Pharmacology Lecture 6

We already said in the previous lecture that depression is a common disease and this disease needs treatment. It's not acceptable to leave a depressed patient without treatment, since in the west; loosing interest in one's own life could easily lead to suicide. However, it is a different story regarding the east; where there is what's so called idea of reference that suicide is against religion so this –suicide- is not of a great issue concerning us, another concern is that the depressed patient if left untreated may either go into bipolar disorder or schizophrenia.

First strategy to tackle the problem of depression is to increase the concentration of certain neurotransmitters in the CNS including: Dopamine, Norepinephrine and serotonin

- Tricycle antidepressants

TCAs are old drugs, which are not selective. They inhibit the reuptake of all 3 neurotransmitters and produce a nice efficacious activity against depression. However being not specific/ selective, they will bind and block Muscarinic acetylcholine receptors, alpha-adrenoreceptors, and certain histamine (H1) receptors therefore producing a variety of BAD side effects:

1. Drug-induced Sedation
2. Orthostatic hypotension
3. Cardiac effects (arrhythmias)
   -Generally, cardiac effects are due to manipulation of muscarinic & adrenergic receptors.
   -Muscarinic receptors (M2) are inhibitory to the heart muscle - bradycardia- while adrenergic receptors (B1) are excitatory to it.
   -In resuscitation, adrenaline and atropine are given. Adrenaline will further activate/ increase activity of adrenergic receptors, whereas Atropine has anti vagal nerve (anti muscarinic) activity on the heart (don't forget that vagus stimulation leads to bradycardia); thus, this increases the heart rate, now, in cases of TCAs, there's chronic blocking of muscarinic receptors in the heart therefore precipitating a chance to develop arrhythmias (tachycardia, palpitations …)

4. Anticholinergic effects: dry mouth, constipation, blurred vision, and urinary retention.

NOTE:
TCAs are not the major class of drugs used in depression but they are still in use –despite having a very bad profile regarding the side effects- because of the heterogeneity of depression, which (heterogeneity) leads to the use of more than a single class of drugs in an attempt to find the most suitable one; i.e. we start with SSRIs, if there's no response, we move to SNRIs, if still there's no response, we use TCAs, so, they are no longer prescribed except in refractory depression (depression not treated by SSRIs and SNRIs).

-SSRIs (Serotonin-specific reuptake inhibitors)

-Inhibit the reuptake of serotonin without seriously affecting the reuptake of dopamine & norepinephrine.
-Increasing serotonin levels in synapses stimulates all the serotonin receptors and this is the goal since serotonin is a mood regulator / stabilizer and increasing its concentration makes the mood better which is very helpful for depressed patients.

- ✓ Side effects: all are due to the increase in concentration of serotonin & thus increased activity on many serotonin receptors:

  - An increase in serotonin levels increases appetite thus patients might gain weight.
  - GI upset –common- including what is called substantial nausea (ladies are more susceptible to depression and nausea, in a 3:1 predilection pattern for ladies & men respectively). High levels of serotonin activate all its receptors in a non-selective fashion, however the stimulation of 5HT2& 5HT3 mainly 5HT3 causes GI disturbances & emesis.

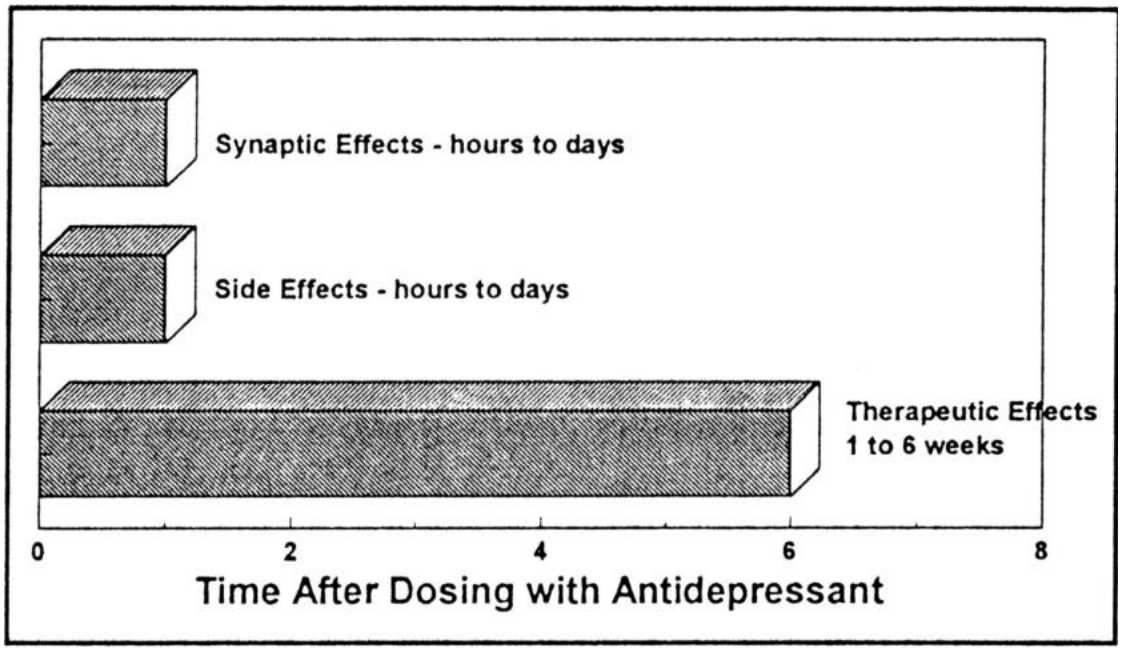
Some may have emesis or diarrhea however **nausea** is the most common.

  - Sexual dysfunction (very common side effect, can reach up to 50% of patients using SSRIs) especially in men.

-Due to the activation of 5HT2 receptors present in the central nervous system including spinal cord.

Recap

Women are more susceptible to depression and mainly suffer from nausea.
Men are more prone to sexual dysfunction.
These 2 previous side effects made the rejection to these drugs high, so how do you convince the patient to take such a drug? By giving a pleasant view about this drug. Here psychotherapy comes in place; successful treatment of depression is mostly based on psychotherapists who will eventually convince the patient to take the drug.



-This diagram shows that side effects occur as soon as hours to days after starting the medication, however therapeutic effects may take up to 6 weeks (4 weeks average) to appear. This even makes it harder for the doctor to convince the patient to take this drug due to the prolonged time the patient suffers from side effects without the appearance of true benefits. This dilemma has to be solved in some way and it is the doctor's responsibility to figure it out.
-One simple way to make the patient take the drug is to not tell him/her about the side effects until he/she actually has them and confronts you. This is the best time to try explaining the side effects and the course of treatment.

*Nausea caused by medication reduces with time

Why do therapeutic benefits of **antidepressants** need 6 weeks (except MAO inhibitors which take from 1-10 days)

- The major & most reliable reason behind this is the concept of auto-receptors, serotonin auto-receptors are (5HT1A, 5HT1B)

*Auto-receptors have a feedback function and are presynaptic.

- Upon starting medication with SSRIs, there will be increase in the levels of serotonin in the synapse & this increase will actually lead to down-regulation of 5HT1A on the presynaptic neuron either by desensitization or by decreasing the number of receptors (5HT1A), thus, there will be disinhibition of the presynaptic neuron –serotonergic neuron- & this will lead to firing of this neuron releasing serotonin to the synapse giving rise to the therapeutic effects, i.e. producing better mood for the patient, which will be fully established after 4-6 weeks of initiation of treatment.
  - Note here that the inhibition of reuptake of serotonin by SSRIs is immediate, however, the clinical effects are delayed, but how does the previous theory explain the delayed onset of therapeutic effects? The downregulation process of 5HT1A is genetic, so, it needs time & it's thought to be one of the explanations.

- Another theory is that with continuous usage of SSRIs, the brain undergoes neurogenesis in order to build more neurons that provide more serotonin activity.

Note: There is slight improvement in the mood of the patients initially but the full effect will take up to 6 weeks.
That's why it is advisable not to switch from one antidepressant to another before using it for a period of **at least 8 weeks.**

- The last symptom of SSRI is that it can develop a discontinuation syndrome with agitation, nausea, disequilibrium and dysphoria.

-Continuously using the drug produces changes in the physiological functions of neurons that lead to discontinuation syndrome upon an abrupt stop of usage.

-Discontinuation syndrome is characterized by the word **F.I.N.I.S.H**

- Flu-like symptoms: fatigue, muscle aches, headache, and diarrhea
- Insomnia: vivid or disturbing dreams
- Nausea
- Imbalance: gait instability, dizziness, lightheadedness, and vertigo
- Sensory disturbance: paresthesia, "electric shock" sensation, and visual disturbance
- Hyper arousal: anxiety, agitation

- Onset: 24-72 hours + Resolution: 1-14 days
- Incidence: ~ 20 - 40 % (who have been treated at least 6 weeks)

- Most antidepressants cause this syndrome upon sudden discontinuation of treatment in adults, so the best choice is tapering (gradually lessen the dose until stopping it).

NOTE: There is no euphoric activity in those drugs. However, dependence is due to the absence of depression (better mood) during treatment, which renders the patient's eager to continue the treatment.

Question: Why are there many drugs belonging to the same class (SSRI) (sertraline which is the most prescribed, escitalopram, paroxetine and fluoxetine)?

-Because every drug is prescribed according to: - it's side effects (these drugs are different in their side effects), -drug-drug interactions and differential diagnosis.

Paroxetine:

- Nice sedating properties (dose at night) offers good initial relief from anxiety and insomnia… so this drug is administered to a patient who's depressed & suffers from anxiety & insomnia.

- Significant CYP2D6 inhibition. This means that is has a high drug-drug interaction hence should not be given to polypharmacy patients (Patients taking more than 5 drugs, usually elderly).

-CYP2D6 is responsible for the metabolism of 25% of all drugs that we know; therefore paroxetine should not be given to patients who are on drugs that are metabolized by this enzyme to prevent accumulation of high levels of these drugs in the blood.

Sertraline (Zoloft):

• Increased number of GI adverse drug reactions.

•Doesn't have the side effects of paroxetine: no sedative activity; actually not all depressed patients have anxiety; some of them sleep for a long time… so, this drug would be suitable for such patients, also, there's no inhibition of CYP2D6 … this explains why it's the most prescribed drug.

Fluoxetine (***Prozac***):

•Most prescribed antidepressant drug in Jordan.

•Secondary to long half-life, less Discontinuation Syndrome. If this drug is stopped, it needs about a week to discard completely from the body & this is helpful for the body to restore its own physiology back to normal during this period.
This mimics tapering; which is very helpful.

•Significant P450 interactions so this may not be a good choice in patients already on a number of meds (drug-drug interactions)

• Initial activation may increase anxiety and insomnia … not a good choice in anxious depressed patients.

• More likely to induce mania than some of the other SSRIs.

To sum up

No one drug is complete in all aspects & none actually is perfect, so the best must be chosen according to the patient's case & there must be always monitoring. Mentioning again that this diversity in treatment is due to the heterogeneity of the disease and the patients having depression as well as to the different mechanisms & effects produced by different drugs.

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

Refer to the table:
-Paroxetine has 18m prescriptions hence the sedative and antianxiety effects of this drug are used, indicating that a lot of patients have anxiety with depression.
-Sertraline has the highest prescriptions since it causes only GI disturbances thus its more tolerable compared to other side effects of other SSRIs.

-All anti depressants have a black box warning: "continuous usage of these drugs increase the incidence of suicide".

As we previously said, this is present mainly in the west, since we have an idea of reference that suicide is against religion and its not humanistic nor ethical in anyway therefore is not even a choice to be considered for many patients.

Finally, you as doctors should use your intelligence to encourage and convince the patients to take the antidepressant regardless of the many side effects it may lead to.

*Note: If the patient has experienced two episodes of major depression, then it's advisable to give an antidepressant life long.

- General physiological note: Don't forget that there are fast neurotransmitters (GABA & Glutamate) & slow neurotransmitters (Serotonin, Dopamine & NE) & the latter take time to actually produce an effect; since they work through G protein coupled receptors not ion channel receptors.

Good luck
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