

CNS

Pharmacology

Modified no. 7

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Antidepressants 2+3



Color code



Slides

Doctor

Additional info

Important

❖ Flow of information in this lecture:

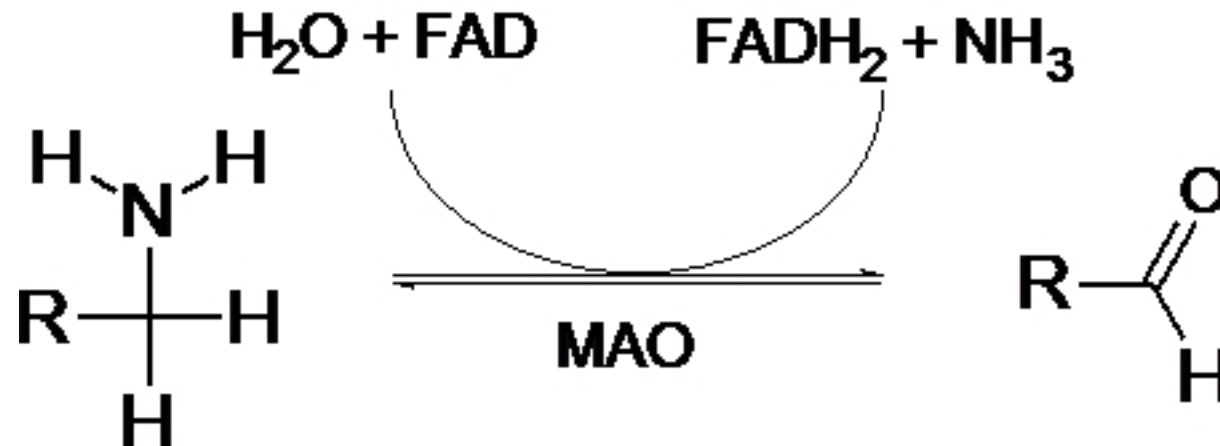
1. Discussing the MOAIs.
2. Discussing the Bupropion.
3. Discussing the TCAs.

Very very easy lecture ! 🙌

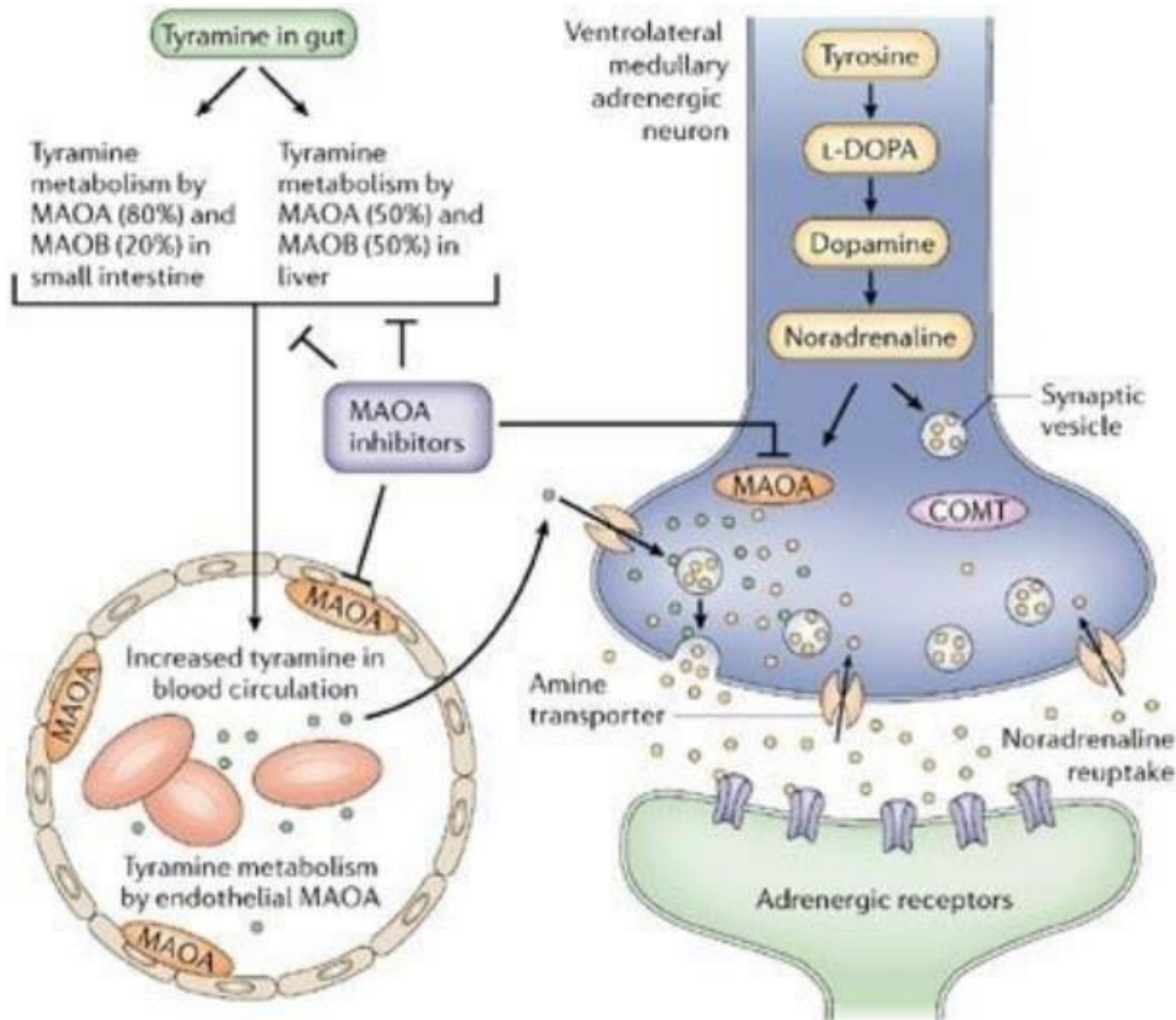
بِسْمِ اللَّهِ نَبْدَأُ

MONOAMINE OXIDASE (MAO) AND DEPRESSION

- MAO catalyze deamination of intracellular monoamines
 - MAO-A oxidizes epinephrine, norepinephrine, serotonin
 - MAO-B oxidizes phenylethylamine
 - Both oxidize dopamine nonpreferentially
- MAO transporters reuptake extracellular monoamine



- We talked about depression and mentioned that there are various theories explaining it. The first theory we discussed was the **monoamine oxidase (MAO) theory**. According to this theory, inhibiting MAO leads to increased levels of norepinephrine, serotonin, and dopamine.
- If we want to increase serotonin, we target MAO-A. If we want to increase dopamine, we target MAO-B.
- When we say that monoamine oxidase (MAO) is going to oxidize dopamine, it means that dopamine levels will decrease. MAO is an enzyme responsible for breaking down neurotransmitters like dopamine, norepinephrine, and serotonin. It does this by oxidizing them, which leads to their inactivation and removal from the brain.



- To understand the situation, the whole idea behind antidepressants is to increase the levels of neurotransmitters like dopamine, norepinephrine, and serotonin. This is exactly what we achieve when using MAO inhibitors.
- However, it's important to note a potential drug-drug interaction because MAO-A is also present in circulation and in the liver. This can lead to significant interactions when discussing MAO itself. (go to the next slide for further explanation 🤔)

MAO-A isn't just found in the brain; it's also present in the **circulatory system** and the **liver**. This matters because:

Metabolism of Other Drugs:

- The liver is responsible for breaking down many medications. Since MAO-A is involved in this process, inhibiting it can **slow down** the breakdown of certain drugs, leading to **higher-than-expected drug levels** in the body. This increases the risk of **side effects** or **toxicity**.

Tyramine Interaction (Food-Drug Interaction):

- MAO-A also helps break down **tyramine**, a substance found in foods like aged cheese, cured meats, and fermented products.
- If MAO-A is inhibited (especially by **non-selective MAO inhibitors**), tyramine builds up in the bloodstream, which can cause a **dangerous spike in blood pressure** (hypertensive crisis).

Drug-Drug Interactions:

- Since MAO-A plays a role in metabolizing neurotransmitters and other substances, **taking MAO inhibitors alongside certain medications (e.g., SSRIs, SNRIs, some painkillers, or decongestants)** can lead to excessive serotonin or norepinephrine levels, potentially causing **serotonin syndrome** or **hypertensive episodes**.

So, when using **MAO inhibitors**, doctors need to be careful about **what other drugs or foods a patient consumes** to avoid these dangerous interactions.

1. Monoamine oxidase inhibitors (MAOI)

- Inhibition of intra-neuronal degradation of serotonin and norepinephrine causes an increase in extracellular amine levels.
- Phenzelzine is a none selective
- Moclobemide is a reversible and selective inhibitor of MAO-A
- Selegiline is a selective for MAO-B
- Side effects:
Blood pressure problems, Dietary requirements, Weight gain, Insomnia, Edema.

- In the previous slide, we discussed different types of MAO inhibitors.
 - **Moclobemide** is a reversible and selective MAO-A inhibitor, **Phenelzine** is a non-selective, **Selegiline**, which is selective for MAO-B, is used to increase dopamine levels in patients with **Parkinson's disease**.
- In Parkinson's, as the effects of **levodopa-carbidopa** start to wear off (a phenomenon known as the "wearing-off" effect), we **augment dopamine activity** by inhibiting MAO-B by **Selegiline**.
- Now, when we talk about **depression**, we focus on **MAO-A**, and **Moclobemide** is the drug used as an **antidepressant**.

Why Do These Drugs Still Exist If We Have Better Options?

- In the **1950s-1960s**, MAO inhibitors were commonly used because the entire theory of depression treatment was built around them. However, their use has significantly decreased because **newer drugs like SSRIs offer better efficacy and safety**.

So, why are MAO inhibitors still available?

- Because they are **non-selective**, meaning we don't typically use them unless the patient is **resistant to other treatments**. If SSRIs don't work, we first try **alternative approaches** like **cognitive therapy, exercise, and lifestyle changes**. If none of these help, and the patient has **treatment-resistant depression**, we then consider MAO inhibitors—but only as a **last resort**.

- One specific case where **MAO inhibitors** may be useful is **atypical depression**.

Atypical depression means that a patient might **appear reactive**—for example, they may **laugh at a joke**, but **deep down, they are still severely depressed**. This type of depression is **more common in teenagers**, and **MAO inhibitors** can be effective in such cases. However, **they are never the first-line treatment**. We start with **SSRIs**, and if the patient doesn't respond after an **8-week trial**, we consider **MAO inhibitors**.

Key Takeaways on MAO Inhibitors:

- **Be aware of food interactions** – especially **cheese** and **tyramine**, which can lead to **hypertensive crises**.
- **Atypical depression** – MAO inhibitors can be used when other treatments fail.
- **Selectivity matters** – MAO-A inhibitors for depression, MAO-B inhibitors for Parkinson's.

So, if you ask me about MAO inhibitors (as the doctor says), the **main things to remember** are the **cheese/tyramine interaction**, their role in **atypical depression**, and the **importance of selectivity** between MAO-A and MAO-B.

Don't give them with serotonin because this could lead to serotonin syndrome.

2. Bupropion

- Good for use as an augmenting agent
- Mechanism of action likely reuptake inhibition of dopamine and norepinephrine
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- No weight gain, sexual side effects, sedation or cardiac interactions
- Low induction of mania
- Does not treat anxiety unlike many other antidepressants and can actually cause anxiety, agitation and insomnia

Bupropion as an Augmenting Agent

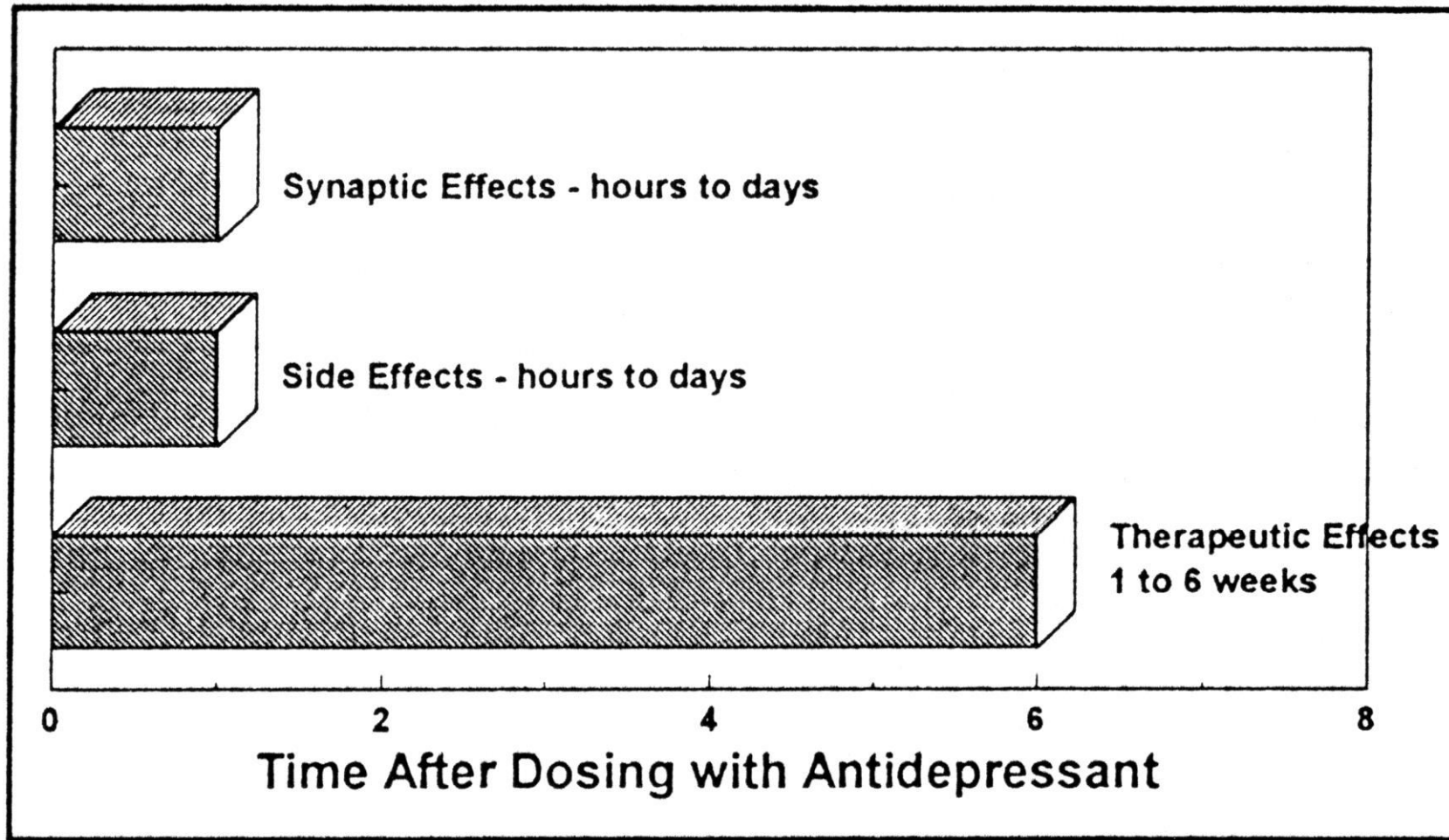
- Bupropion can enhance serotonin activity indirectly when used as an **augmenting agent**. This means that when combined with SSRIs, it provides **additional benefits** by increasing dopamine and **norepinephrine** levels while allowing SSRIs to enhance serotonin activity.
- This combination **resembles the effects of MAO inhibitors** but **without** the dietary restrictions (cheese effect) or blood pressure complications.
- Bupropion is **not** typically used as a **standalone antidepressant**. Instead, it is most effective as an **augmenting agent**. The primary drugs it augments are SSRIs. Why? Because bupropion's mechanism of action involves **inhibiting the reuptake of dopamine and norepinephrine**, with **no direct effect on serotonin**. This makes it a favorable option since it **does not contribute to serotonin syndrome, weight gain, sexual dysfunction, sedation, or cardiac interactions**. However, it is considered a **relatively weak antidepressant on its own**.
- Additionally, bupropion has a **low risk of inducing mania**, but because it increases dopamine and norepinephrine, it is generally **avoided in bipolar mania**, where elevated levels of these neurotransmitters can be problematic.

In summary: Who am I, Bupropion ?

- I am a drug that **inhibits the reuptake of dopamine and norepinephrine.**
- However, I am not a highly effective antidepressant on my own—I work best when combined with another antidepressant that targets serotonin.
- The good news is that I do not increase serotonin levels by myself. Instead, I elevate dopamine and norepinephrine while avoiding common side effects such as weight gain, sexual dysfunction, sedation, or cardiac interactions.
- My potential downside? A low risk of inducing mania due to my effects on dopamine and norepinephrine. I also **do not have anti-anxiety properties.**
- In my early stages of use, I may cause **agitation, insomnia, and anxiety** before my full effects are felt, which usually takes about **4–6 weeks.**

Low Induction of Mania & Manic Episodes:

- Bupropion has a low risk of triggering manic episodes compared to other antidepressants.
- A manic episode is a period of extremely elevated mood, energy, and impulsivity, often seen in bipolar disorder. Symptoms include decreased need for sleep, racing thoughts, risky behavior, and even delusions or hallucinations in severe cases.
- Although bupropion increases dopamine and norepinephrine, which can contribute to mania, it is generally considered to have a lower risk of inducing it compared to other antidepressants like SSRIs or SNRIs.
- However, it is still not recommended for patients with bipolar disorder, especially those prone to mania, because any drug that boosts dopamine and norepinephrine can still potentially trigger manic episodes.



Onset of action of antidepressants. Synaptic effects and side effects of antidepressants begin before therapeutic effects are observed.

NOT REQUIRED

- Following the initiation of the antidepressant drug treatment there is generally a therapeutic lag lasting for 3-4 weeks.
- 8 weeks trial, then you allow to switch to another antidepressant.
- Partial response then add one another drug from different class.

NOT REQUIRED

- if the initial treatment was successful then 6-12 maintenance periods.
- If the patient has experience two episodes of major depression, then it is advisable to give an anti depressant life long.

3. Tricyclic antidepressant (Amitriptyline)

- TCAs inhibit serotonin, norepinephrine, and dopamine transporters, slowing reuptake.
- With a resultant increase in activity.
- Muscarinic acetylcholine receptors, alpha-adrenoceptors, and certain histamine (H1) receptors are blocked.

Side effects:

- (1) drug-induced Sedation
- (2) Orthostatic hypotension
- (3) Cardiac effects
- (4) Anticholinergic effects dry mouth, constipation, blurred vision, urinary retention

Tricyclic Antidepressants (TCAs):

Mechanism of Action (MOA):

TCAs cause non-selective reuptake inhibition of norepinephrine (NE), dopamine, and serotonin, increasing their activity in the synapse. They are effective as antidepressants.

Side Effects:

The side effects of TCAs arise from their binding to various other receptors:

1. **Sedation** – Due to **histamine receptor blockade** (antihistamine effect).
 2. **Orthostatic hypotension** – Caused by **alpha-1 adrenergic blockade**.
 3. **Cardiac effects** –inhibiting the vagal nerve, leading to **palpitations** and **tachycardia**.
- In cases of **poisoning**, TCAs can cause **severe arrhythmia** with **QT interval and QRS complex elongation**. However, they do not cause Torsades de Pointes. (Pay attention, there is a difference between cardiac effects as a side effect and those occurring in a poisoning situation)
4. **Atropine-like effects** – Due to **muscarinic receptor blockade**, leading to **dry mouth, constipation, blurred vision, and urinary retention**.

Uses:

- Due to their side effects and drug-drug interactions , TCAs are rarely used. They are **primarily prescribed to treat resistant depression** when other drugs, such as SSRIs, SNRIs, MAO inhibitors, or bupropion, are ineffective.
- Additionally, TCAs can sometimes be used in **fibromyalgia** (e.g., **amitriptyline**) as pain management is sometimes linked to depression.

Important Note !!!! :

Do NOT combine TCAs with other serotonin-enhancing drugs, as this can lead to **serotonin syndrome**.

« يَا أَيُّهَا الَّذِينَ آمَنُوا اذْكُرُوا اللَّهَ ذِكْرًا كَثِيرًا »

- سُبْحَانَ اللَّهِ
- الْحَمْدُ لِلَّهِ
- لَا إِلَهَ إِلَّا اللَّهُ
- لَا حَوْلَ وَلَا قُوَّةَ إِلَّا بِاللَّهِ
- سُبْحَانَ اللَّهِ وَبِحَمْدِهِ
- سُبْحَانَ اللَّهِ الْعَظِيمِ
- أَسْتَغْفِرُ اللَّهَ الْعَظِيمَ
- لَا إِلَهَ إِلَّا أَنْتَ سُبْحَانَكَ إِنِّي كُنْتُ مِنَ الظَّالِمِينَ.

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→V2			
V2→V3			



امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!