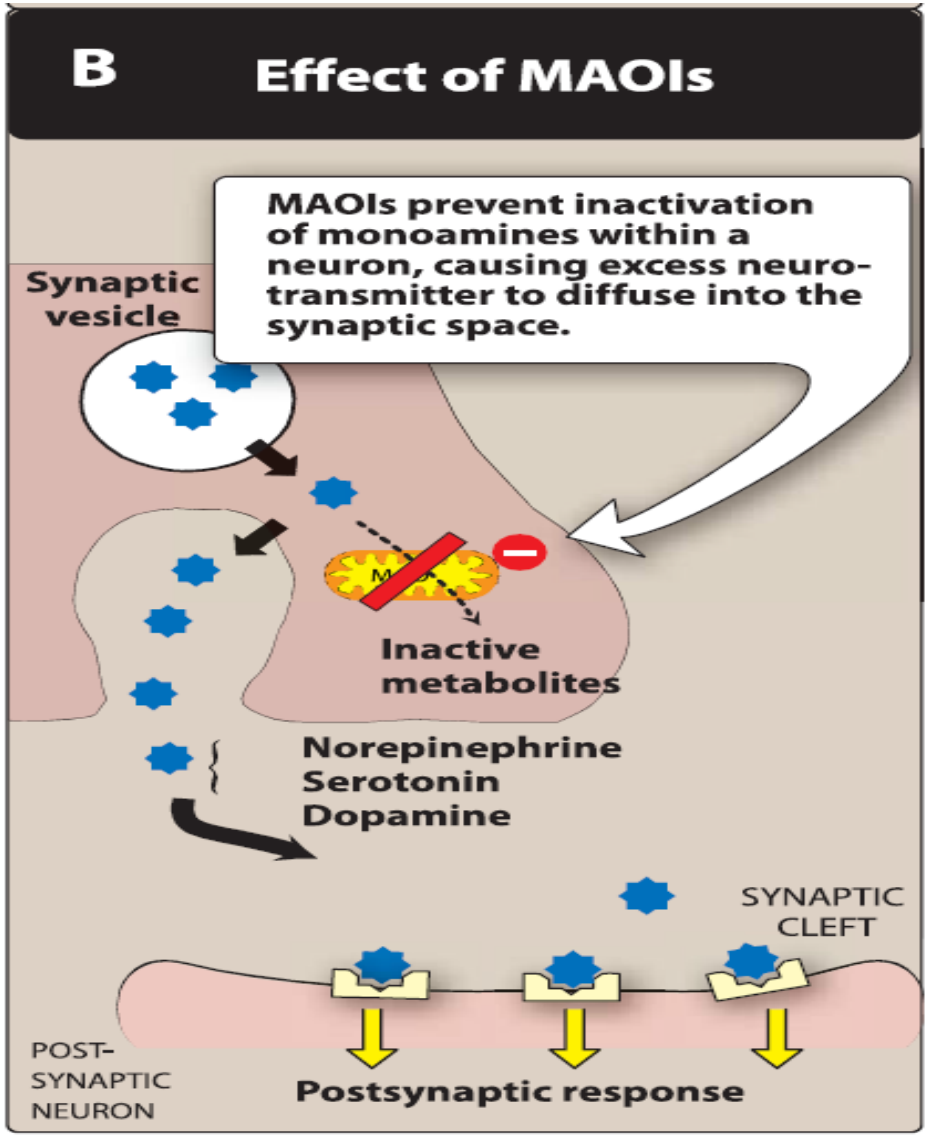
The MAOIs may **irreversibly** or **reversibly** inactivate the enzyme, permitting neurotransmitters to **escape degradation**.

The four MAOIs **currently** available for the treatment of depression include **phenelzine tranylcypromine, isocarboxazid, and selegiline**.

Selegiline is also used for the treatment of **Parkinson's disease**.

5. MONOAMINE OXIDASE INHIBITORS





5. MONOAMINE OXIDASE INHIBITORS

A. Mechanism of action

Most MAOIs, such as phenelzine, form **stable complexes** with the enzyme in the **brain**, causing **irreversible** inactivation.

This results in **increased stores** of norepinephrine, serotonin, and dopamine within the neuron synaptic space.

These drugs also inhibit **MAO** in the **liver and gut** which catalyzes the oxidative deamination of drugs and potentially toxic substances, such as **tyramine**, which is found in certain foods.

The MAOIs, show a **high incidence** of drug-drug and drug-food **interactions**.

5. MONOAMINE OXIDASE INHIBITORS

B. Therapeutic uses

The MAOIs are indicated for **depressed patients** who are unresponsive or intolerant of other antidepressants.

Because of their **risk for drug-drug and drug-food interactions**, MAOIs are considered last-line agents in many treatment settings.

5. MONOAMINE OXIDASE INHIBITORS

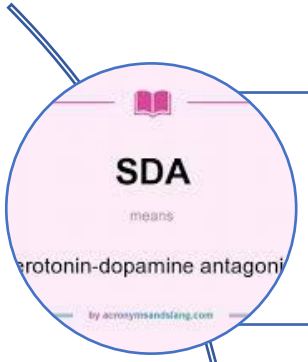
5. MONOAMINE OXIDASE INHIBITORS

C. Adverse effects

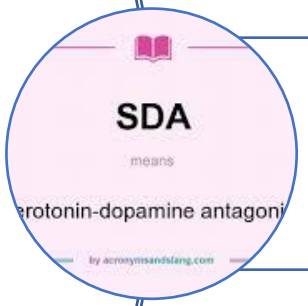
MAOIs **prevent** the **degradation** and **elevate** the level of **tyramine** within some foods, which act as **catecholamines releasers** that result in a **hypertension crisis**.

Other adverse effects include drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation.

6. SEROTONIN-DOPAMINE ANTAGONISTS



While **60% to 80**% of patients **respond** favorably to antidepressants, **20% to 40%** experience a **partial or poor response** to monotherapy.



SDAs, or **atypical antipsychotics**, are occasionally used as **adjunctive** treatments to antidepressants in **partial responders**.

SDAs include: **Aripiprazole, brexpiprazole, and quetiapine**

THANK YOU FOR YOUR ATTENTION