بسم الله الرحمن الرحيم

Antidepressants pt.1

FINAL | Lecture 1

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

Written by: Hala Sweidan
Raneem AH

Reviewed by: Roaa Maakoseh

PHARMACOLOGY

رحلة اليقين مع سورة يس

بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

وَإِذَا قِيلَ لَهُمْ أَنفِقُواْ مِمَّا رَزَقَكُمُ ٱللَّهُ قَالَ ٱلَّذِينَ كَفَرُواْ لِلَّذِينَ ءَامَنُوٓاْ أَنُطْعِمُ مَن لَّوْ يَشَآءُ ٱللَّهُ أَطْعَمَهُۥٓ إِنْ أَنتُمْ إِلَّا فِي ضَلَٰلٍ مُّبِينٍ (٤٧)

{ وَإِذَا قِيلَ لَهُمْ أَنْفِقُوا مِمَّا رَزَقَكُمُ اللَّهُ } أي: من الرزق الذي منَّ به الله عليكم، ولو شاء لسلبكم إياه، { قَالَ الَّذِينَ كَفَرُوا لِلَّذِينَ آمَنُوا } معارضين للحق، محتجين بالمشيئة: { أَنُطْعِمُ مَنْ لَوْ يَشَاءُ اللَّهُ أَطْعَمَهُ إِنْ أَنْتُمْ } أيها المؤمنون { إِلَّا فِي ضَلَالٍ مُبِينٍ } حيث تأمروننا بذلك.وهذا مما يدل على جهلهم العظيم، أو تجاهلهم الوخيم، فإن المشيئة، ليست حجة لعاص أبدا، فإنه وإن كان ما شاء الله كان، وما لم يشأ لم يكن، فإنه تعالى مكَّن العباد، وأعطاهم من القوة ما يقدرون على فعل الأمر واجتناب النهي، فإذا تركوا ما أمروا به، كان ذلك اختيارا منهم، لا جبرا لهم ولا قهرا.

Antidepressants

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

Dr Malek Zihlif

قال رسول الله ﷺ:

"اللَّهُمَّ إني أعوذُ بك من العجزِ والكسلِ، والجبنِ والبخلِ، والهرمِ، وعذابِ القبرِ، اللهم آتِ نفسي تقواها، وزكِّها أنت خيرُ من زكَّاها، أنت وليُّها ومولاها، اللهم إني أعوذُ بك من علمٍ لا ينفع، ومن قلبٍ لا يخشع، ومن نفسٍ لا تشبع، ومن دعوةٍ لا يُستجاب لها.

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.**

❑ **Depression is an important topic that medical students must pay attention to,** because **the prevalence of depression among medical students is unfortunately high.**

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 is mainly associated with changes in three key neurotransmitters: **dopamine, norepinephrine (NE), and serotonin**, which are essential for our personality , motivation, and attention. Others as (endorphins, enkephalins, GABA) are involved, but the main focus remains on these three neurotransmitters.
- The **interaction and balance between these three neurotransmitters** play a key role in shaping . However, Depression results from the **imbalance and interaction** between these neurotransmitters, not a single one alone.
- Depression is not about personality itself, but about how these neurotransmitters influence **the level of motivation within that personality**

Depression

- **Symptoms**
  - **Cognitive**
    - **Thoughts of hopelessness, poor confidence, negative thoughts.**
  - **Emotional**

    Feeling sad, unable to feel pleasure, irritability
  - **Psychomotor/Physical**
    - **Decreased libido, energy**
    - **Sleep changes (70% less, 30% more)**
    - **Appetite changes (70 % less, 30 % more)**

❑ The symptoms overlap due to an imbalance in the three neurotransmitters.

Depression: Treatment

- **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**

❑ There are two levels of depression: **minor** and **major**. We mainly focus on **major depression**, since a large percentage of people may fall under minor depression – من قانون الضمان للكشرة الأردنية:).

لا إله إلا الله العظيم الحليم،"
لا إله إلا الله رب العرش العظيم،
لا إله إلا الله رب السماوات ورب الأرض
"ورب العرش الكريم

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

Check next slide please

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

Drugs classifications

- There are **millions of prescriptions** for antidepressants, and it is often said that a large proportion of people in the USA take them. You do **not need to memorize all drug names**, but you should understand the **main classes and how they work**.
- The major types of antidepressants include:

1-SSRIs (Selective Serotonin Reuptake Inhibitors) → most common
2-SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors)
3-NDRIs (Norepinephrine-Dopamine Reuptake Inhibitors)
4-TCAs (Tricyclic Antidepressants)
5-TeCAs (Tetracyclic Antidepressants)

- **Trazodone** → a newer drug that acts as a **5-HT2A receptor antagonist**

- In general, antidepressants work by **increasing neurotransmitter levels**:

Increase **serotonin alone** → SSRIs
Increase **serotonin + norepinephrine** → SNRIs
Increase **norepinephrine + dopamine** → NDRIs

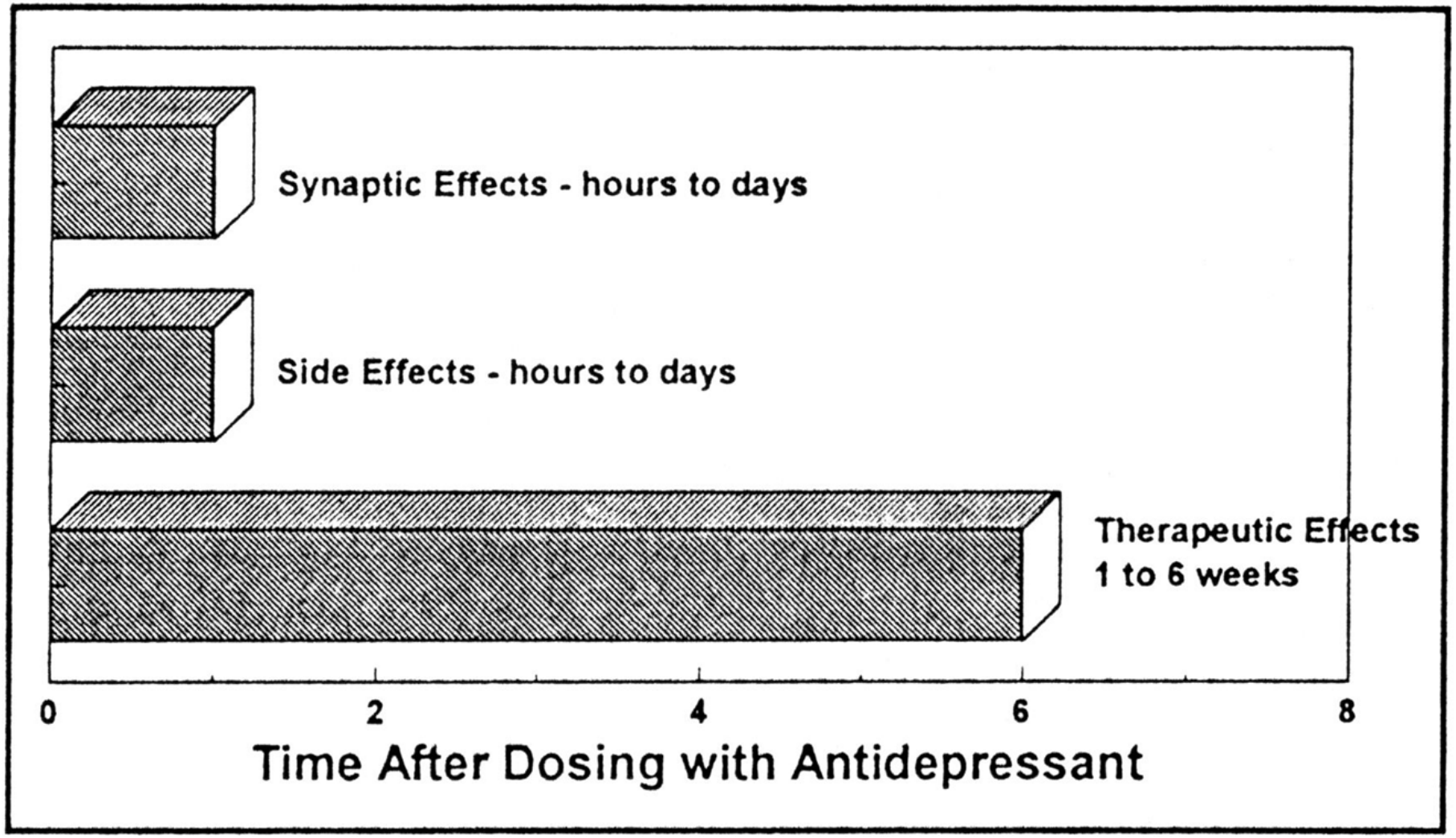
- Most of this is achieved through **reuptake inhibition**
- If we need to increase **all three neurotransmitters (serotonin, norepinephrine, dopamine)**, we use **MAO inhibitors (Monoamine Oxidase Inhibitors)** *(not shown in the table)*.
- When are MAO inhibitors used?

In cases like **atypical depression**, where increasing serotonin and norepinephrine alone is not enough.

- Atypical depression: the patient may **appear reactive (laughs, interacts)**, but internally is severely depressed and may have **suicidal thoughts**. This type is **more resistant** and may require increasing all three neurotransmitters.
- Typical depression symptoms:

Loss of interest , Loss of emotional feeling , Social withdrawal (e.g., sitting alone) and **Suicidal thoughts (most important symptom).**

Check next slide please



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

Antidepressants: Onset, Side Effects, and Compliance

- Antidepressants require **time to produce their full clinical effect**, usually about **1–6 weeks**. Although the **synaptic changes** (increased serotonin and norepinephrine due to reuptake inhibition) occur within **hours to days**, this early effect is not responsible for the actual improvement. The **true therapeutic effect is delayed..**
- During this early period, **side effects appear before any clinical improvement**, which creates a major challenge. Common side effects include **nervousness, insomnia, nausea, and vomiting**, as well as a significant **decrease in sexual function (50–70%)** , this occurs because increased serotonin can suppress dopamine activity, leading to **reduced libido and sexual dysfunction**. These side effects can start within **hours to days** after beginning treatment. Aka before the therapeutic effects.
- This situation is particularly difficult because the patient is already **depressed**, meaning they do not feel improvement, yet they are experiencing unpleasant side effects. As a result, many patients may be tempted to **stop the medication early**.
- Therefore, the role of the doctor is crucial. It is not enough to simply prescribe medication and send the patient home. The doctor must **explain the delay in therapeutic effect**, reassure the patient, and encourage them to continue treatment. Additional support, such as **cognitive behavioral therapy (CBT)**, is important to improve outcomes. The doctor should also help the patient build **trust in themselves and trust in Allah's plan...**

قال رسول الله ﷺ: "عجبًا لأمرِ المؤمنِ، إنَّ أمرَه كلَّه له خيرٌ، وليس ذلك لأحدٍ إلا للمؤمنِ: إن أصابته سرَّاءُ شكرَ فكان خيرًا له، وإن أصابته ضرَّاءُ صبرَ فكان خيرًا له.

- A key concept in treatment is **compliance**, which means that the patient takes the medication as prescribed. Good compliance is essential for successful treatment, because without it, even the most effective medications will not work.

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)**

Check next slide please

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**

Monoamine hypothesis & Neurotrophic Hypothesis

- **Why antidepressants take 1-6 weeks to work?**
- Antidepressants increase **serotonin, norepinephrine, and dopamine** in the synapse within **hours to days**, but the patient does not feel better immediately. This means that increasing neurotransmitters alone is **not enough** to explain the antidepressant effect.
- The **monoamine hypothesis** says that depression is due to a deficiency in one of these three neurotransmitters. So theoretically, when we increase them, the patient should improve quickly. However, this does **not happen in reality**, so this theory is incomplete.

- To explain this delay, we use the **neurotrophic hypothesis**. This states that depression is associated with:

Low BDNF
Low tyrosine kinase receptor activity
Low protective factors against apoptosis in the brain.

BDNF: Brain-derived neurotrophic factor

Continue...

Monoamine hypothesis & Neurotrophic Hypothesis

- There is **no direct way** to increase these factors quickly. However, when the patient takes antidepressants for a **long period**, these factors gradually increase.
- To achieve an antidepressant effect, (BDNF) must be increased. This typically requires **continuous treatment** with drugs that elevate levels of serotonin, norepinephrine, and dopamine.
- This slow increase is called **brain plasticity**, meaning the brain needs time to **adapt and recover its normal function**. Therefore, the treatment effect depends on this slow process, not the immediate increase in neurotransmitters in synapses !

🔴 **High-yield point:**

Do not judge the treatment before 8 weeks, because the goal is to **restore brain plasticity**, not just increase neurotransmitters in synapses (which mainly causes side effects early).

Relating to Cancer

❑ Most types of cancers metastasize to bone, stomach, liver (like: triple positive breast cancer).

❑In triple-negative breast cancer (TNBC), there is a higher tendency for metastasis to the brain. Experimental studies suggest that TNBC cells:
- **Proliferate in the presence of BDNF** within the brain microenvironment.
- **Die in the presence of VEGF**

For **metastasis** to occur, cancer cells require a **receptive microenvironment** at the microscopic level. In TNBC brain metastasis, BDNF acts as a supportive factor in this environment.

Incresing the concentration of BDNF is our goal for treatment of depression

VEGF: vascular endothelial growth factor

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**

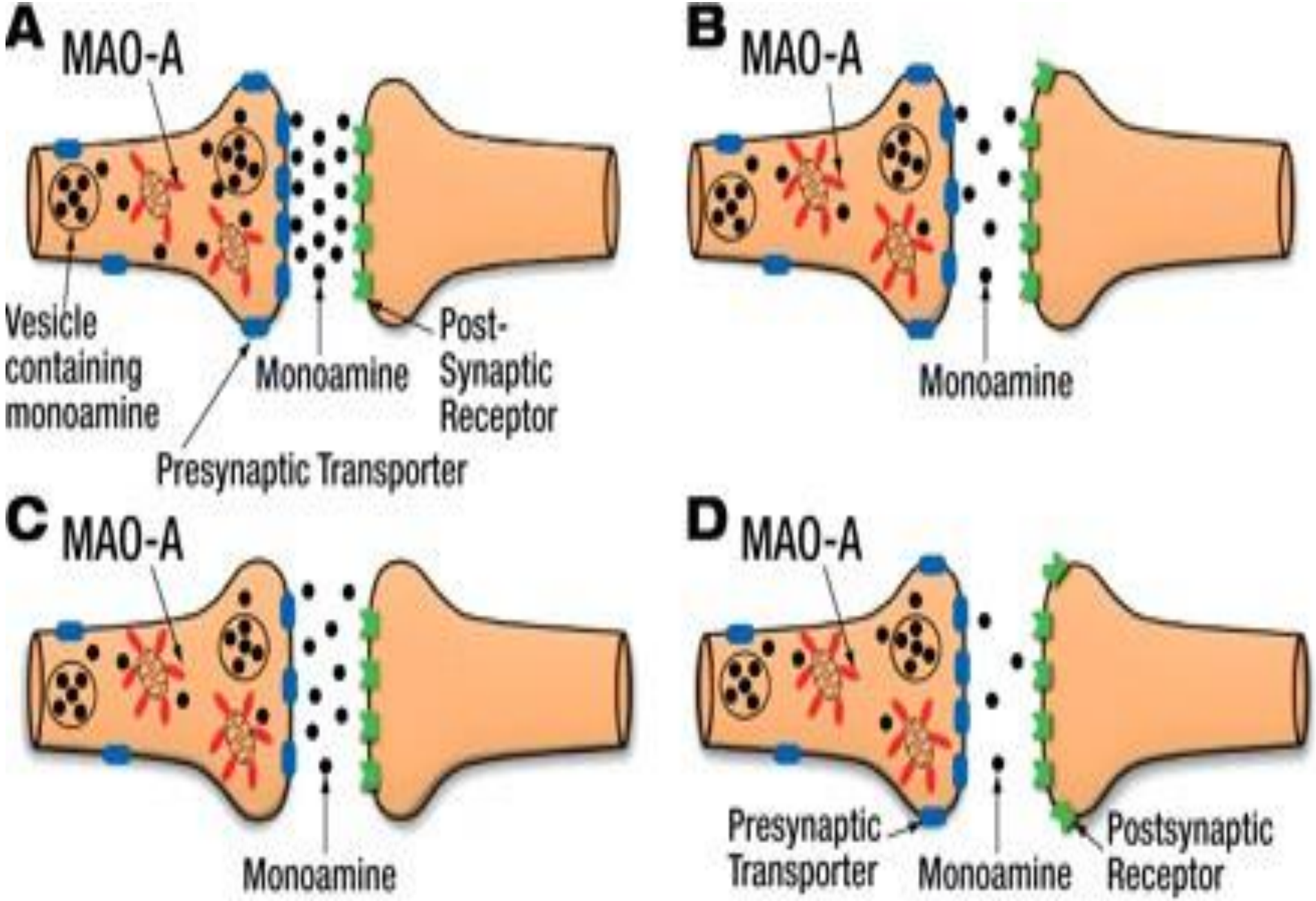
Neurotrophic Hypothesis

- **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**

وما الخوفُ إلاّ ما تخوّفه الفتى

!وما الأمنُ إلاّ ما يراهُ الفتى أمْنا


A
MAO-A
Vesicle containing monoamine
Monoamine
Post-Synaptic Receptor
Presynaptic Transporter
B
MAO-A
Monoamine
C
MAO-A
Monoamine
D
MAO-A
Presynaptic Transporter
Monoamine
Postsynaptic Receptor

Tricycle 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) Anticholinergeric effects dry mouth, constipation,blurred vision, urinary retention

SSRIs (Serotonin-specific reuptake inhibitors)

inhibits the reuptake of serotonin without seriously effecting the reuptake of dopamine & norepinephrine.

- **Most common side effects include GI upset, sexual dysfunction (30%+!), anxiety, restlessness, nervousness, insomnia, fatigue or sedation, dizziness**

more

Sedation and insomnia **Both** occur because of **personal variations.**

Restlessness, nervousness, anxiety are the result of increasing serotonin concentration, (remember it's jobs slide 5!).

Most important side effect is changing personality (disconnected from themselves) with long term use.

So it's not recommended to be used for long period of time.

- **Can develop a discontinuation syndrome with agitation, nausea, disequilibrium and dysphoria**

Serotonin syndrome

the case when patient had taken large dose of SSRI he will have:
Nervousness, Very high temperature and it leads to death.

So never ever give 2 drugs that increase serotonin concentration
(never combine SSRI & SNRI for example)

NOTES:

- **Drug companies hidden the personality changing effect and the placebo effect**

Placebo effect is more effective than pharmacological effect of SSRI in minor and moderate depression but not severe depression
Placebo role in cognitive therapy, self motivation.
Don't give SSRI for minor depression, placebo is enough.

- **In major depression drug effect is higher than placebo effect(placebo effect is not enough)**
  SSRI → 30-40% the pharmacological response
  SSRI +CBT(cognitive behavioral therapy) → 65%

SSRI/SNRI Discontinuation Syndrome in **Adults**

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

- **F**lu-like symptoms: fatigue, muscle aches, headache, diarrhea
- **I**nsomnia: vivid or disturbing dreams
- **N**ausea
- **I**mbalance: gait instability, dizziness, lightheadedness, vertigo
- **S**ensory disturbance: paresthesia, "electric shock" sensation, visual disturbance
- **H**yperarousal: anxiety, agitation
- Onset: 24-72 hours + Resolution: 1-14 days
- Incidence: ~ 20 - 40 % (who have been treated at least 6 weeks)

- Not all symptoms are presented, there is variability
- The discontinuation syndrome happen due to **physical dependence**
- No addiction

Why there are many of them

Paroxetine: Sedating properties (dose at night) offers good initial relief from anxiety and insomnia (anti histamine)

Significant CYP2D6 inhibition

Zoloft

Sertraline: Increased number of GI adverse drug reactions

No sedative effect, not given to pt. with ulcer.

The best

Fluoxetine Secondary to long half life, less Discontinuation Syndrome

Significant P450 interactions so this may not be a good choice in pts already on a number of meds

Easy tapering, no Discontinuation syndrome

Initial activation may increase anxiety and insomnia More likely to induce mania than some of the other SSRIs

قال رسول الله ﷺ: "مَن رأى منكم مُنكرًا فليُغيِّره بيده، فإن لم يستطع فبلسانه، فإن لم يستطع فبقلبه، وذلك أضعف الإيمان.

PHARMACOLOGY

QUIZ

LECTURE 1

External Resources

رسالة من الفريق العلمي

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار،
أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.

- ﴿إِنَّمَا ذَٰلِكُمُ الشَّيْطَانُ يُخَوِّفُ أَوْلِيَاءَهُ فَلَا تَخَافُوهُمْ وَخَافُونِ إِن كُنتُم مُّؤْمِنِينَ﴾ [آل عمران: 175]

﴿وَلَا تَهِنُوا وَلَا تَحْزَنُوا وَأَنتُمُ الْأَعْلَوْنَ إِن كُنتُم مُّؤْمِنِينَ﴾ [آل عمران: 139] لماذا يريد الشيطان حزن المؤمن ؟

إضعاف الإرادة: الحزن يُوهن العزم ويقطع المؤمن عن سيره إلى الله.

التشويش: إبعاد المؤمن عما فيه مصلحته.

الخوف: التخويف هو وسيلة الشيطان لبث الحزن.

السبيل للوقاية : "وَعَلَى اللَّهِ فَلْيَتَوَكَّلِ الْمُؤْمِنُونَ"

- قال رسول الله صلى الله عليه وسلم: "انظروا إلى من هو أسفل منكم، ولا تنظروا إلى من هو فوقكم فهو أجدر أن تزدروا نعمة الله عليكم.
- قال رسول الله ﷺ:

"المؤمن القوي خير وأحب إلى الله من المؤمن الضعيف، وفي كلٍ خير. احرص على ما ينفعك، واستعن بالله ولا تعجز. وإن أصابك شيء فلا تقل: لو أني فعلت كان كذا وكذا، ولكن قل: قدّر الله وما شاء فعل، فإن لو تفتح عمل الشيطان."

.اللهم اجعل كلمة الإسلام هي العليا، وكلمة أعداءه هي السفلى، اللهم رد عنا كيدهم، وفل حدهم، وأنزل عليهم بأسك الذي لا يُرد عن القوم المجرمين

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

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