CENTRAL NERVOUS SYSTEM

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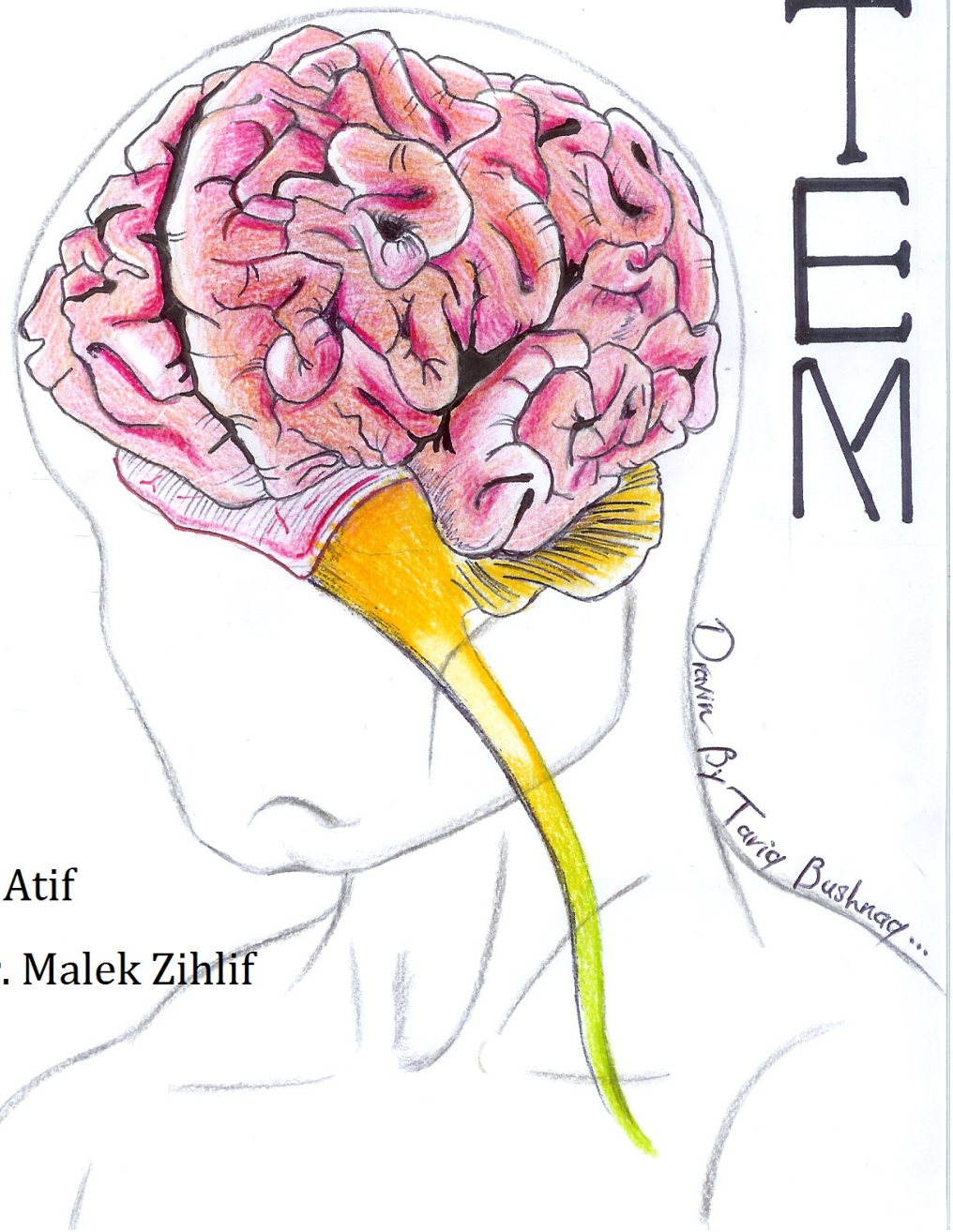

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ANTIDEPRESSANTS

- Last lecture we started talking about depression, we will continue:
- Serotonin, dopamine, norepinephrine are linked toward mood, awareness, happiness, sleep, sexuality and movement.
- Antidepressant drugs take long time to have an effect
- Most of these drugs increase neurotransmitters in the synapse, however the effect takes place within 4-8 weeks (mainly 8 weeks)
- Not only neurotransmitters in the synapse produce anti-depression, there is something called **brain derived neurotropic factor** (neurotropic means: having activity in growth and elasticity of the neurons)
- **The bottom line** :
    - Antidepressants will NOT work within 1 or 2 weeks, **you need at least 8 weeks to say whether it works or not**, so don't think about changing the drug or adding another drug or stopping the drug before 8 weeks.
    - The **side effects of these drugs start on day one immediately.**

  And this is the complexity of the story of treating bipolar, schizophrenia and depression.
- Here we notice the importance of **compliance** in treatment, you should convince a depressed patient to take a drug which will take a long time to work but with side effects in the next day, these side effects are not only nausea and vomiting, they are major side effects that affect the life of the patient.

- **How do we treat depression?**
- By drugs activating serotonin, dopamine and norepinephrine.
- they are 5 groups (you may see them 7 in other places) :
    - **Serotonin selective reuptake inhibitor (SSRI) :** increase serotonin only in the synapse
    - **Serotonin norepinephrine reuptake inhibitor (SNRI) :** increase serotonin and norepinephrine in the synapse
    - **Dopamine norepinephrine reuptake inhibitor (DNRI) :** increase dopamine and norepinephrine in the synapse
    - **Monoamine oxidase inhibitors (MAO inhibitors) :** inhibit every single monoamine oxidase thus increasing all (serotonin, dopamine and norepinephrine)

- **5HT2A antagonist :** serotonin receptor antagonist.
  A new drugs which are becoming very famous for treatment of depression (maybe you will notice it is weird to use serotonin antagonist in the last group although in the previous groups we tend to increase serotonin, but both producing similar activity! . so yes we know things but we don't know many things. And this is the complexity of the story)

- Back to the origin of pharmacology, receptors have specific activity with specific tissue, specific site and specific condition.

• Selective serotonin reuptake inhibitors (SSRI) :

- The most important group

- Inhibit the reuptake of serotonin without affecting the reuptake of dopamine and norepinephrine.

- This mechanism increases the serotonin causing better mood and remold bringing back the patient into normal condition.

- "Is it enough?" this is the hard question, we decide the answer by knowing the effectuation and response of these drugs on patients, in the best cases we have 50% response however if you give a placebo the response in 35% ! . And if we combine SSRI with psychotherapy or behavioral therapy the 50% will become 70%. There is a psychological issue within the treatment of depression; this means we can treat the patient only by telling him he is taking antidepressant. Psychology is very complex!

- As we said SSRI is effective in 50% of cases, so we may add another drug or use another drug from other groups.

- Side effects :
  1- **related to GI** : they cause **nausea** (5HT3 receptor is responsible for it) , mainly in ladies
  2- **sexual dysfunction** : (5HT2 receptor is responsible for it) sexuality is linked

toward serotonin so anything increases serotonin in the synapse will produce sexual dysfunction

NOTE : **the main side effect of SSRI, SNRI and MAO inhibitors is sexual dysfunction**

3-**anxiety** : 5HT2 receptor is responsible for it
4-**restlesness and nervousness**
5-**insomnia** : 5HT2 receptor is responsible for it
6- **sedation**
7-**dizeness**

- Antidepressant are good drugs for depression but we need to **monitor the patient** and **convince him to take the drug**

- The effect of the drug needs 8 weeks but the side effects start from day one

- Antidepressant effect due to 5HT1 receptor, but the side effects are due to 5HT2 and 5HT3 receptors, and others.

- You can't stop the drug before 8 weeks, if you stop it you will have **FINISH** (F: flu like syndrome , I: insomnia , N:nasea , I: imbalance , S: sensory disturbances , H: hyperarousal means anxiety)

- All antidepressants and antipsychotic have **discontinuation withdrawal syndrome,** depending on the half-life of the drug, drugs with long half-life you may not even see this syndrome, but drugs with short half-life you will suddenly have the syndrome after stopping the drug.
  The drug needs 4 to 5 half-lives to take off from the body, and this explains the relation between the half-life and discontinuation syndrome above.

- Antidepressant therapy is NOT for life (we stop it after one year through gradual reduction, otherwise the patient will suffer from discontinuation syndrome) but antipsychotic therapy is for life.

- The onset is within 24-72 hours, resolution finishes within 1 or 14 days, incidence 20-40% of the patients, so the drug is not easy to deal with.

- All SSRI drugs are **equally effective** in treating depression, so we choose according to the side effects.

- 3 most important SSRI drugs:
  1- **paroxetine (Prozac):**
  very famous drug , sedating properties (dosing at night) offers good initial relief from anxiety and insomnia.
  so we give to **depressed patient with insomnia or anxiety** , however this drug has CYP2D6 inhibition and this makes it not a great drug because CYP2D6 metabolizes 25% of the drugs so with paroxetine we will have many drug-drug interaction.

  2- **Sartaline :**
  NO sedation activity , NO antianxiety activity , NO effect on CYP2D6 . It is a great drug but has GI adverse reaction, it is very nauseatic drug "causes nausea" and some patients can't tolerate it.

  3- **Fluoxetine :**
  secondary to long half-life (has long half-life) ,so has an advantage which is less discontinuation syndrome. However the disadvantage is having significant p450 interactions so they may not be a good choice for patients already on medications.

- Let's talk a little bit about clinical pharmacology, a patient comes to you and he is already taking many drugs, fluoxetine and paroxetine are not great drugs, so we give sartaline but if the patient couldn't tolerate it we switch to another group. It is all about interactions and side effects.

- We always start treating depression with SSRI, if it doesn't work we switch to another group.

• Serotonin norepinephrine reuptake inhibitor (SNRI):

- Inhibit serotonin and norepinephrine reuptake

- Slightly higher efficacy and fewer side effects than SSRI

- Side effects are : **sexual dysfunction** , **significant nausea**

- Example of SNRI : **Venlafaxine** (very nauseatic drug), some studies say it has greater efficacy than SSRI, however other studies say they have some efficacy. Sexual dysfunction is less than SSRI, but nausea is more.

- They can cause bad discontinuation syndrome, because it affects both serotonin and norepinephrine

- They increase blood pressure by 10 mmHg (as a result of increasing norepinephrine)

- Tapering is recommended after 2 weeks of administration

• Monoamine oxidase inhibitors (MAO inhibitors):

- Characterized deamination of intracellular monoamine

- **Monoamine oxidase A (MAO A) :** oxidize epinephrine, norepinephrine and serotonin, so we inhibit it to increase them to treat **depression**.

- **Monoamine oxidase B (MAO B):** hydrolyze Phenethylamine which is linked toward dopamine, so we inhibit it to increase dopamine and treat **Parkinson**.

- Example of MAO inhibitors :
  1- **phenelzine :**
  non selective and irreversible, so it can't treat Parkinson or depression, we don't use it anymore
  2- **moclobemide :**
  reversible and selective toward MAO A, so used to treat depression.
  3**- selegiline** :
  reversible and selective toward MAO B, used to treat Parkinson disease.

- We increase norepinephrine by preventing its metabolism so we will have side effects : **blood pressure problem, dietary requirement, weight gain, insomnia and edema.**

- They increase blood pressure by 15 mmHg (increase it more than SNRI)
- To clarify what do we mean by dietary requirements, MAO is found in the liver and intestines, it metabolizes Tyramine (found in liver, cheese and alcohol) , so if the patient is taking MAO inhibitors and eating food with tyramine, this tyramine won't be metabolized and it will build up in the body,(tyramine acts as a catecholamine releasing agent. wiki) , so this will increase the norepinephrine more and more causing **hypertensive crisis,** so the patient should avoid tyramine specially with the non-selective type of drugs (phenelzine),but in selective types the risk is less because tyramine will have an alternative pathway for metabolism (if A is inhibited tyramine will be metabolized by B, and vice versa).

- **The old drugs :**
- **Tricycle antidepressant :**
  - they used to be used in 50s and 60s to treat depression
  - They inhibit dopamine, norepinephrine and dopamine transporters, slowing their reuptake.
  - They are non-selective at all (they bind to different receptors: muscarinic receptors, alfa receptors and histamine (H1) receptors)
  - If they bind to H1 receptors, they cause **sedation**
  - If they bind to adrenergic alfa 1 receptors, they cause **orthostatic hypotension**
  - if they bind to muscarinic receptors, they cause **blurred vision, constipation, dry mouth** and **urinary retention**
  - We use them if the previous groups fail to treat depression, but this is not common.
  - Example of tricycle antidepressant : **Amitriptyline**
  - In all cases don't use those drugs together, because this will cause **serotonin syndrome**, it is life threatening situation that causes hyperthyroidism and hypertensive crisis leading to coma. So, don't combine drugs that work on serotonin together, (for example combining MAO inhibitor and tricycle antidepressant is the worst thing to do).

- **Combination therapy :**
- **5HT2 antagonist :**
  - Inhibition of 5HT2A receptors in both animals and humans associated with substantial antianxiety, antipsychotic, and antidepressant.
  - Examples for 5HT2A antagonist : **Mirtazapine** and **Trazodone**
  - They don't increase the level of serotonin highly, so they are a good choice to be **combined with SSRI, SNRI and MAO inhibitor**. Also they **can be used alone.**
  - They **don't affect sexuality** , however they bind to H1 receptor causing **sedation or insomnia.**

- **Buproprion:**
  - Has different mechanism of action, used as **augmented agent**, and this is our second choice in combination therapy to increase the activity of SSRI, SNRI , MAO inhibitor, and tricycle antidepressant (producing augmented activity)
  - It inhibits the reuptake of dopamine and norepinephrine, but doesn't affect the serotonin level, so the idea of serotonin syndrome can't occur.
  - No weight gain, No sexual side effects (NO sexual dysfunction), but sedation and cardiac interaction is there.
  - It is <u>not</u> active alone, because it has low efficacy.

- **Clinical pharmacology :**
- time after dosing with antidepressant, therapeutic effect is going to take 1 to 6 weeks however the side effects and synaptic effect begins before therapeutic effects are observed, so your mission is to convince your patient to take those drugs.
- We start with **8 weeks trial**, throw the 8 weeks don't stop the drug, or add another drug or switch to another drug.
- If we have partial response we add another drug from different class (combination therapy), if there is NO response we switch to another drug.

- If the initial treatment was successful then we give 6-12 maintenance period (6-12 months) , then after 12 months we **taper** to stop the drug (we don't stop it immediately).

- If the patient has experienced two episodes of major depression (**relapse**), then it is advisable to give an anti-depressant life-long.

- All antidepressants now carry a “black box” warning that they may lead to suicidal thoughts/behavior.

THE END

**"عندما نعيش لذواتنا فحسب، تبدو لنا الحياة قصيرة ضئيلة، تبدأ من حيث بدأنا نعي، وتنتهي بانتهاء عمرنا المحدود.
أما عندما نعيش لغيرنا، أي عندما نعيش لفكرة، فإن الحياة تبدو طويلة عميقة، تبدأ من حيث بدأت الإنسانية، وتمتد بعد مفارقتنا لوجه هذه الأرض"**

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