

# Pharmacology

Modified no.6

الكاتب: علاء خضر و ليث الخزاعلة  
المدقق: ميس قشوع و أحمد الرشيد  
الدكتور: مالك زحلف

# Antidepressants (1)



## Color code

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Slides



Doctor



Additional info



Important

❖ Flow of information in this lecture:

1. Intro for depression and Antidepressants.
2. Discussing the 3 theories about how anti-depressants work.
3. Discussing Antidepressants (SSRI, SNRI and MOAI).

بِسْمِ اللّٰهِ نَبْدَأُ

Welcome to first lecture of the final. WE are going to discuss Anti-depressants, these drugs are very complex and in this lecture we are gonna just scratch the tip of the iceberg. However, before proceeding , we need to keep in mind **some important concepts** to further increase our understanding:

- ❑ There many theories how anti-depressants work, but we will mainly focus on 3. All of them give somewhat explanation but not fully.
  - Monoamine oxidase theory
  - Neurotrophic Theory
  - Serotonin receptors theory
- ❑ Placebo effect: placebo can work effectively as actual drugs and even that anti-depressants are most widely prescribed drugs world wide!
- ❑ These drugs can change our personalities and lead to change in our ideas and thoughts.
- ❑ These drugs mainly work on 3 neurotransmitters:
  - Dopamine: Dopamine plays a crucial role in motivation, reward, and pleasure.
  - Norepinephrine: This neurotransmitter is involved in the body's stress response and affects attention and responding actions in the brain.
  - Serotonin: This neurotransmitter is linked to mood regulation, social behavior, and feelings of well-being.

# Antidepressants

**The optimal use of antidepressant required a clear understanding of their mechanism of action, pharmacokinetics, potential drug interaction and the differential diagnosis of psychiatric illnesses.**

# Depression

## A World Health Organization (WHO) Prediction

- Depression is currently the **FOURTH** most significant cause of suffering and disability worldwide
- and, sadly, It will be the **SECOND** most debilitating human condition by the year 2020.

Drug	Brand	Class	2007 Prescriptions (in millions)
Sertraline	Zoloft	SSRI	29.652
Escitalopram	Lexapro	SSRI	27.023
Fluoxetine	Prozac	SSRI	22.266
Bupropion	Wellbutrin	NDRI	20.184
Paroxetine	Paxil	SSRI	18.141
Venlafaxine	Effexor	SNRI	17.200
Citalopram	Celexa	SSRI	16.246
Trazodone	Desyrel	SRI	15.473
Amitriptyline	Elavil	TCA	13.462
Duloxetine	Cymbalta	SNRI	12.551
Mirtazapine	Remeron	TeCA	5.129
Nortriptyline	Pamelor	TCA	3.105
Imipramine	Tofranil	TCA	1.524

- As you can see, there are millions of prescriptions for these drugs, and there are many different medications. We are not required to know all of them; we just need to focus on the most important ones, which are highlighted in red boxes.
- These drugs are prescribed to hundreds of millions of people worldwide, so it is essential to understand them.
- In terms of clinical pharmacology, why do we really prescribe these drugs? Where will we be at the end of the day?

# Chemical “Jobs”

## Dopamine

- Attention
- Pleasure
- Emotions
- Reward
- Motivation
- Movement

## Norepinephrine

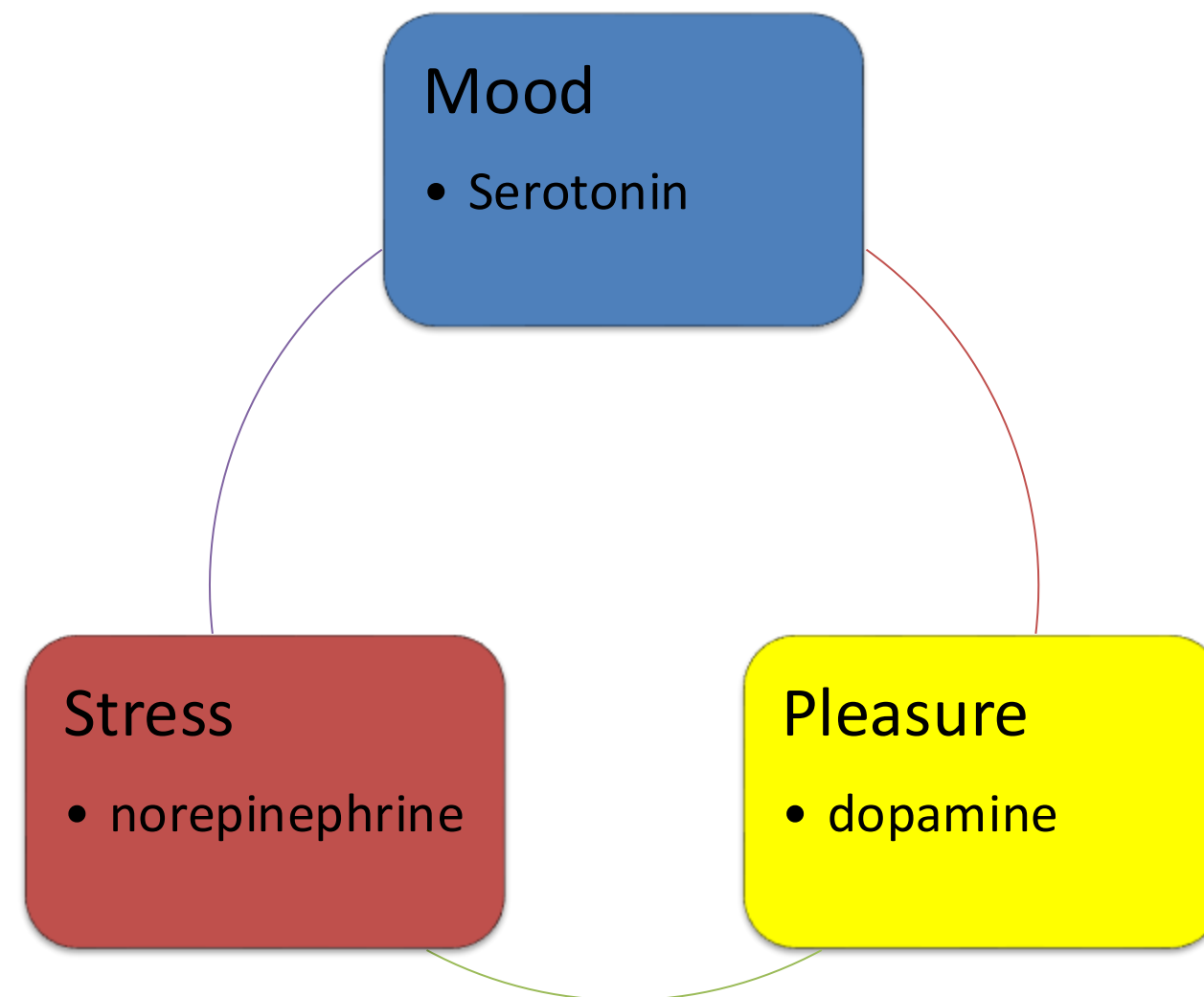
- alertness
- Observance
- Daydreaming
- Heart/BP rates
- Stress

## Serotonin

- Regulates mood
- sleep
- emesis
- sexuality
- Appetite
- impulsiveness/  
aggression

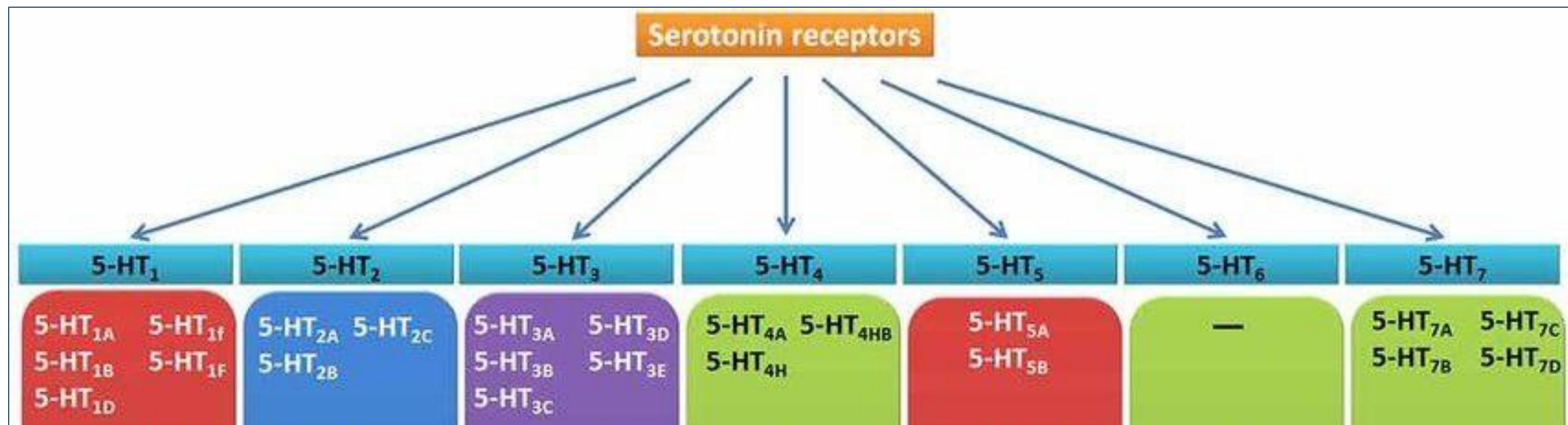
Depression depends mainly on three chemicals: dopamine, norepinephrine, and serotonin. They are regulators of our personality and mood. They control mood, tranquilization, and depression. Our personalities are built from these three neurotransmitters, and the major problem is that these neurotransmitters overlap, and we are dealing with the CNS; we can't get a lot of information from the CNS, and we can't manipulate things (rats don't have the same mind as we do).

Tranquilization: (of a drug) have a calming or sedative effect



There are seven main types of serotonin receptors, each with several subtypes, and these can be either excitatory or inhibitory. The 5-HT<sub>1</sub> and 5-HT<sub>5</sub> types are primarily inhibitory, while the other types—5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub>—are mostly excitatory.

- Each type and subtype of serotonin receptors has different functions that can either increase or decrease specific actions depending on their location in the brain. Therefore, when we aim to increase serotonin levels, we cannot simply instruct a drug to target a specific receptor.
- For instance, to enhance pleasure for a patient, we cannot just administer dopamine. This is because dopamine can interfere with the synthesis of norepinephrine and epinephrine and can also impact serotonin release. While pleasure is influenced by mood, mood itself is regulated primarily by serotonin. Understanding this interplay is complex, showing the challenges of treating depression issues.



# Depression

- **Symptoms:**

1. **Cognitive**

- Thoughts of hopelessness, poor confidence, negative thoughts.

2. **Emotional**

- Feeling sad, unable to feel pleasure, irritability.

3. **Psychomotor/Physical**

- Decreased libido, energy
- Sleep changes (70% less, 30% more)
- Appetite changes (70 % less, 30 % more)

# Depression: Treatment

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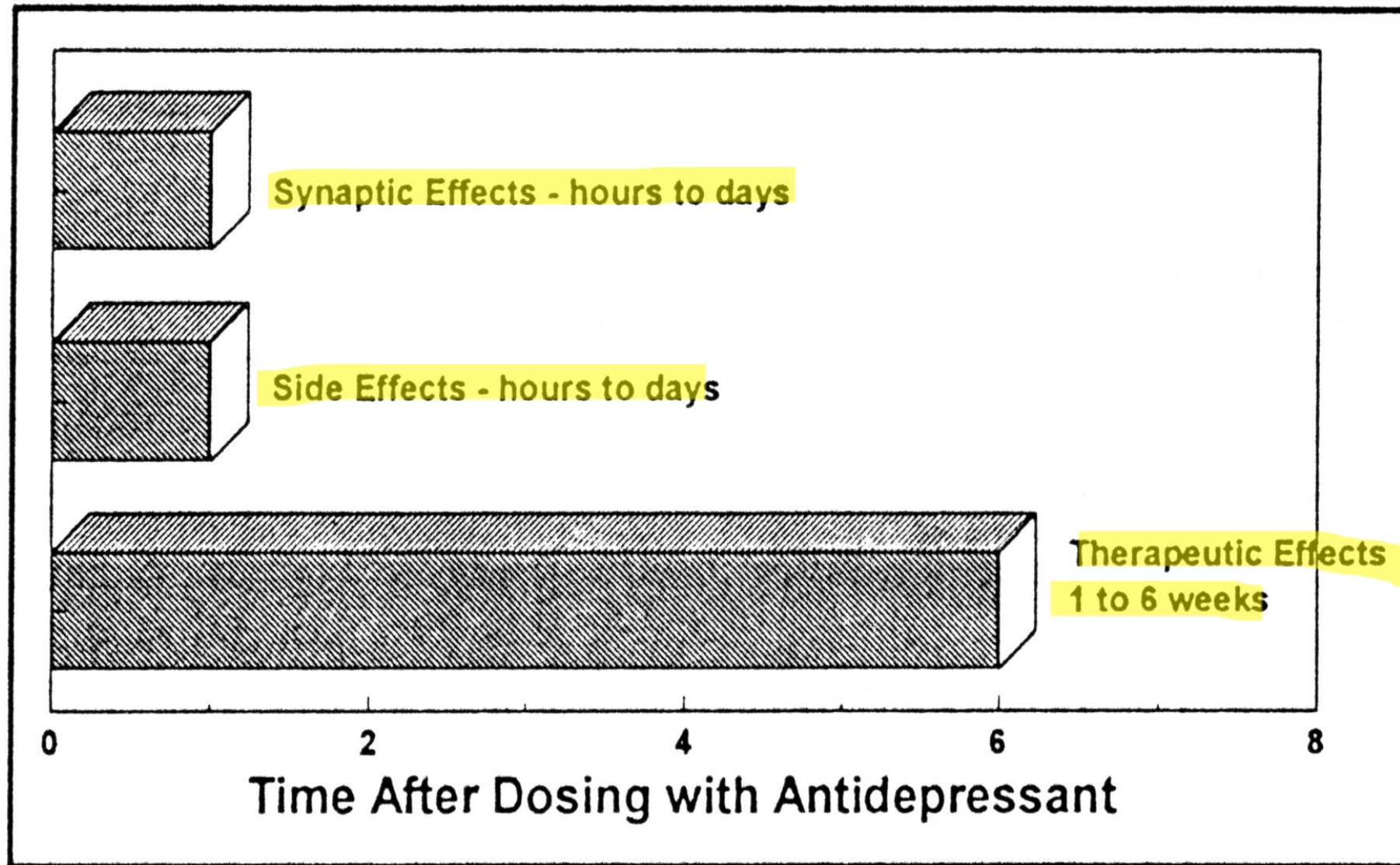
- **Antidepressant Medications**
  - **Selective serotonin reuptake inhibitor(SSRI's) are first line of treatment**
- **Psychotherapy**
  - **Usually individual psychotherapy**
  - **Cognitive behavioral therapy has most evidence for efficacy of treatment**
- **Sometimes exercise or body awareness has been found to helpful**

**Now, Lets discuss the 3 theories about how  
anti-depressants work 😁**

# 1. Monoamine hypothesis of depression

- The monoamine hypothesis grew originally out of associations between the clinical effects of various drugs that cause or alleviate symptoms of depression and their known neurochemical effects on monoaminergic transmission in the brain.
- The monoamine hypothesis of depression suggests that depression is related to a deficiency in the amount or function of cortical and limbic serotonin (5 - HT), norepinephrine(NE), and dopamine (DA).

- The monoamine oxidase theory suggests that depression is caused by a deficiency of these monoamine neurotransmitters in the brain. Although this theory is not completely correct, we are still using it since there is no other real theory. A depressed patient would have less serotonin or dopamine, and our role is to increase them in their brain.



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

- We give drugs that increase synaptic levels of serotonin (5-HT), norepinephrine (NE), and/or dopamine (DA) almost immediately by inhibiting their reuptake; however, we have a synaptic effect before the clinical effect.
- The clinical effects (i.e., improvement in mood and other depressive symptoms) typically take 4-6 weeks to manifest. However, side effects often appear **earlier** than therapeutic effects.
- Therefore, if the theory is true, the patient should be relieved from depression immediately after you increase these neurotransmitters (NE, 5-HT, DA). But the truth is the patient needs at least 6 weeks to observe the therapeutic effect, while the side effects or synaptic effect would happen within days.

## **Monoamine hypothesis of depression**

- The chronic activation of monoamine receptors by antidepressants appears to increase in BDNF transcription**
- One of the weaknesses of the monoamine hypothesis is the fact that amine levels increase immediately with antidepressant use, but maximum beneficial effects of antidepressants are not seen for many weeks**
- The time required to synthesize neurotrophic factors has been proposed as an explanation for this delay of antidepressant effects**

## 2. Neurotrophic Hypothesis

- Depression appears to be associated with a drop in brain-derived neurotrophic factor (BDNF) levels in the cerebrospinal fluid and serum as well as with a decrease in tyrosine kinase receptor B activity
- BDNF is thought to exert its influence on neuronal survival and growth effects by activating the tyrosine kinase receptor B in both neurons and glia

- Another theory points that depression is associated with a decrease in neurotrophic factors, particularly BDNF, in certain brain regions, such as the hippocampus and prefrontal cortex.
- Thus, the theory suggests that when treating depressed patients, we are trying to increase the levels of BDNF, but BDNF needs time to increase, and the plasticity of the brain also needs time to heal itself.

# Neurotrophic Hypothesis

- Animal and human studies indicate that stress and pain are associated with a **drop in BDNF levels** and that this loss of neurotrophic support contributes to atrophic structural changes in the hippocampus and perhaps other areas such as the medial frontal cortex and anterior cingulate
- Studies suggest that major depression is associated with substantial loss of volume in the hippocampus, anterior cingulate and medial orbital frontal cortex
- you should prescribe these drugs for 6 weeks to determine if they are responding well or not.

### 3. Serotonin Receptor Dysregulation

- Another theory, known as the **Serotonin Receptor Dysregulation Hypothesis**, was introduced in 2022. It suggests that depression is not solely caused by a deficiency of serotonin. Instead, it involves dysfunction in specific serotonin (5-HT) receptors, which become desensitized within the lipid membrane.
- The idea is that serotonin receptors, which are G-protein coupled receptors (GPCRs) need to be regularly activated, by serotonin and norepinephrine, to become more localized on the surface of the lipid membrane rather than deep within it. This activation leads to the triggering of various intracellular pathways via second messengers like cAMP.
- Structural studies of GPCRs indicate that serotonin receptors can activate different intracellular pathways through these second messengers. [PaperLink](#)

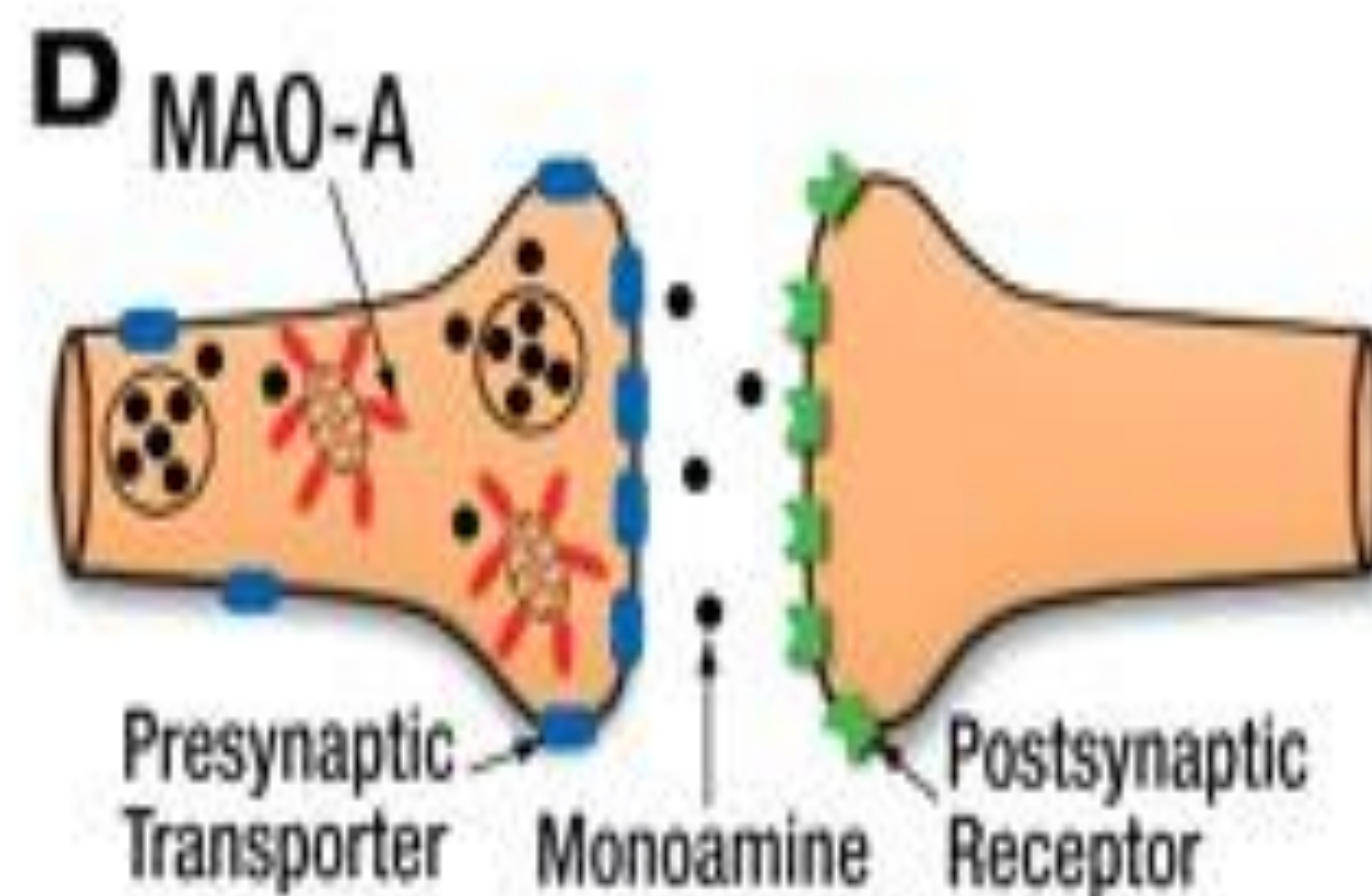
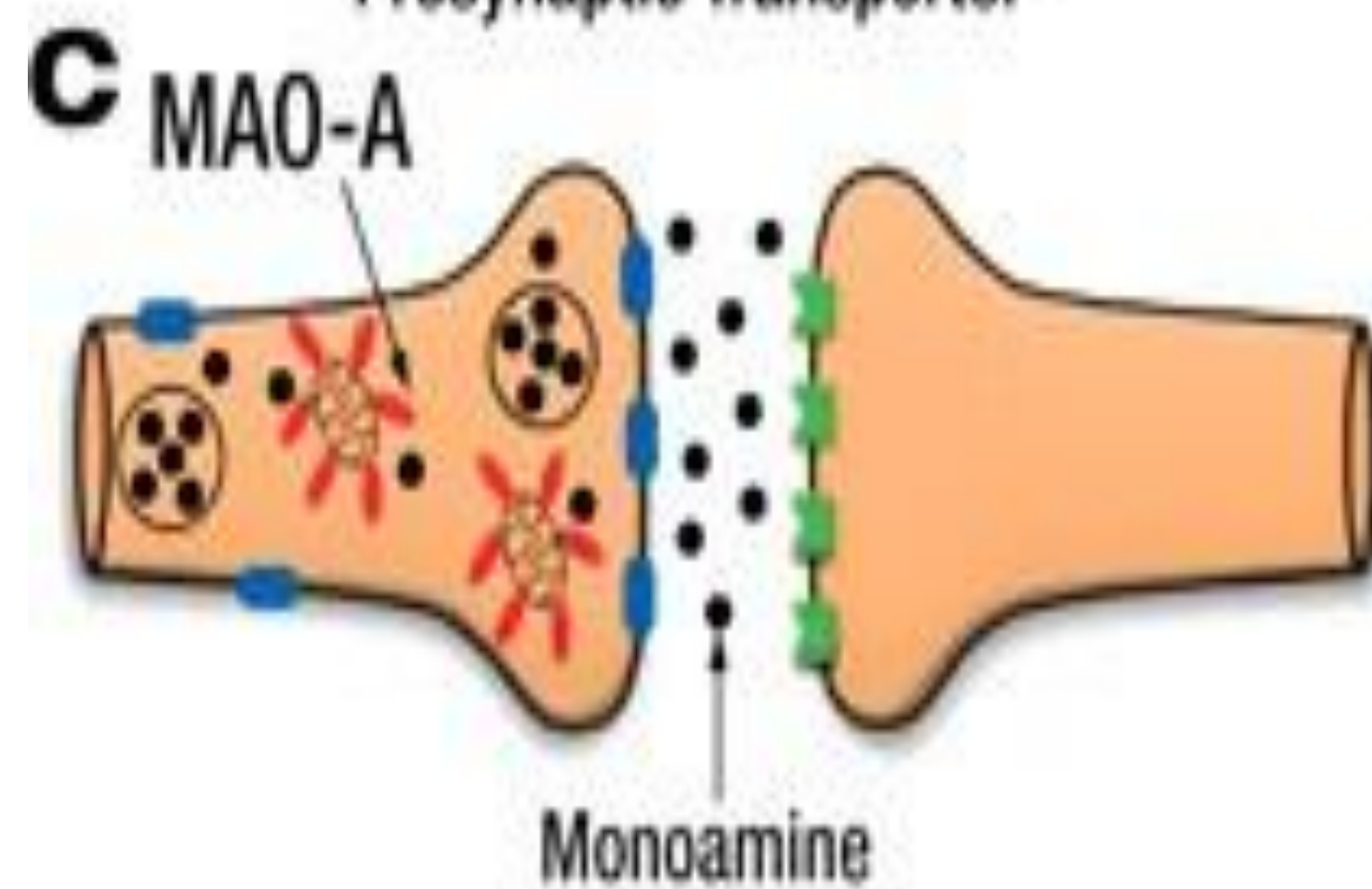
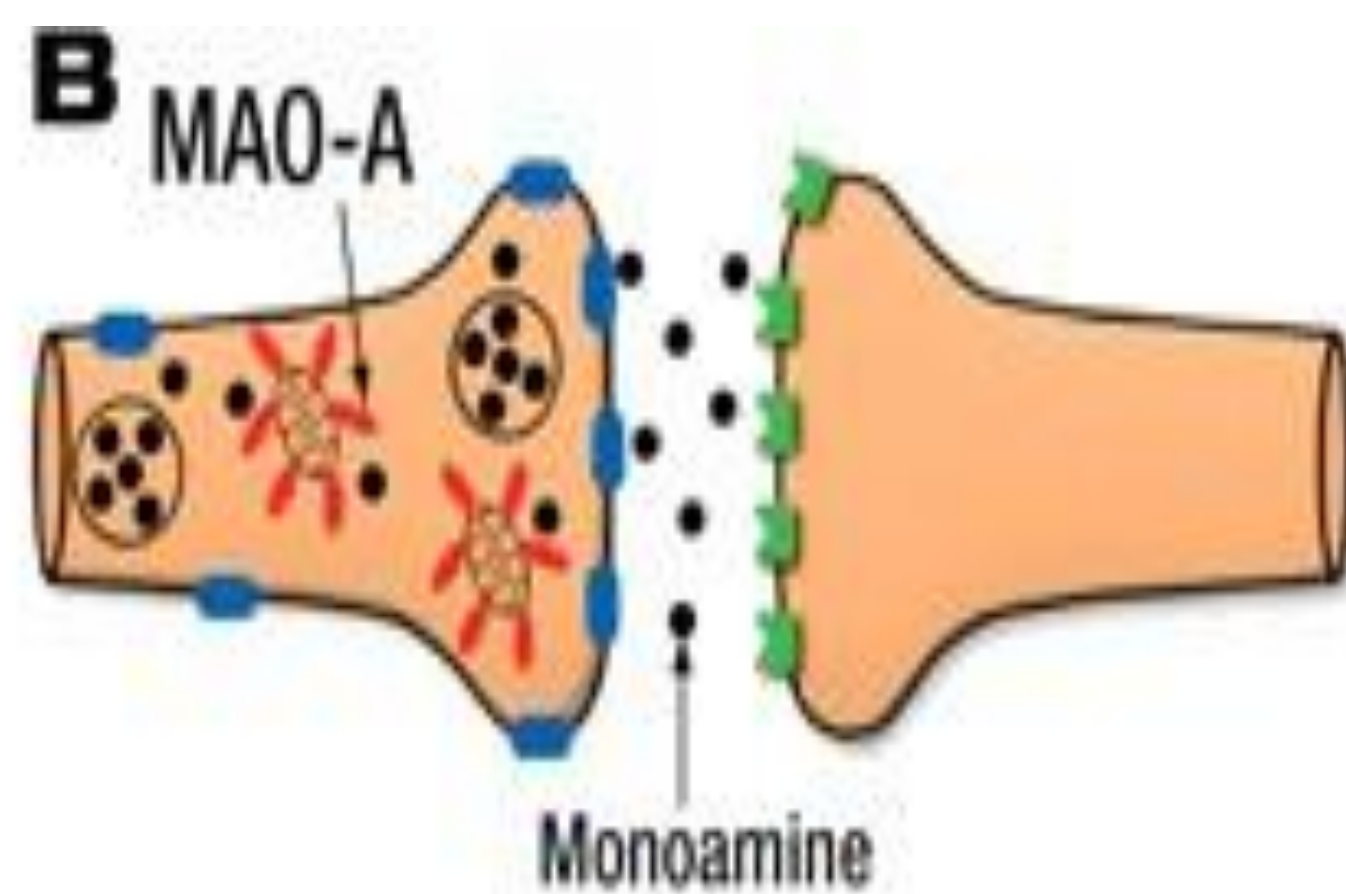
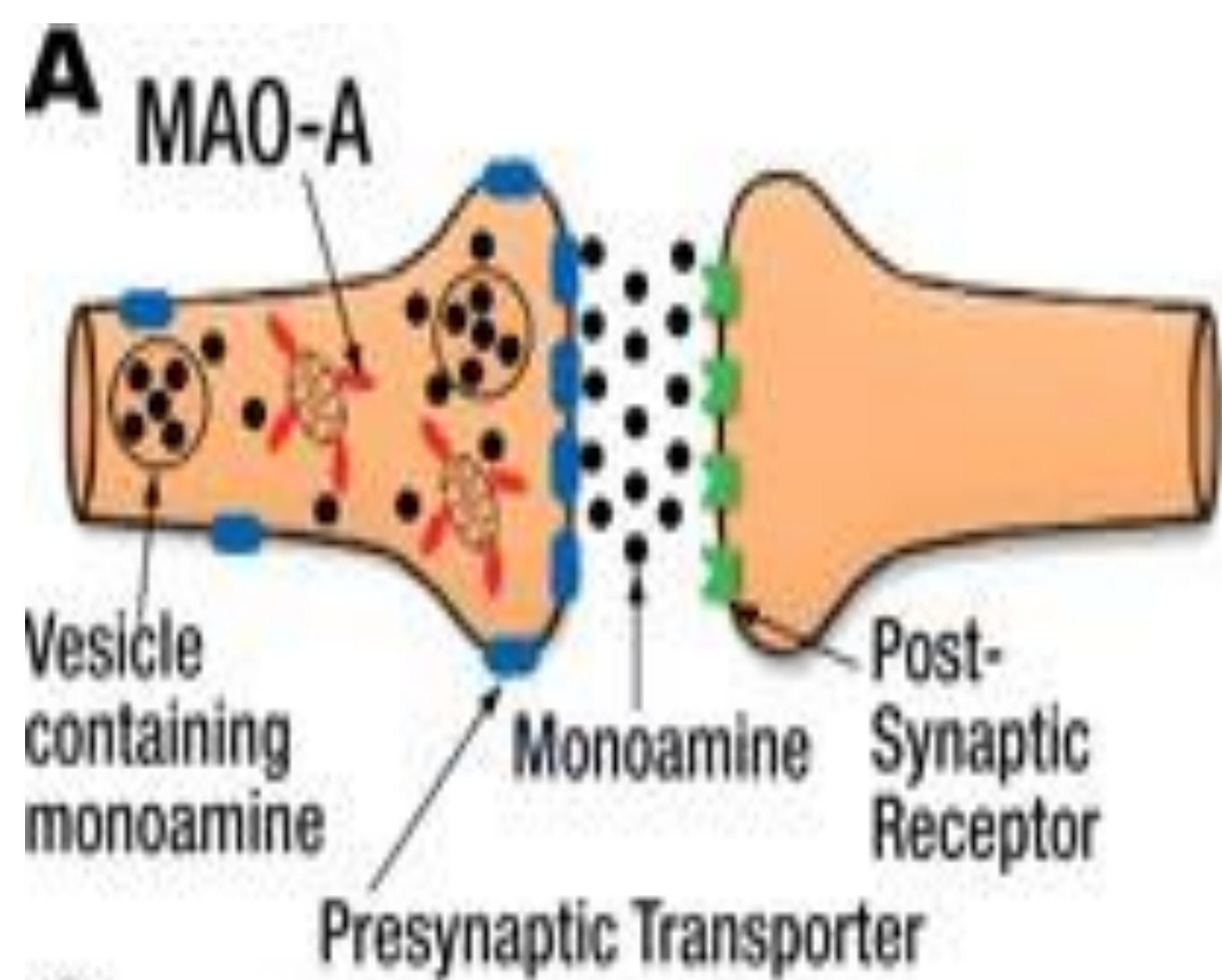
**Overall, all the theories suggest that there is something in the brain that is changing in depression, but this change is not limited to just the level of neurotransmitters.**

# Are Anti-depressants useless? 😱

- Antidepressants are not always effective. In some cases, placebos can be equally or even more effective than antidepressants. Does this mean that antidepressants are useless? Not so much, they do have an impact. However, analytic data that shows placebos being more effective are often disregarded or not approved for reasons that remain unclear (💊💰).
- Overall, research indicates there is only a 3 percent difference in outcomes between antidepressants and placebos.
- To illustrate this more clearly:
  - If we have 100 patients taking antidepressants and 100 patients taking placebos, we would see the following results as an example:
    - Patients relieved by antidepressants: 33.3%
    - Patients relieved by placebos: 30%

- The question then arises: if antidepressants provide only a modest benefit over placebo, why are they still widely used?
- The answer lies in the complex overlap of pharmacology and clinical psychology. The placebo effect itself is a powerful phenomenon in neuroscience by how patients deal with name of drug or say they are depressed while they are not. The doctor claims that at least 50% of the drugs effect comes from placebo.
- **Therefore, we use a combination of both: 1) drugs (anti-depressant) and 2) psychotherapy to which will result in a response rate of 70%. If we use Psychotherapy without drugs, 40% of patients will respond. Thus, drugs provide an increase of 30% in response.**

**The ultimate rule: Prescribe antidepressants even if it is not useful because the placebo effect alone can help improve the patient.**



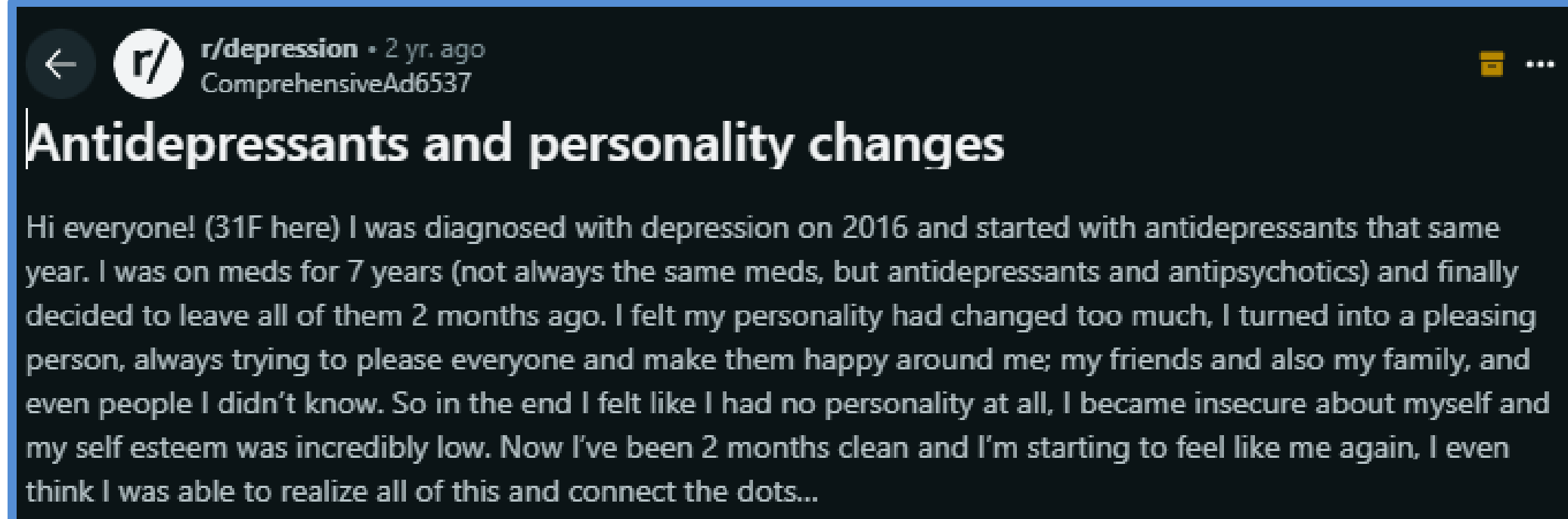
**Now, Lets start discussing Antidepressants** 

# 1. SSRIs (Serotonin-specific reuptake inhibitors)

- Inhibits the reuptake of serotonin without seriously affecting the reuptake of dopamine & norepinephrine.
- **Most common side effects:** include GI upset, sexual dysfunction (30%+!), anxiety, restlessness, nervousness, insomnia, fatigue or sedation, dizziness. Increasing level of serotonin at different type of receptors can lead to many effects as some receptors are inhibitory and others are excitatory.
- **Withdrawal Symptoms:** Can develop a discontinuation syndrome with agitation, nausea, disequilibrium and dysphoria. They are always opposite the effects that you are being treated for.

# SSRI & Personality Changes

- ❑ Personality change is a significant effect associated with these drugs, as neurotransmitters regulate our mood and feelings of pleasure, which directly impacts our personality and brain function.
- ❑ Additionally, alterations in brain plasticity can also influence personality.
- ❑ Selective Serotonin Reuptake Inhibitors (SSRIs) can lead to an increase in the experience of ideas of reference in patients.
- ❑ Therefore, antidepressants should only be used when benefits outweigh the risks.

A screenshot of a Reddit post from the subreddit r/depression. The post is titled "Antidepressants and personality changes" and was posted 2 years ago by user ComprehensiveAd6537. The text of the post describes a personal experience of a 31-year-old female who was diagnosed with depression in 2016 and started on antidepressants. She mentions being on medication for 7 years, including antidepressants and antipsychotics, and finally decided to stop them 2 months ago. She describes how her personality changed significantly while on medication, becoming a "pleasing person" who always tried to please everyone, leading to a loss of self-identity and low self-esteem. She now feels like herself again after 2 months off medication and reflects on how deeply drugs can alter one's thoughts and perspectives on life.

← r/ depression • 2 yr. ago  
ComprehensiveAd6537

## Antidepressants and personality changes

Hi everyone! (31F here) I was diagnosed with depression on 2016 and started with antidepressants that same year. I was on meds for 7 years (not always the same meds, but antidepressants and antipsychotics) and finally decided to leave all of them 2 months ago. I felt my personality had changed too much, I turned into a pleasing person, always trying to please everyone and make them happy around me; my friends and also my family, and even people I didn't know. So in the end I felt like I had no personality at all, I became insecure about myself and my self esteem was incredibly low. Now I've been 2 months clean and I'm starting to feel like me again, I even think I was able to realize all of this and connect the dots...

This is a Reddit post that describes someone's experience with how their personality has changed due to drug use. As you read further through the posts, you notice a significant amount of suicidal thoughts and letters, prompting reflection on how deeply drugs can alter one's thoughts and perspectives on life.

# SSRI/SNRI Discontinuation Syndrome in **Adults**

## F.I.N.I.S.H.

- Flu-like symptoms: fatigue, muscle aches, headache, diarrhea
- Insomnia: vivid or disturbing dreams
- Nausea
- Imbalance: gait instability, dizziness, lightheadedness, vertigo
- Sensory disturbance: paresthesia, “electric shock” sensation, visual disturbance
- Hyperarousal: anxiety, agitation
- Onset: 24-72 hours + Resolution: 1-14 days
- Incidence: ~ 20 - 40 % (who have been treated at least 6 weeks)

Drug name	Commercial name	Drug class	Total prescriptions
Sertraline	Zoloft	SSRI	33,409,838
Citalopram	Celexa	SSRI	27,993,635
Fluoxetine	Prozac	SSRI	24,473,994
Escitalopram	Lexapro	SSRI	23,000,456
Trazodone	Desyrel	SARI	18,786,495
Venlafaxine (all formulations)	Effexor (IR, ER, XR)	SNRI	16,110,606
Bupropion (all formulations)	Wellbutrin (IR, ER, SR, XL)	NDRI	15,792,653
Duloxetine	Cymbalta	SNRI	14,591,949
Paroxetine	Paxil	SSRI	12,979,366
Amitriptyline	Elavil	TCA	12,611,254
Venlafaxine XR	Effexor XR	SNRI	7,603,949
Bupropion XL	Wellbutrin XL	NDRI	7,317,814
Mirtazapine	Remeron	TeCA	6,308,288
Venlafaxine ER	Effexor XR	SNRI	5,526,132
Bupropion SR	Wellbutrin SR	NDRI	4,588,996
Desvenlafaxine	Pristiq	SNRI	3,412,354
Nortriptyline	Sensoval	TCA	3,210,476
Bupropion ER	Wellbutrin XL	NDRI	3,132,327
Venlafaxine	Effexor	SNRI	2,980,525
Bupropion	Wellbutrin IR	NDRI	753,516

- The medications you should know from the previous table are **sertraline (zoloft)** , **citalopram**, **fluoxetine**, **escitalopram**, **paroxetine**; the first one is the best seller. All of them belong to the **SSRI** family.
- If they all bind to the same receptor, why do we have four or five drugs then?
  - ✓ Because the **major depression patients** that we intend to intervene on are heterogeneous patients, meaning there are genetic differences among them. This implies that their serotonin receptors also differ genetically (polymorphism). This leads to variations in the activity of binding of these drugs, and even the level of serotonin differs among them, resulting in varying degrees of depression.
- So, how do we treat these patients?
  - ✓ **Based on the trial therapy**: when a patient comes, I prescribe the best one among them (**sertraline**) and start with it, waiting six weeks. The response rate is about 30%, and with the addition of 40% from psychotherapy, as mentioned previously, the overall response becomes 70%, leaving 30% unresolved. What do I do with them? I use a **second drug from the same family or from another family**. This is because, although drugs from the same family bind to the same receptor, as mentioned, due to genetic differences, the mode of binding and the effect vary.

# Why there are many of them

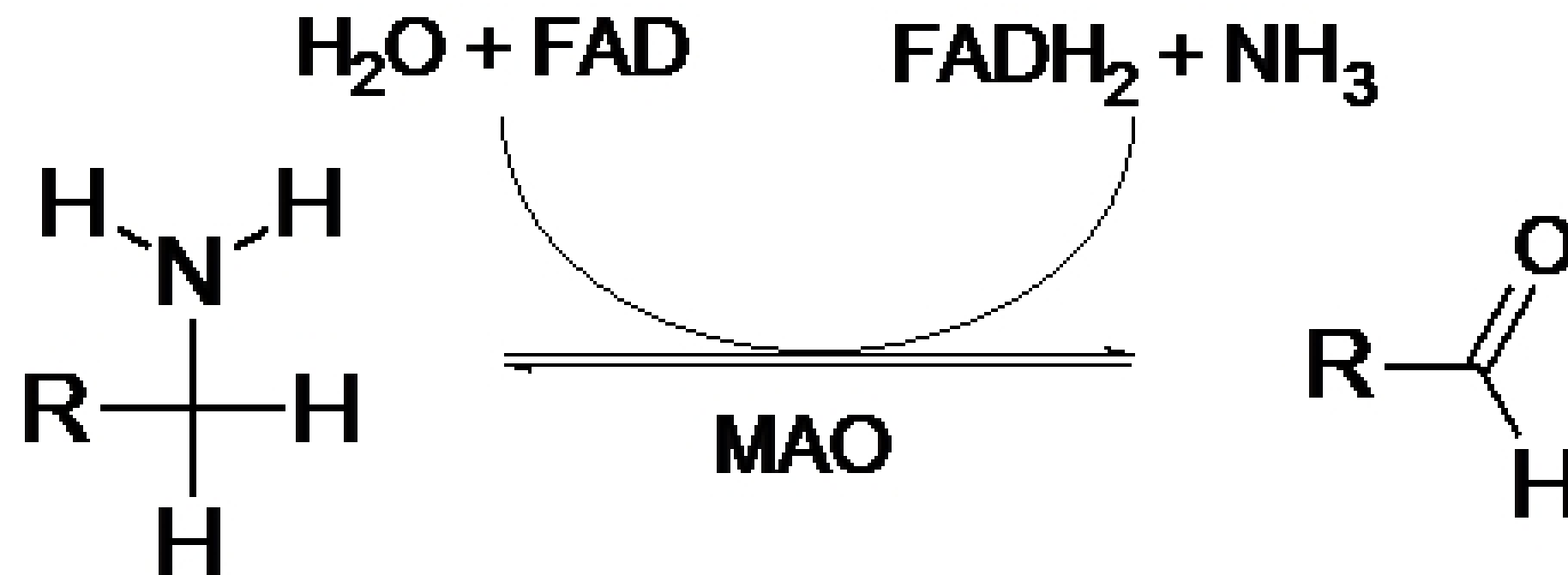
- 1. Paroxetine:** Sedating properties (dose at night) offers good initial relief from anxiety and insomnia. So, a patient presenting with sleep problems, anxiety, and depression is treated with paroxetine. **Exhibits Significant CYP2D6 inhibition**
- 2. Sertraline:** Increased number of GI adverse drug reactions. Therefore, for patients with gastrointestinal issues, sertraline is avoided.
- 3. Fluoxetine:**
  - Secondary to long half life (approximately one week), which is why it is given in lower doses and has less discontinuation Syndrome compared to other SSRIs.
  - **It has significant P450 interactions, making it a less favorable choice for patients already on multiple medications.**
  - Initial activation may increase anxiety and insomnia (side effects seen with all SSRIs but more pronounced with fluoxetine). **And more likely to induce mania (anxiety, insomnia) than some of the other SSRIs.**

## 2. Serotonin/Norepinephrine reuptake inhibitors (SNRIs)

- SNRIs are used when the patient has **total depression**, where they appear emotionally flat and unresponsive. In addition to improving mood and energy levels, norepinephrine motivates patients to be more productive
- **Slightly greater efficacy than SSRIs** with a response rate reaching 40%.
- Slightly fewer adverse effects than SSRIs.
  - **Venlafaxine**
  - **Duloxetine**
- Side effects:
  1. Can cause a 10-15 mmHG dose-dependent increase in diastolic BP (which requires regular monitoring of the patient's blood pressure). This side effect is specifically important among Jordanians (since we are always angry, and we have a high population of smokers)
  2. May cause **significant nausea**.
  3. Can cause a **bad discontinuation syndrome**, and tapering is recommended after 2 weeks of administration.

# MONOAMINE OXIDASE (MAO) AND DEPRESSION

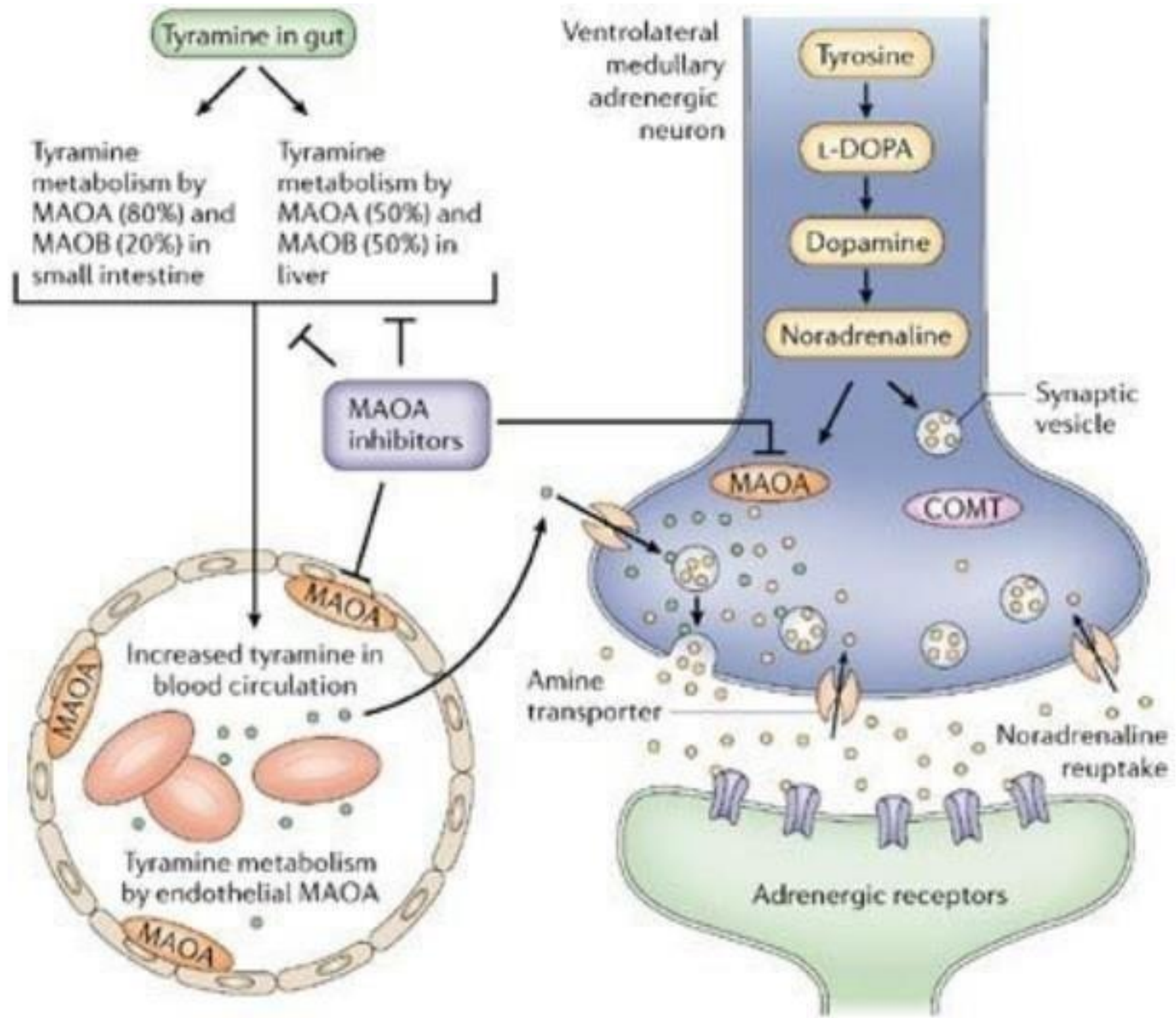
- MAO catalyze deamination of intracellular monoamines
  - MAO-A oxidizes epinephrine, norepinephrine, serotonin
  - MAO-B oxidizes phenylethylamine
  - Both oxidize dopamine nonpreferentially
- MAO transporters reuptake extracellular monoamine



### 3. 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.

- A patient with **depression** who can laugh at a joke despite their condition is classified as having **atypical depression**. These patients typically **do not respond to any medications except MAOIs**.
- **MAO Mechanism of Action (MOA):**
  - MAOIs work by **inhibiting monoamine oxidase (MAO)**, an enzyme responsible for the **metabolism of monoamines** (such as serotonin, dopamine, and norepinephrine). By blocking this enzyme, **monoamine levels increase significantly** because their **metabolism is completely inhibited**. This leads to a **strong and substantial rise** in neurotransmitter availability, resulting in a more pronounced mood-stabilizing effect.
- Pay attention here; we don't increase the level of monoamines in synaptic cleft we allow the vesicle to take up a larger amount of monoamines.
- There is significant interaction with **tyramine**, which is present in some fermented products such as alcohol, cheese and (جميد). If a patient on an **MAOI** ingests tyramine, the tyramine will not be metabolized and will reach the brain, leading to increased levels of norepinephrine and potentially triggering a **hypertensive crisis**.



## 4. 5-HT<sub>2</sub> antagonists

- **Nefazodone, Trazodone, mirtazapine.**
- Inhibition of 5-HT<sub>2A</sub> receptors in both animal and human studies is associated with substantial antianxiety, antipsychotic, and antidepressant effects
- Nefazodone is a weak inhibitor of both SERT and NET, whereas trazodone is also a weak but selective inhibitor of SERT

The doctor skipped this slide

## 5-HT<sub>2</sub> antagonists- Clinical uses

- **Depression:** Mirtazapine can be advantageous in patients with depression having sleep difficulties
- Low doses of trazodone (50-100 mg) have been used widely both alone and concurrently with SSRIs or SNRIs to treat insomnia

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## 5-HT<sub>2</sub> antagonists

- 1) Sedation : necessitates dosing at bedtime
- 2) Dose-related GIT SEs
  - 1) weight gain (mirtazapine)

## **5. 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**

## 6. Bupropion

- 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.

## The doctor read slide

- 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.
- 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 antidepressant life long.

- When treating depression, SSRIs (Selective Serotonin Reuptake Inhibitors) should not be combined with other SSRIs, as this can lead to **Serotonin Syndrome**—a dangerous condition caused by excessive serotonin levels, leading to severe agitation and high blood pressure.
- If a patient takes an **overdose of SSRIs or is prescribed two SSRI drugs together**, they may develop **Serotonin Syndrome**. Additionally, **using MAOIs** (Monoamine Oxidase Inhibitors) **can also cause this syndrome**, even without combining them with other medications.
- **To avoid this risk**, when an additional medication is needed, Bupropion is used. **Bupropion is an NDRI** (Norepinephrine-Dopamine Reuptake Inhibitor), meaning it does not affect serotonin levels, making it a safer option.

**Do not combine an SSRI with another SSRI or any two drugs that affect the same neurotransmitter (e.g., N with N) to ensure patient safety.**

اللَّهُمَّ انزل رحمتك على عبادك في غزوة وجميع  
المستضعفين من المسلمين ، اللهم عليك  
بالظالمين المعتدين ، اللهم لا ترفع لهم راية ، ولا  
تحقق لهم غاية ، واجعل تدبيرهم في تدميرهم .



VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	10	Serotonin has seven main types	highlighted
V2→V3			



امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!