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

ANTIDEPRESSANTS

Dr Qassim A zigam

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**.
- **Mania** is characterized by the **opposite** behavior.

SIGNS AND SYMPTOMS 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

Mania is characterized by:

- Enthusiasm, anger, rapid thought and speech patterns
- Extreme self-confidence
- Impaired judgment

TYPES OF DEPRESSION

Types of Depression:

- **Major depression**, which includes symptoms of depression most of the time for **at least 2 weeks** that typically interfere with one's ability to work, sleep, study, and eat.
- **Persistent depressive disorder** (also called dysthymia), which often includes **less severe symptoms** of depression that last much **longer**, typically for **at least 2 years**.
- **Perinatal depression**, which occurs when a woman experiences major depression during **pregnancy** or after **delivery** (postpartum depression).
- **Seasonal affective disorder**, which comes and goes with the **seasons**, typically starting in **late autumn** and **early winter** and going away during spring and summer.
- **Depression with symptoms of psychosis**, which is a severe form of depression where a person experiences **psychosis symptoms**, such as **delusions** (false fixed beliefs) or **hallucinations** (hearing or seeing things that others do not see or hear).

TYPES OF DEPRESSION

Delusions

Fixed, false beliefs, cannot be corrected by logic and **are not consistent with culture and education** of the patient.

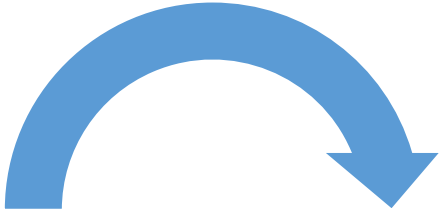
Hallucinations

False sensory perception experienced **without real external stimulus.** They are usually experienced as originated in the outside world not within the mind as imagination.

Illusions

Misperception of real external stimulus. Most likely to occur when general level of sensory stimulation (consciousness) is reduced.

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**.

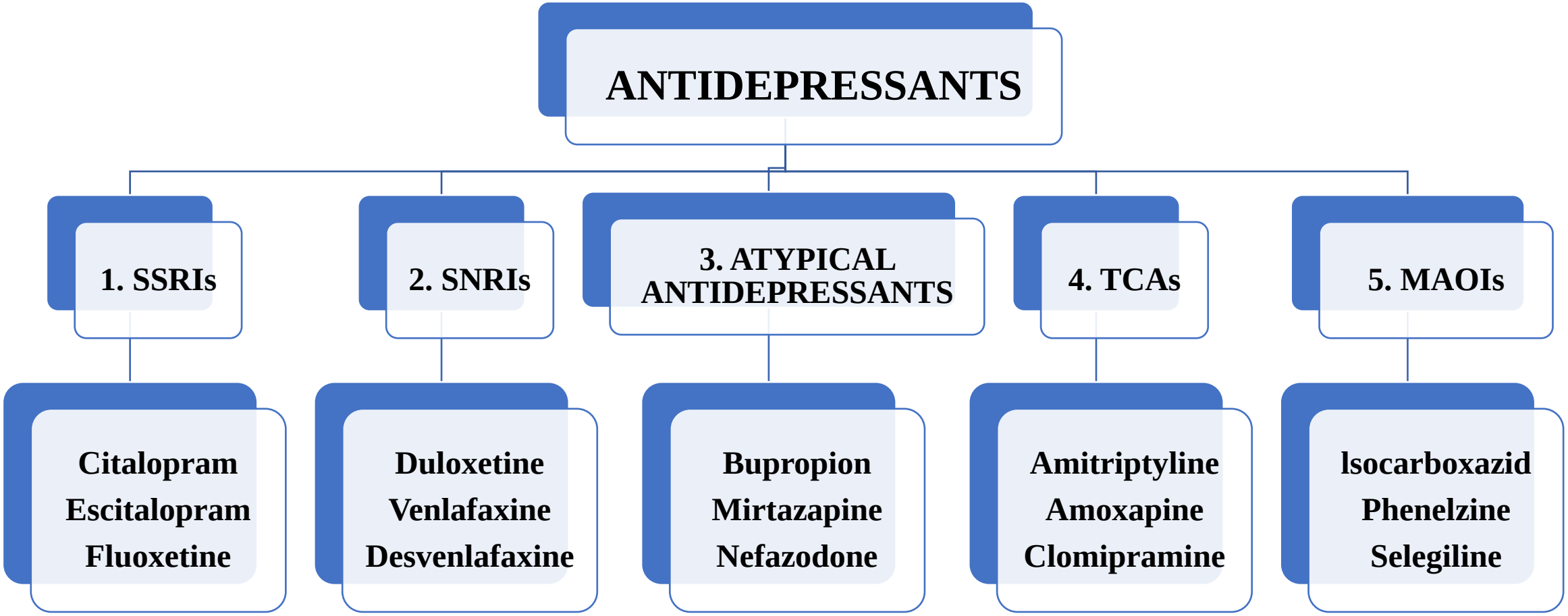
According to the hypothesis, a **functional decrease** in the activity of such **amines** is thought to result in **depression**; a functional increase in activity results in mood elevation.

THE AMINE HYPOTHESIS OF MOOD

Difficulties with this hypothesis include:

- **Postmortem** studies do **not** reveal any **decreases** in the brain levels of NE or 5-HT in patients suffering from depression.
- Although antidepressant drugs may cause changes in brain amine activity **within hours**, **weeks** may be required for them to achieve clinical effects.
- Most antidepressants ultimately cause **downregulation** of amine receptors.
- At least 1 effective antidepressant, **bupropion**, has minimal effects on brain NE or 5-HT.

ANTIDEPRESSANT DRUGS



SELECTIVE SEROTONIN REUPTAKE INHIBITORS

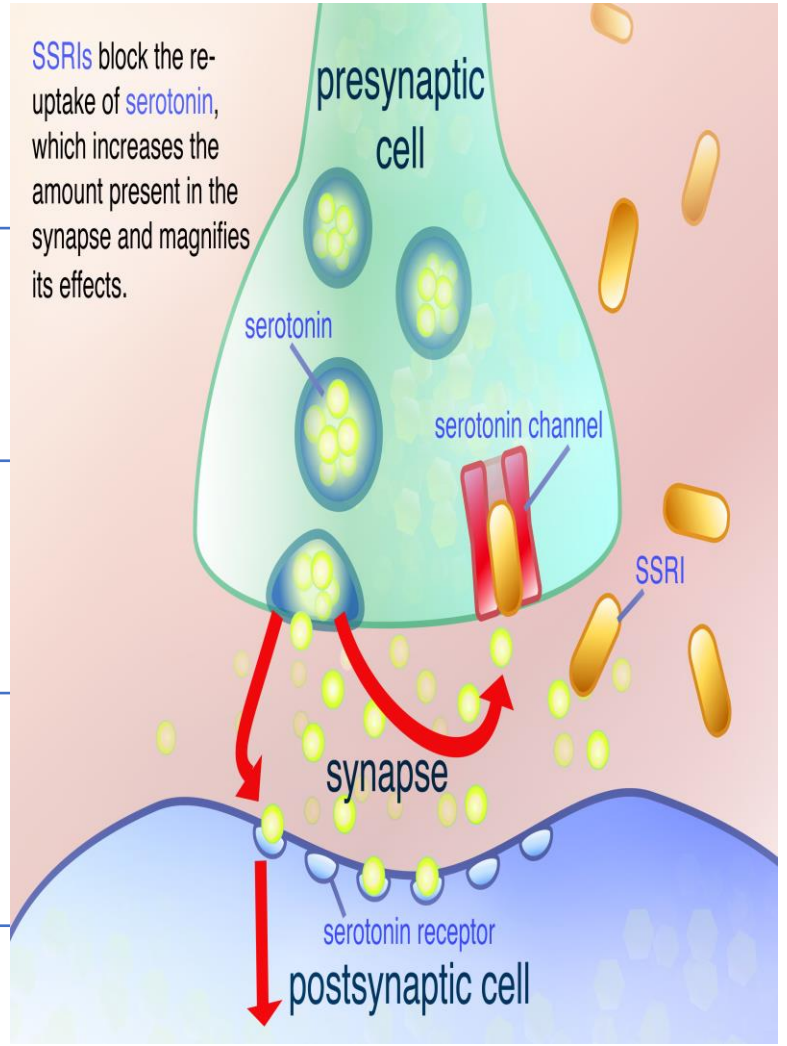
They specifically **inhibit serotonin reuptake,** having 300-3000 fold **greater selectivity** for the **serotonin** transporter, as compared to the **norepinephrine** transporter.

The SSRIs have **little** blocking activity at **muscarinic**, **α-adrenergic**, and **H1 receptors**.

Therefore, common **side effects** associated with TCAs, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are **not commonly** seen with SSRIs.

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**.



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.

B. Therapeutic uses

The **primary indication** for SSRIs is **depression**. **Other** psychiatric disorders also respond favorably to SSRIs, including obsessive-compulsive disorder, panic disorder,

generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder, and **bulimia nervosa (only fluoxetine is approved for bulimia).**

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

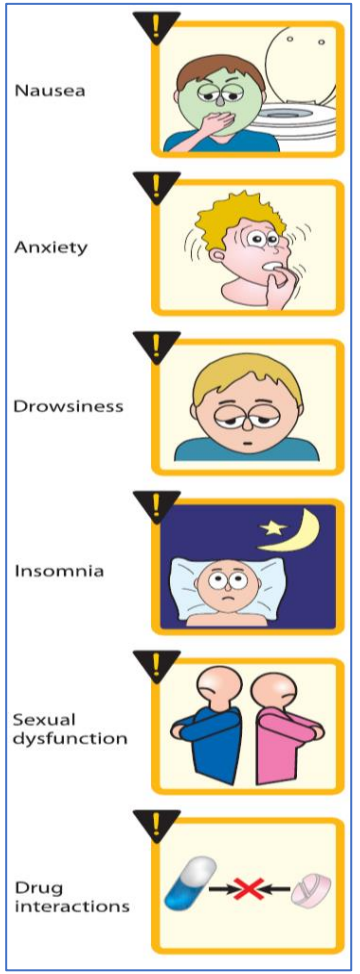
C. Pharmacokinetics

- **All** of the SSRIs are well absorbed after **oral** administration.
- **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).
- The plasma **half-lives 16-36** hrs.
- **Metabolism** by **cytochrome** P450 enzymes and glucuronide or sulfate **conjugation** occur extensively.
- **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).

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

D. Adverse effects

- SSRIs are considered to have fewer such as headache, sweating, anxiety and agitation, hyponatremia.
- GITeffects (nausea, vomiting, and diarrhea)
- Weakness and fatigue, sexual dysfunction, changes in weight, sleep disturbances (insomnia and somnolence), and potential for drug-drug interactions.

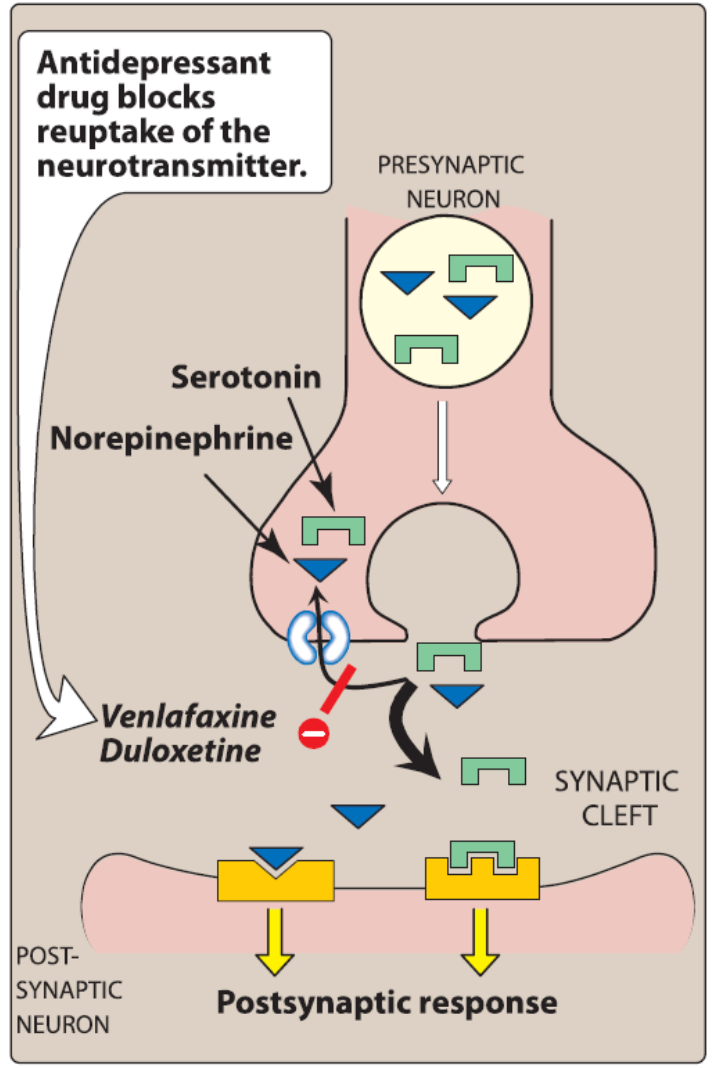


E. Discontinuation syndrome

- This occurs after their **abrupt withdrawal**, particularly the agents with **shorter half-lives** and **inactive** metabolites.
- **Fluoxetine** has the **lowest risk** of causing an SSRI discontinuation syndrome due to its longer half-life and active metabolite.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

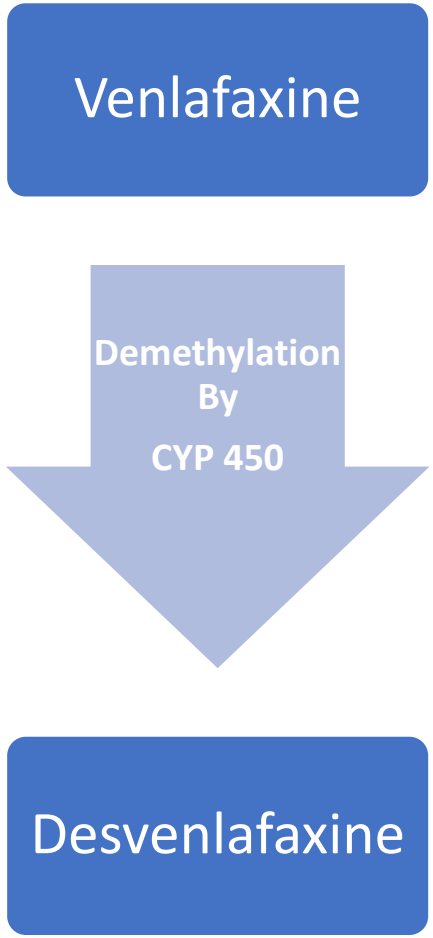
- These drugs **inhibit the reuptake** of **both** serotonin and norepinephrine and, thus, are termed SNRIs.
- Examples of SNRIs are **Venlafaxine**, **desvenlafaxine**, and **duloxetine**
- Depression is often accompanied by **chronic pain**, such as backache, muscle aches, and diabetic neuropathy for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



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.
- Venlafaxine has **minimal** inhibition of the CYP450 isoenzymes and is a **substrate** of the CYP2D6 isoenzyme.
- **Desvenlafaxine** is the **active**, **demethylated** metabolite of venlafaxine.
- 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.



SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

B. Duloxetine

- It **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**.
- **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.
- Duloxetine is a moderate **inhibitor** of CYP2D6 isoenzymes and may increase concentrations of drugs metabolized by this pathway, such as **antipsychotics**.

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

ATYPICAL ANTIDEPRESSANTS

A. 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.
- Bupropion should be **avoided** in patients at risk for **seizures** or those who have eating disorders such as **bulimia**.

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.

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 and nortriptyline, protriptyline.

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

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**.

TRICYCLIC ANTIDEPRESSANTS

B. Actions

- The TCAs **improve mood**, 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** the dosage.
- **Tapering** of these agents is recommended to **minimize discontinuation syndromes** and cholinergic rebound effects.

C. 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**.

TRICYCLIC ANTIDEPRESSANTS

D. Pharmacokinetics

TCAs are well absorbed upon **oral** administration with **low** and **inconsistent bioavailability**.

These drugs are **metabolized** by the hepatic **microsomal** system and **conjugated** with glucuronic acid.

Ultimately, the TCAs are **excreted** as inactive metabolites via the **kidney**.

TRICYCLIC ANTIDEPRESSANTS

E. Adverse effects

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

These agents affect cardiac conduction **similar to quinidine** and may precipitate life-threatening arrhythmias in an overdose situation.

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**.

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.

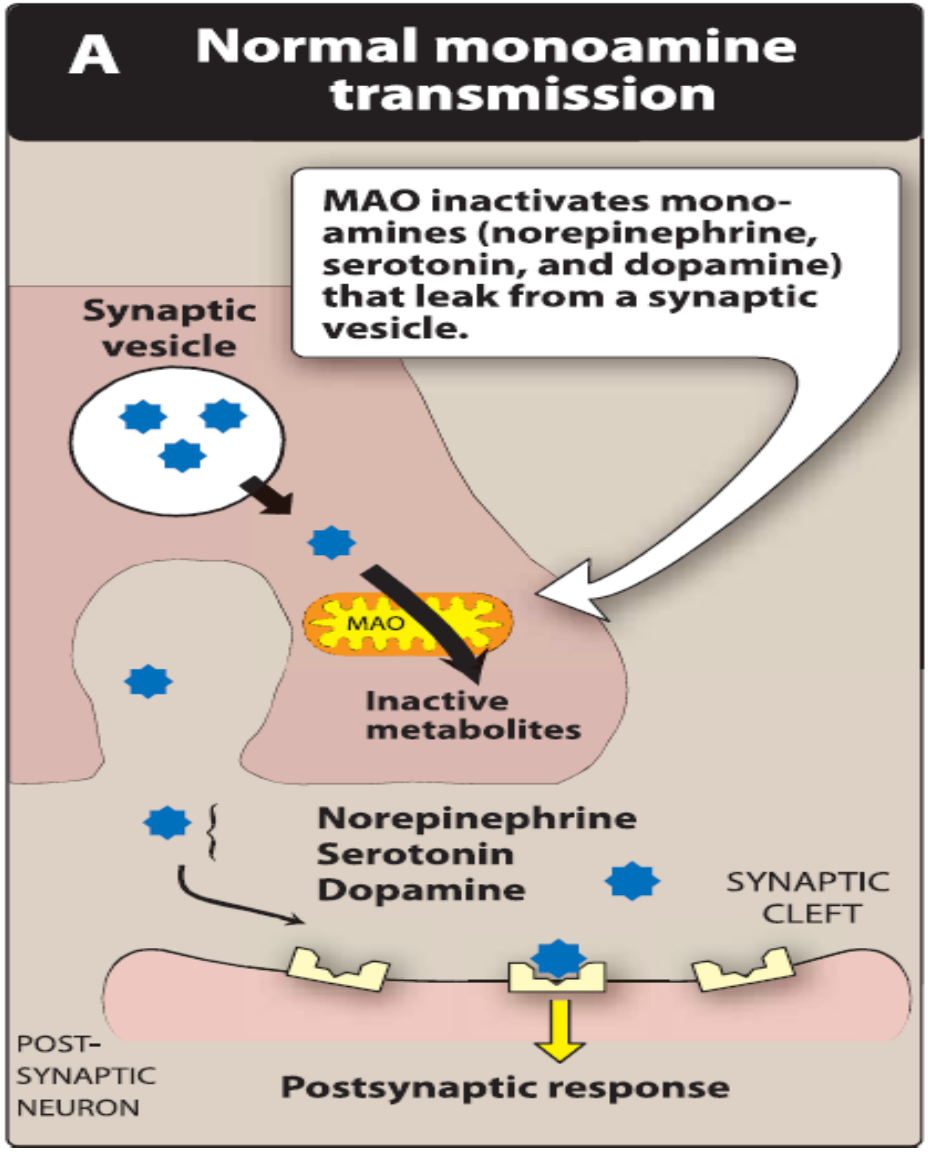
The MAOIs may **irreversibly** or **reversibly** inactivate the enzyme, permitting neurotransmitters to **escape degradation**.

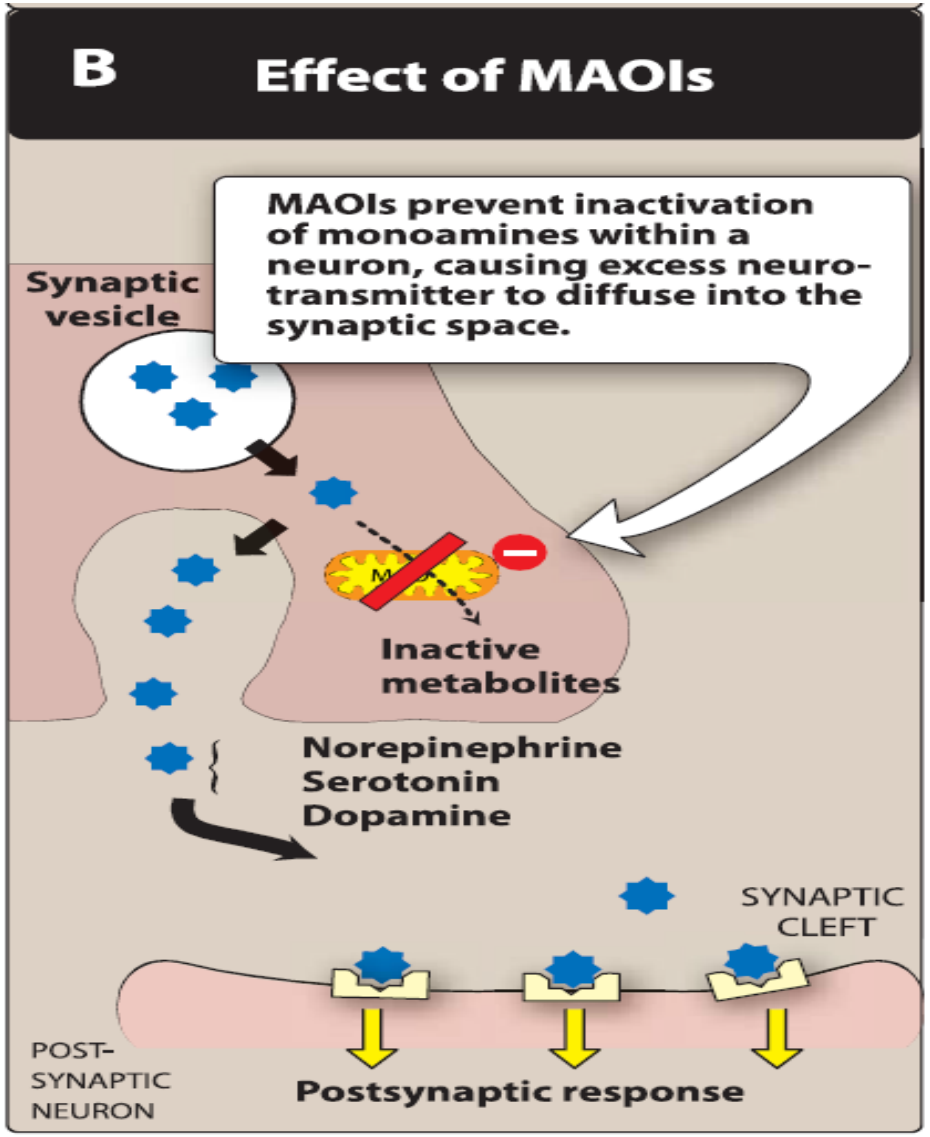
The four MAOIs **currently** available for the treatment of depression include **phenelzine tranylcypromine, isocarboxazid, and selegiline**.

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

Use of MAOIs is **limited** due to the **complicated** dietary restrictions required while taking these agents.

MONOAMINE OXIDASE INHIBITORS





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**.

MONOAMINE OXIDASE INHIBITORS

B. Actions

Although MAO is fully inhibited after **several days** of treatment, the antidepressant action is delayed for **several weeks**.

Selegiline and **tranylcypromine** have an **amphetamine-like** stimulant effect that may produce agitation or insomnia.

C. 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.

MONOAMINE OXIDASE INHIBITORS

D. Pharmacokinetics

- These drugs are **well absorbed** after **oral** administration.
- Enzyme **regeneration**, when irreversibly inactivated, varies, but it usually occurs **several weeks** after the termination of the drug.
- Thus, when **switching** antidepressant agents, a **minimum of 2 weeks** of delay must be allowed after the termination of MAOI therapy and the initiation of **another antidepressant** from any other class.
- MAOIs are hepatically **metabolized** and **excreted** rapidly in the urine.

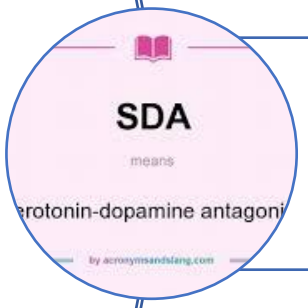
MONOAMINE OXIDASE INHIBITORS

E. Adverse effects

- MAOIs **pre** … act as **cate** … ne foods, which
- **Other** adve … sion, dry mouth, and constip …
- SSRIs shou … **syndrome**.
- Both SSRIs … administer … e other type is

SEROTONIN-DOPAMINE ANTAGONISTS

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



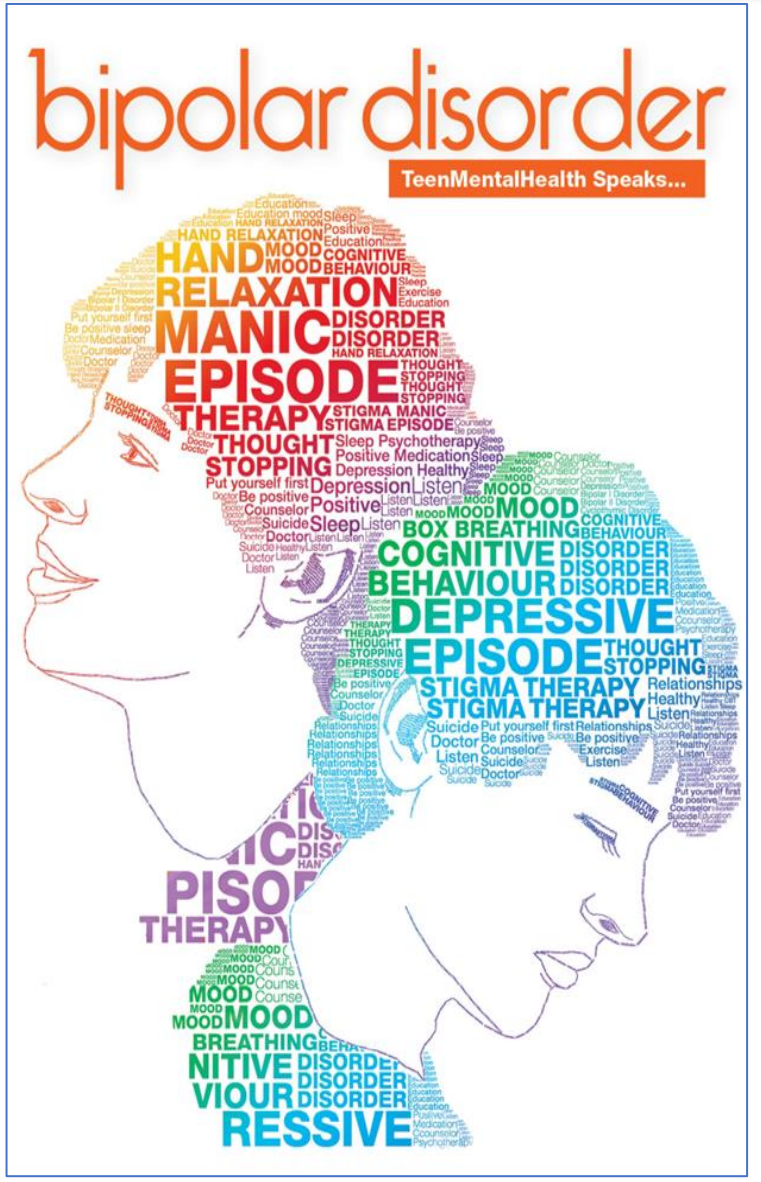
SDAs, or **atypical antipsychotics**, are occasionally used as **adjunctive** treatments to antidepressants in **partial responders**.

Aripiprazole, brexpiprazole, quetiapine, and the combination of fluoxetine and olanzapine are approved for use as **adjuncts** in major depressive disorder (MDD).

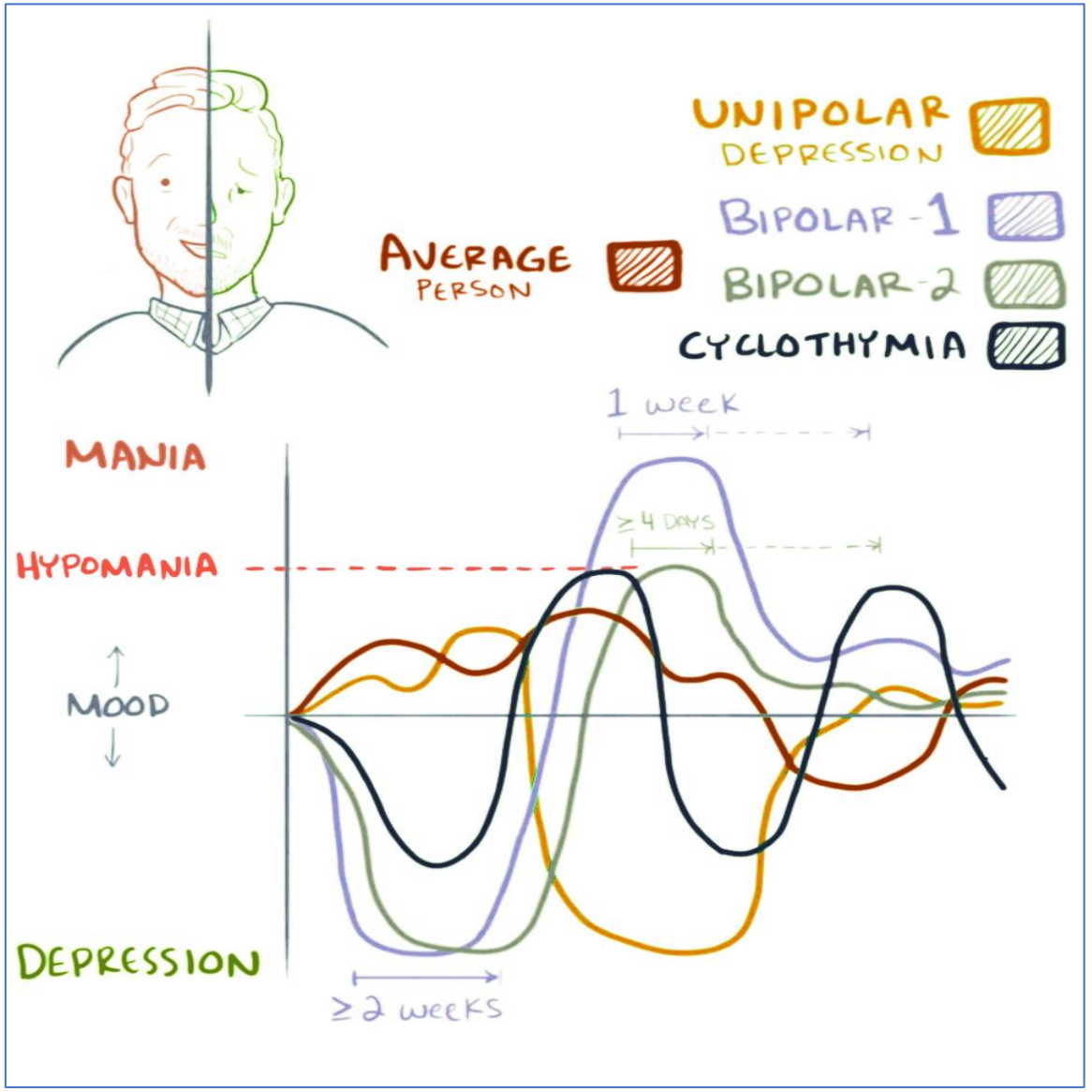
MANIA AND BIPOLAR DISORDER

Bipolar disorder (manic-depressive illness) is a mental illness that causes **unusual shifts** in mood, energy, activity levels, concentration, and the ability to carry out day-to-day tasks.

There are **three types** of bipolar disorder: **Bipolar I disorder, Bipolar II disorder, and Cyclothymic disorder**



MANIA AND BIPOLAR DISORDER



MANIA AND BIPOLAR DISORDER

There are **three types** of bipolar disorder.

Bipolar I disorder is defined by **manic** episodes that last at **least 7 days** or by manic symptoms that are so severe that the person needs **immediate hospital care**. Usually, **depressive episodes** occur as well, typically lasting at least **2 weeks**.

Bipolar II disorder is defined by a pattern of **depressive episodes** and **hypomanic episodes**, but the episodes are less severe than the manic episodes in bipolar I disorder.

Cyclothymic disorder (also called cyclothymia) is defined by **recurrent hypomanic** and **depressive symptoms** that are not intense enough or do not last long enough to qualify as hypomanic or depressive episodes.

TREATMENT OF MANIA AND BIPOLAR DISORDER

A. Lithium

- Lithium is effective in **treating 60% to 80%** of patients exhibiting mania and hypomania.
- At a neuronal level, lithium **reduces excitatory** but **increases inhibitory** neurotransmission.
- The **therapeutic index** of lithium is extremely **low**, and lithium can be toxic.
- **Common adverse effects** may include headache, dry mouth, polydipsia, polyuria, polyphagia, GI distress, fine hand tremor, dizziness, fatigue, dermatologic reactions, and sedation.
- **Thyroid function** may be **decreased** and should be **monitored**.
- Lithium is **renally** eliminated, and it may be the best choice in patients with **hepatic impairment**.

TREATMENT OF MANIA AND BIPOLAR DISORDER

B. Other drugs

- Several antiepileptic drugs, including carbamazepine, valproic acid, and lamotrigine are approved **as mood stabilizers** for bipolar disorder.
- Other agents that may **improve manic symptoms** include the **older** antipsychotics (chlorpromazine and haloperidol).
- The **atypical antipsychotics** risperidone, olanzapine, ziprasidone, aripiprazole, asenapine, cariprazine, and quetiapine are also used for the **management of mania**.
- Quetiapine, lurasidone, and the combination of olanzapine and fluoxetine have been approved for **bipolar depression**.

THANK YOU FOR YOUR ATTENTION