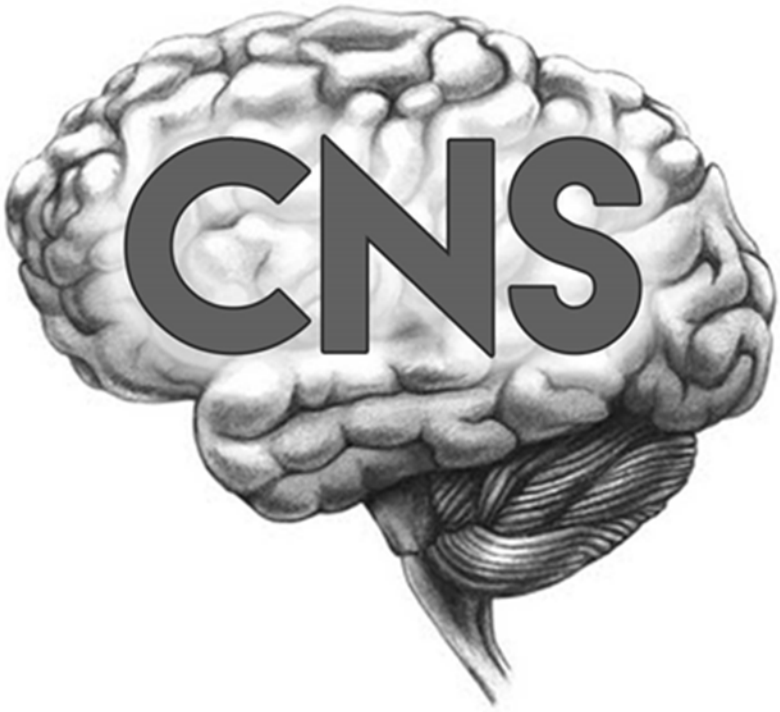


# PHARMACOLOGY

☑ Sheet ○ Slide ○ Handout

Number

1

Subject

General concepts about CNS pharmacology and depression

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*Notes:*

- *This sheet was written according to section 3 recording.*
- *The First 4 and half pages are not included in the final exam; however it is really important to go through them.*
- *The sheet is very easy and it only contains simple and general information.*

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# ♣ General concepts about CNS pharmacology:

## I. Tolerance, dependence and addiction:

### ❖ Tolerance:

- Simply it is the body response towards a drug -most cases agonist- in which it decreases the number of drug's receptors. Thus the dose, which the patient is used to take, will not be effective any more.
- It is a physiological change, mostly related to receptors.
- Most of the drugs that develop tolerance are agonists -not antagonists-.
- Because most of the drugs used in psychological disorders are agonists like the narcotics, anxiolytics and hypnotics; tolerance is seen with most of them when used for long time. So the first rule when using such drugs is that to **avoid prolonged use**.
- **Example:**

→ A patient takes lorazepam one pill daily as a hypnotic, the effect is seen during the first week only and then this one pill will not produce any effect → the reason behind that is tolerance!

***Hypnotics are not used for more than two weeks due to tolerance***

→ To avoid tolerance, dependence and addiction, hypnotics are not used for more than two weeks.

→ And keep in mind that using hypnotics is just kind of symptomatic treatment for a major underlining disease that you should look for.

→ To avoid tolerance→ avoid prolonged continuous use.

### ❖ Physical dependence:

- It means that the body is theoretically *"built with the drug"* as if the drug became part of the body due to physiological changes. And stopping the drug abruptly is going to cause withdrawal symptoms (discontinuation symptoms).
- Tolerance is different from physical dependence

- **Example:**
  - → Adrenal crisis is an example on withdrawal reaction in which the sudden termination of corticosteroidal use results in severe dangerous symptoms because the body in such case depends on exogenous sources of corticosteroids and the adrenal gland is atrophic. To avoid such withdrawal reactions, the drug is terminated gradually -tapering the dose- to give enough time for the adrenal glands to start working properly.

    ***Thus to avoid withdrawal reactions, taper the dose gradually.***

## ❖ Addiction:

- It is **psychological** dependence;
  - → Psychological and behavioral syndrome manifested by drug seeking behavior, loss of control of drug use, and **continued use despite adverse effects.**
  - → Mostly it is caused by the euphoria induced by the drug.

- Some drugs may develop more than one of these phenomena (i.e. tolerance, addiction and physical dependence) at the same time while others may not. In other words, a drug that develops one of these phenomena does not necessarily mean that it develops the other two.

***They are separate phenomena.***

- Examples:
  - → The beta-agonist salbutamol develops tolerance but not dependence nor addiction.
  - → On the other hand, the antipsychotics develop physical dependence but not addiction nor tolerance.
  - → Cannabis which binds to Cannabinoid receptors does not develop dependence or tolerance but they develop psychological dependence -addiction- as they cause a degree of euphoria.

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# II. General notes:

- The most prescribed drugs in the world are hypnotics specially lorazepam. In Australia for example, 1/5 of the population suffers from sleeping disorder.

- The second most prescribed drugs are anti-depressants.
- Do not use any euphoric drug in treatment except in very specific medical conditions.
- Smoking causes addiction - as nicotine has little euphoric action-and a small degree of physical dependence.
- Morphine works on μ-opioid receptors. While Benzodiazepines and barbiturates both of them work on GABA receptors.

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## III. Analgesics:

***The three magical drugs: Aspirin, cortisone and Morphine.***

- Remember that each drug has a ceiling effect -E max-:
- Paracetamol reliefs only **mild pain** so it cannot be used for moderate pain like toothache for example.
- Non steroidal anti-inflammatory drugs (NSAID) relief moderate pain which means that they have higher ceiling than paracetamol.
- Narcotics have very high ceiling -much more than that of NSAID- , actually they have an endless peak or ceiling.
- Thus these three drugs have different ceilings, so different uses :
  - → Mild pain: paracetamol
  - → Moderate: NSAID
  - → Severe: narcotics
- **Narcotics :**
  - → Narcotics that are used in Jordan are: Morphine, pethidine (known also as meperidine) and fentanyl.

1. **Morphine:**
   - *"There is no drug in life as morphine; it is one of the three magical drugs."*
   - It is very powerful drug with endless ceiling which means that the more you give your patient, the more the effect will be.
   - However; morphine as a pain killer develops tolerance with the continuous use that is why it is not used for a long time.
   - It is highly euphoric drug, so the patient who was given morphine, is aware of the pain but they are not feeling that it is unpleasant. *This effect is produced by all opioids but morphine still the magical one.*
   - Morphine has a **dilation activity** on the vessels especially the pulmonary vessels that's why it is used in pulmonary embolisms.
   - Has a long activity -up to 6 hours-.
   - It also has a sedative activity.

- **NOTE**: Naloxone is the opioid antagonist.

2. **Fentanyl:**
    - Has shorter activity than morphine so it is used in theater rather than morphine.
    - Fentanyl is 100 times more potent -not efficacious- than morphine.
    - Faster in producing the effect than morphine.
    - It produces effects faster and finishes faster→so used in operations and pre-operational*. But why this is important in operations?*
        - → Because it is important that the patient wakes up after the surgery by a short period of time. If he was given morphine, the patient will be under morphine's effects -specially the sedative- for around three hours which is not preferred after surgeries. *But still Morphine can be used in case of very long operations.*
        - → This is also important as it gives you the ability to titrate the dose as it is needed.
    - Fentanyl has a sedative activity also, but lasts for around 1 hour.
    - → **Note that** even if the patient is on anesthesia during the operation, he still can be hurt. So it is important to give him an analgesic and more specifically an analgesic that works and finishes fast which is fentanyl.
    - → If the patient is feeling pain during the operation, his vital signs will show that -his heart rate will increase for example-.

***So fentanyl is preferred on morphine in threats because its effects come fast and go fast.****

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## IV. Balanced anesthesia:

Previously, anesthesia was achieved by using a single agent only -*ether or chloroform-.* This has a mortality rate around 1/1000.

The reason behind this significant mortality rate is that anesthesia is achieved by giving a **large dose of single agent** → thus being on **the edge of the third stage**→ so it has really high chance in developing fourth stage anesthesia in which the patient will be dead because of respiratory depression. In other words, if you build anesthesia in a major surgery only on a single agent, you are really close to respiratory depression -i.e. fourth stage- .

***Remember:***

***Potency: is a measure of the amount of the drug necessary to produce an effect of given magnitude.***

***Efficacy: is the magnitude of response a drug causes when it interacts with a receptor.***

***To avoid this risk, don't give too much anesthesia*.***

But how is that?

Use a combination of **anesthetic agent *-lower dose of course-*, analgesic, muscle relaxant and anxiolytic**:

- Muscle relaxant→to reduce muscles reflexes and cause muscle relaxation. Example: pancuronium, ipratropium etc…
- Analgesic→ to suppress the pain, this is usually fentanyl.
- Anxiolytic →to calm down the patient and cause sedation.

### 3. Meperidine or pethidine:

- **It is used in obstetrics** as it has the least effect on the fetus compared with other narcotics. *All studies showed that the effects of pethidine on fetuses are minimal.*
- No other opioid is used in obstetrics.
- Meperidine is not used in procedures other than obstetrics. But in case it was used, it should not be used for longer than 3-5 days only because it has a toxic metabolite -3-methyl meperidine- that accumulates with repetitive use.
- Thus it is used in delivery because:

→ Its minimal effect on fetus.

→ Used for 2-3 hours so there is no risk for toxic metabolite accumulation.

- Due to the combination of the drugs that were used during the operation some patients may suffer from **post-operational hypothermia** so they start to shiver:

→ In such case; firstly we just cover the patient with blanket trying to rise his body temperature. If this was not useful then **the drug of choice of hypothermia is IV pethidine.**

→ The mechanism by which pethidine treats hypothermia is unknown.

** End of the material that is not included in the final exam**

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## ♣ Psychological disorders:

*"The optimal use of antidepressant requires a clear understanding of their mechanism of action, pharmacokinetics, potential drug interaction and the deferential diagnosis of psychiatric illnesses."*

*"Depression sadly, will be the SECOND most debilitating human condition by the year 2020."*

- The first step required to treat a psychiatric patient is to know about the patient. We cannot prescribe an anti-depressant to a patient without seeing them.
- Anti-depressants are very popular and commonly used drugs so it is very important to know about them.
- Because the drugs have many side effects and drug-drug interactions, and the disease itself is heterogeneous, the treatment is very complicated. Every single patient has a different way in being depressed because every human has a different personality, thus a different way in treatment.
- Thus each patient with depression, schizophrenia, bipolar mania or obsessive disorder has a different situation than the other.
- The typical presentation of a depressed patient is being inactive, wants to be alone with loss of interest in anything. *(Feeling sad, unable to feel pleasure, irritability).*
- However; depression may manifest in atypical way in which the patient will not show signs of depression and continues his life normally but deep inside he is really depressed.
- Psychomotor/Physical symptoms of depression:
  - → Decreased libido, energy.
  - → Sleep changes (70% less, 30% more).
  - → Appetite changes (70 % less, 30 % more).
- So you can notice from these symptoms that depression is a heterogeneous disease, so there is no specific differential diagnosis for such disease.
- The personality and behavior of the human depends on three molecules that interact in different manners in each one of us; these molecules are:
  1. Dopamine.
  2. Serotonin
  3. Norepinephrine.

- The function of these neurotransmitters:

| Dopamine : | Nor-epinephrine | Serotonin |
|---|---|---|
| Attention | alertness | Regulates mood |
| Pleasure | Observance | sleep |
| Emotions | Daydreaming | emesis |
| Reward | Heart/BP rates | sexuality |
| Motivation | Stress | Appetite |
| Movement | | Impulsiveness/ aggression. |

- You can notice that these functions are really interconnected with each other which means that each function out of these is a result of the interaction between the three neurotransmitters.
- However, serotonin by itself is an important factor in controlling Mood, impulsiveness and aggression which are really important determinants in psychotic disorders.
- Due to these multiple effects of serotonin, nor-epinephrine and dopamine; any drug that deals with them will have many side effects -mainly related to behavior, sexuality and GI-.

## ❖ Theories explaining depression:

- **From physiological side of view:**
  Depression can be defined as:

→ Decrease in serotonin level in the brain.
→ Decrease in serotonin and dopamine levels in the brain.
→ Decrease in serotonin, dopamine and nor-epinephrine levels in the brain.

  - All of which are correct definitions.
  - From here the first theory about depression appeared;

### Monoamine hypothesis of depression

- Monoamine oxidase is an enzyme responsible for the metabolism of serotonin, dopamine and nor-epinephrine -monoamines-.
- By using monoamine oxidase inhibitors (MAOI) in depressed patients, 50% of them showed improvement after 2 weeks. **Based on that it was established that depression is related to decreased levels of serotonin, dopamine and nor-epinephrine.** The other 50% showed no improvement.

- *"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)".* *From slides*
- So this theory was able to explain that depression is related to reduced amounts of serotonin, dopamine and nor-epinephrine. But it was not able to explain why the response appears after two weeks although levels of the three molecules were already elevated before these two weeks →so the second theory originated:

## 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.*
- *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.*
- *Studies suggest that major depression is associated with substantial loss of volume in the hippocampus, anterior cingulate and medial orbital frontal cortex".* *From slides*
- In other words; the depressed patient has atrophy in the hippocampus, anterior cingulate and medial orbital frontal cortex.
- So when giving MAOI, levels of serotonin will be elevated but with no effect at the beginning of the treatment as the hippocampus, anterior cingulate and medial orbital frontal cortex need time to return back to their normal state. And they return to their normal state by the action of BDNF which increases the communication between neurons.
- All anti-depressants need around 10-14 days to show effects.

→ Thus the first theory explained that depression is related to reduced level of NE,DA and 5-HT.While the second one explained why the effect of antidepressants requires at least 2 weeks to appear.

***Based on these two theories all anti-depressants work by increasing the level of 5-HT, NE and DA.***

***Sorry for any mistakes,***

***Wish you all best of luck~***