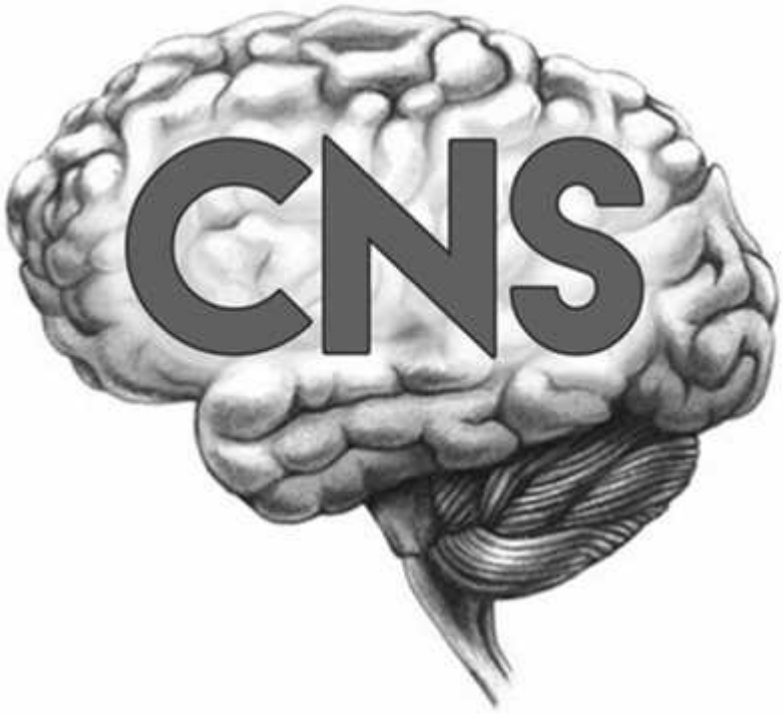


# PHARMACOLOGY

☑ Sheet ○ Slide ○ Handout

Number

2

Subject

## Antidepressants

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Date: **00/00/2016**

Price:

*Notes:*

- *This sheet was written according to section 3 recording.*
- *Before you start studying this sheet remember that there are so many people suffering from depression and one day some will come to YOU seeking help and asking you to make them smile again. Remember them then study this sheet with passion.*

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# *How to treat depression:*

## 1- Behavioral therapy is a must!

→ Behavioral therapy increases the percentage of response from 40% -with drugs only- up to 65-70%.

→ Treating a depressed patient with drugs only is a **complete failure.**

→ Exercise or body awareness has been found to helpful.

## 2- Antidepressants drugs:

### ➢ General view on these drugs:

This slide shows the number of prescriptions of each anti-depressant per year in US. *Of course the numbers are not for memorization; just take a look on these numbers to have an idea about the tremendous use of these drugs.*

| Drug name | Commercial name | Drug class | Total prescriptions |
|---|---|---|---|
| Sertraline | Zoloft | SSRI | 33,409,830 |
| Citalopram | Celexa | SSRI | 27,993,635 |
| Fluoxetine | Prozac | SSRI | 24,473,994 |
| Escitalopram | Lexapro | SSRI | 23,000,156 |
| 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 | Sensaval | TCA | 3,210,476 |
| Bupropion ER | Wellbutrin XL | NDRI | 3,132,327 |
| Venlafaxine | Effexor | SNRI | 2,980,525 |
| Bupropion | Wellbutrin IR | NDRI | 761,616 |

- The number one drug is Sertraline -Zoloft- →around 33milion prescription.
- The second one is citalopram → around 27 million prescription.

- Flouxetine (Prozac) →24 million prescription, commonly used in Jordan.
- Escitalopram (lexapro)→23 million prescription.
- Trazodone →is a new drug that is becoming popular,18 million prescription.
- Bupropion →also is becoming popular,15 million prescription.
- Duloxentine.
- Paroxetine.
- Amitriptyline → an old antidepressant.

### ➢ Antidepressants classes:

All antidepressants are classified into 5 classes; these classes are:

1) **Serotonin reuptake inhibitors** (SSRI) -*these are the top guys-.*
2) **Serotonin nor-epinephrine reuptake inhibitors** (SNRI); venlafaxine.
3) **Serotonin antagonist reuptake inhibitors** (SARI); trazodone is one of them.
4) **Nor-epinephrine-dopamine reuptake inhibitors** (NDRI); Bupropion.
5) **Tricyclic antidepressants.**
6) **Monoamine oxidase inhibitors**, used in specific cases of depression; thus they are not so popular.

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## 1) Selective Serotonin reuptake inhibitors (SSRI):

We will discuss three drugs of SSRI:

A. **Sertraline ( Zoloft).**
B. **Flouxetine (Prozac);** the most used one in Jordan.
C. **Paroxetine.**
D. Citalopram is one of the SSRI that is used commonly. *We will not discuss it.*

→ These four drugs are the most prescribed drugs in Jordan.

**SSRIs are the first line treatment along with psychotherapy -behavioral therapy- .**Always we start treatment by selective serotonin reuptake inhibitor (SSRI).

## ❖ Mechanism of action:

Inhibit the reuptake of serotonin without seriously affecting the reuptake of dopamine & nor-epinephrine. Thus, they cause an elevation in serotonin levels resulting in:

- Increase in the motivation and improve the mood.
  **But at the same time;**
- Elevated levels of serotonin cause sexual dysfunction, increase the emesis -vomiting-and cause diarrhea.
- So, you increased serotonin to improve the mood but with many other adverse effects.

- **NOTE:** depression is more common among females than males.

- So in general SSRIs' most common side effects are:
  - → GI upset.
  - → Sexual dysfunction, this is the most common side effect appears in more than 30% of the patients.
  - → Anxiety, restlessness and nervousness.
  - → Insomnia -due to increased aggression by elevated levels of serotonin-.
  - → Fatigue or sedation.
  - → Dizziness.
- The side effects appearance depends on the patient him/herself; some patients may develop none of these side effects while others will develop most of them.
- As you can see it is not a simple issue to give SSRI due to the many side effects.
- All anti-depressants cause **with-drawl symptoms** -AKA discontinuation syndrome- when stopped abruptly **after one month or more**.
  - → For simplicity, the with drawl symptoms are gathered in the word **"FINISH":**
    - ❖ **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, dysphoria.
  - → The Incidence of these symptoms is: around 20 - 40 % (of those who have been treated at least 6 weeks).

→ Such syndrome starts within 24-72 hours *-according to the drug-* after stopping the drug and resolve by itself within 1-14 days.

→ **NOTE:** Even within the same group, drugs have some differences between them, for example some may have with drawl reaction more severe than others.

*Now we will discuss every drug by itself;*

## A- Paroxetine:

- The most important characteristic in it is that it is **the least SSRI to produce insomnia;** thus its sedating properties (dose at night) offer good initial relief from anxiety and insomnia.
- On the other hand, it is not used that much because of its **significant CYP2D6 inhibition.** So it is not a good choice for those over 50 years of age -i.e. poly pharmacy- due to the high potential of drug-drug interaction.
- Remember that CYP2D6 is responsible of metabolism of around 25% of the drugs.
- So Paroxetine is a good choice when:

I. The patient suffers from insomnia -and he/she is not taking many drugs concurrently-.

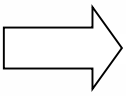
II. When a patient develops insomnia from other SSRIs –Zoloft or Prozac-.

- So if a patient develops insomnia from one of the SSRIs do not change the whole class of drugs, you firstly change the drug within the same group. So stick to SSRI and use Paroxetine- instead of Zoloft or Prozac- but keep an eye on the drugs that your patient is taking.

## B- Sertraline (Zoloft):

- Why Zoloft is the most prescribed drug?
  - → Because it is **the most tolerable** one among anti-depressants; the insomnia induced by it is more tolerated than that produced by other drugs. In addition; it **does NOT have that much drug-drug interactions**→ Thus we start with Zoloft.
  - → **Zoloft is the best to start with.** But this does not mean that it does not have side effects.

- its main **side effects** are:
  1) Nausea.
  2) vomiting
  *3)* Diarrhea.
  *4)* Dry mouth.
  *5)* Headache.
  *6)* Sexual dysfunction.



***GI upset In general***

****Usually, doctors prescribe as a first choice, Sertraline or Flouxetine. ****

## c- Flouxetine (Prozac):

- Why NOT to start with Prozac?

  *Because of its **significant P450 interactions** so this may not be a good choice in patients already on a number of medications.

  *Also, Its Initial activation may **increase anxiety and insomnia** which is dangerous in case of bipolar mania misdiagnosed as depression. *To understand this, we need to understand bipolar mania;*

  - → **Bipolar mania:** is psychological disorder characterized by cycles of depression followed by mania and so on….
  - → And many of bipolar patients will come to doctors to complain about their depression -*they will not tell the whole story of their cycles*- . And based on that doctors will diagnose them with depression. Thus if they were given Prozac their mania is going to be even worse than before by the increased level of anxiety induced by Prozac. So because of the high incidence of misdiagnosing bipolar disorder as depression, Prozac is not preferred as first choice

- Based on that;

  ****Do not start with Prozac.****

- Prozac side effects: more anxiety and anorexia than other SSRIs.

## ❖ Strategy and response:

- If there were 200 depressed patients and half of them were given antidepressants as a treatment while the other half were given placebo. The results would be:
  - → 45% of those given real drugs will respond.
  - → 30% of the patients on placebo will respond as well.
  - → Patients on placebo think that they are taking drugs but in reality they do not. So what is really happening is that they are motivating themselves by themselves.
- So you can conclude that there is something in the physiology of depression that does not depend on chemicals or drugs, there is endogenous something that is really important. So once again remember that behavioral therapy is a must.
- From such studies , it was established that giving an antidepressant along with psychological treatment will increase the percentage of response as follows:
  - → Antidepressant+ behavioral therapy= 30% +45%= increasing the percentage of response up to 75%.
  - → Based on the previous information, the first strategy in the treatment of depression is: **SSRI with psychotherapy.**

- Now; if your patient did not respond to the treatment by SSRI along with psychotherapy→ you need to change the strategy.
- But when to change , or how long we should wait a patient on SSRI to tell whether he is responding or NOT:
  - → At least you should wait **eight weeks** as the maximal benefit of antidepressant drugs appears after 6 weeks up to 8 weeks. *The reason behind this is explained by the neurotrophic theory (sheet 1).*

***Do NOT change the antidepressant used before eight weeks. ***

***Do NOT judge that your patient is responding to the drug or not before eight weeks. ***

- And due to the with drawl symptoms associated with antidepressants; if you want to change the drug you need to **taper the dose gradually** and at the same time you add the new drug to the regimen.

## 2) Serotonin nor-epinephrine reuptake inhibitors (SNRI):

- SNRIs have Slightly greater efficacy than SSRIs.
- Slightly fewer adverse effects than SSRIs *-but they still have-.*

- Two drugs that are mainly used from this group, these are:

1. **Venlafaxine**, as mentioned before it has around 16 million prescription because patients who do not respond to SSRI are given venlafaxine.
2. **Duloxetine.**

- **Side effects:**
  1. SNRIs increase the level of serotonin as well as nor-epinephrine thus the blood pressure will rise; they can cause a 10-15 mm HG dose dependent increase in **diastolic** blood pressure -not systolic-. And because this increase is in the diastolic pressure then it is significant and may be dangerous.
  2. May cause **significant nausea**, *the most nausea inducing drugs among antidepressants are SNRIs*.
  3. Can cause a **bad discontinuation syndrome**, and taper recommended **after 2 weeks** of administration ONLY -not 6 weeks as in SSRI-because you are dealing with two factors serotonin and nor epinephrine not only serotonin as in SSRI.
  4. Venlafaxine appears to induce mania more than SSRI in bipolar patients

***Thus, do not start with SNRI***
***SNRIs are the second strategy to use; not the first***

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*Around 20% of depressed patients do not respond to SSRI and SNRI. In such case, move on to the next strategy.*

## 3) 5-HT2 antagonists reuptake inhibitors (SARI):

- This third strategy is a new strategy that was discovered in 2004.
- The drugs of this group are:
  - Nefazodone.
  - Trazodone.-*just memorize this*-
  - Mirtazapine.

### ❖ Mechanism of action:

- Inhibition of 5-HT2A receptors in both animal and human studies is associated with substantial antianxiety, antipsychotic, and antidepressant effects

- Nefazodone is a weak inhibitor of both SERT -serotonin transporter- and NET nor-epinephrine transporter-, whereas trazodone is also a weak but selective inhibitor of SERT.

- There are many subtypes of serotonin receptors:

  → 5-HT**1** subtype is the one that is responsible for therapeutic effects of increasing intra-synaptic serotonin levels by antidepressant drugs. So when serotonin binds to 5-HT1 receptors, it increases motivation, regulates the mood ….etc. -i.e. produces the therapeutic effects-.

  → Whereas when serotonin binds to 5-HT**2** receptors → side effects of increased serotonin levels are produced.

  → This explains how antidepressants have their therapeutic effects and the adverse effects discussed earlier.

  → From here the idea of 5-HT2 antagonist originated. why not to produce a drug that blocks 5-HT2 selectively without affecting 5-HT1 receptors and at the same time increase the serotonin levels!

***So Trazodone was the result***

- **Trazodone** :

→ Blocks 5-HT2 serotonin receptors.

→ Inhibits SERT and NET.

→ So it increases the levels of serotonin and at the same time blocks serotonin receptor reasonable for the side effects -i.e. 5-HT2-. Thus, we will have the therapeutic effects **WITHOUT** the side effects.

- Based on their mechanism of action, you can conclude that these drugs do **NOT** produce sexual dysfunction and anxiety and cause **less nausea and vomiting -or GI upset-** or any of the side effects caused by the elevated levels of serotonin.
- They have an activity on alpha 1 receptors and histamine receptors. *Keep this mind.*

***But why not to use trazodone from the beginning?***

- Firstly, it is a new drug.
- Secondly, trazodone still has side effects produced by its other mechanisms of action!
  1. They are very sleepy drugs, **very sedative** because they have an effect on histamine receptors:
     - → They result in **dizziness** in most cases.
     - → So it is not practical to use them in old ages mainly as most of elderly suffer from dizziness so giving them sedative drug is going to make things even worse. But other than this, they are considered a good choice due to the fewer side effects.
     - → However, this effect (i.e. sedation) may be good in some cases such as :
       - © Mirtazapine can be advantageous in patients with depression having sleep difficulties.
       - © Low doses of trazodone (50-100 mg) have been used widely both alone and concurrently with SSRIs or SNRIs to treat insomnia.
  2. They cause **weight gain** but less than other drugs.
  3. It may cause **orthostatic hypotension** because, as mentioned, they have an activity on alpha 1 receptors.

- to summarize things, SARI:
  - ❖ cause sedation and dizziness.
  - ❖ Orthostatic hypotension.
  - ❖ Little weight gain.

**BUT**

  - ❖ **NO** sexual dysfunction or anxiety.
  - ❖ **Less nausea and vomiting.**

*If the patient did not respond to all these strategies, do not lose hope; you still have another one.*

## 4) Tricyclic antidepressants:

- Ami**tri**ptyline is the tricyclic antidepressants used.
- Used for resistant patient who does not respond to other strategies as they are more effectious than other anti-depressants.
- They are **NOT** selective at all;
  - → They inhibit serotonin, nor-epinephrine, and dopamine transporters, slowing reuptake with a resultant increase in activity.
  - → Muscarinic acetylcholine receptors, alpha-adrenoceptors, and certain histamine (H1) receptors are also blocked.
  - → Thus they are more efficacious.

- **Side effects:**
  1. **Drug-induced Sedation**→ by blocking histamine receptors.
  2. **Orthostatic hypotension**→ by blocking alpha receptors.
  3. **Cardiac effects**→ by the action on alpha receptors.
  4. **Anti-cholinergic effects**; dry mouth, constipation, blurred vision, urinary retention -Atropine like effects-.

## 5) Monoamine oxidase inhibitors (MAOI):

- Patients who suffer from **atypical depression** do not respond to any of the strategies mentioned. In such case Monoamine oxidase inhibitor (MAOI) is the drug of choice. In other words; in atypical depression we start with MAOIs.
- These drugs are not widely used as they are really bad drugs. *Not used except in atypical depression.*

## ❖ Mechanism of action:

- MAO catalyzes deamination of intracellular monoamines;
  - → MAO-A oxidizes epinephrine, nor-epinephrine, serotonin
  - → While MAO-B oxidizes phenylethylamine.
  - → Both oxidize dopamine non-preferentially
- MAO transporters reuptake extracellular monoamine.
- Thus these drugs increase the level of serotonin and nor-epinephrine by inhibiting their metabolism. These drugs are **Non selective.**

## ❖ Side effects:

1) Blood pressure problems due to blocking alpha 1 receptors. - → causing **orthostatic hypotension**. -remember that this side effect is also seen in SNRI
2) Weight gain.
3) Insomnia.
4) Edema.
5) Require dietary restriction:
   - → Patients on **nonselective MAOI** -i.e. that inhibit both MAO A and B- should not eat cheese or any food that contains tyramine because tyramine is metabolized by MAO -mainly B -in the GI tract thus when the patient is taking MAOI →tyramine will not be metabolized → build up of tyramine → resulting in excessive release of nor-epinephrine →hypertension crisis.
   - → To avoid this effect of MAOI, give **reversible and selective MAOI** -i.e. that works on MAO A only not B-→ thus the metabolism of tyramine will not be affected and no need for dietary restriction.

***This drug is moclobemide***

- **NOTE:** Phenalzine is non selective MAOI; so it is contraindicated to take cheese or any tyramine containing food with such drug. It is no longer used for this reason as we have a better choice.
- **We conclude that :**

***the drug of choice for atypical depression is molobemide.***

## 6) Buproprion:

- Good as an **augmenting agent not as mono-therapeutic agent** ; When the patient is not responding to any antidepressant drugs or when there is initial response then the response started to decrease →augmentation is the solution. Augmentation is made by giving a drug that does not affect serotonin -to prevent the occurrence of serotonin syndrome- along with other antidepressant.

***Buproprion is the augmenting agent***

- Mechanism of action : reuptake inhibition of dopamine and nor-epinephrine -no effect on serotonin-
- **No** weight gain, sexual side effects, sedation or cardiac interactions
- Why buproprion is the ONLY agent for augmentation?

Because all other antidepressants increase the level of serotonin, thus using two drugs that elevate serotonin will result in **serotonin syndrome**; so you cannot combine:

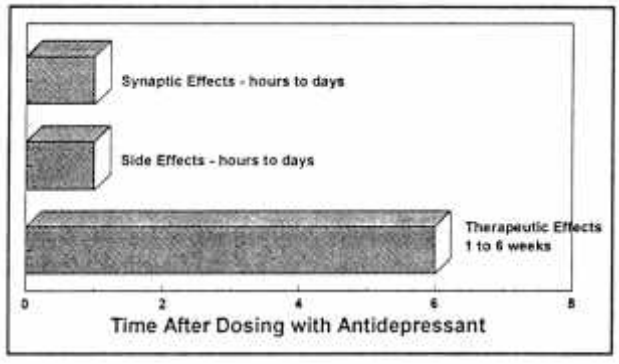
- → SSRI with SNRI.
- → SSRI and TCA.

***Extra note: Serotonin syndrome (SS) is a group of symptoms that may occur following use of certain serotonergic medications or drugs. The degree of symptoms can range from mild to severe. Symptoms include high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhea. Body temperature can increase to greater than 41.1 °C (106.0 °F). Complications may include seizures and extensive muscle breakdown.***

***Wikipedia***

## ➢ General notes:

- Synaptic effects of antidepressants appear **within hours**.
- Therapeutic effects appear **within WEEKS**.
- The side effects appear **within hours to days**.
  - → So it is your job to convince your patient to take such drugs despite the side effects and the




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

long time to achieve the indented effects. You have to persuade the patient take a drug whose side effects appear before its effects.

- If the initial treatment was successful, then the patient should continue using the drugs for 6- 12 months. And do not forget that when you want to stop the drug →**you MUST taper the dose**.
- If the patient has experienced two episodes of major depression, then it is advisable to give an anti-depressant lifelong.

***Sorry for any mistakes,***

***Wish you all high dose of luck ~***