بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

Antidepressants (pt.3)

FINAL | Lecture 3

﴿إِنِّي تَوَكَّلْتُ عَلَى اللَّهِ رَبِّي وَرَبِّكُمْ ۚ مَّا مِن دَابَّةٍ إِلَّا هُوَ آخِذٌ بِنَاصِيَتِهَا ۚ إِنَّ رَبِّي عَلَىٰ صِرَاطٍ مُّسْتَقِيمٍ﴾

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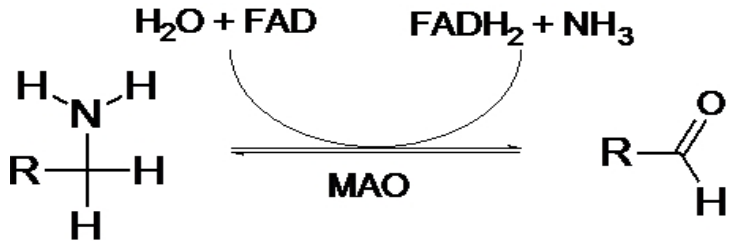
PHARMACOLOGY

Monoamine oxidase (MAO) and depression

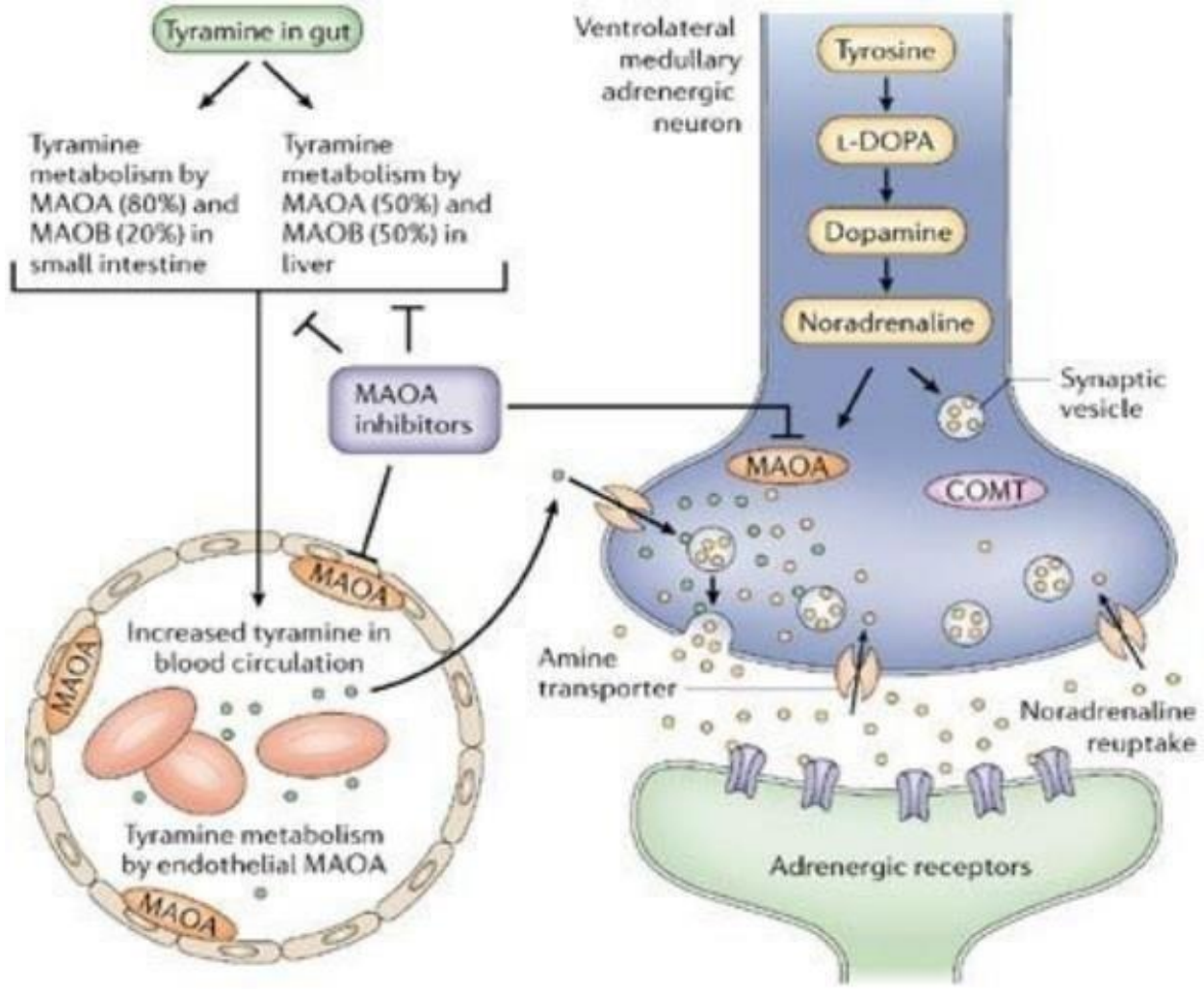
- **Depression** can be explained by several theories, one of which is the **Monoamine Oxidase (MAO) Theory.** According to this theory **MAO inhibitors increase** the levels of key **neurotransmitters** —**norepinephrine**, **serotonin**, and **dopamine**— by **preventing** their **breakdown**.
- MAO catalyze deamination of intracellular monoamines
  - MAO-A oxidizes epinephrine, norepinephrine, serotonin
  - MAO-B oxidizes phenylethylamine
  - Both oxidize dopamine nonpreferentially
- Targeting **MAO-A** primarily increases **serotonin** levels.
- Targeting **MAO-B** primarily increases **dopamine** levels
- MAO transporters reuptake extracellular monoamine.



Monoamine oxidase (MAO) and depression

- The main goal of **antidepressants** is to **increase neurotransmitter** levels, including **dopamine**, **norepinephrine**, and **serotonin**. This is precisely the effect achieved by **MAO inhibitors.**

- However, **caution** is needed because **MAO-A** is also **present** in the **circulation** and **liver**, which can lead to significant **drug-drug interactions**. Therefore, **potential interactions** should always be considered when using **MAO inhibitors.** Click HERE



Monoamine oxidase inhibitors (MAOI)

- **Inhibition of intra-neuronal degradation of serotonin and norepinephrine causes an increase in extracellular amine levels.**
- **Phenelzine** is a none selective
- **Moclobemide** is a reversible and selective inhibitor of MAO-A (the main drug used)
- **Selegiline** is a selective for MAO-B

  Selegiline, a selective **MAO-B** inhibitor, is used to increase **dopamine** levels in patients with **Parkinson's disease**. In Parkinson's, when the effects of **levodopa-carbidopa** begin to **diminish** ("**wearing-off**" effect), **Selegiline** helps **augment dopamine** activity by inhibiting **MAO-B**. (Lecture 8)

- Side effects:

  Blood pressure problems, Dietary requirements, Weight gain, Insomnia, Edema

Monoamine oxidase inhibitors (MAOI)

Why MAO Inhibitors Are Still Used

In the 1950s–1960s, MAO inhibitors were commonly prescribed because depression treatment was centered around them. However, **newer drugs**, such as **SSRIs**, are **safer** and more **effective**, so MAO inhibitors are **rarely first-line**.

Current role:

- **Reserved for treatment-resistant cases:** Only considered if **SSRIs**, **cognitive therapy**, **exercise**, and **lifestyle** interventions fail.
- **Atypical depression:** Can be useful for patients who appear **emotionally reactive** (e.g., laughing at jokes) but are **deeply depressed**. More common in teenagers. MAO inhibitors are never **first-line**; **SSRIs** are tried first for 8 weeks.

Selectivity:

- **MAO-A** inhibitors → **depression**
- **MAO-B** inhibitors → **Parkinson's disease**

Drug & food interactions:

- Avoid foods high in **tyramine** (aged cheese) → risk of **hypertensive crisis.** **IMPORTANT!** **See slide 4**
- Avoid combining with **serotonergic drugs** → risk of **serotonin** syndrome. **IMPORTANT!**

Clinical use:

- Mainly for **atypical depression** or **treatment-resistant** cases
- Always consider **safer alternatives first**

Buproprion

- Good for use as an augmenting agent
- Mechanism of action likely reuptake inhibition of dopamine and norepinephrine
- 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

Buproprion / Further Explanation

Mechanism of Action:

- Inhibits the **reuptake** of **dopamine** and **norepinephrine**.
- **Indirectly enhances serotonin activity** when **combined** with **SSRIs**, providing **synergistic** antidepressant effects.
- This synergism works similarly to **MAO inhibitors** but **without dietary restrictions** (no "cheese effect") or blood pressure complications.

Clinical Use:

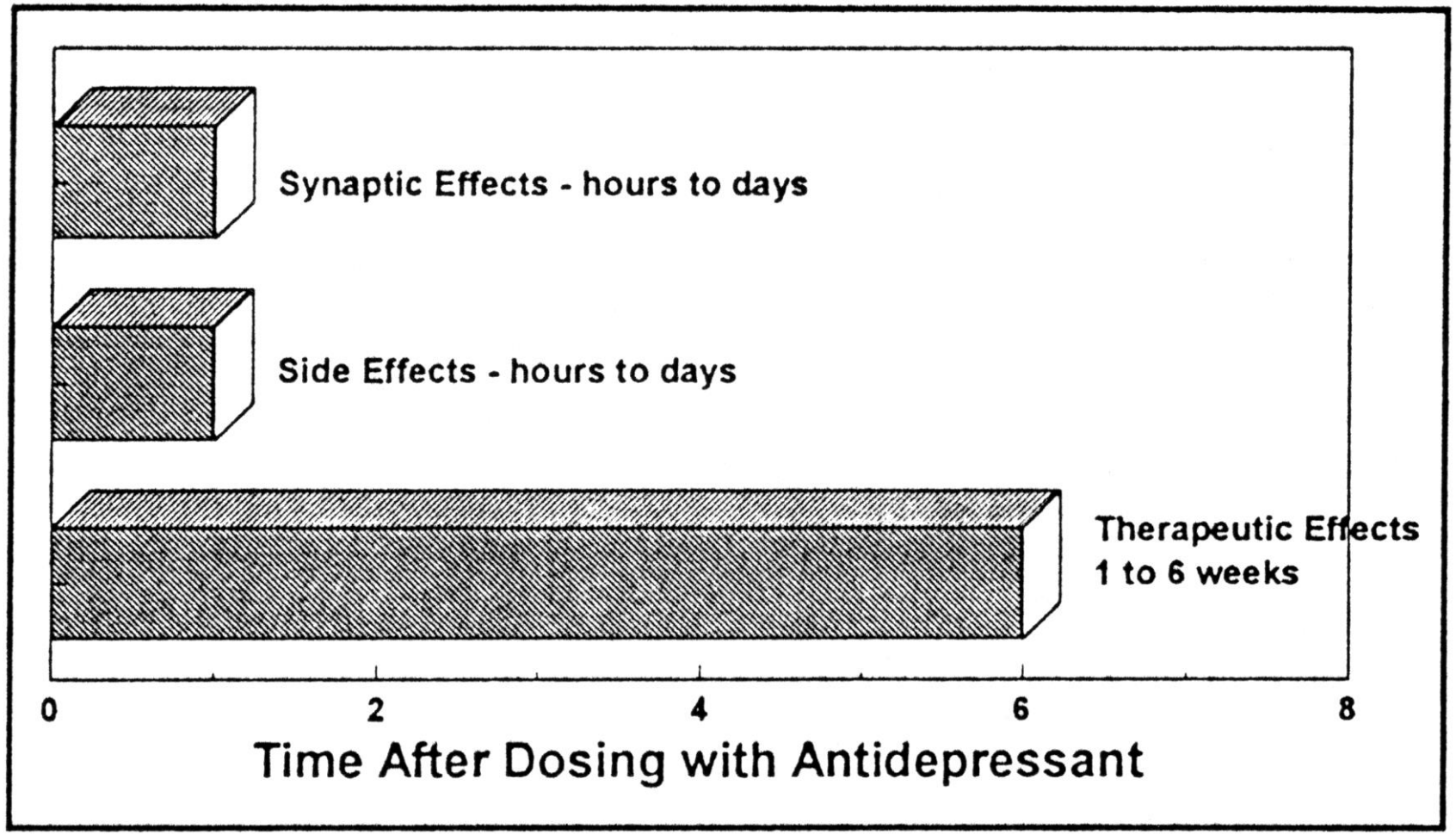
- **Not** typically used as a **standalone antidepressant**; most effective when **augmenting** SSRIs.
- Favors **combination therapy** because it does **not increase serotonin directly,** minimizing risk of **serotonin syndrome.**
- **Avoided** in **bipolar mania**, as increasing **dopamine** and **norepinephrine** can trigger manic episodes

Advantages:

- **Avoids** common SSRI side effects: **weight gain, sexual dysfunction, sedation, and cardiac interactions.**
- **Low** risk of inducing **mania** (increases dopamine & norepinephrine)

Potential Downsides / Early Effects:

- May **initially** cause **agitation, insomnia, or anxiety mania** (as it increases dopamine & norepinephrine)**.**
- Full **therapeutic effects** typically **take 4–6 weeks.**



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

Management – NOT REQUIRED

- Following the initiation of the antideppresant dryg treatment there is generally a therapuetic 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.
- 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.

Tricycle antidepressant (Amitriptyline)

- **TCAs** cause non-selective **inhibition of serotonin, norepinephrine, and dopamine transporters, slowing reuptake.**

- **with a resultant increase in activity.**

- They are effective as **antidepressants**.

- **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) Anticholinergeric effects dry mouth, constipation, blurred vision, urinary retention

➢ 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.

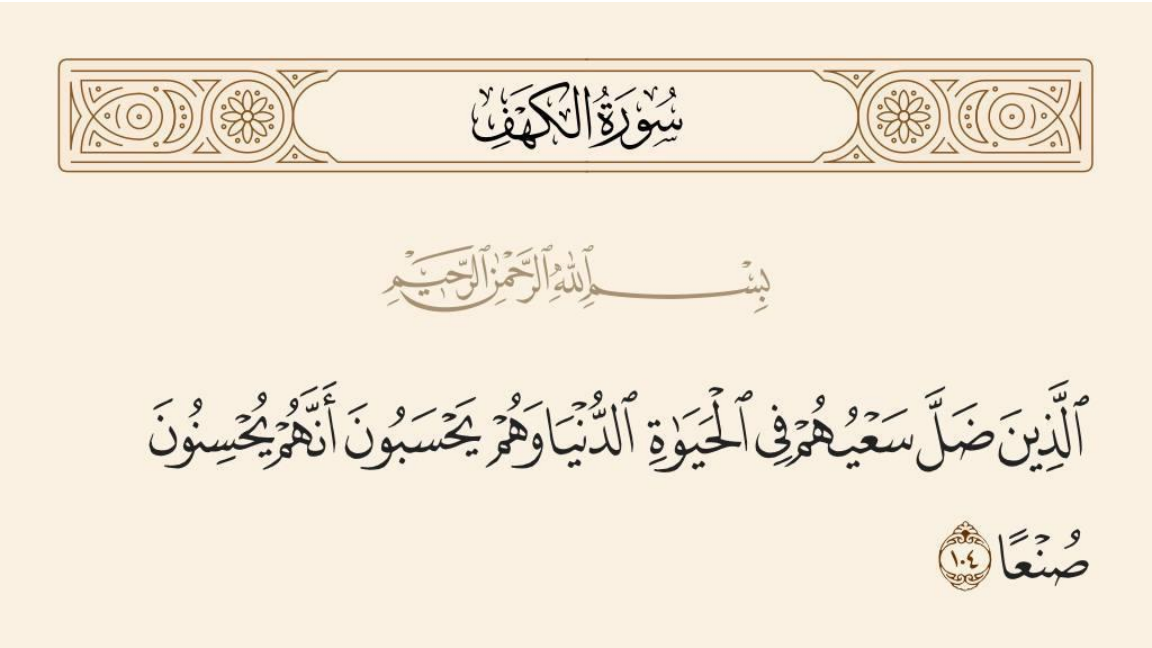
IMPORTANT NOTE:

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

PHARMACOLOGY QUIZ

LECTURE 3

رسالة من الفريق العلمي



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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			