Antidepressants - Lecture 1

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Antidepressants

- This lecture is a very important one, as it's talking about a family of drugs that are the most used drugs in the whole life!
- The very high prevalence of depression makes it that every doctor and in all specialties will have to deal with these drugs, thus the importance of the lecture.
- There's a dilemma about depression and whether it's a physical disease or a *disorder of the soul*, at least which of these comes first, as a lot of research papers show that depressed people have shrinkage in their hippocampus but still we are not sure if that happened first and then the person became depressed, or depression came first and caused it to shrink?
- Depression has many types, many of which don't even need drug treatment yet the patients are also given drugs as "drugs always win - placebo". Depression is also a multi-factorial disease that shows large heterogeneity between people.

Dr Malek Zihlif

Antidepressants the most used drugs in life!

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.

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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. COVID-19 made it even worse**

These numbers are way higher now

Don't memorize anything from here.

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

Depression is a mood disease, and we need to balance these 3 neurotransmitters in order to regulate the mood of our patient.

Chemical "Jobs"

Dopamine

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

we're not interested in this part today

Norepinephrine

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

Serotonin

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

Monoamine hypothesis of depression

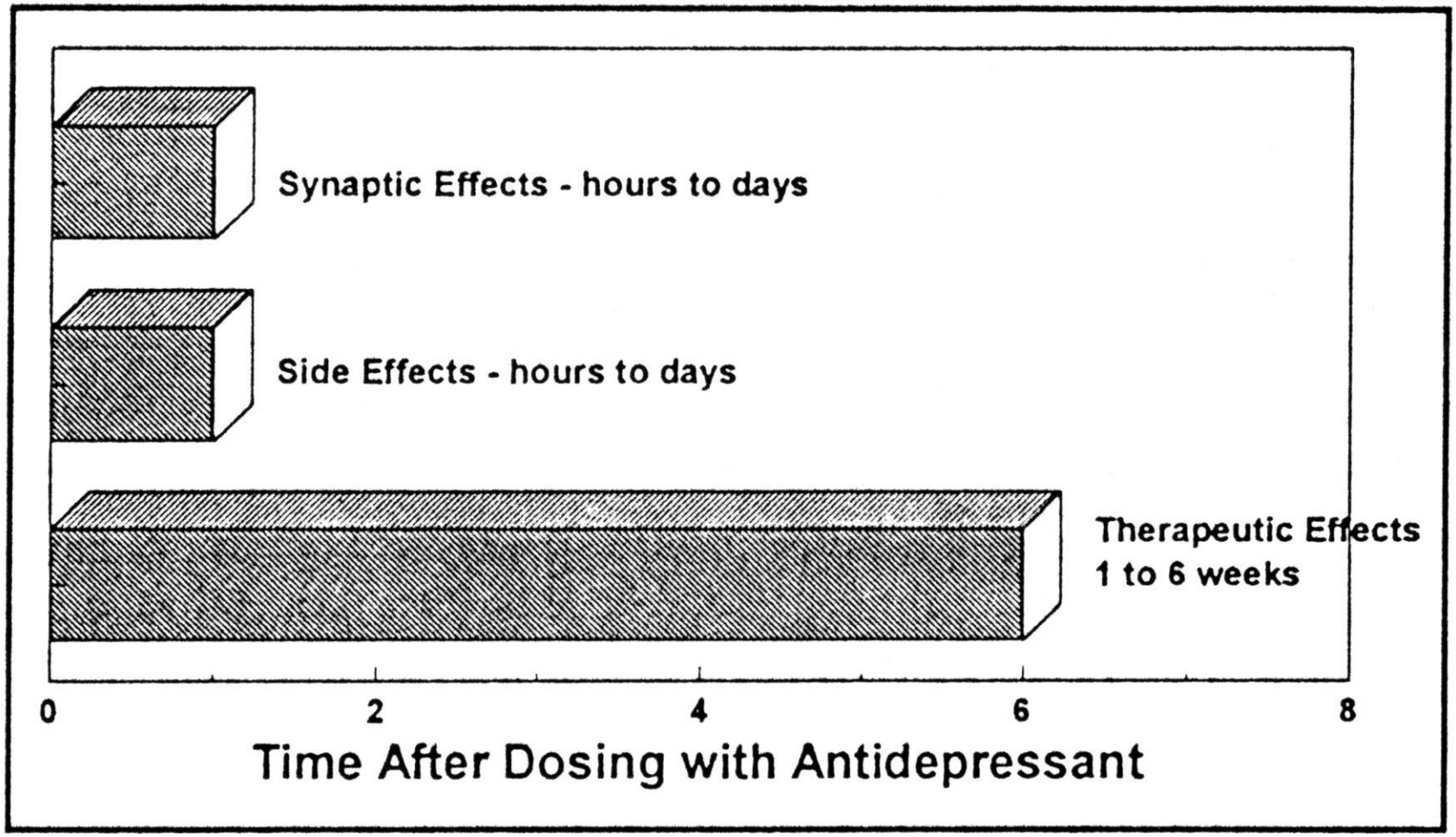
- **The monoamine hypothesis grew originally out of associations between the clinical effects of various drugs that cause or alleviate symptoms of depression and their known neurochemical effects on monoaminergic transmission in the brain**

- **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)**

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 this point shows the weakness of the hypothesis (this is not always the case, depending on the type of depression, that's why this hypothesis is still viable)
- The time required to synthesize neurotrophic factors has been proposed as an explanation for this delay of antidepressant effects



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

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 which causes a decrease in the plasticity of the brain (Neural plasticity) or the communication ability of the brain which we discovered to be reduced in depression patients.**

- **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. Antidepressants take 2 weeks to increase the expression of BDNF at the gene level, that's the reason of their delayed effect.**

Dr reminds us that its of our responsibility to keep in touch with the patient, maybe even giving him behavioral medicine so we help him wait the 2-3 weeks it takes for the drug to give its effect while bearing its side effects.

To show you the importance of BDNF; take breast cancer as an example, it targets the bone and rarely the liver when it undergoes metastasis.
But there's one variant of breast cancer that goes to the brain; **Triple-negative breast cancer (TNBC)** why does it behave that way?

Just because cancer cells are always looking for what stimulates their growth and survival, these malignant cells don't even respond to vascular epithelial growth factor, **they only respond to BDNF**!
Which again shows us how important BDNF is to the brain tissue.

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**

Depression

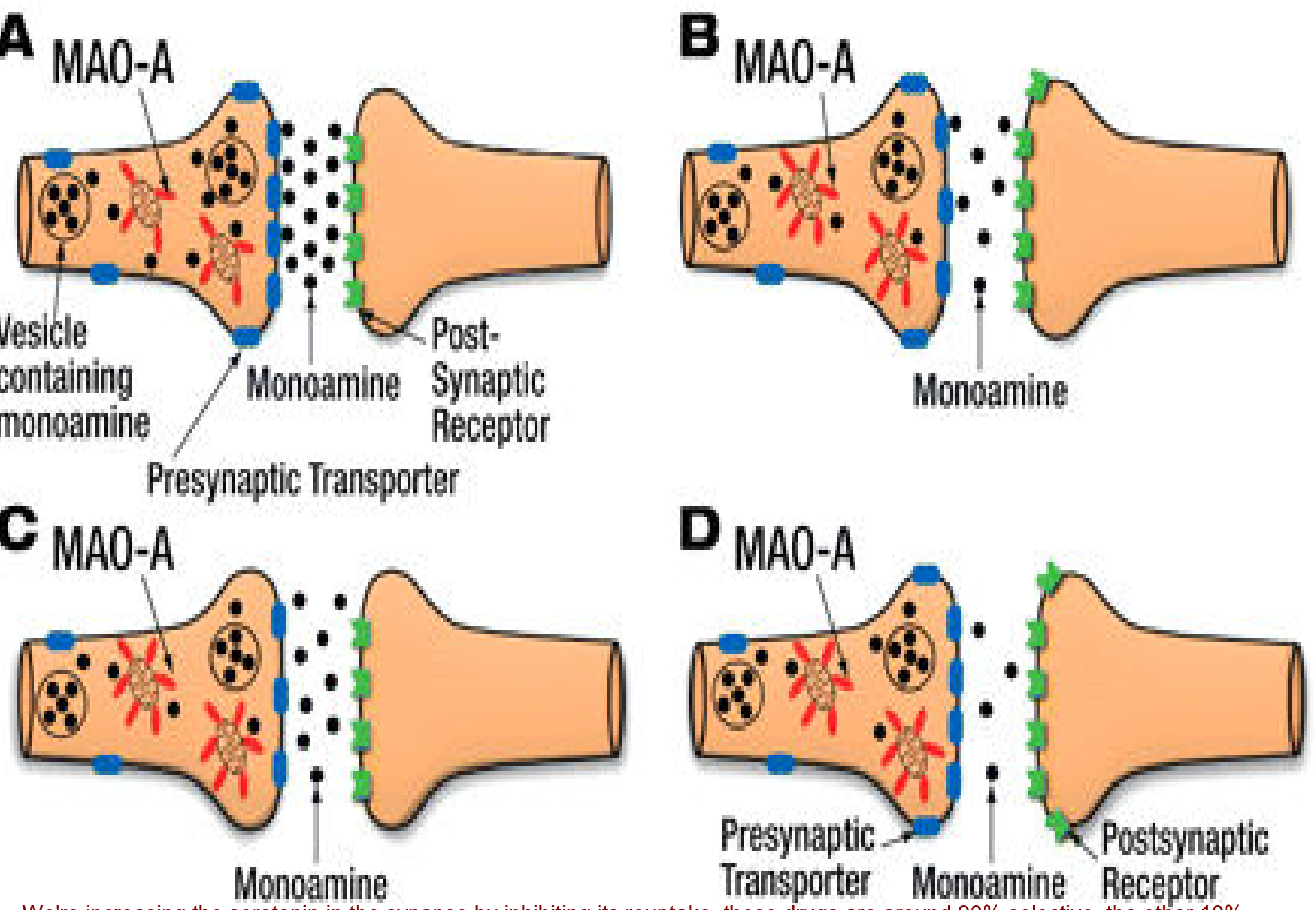
- **Symptoms**
  - **Cognitive**
    - **Thoughts of hopelessness, poor confidence, negative thoughts.**
  - **Emotional**

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

Depression: Treatment

- Antidepressant Medications (Aroud 40% response, low relapse rates)
  - Selective serotonin reuptake inhibitor (SSRI's) are first line of treatment -the golden standard-(Remember, serotonin regulates the mood)
- Placebo effect was almost as effective as the drugs in the treatment of depression, the only drawback of placebo was in its relapse rates. (~30-35% response, more relapse)
- Psychotherapy (using both; placebo effect and the drug effect)
  - Usually individual psychotherapy
  - Cognitive behavioral therapy has most evidence for efficacy of treatment. (~70% response, low relapse)

- Sometimes exercise or body awareness has been found to helpful.



We're increasing the serotonin in the synapse by inhibiting its reuptake, these drugs are around 90% selective, the other 10% might bind to dopamine / NE reuptake channels.

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 These drugs are metabolized by cyp450 in the liver, and the variation of their activity will produce variability in the side effects a patient will experience.**

  As these side effects depend on how much of the drug will reach the brain which is heavily affected by the first pass metabolism, a poor metabolizer as an example will have more drug reaching the brain thus worse side effects compared to a fast metabolizer whose brain will be exposed to way less concentrations.

  Note: **GI effect will take 1 week and will then go**, something similar to tolerance but **IT ONLY HAPPENS** in regard to SSRI's effect on the **GI tract. (Other effects including side effects don't exhibit tolerance)**

- **Can develop a discontinuation syndrome with agitation, nausea, disequilibrium and dysphoria (This is because of its physical dependence)**
  Note: these drugs don't have any form of psychological dependance.

-Serotonin in the CNS has many receptors (These receptors are GPCR), that can be either excitatory or inhibitory.

-The effect we're looking for in depression treatment is excitation, which is the result of activating **(5-HT1) receptor**, this will increase the motivation, alertness, the connectivity and communication in the brain, the levels of BDNF thus increasing the neural placticity.

-SSRI's side effects on the other hand are the result of binding to **(5-HT2) receptor**, this binding for example is responsible for the increased appetite, decreased sexual activity and more side effects!

Dr will continue from here in the next lectre.

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

(2) Cardiac effects

(3) Anticholinergeric effects dry mouth, constipation,blurred vision, urinary retention