بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

Antidepressants (Pt.2)

FINAL | Lecture 2

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

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PHARMACOLOGY

رحلة اليقين مع سورة يس

بِسۡمِ ٱللَّهِ ٱلرَّحۡمَٰنِ ٱلرَّحِيمِ

وَيَقُولُونَ مَتَىٰ هَٰذَا ٱلۡوَعۡدُ إِن كُنتُمۡ صَٰدِقِينَ ﴿٤٨﴾ مَا يَنظُرُونَ إِلَّا صَيۡحَةٗ وَٰحِدَةٗ تَأۡخُذُهُمۡ وَهُمۡ يَخِصِّمُونَ ﴿٤٩﴾
فَلَا يَسۡتَطِيعُونَ تَوۡصِيَةٗ وَلَآ إِلَىٰٓ أَهۡلِهِمۡ يَرۡجِعُونَ ﴿٥٠﴾

{وَيَقُولُونَ} على وجه التكذيب والاستعجال: {مَتَى هَذَا الْوَعْدُ إِنْ كُنْتُمْ صَادِقِينَ} قال الله تعالى: لا يستبعدوا ذلك، فإنه [عن] قريب.

{مَا يَنْظُرُونَ إِلَّا صَيْحَةً وَاحِدَةً} وهي نفخة الصور {تَأْخُذُهُمْ} أي: تصيبهم {وَهُمْ يَخِصِّمُونَ} أي: وهم لا هون عنها، لم تخطر على قلوبهم في حال خصومتهم، وتشاجرهم بينهم، الذي لا يوجد في الغالب إلا وقت الغفلة.

وإذا أخذتهم وقت غفلتهم، فإنهم لا ينظرون ولا يمهلون {فَلَا يَسْتَطِيعُونَ تَوْصِيَةً} أي: لا قليلة ولا كثيرة {وَلَا إِلَى أَهْلِهِمْ يَرْجِعُونَ}.

SSRI Usage in Depression

Some notes to recall from the previous lecture:

- SSRIs are the first-line and most prescribed treatment for depression.
- The synaptic effect can occur within days or hours, meaning that the side effects will also manifest within days or hours as a consequence.
- The desired therapeutic effect, however, takes 1-6 weeks. (Dr. Malik said that realistically we need 4 weeks to see activity, and 6 weeks for maximal activity.)
- The trial period is 8 weeks (this is universal across all anti-depressants, not just SSRIs), and only after the trial period we can decide whether the anti-depressant is working or not.

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**
  - An increase in serotonin does not carry an antagonistic effect nor an agonistic effect; it results in "Modulation", meaning it can result in an increase or decrease of an effect. This explains why some of the side effects are self-conflicting; it's a natural consequence of every human being different, and processing drugs differently, as such, we can see that some patients suffer from insomnia, and others are sedated.
- **Can develop a discontinuation syndrome with agitation, nausea, disequilibrium and dysphoria**

Two Other Side Effects

- The first is a change in a personality, where your own nature changes. In most people, this is a good change; they become more motivated, start planning, etc. However, in about 30% of people, they end up feeling disconnected from themselves, as if they're a completely different person. The direct reason for this is the continuous increase of serotonin (over a period of years) leading to "flattened feelings" (as the doctor described it). This is a long-term effect.
- The second side effect (which occurs in the short-term), which is a **black box warning**, is the potential increase in suicidal thoughts (to be specific, the black box notes the increase in suicide rates in patients who follow the medication).
  The reason behind this will be addressed in the next slide.

Note: when we talk about SSRI side effects, we generally mean most anti-depressants.

Suicidal Thoughts

- CNS medications are very complicated and have a lot of intricate details. In young adults (18-24), the CNS is in its “prime”, and serotonin levels are inherently high.

- When such patients experience depression or suicidal thoughts, they may opt to take SSRIs, increasing serotonin (which is already high in a young adult). SSRIs increase anxiety, restlessness, and thinking motivation, which naturally increases the frequency of suicidal thoughts.

- This made SSRIs hold a black box warning in many countries.

Suicidal Thoughts

If SSRIs can increase suicidal thoughts, why would we use them to treat a depressed, potentially suicidal patient?

Although their usage is not recommended in any country, Muslim countries do not have the black box warning. This is because Muslims have an idea of reference "الانتحار حرام", so their motivation for suicide is inherently low.

However, in countries such as South Korea (East Asian countries notoriously have low rates of a religious population relative to the rest of the world) suicide rates are very high, which is why these countries have a black box warning. This ties into the point of the effects of CNS medication differing between individuals, and as suicide rates are lower in Muslim countries, they are still used and the black box warning was deemed unnecessary.
(Remember that their usage is not recommended at all)

The discontinuation of SSRIs and avoidance of long-term side effects

After we give the drug and have passed the trial period, we observe the patient.

- If he has experienced one major depression attack within a one-year time period, then we discontinue the drug by tapering throughout a year. This is to avoid the flattening of feelings that causes a self-disconnect as we mentioned previously.
- If he has experienced two or more major attacks within the year, then it is advised that we continue the medication throughout his entire life. Although we mentioned that we want to avoid the long-term side effects, we must measure the benefit-to-risk ratio, and It would be better to imminently deal with the major depression.

Serotonin/Norepinephrine reuptake inhibitors (SNRIs)

- Slightly greater efficacy than SSRIs

  Use SNRIs when the patient is unresponsive to SSRIs after 8 weeks.

- Slightly fewer adverse effects than SSRIs
  - Venlafaxine
  - Duloxetine

1. Can cause (in around 10% of patients) a 10-15 mmHg dose dependent increase in diastolic BP. (↑NE → Sympathetic Activation → Vasoconstriction → ↑BP). So make sure to monitor patients' BP.
2. May cause significant nausea,

   Serotonin alone causes nausea and GI disturbances; with NE, the effect is amplified.
3. Can cause a bad discontinuation syndrome, and taper recommended after 2 weeks of administration (because you've interfered with NE levels alongside Serotonin)

Transitioning from SSRI to SNRI

- NEVER give patients multiple serotonin-raising drugs (risk of serotonin syndrome).
- When transitioning a patient from SSRIs to SNRIs, you must allow for a 5-half-life "washing period" between the discontinuation of the SSRI and the initiation of the SNRI. This is to ensure SSRI levels reach insignificant, subtherapeutic levels in the blood, because otherwise the discontinued drug and the initiated drug would have an additive effect, and increase the risk of Serotonin Syndrome.
- So, the plan is: If SSRIs are ineffective after 8 weeks, taper it over a 2-week period, and start your patient on an SNRI after 1-2 weeks.
- Example: Fluoxetine's half-life is 36 hours, 5-half-lives would be 7.5 days, and with norfluoxetine (Fluoxetine's active metabolite) the period of significant drug effect extends even more, necessitating a longer “washing period”.

- Following the initiation of the antidepressant drug treatment, there is generally a therapuetic 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 anti depressant life long.

Atypical Antidepressants Trazodone & Mirtazapine

Previously discussed antidepressants worked by inhibiting serotonin reuptake, thereby increasing synaptic serotonin level. Trazadone & (most importantly) Mirtazapine instead "inhibit feedback inhibition" of serotonin release by:

1. Blocking specific receptor pathways that normally limit the beneficial serotonergic response, thereby indirectly increasing serotonin levels in the synapse (5-HT2A, 5-HT2C, 5-HT3 receptors).

2. They have antagonistic effects on α-2 receptors.

Elaboration: Clonidine (*recall CVS*) is an α-2 agonist used to treat hypertensive patients by reducing sympathetic outflow centrally. Its main adverse reaction is depression. Antagonism of α-2 receptors results in the exact opposite, an antidepressive effect.

Atypical Antidepressants Trazodone & Mirtazapine

- In contrast to Mirtazapine, Trazadone also has a unique sedative effect because it antagonizes H1 receptors (acts as an antihistamine, therefore also used as a hypnotic), which further adds to why it is widely prescribed.
- Literature says these drugs must not be given alongside SSRIs, although that is not an uncommon practice. That is because their mechanism of action is not fully understood, and they are classically not as impactful to serotonin levels as other drugs.
- You should know Bupropion (to be explored later) can be given alongside other drugs (except MAO inhibitors) as it does not raise serotonin levels.

PHARMACOLOGY QUIZ LECTURE 2

واحنا بندرس محاضرة عن الاكتئاب،

نسأل الله أن يرحم زميلتنا روضة رحمةً واسعة، ويغفر لها، ويتجاوز عنها، ويجعل ذكرها الطيب باقيًا.

روضة، التي كان من آخر وصاياها: "تبرعوا بأعضائي"، نسأل الله أن يجعل ذلك في ميزان حسناتها، فادعوا لها.

وإن أثقلتكم الأيام يومًا، فتذكّروا أن طلب العون ليس منقصة، وأن الحديث عمّا في القلب ليس ضعفًا
رحمك الله يا روضة.

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