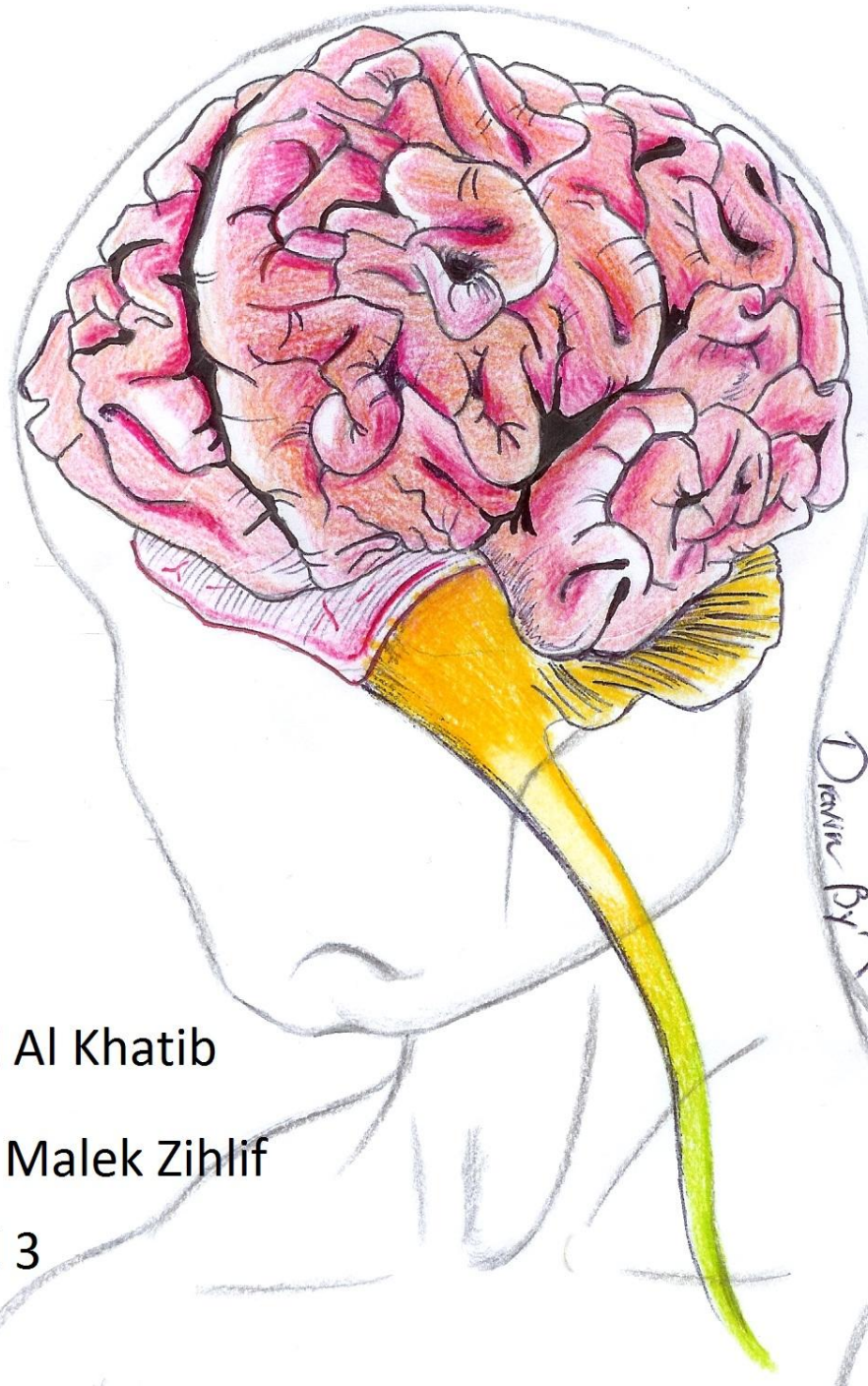
CENTRAL NERVOUS SYSTEM

- ○ Handout
- ● Sheet
- ○ Slide

- ○ Anatomy
- ○ Physiology
- ○ Pathology
- ○ Biochemistry
- ○ Microbiology
- ● Pharmacology
- ○ PBL



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Lec #: 2 and 3

Opioids

Firstly you will be glad to know that this sheet (10 pages) is actually two lectures and a summary =D omgthxAseilyoudabestheeh

Last lecture, we explained the difference between physical dependence and addiction. And we said that physical dependence means that the body is relying on an exogenous material for normal function, so if you stop it abruptly, the body can't find it so there would be withdrawal symptoms. Whereas addiction is the belief of a patient that he can't live without these drugs. He links those drugs to happiness or relaxation (like in the case of smoking).

We said also that opioids produce an acute reaction that's characterized by analgesia, respiratory depression, euphoria, relaxation and sleep, tranquilization, a decrease blood pressure, constipation, pupillary constriction, hypothermia (only a slight decrease in the body's temperature), drying of secretions, flushed and warm skin.

And when you stop them they will produce the completely opposite symptoms, this is called "withdrawal syndrome".

Note that the body can't build tolerance against pupillary constriction and constipation.

We have separated opioids into two groups: strong opioids and weak opioids.

- Strong opioids are morphine, methadone, fentanyl and meperidine.
- Weak opioids are codeine and tramadol.

Strong Opioids

Morphine:

- Morphine has a cardiovascular application which is the treatment of pulmonary edema. The drug of choice to treat pulmonary edema is **Furosemide**, but if the patient is very anxious, has dyspnea that's too severe and is not responding to furesemid, we use morphine. (Actually, morphine has been used to treat pulmonary edema for many years but the new guidelines tell us to try furosemide first and then morphine)
- Morphine is the main drug to be used in cases of **severe** chronic pain (cancer patient being the most important example).

- It can be taken orally, rectally, IV, IM and all other routes, so it's a simple drug.
- Morphine has a small problem that we'll see only in cases of renal failure (or renal compromised patients) and not in the normal population. This problem is the metabolites of the morphine. For morphine to be metabolized it needs to be glucuronidated (which means adding glucuronic acid to it) to form morphine-3-glucuronide which can be toxic towards the brain and produce confusion and seizures as it builds up in the body.
- So what to do with the patients who have a severe chronic pain (or generally, need opioids) and are renally compromised?
  Simply, we either decrease the dose of morphine or use another drug with similar activity and here it's **oxycodone**. However, oxycodone isn't found in Jordan (it's found in the US and very popular there), so we use another drug called **hydromorphine**.
  * Note 1: Oxycodone was introduced to the market as a drug that doesn't cause addiction but this is not true. At the end of the day you'll find yourself addicted just like morphine.
  *note 2: What applies for morphine also applies for oxycodone (except the renal compromised part).
- Doctor read from the slides :
  - ☒ Morphine has 2 biologically active metabolites, morphine-6- glucuronide and morphine-3-glucuronide.
  - ☒ Morphine-6-glucuronide binds to the opioid receptor and is believed to contribute to the effects of the parent compound. Morphine-3-glucuronide does not bind to the receptor and is believed to contribute in some cases to adverse effects such as myoclonus and confusion.

Fentanyl:

- ✓ It's a very potent drug: 100 times more potent than morphine. Which means that 10 mg of morphine is equivalent to 0.2 mg of fentanyl or even less. So the amount of fentanyl that produces analgesia is very low compared to morphine. (but the E_{max} or efficacy is similar for both)
- ✓ It's important to you in the clinic, it's the drug that can work fast and finish fast (it's an emergency drug)
- ✓ Where do you think we need an opioid that can work fast and finish fast?

During operations.
Anesthesia during operations can't produce enough analgesia, that's why we need to supplement it with an analgesic agent that is going to be an opioid because we have no other choice (we give the patient undergoing an operation an anesthetic agent, muscle relaxant, hypnotic and analgesic). You know that your patient is suffering when there's **tachycardia,** in this case you have to **act fast**. We need an opioid that starts fast and finishes fast (you don't need it to last long because you won't make the patient sleep for more than 4-5 hours). All strong opioids won't give you a fast action **except fentanyl;** it starts working within 1 minute after IV administration. Also, all other opioids have relatively long half life (3-4 hours) except fentanyl that has a half life of 30-60 minutes, so maximally the effect of this drug will finish after one hour. So, the **drug of choice** during operations is fentanyl.
*note: we also give morphine so it will start working when fentanyl ends.

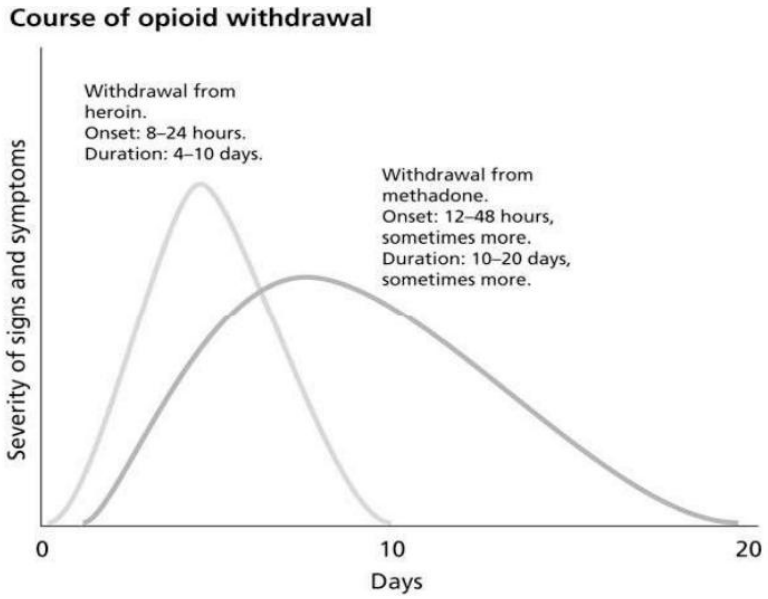
Meperidine (also called: pethedine):

- It used to be the drug of choice for years but we found that it produces toxic metabolites that may produce CNS problems. So now it shouldn't be used for more than three days because metabolites will start to build up after that.
- It's the drug of labor. But why did we choose it and not any other opioid?
  As we said at the beginning of the lecture, opioids produce respiratory depression. So if they crossed the placenta they may produce respiratory depression or stress on the fetus and this drug is the least to produce such a stress. Henceforward, meperidine is the drug of choice in delivery.
- Another application for meperidine is to reduce shivering after operations.
  Many of the drugs that we use during operations and in anesthesia may result in a new dead-point for the temperature center of the brain and this will produce an elevation in the body's temperature after an operation. When the patient is febrile he starts shivering (his body's temperature will not reach a very high value but sometimes it really produces shivering). If there wasn't any other obvious reason for this elevation in the body's temperature, doctors will try to cover the patient and warm him up. If this didn't work they'll give him an opioid (since they produce hypothermia as we mentioned at the beginning of the lecture) and meperidine is the most effective one in this case.

- Reading from the slide: with repetitive large doses, there will be an accumulation of the toxic metabolite normeperidine (normeperidine) that causes CNS hyper-excitability, subtle mood changes, Tremors, Multifocal myoclonusand Seizures.
- It's completely contraindicated in renal failure patients.

Methadone:

- It's a great drug. However, since 2006 it's been linked to death, so we don't really use it anymore in the clinic but it still has an application in countries like US and Canada in what is so called "methadone maintenance clinic ".
- So, what do we mean by methadone maintenance clinic?
  Americans found a solution for heroin addiction; they can't stop it so they maneuver around the story through giving a drug like methadone. Why did they choose methadone? Because it has a lower euphoric activity than heroin that can cover the μ-receptors (occupy them), so when the patient takes heroin it won't find a place to bind and produce euphoria. At the same time, they have to choose a drug with a sustained activity and this is what makes methadone special, it has a long half life. So the patient doesn't need to be dosed more than two times a day.
  These clinics are found in places that have a high percentage of heroin addicts and criminals. They have registered heroin addicts who come to the clinic twice a day to take the drug to produce what is so called "sustained occupation of the receptors". This is going to take time (minimally 6 months) and has to be linked with psychotherapy to convince the patient that he's not a heroin addict.



*note in the figure above that if the patient is taking heroin he's going to suffer from withdrawal symptoms very quickly (within 8-24 hours) that last for 4-8 days. While in case of methadone: within 12- 47 hours and the withdrawal lasts for 10-20 days.

- Methadone has another activity which is blocking NMDA receptors (blocking them produces analgesia or, generally speaking, an inhibitory activity).
- Another mechanism of action methadone has is inhibiting monoamine oxidase reuptake transporter. So there is going to be more serotonin and dopamine within the synapse.
- This mixed mechanism of action is making methadone special in many cases. These mechanisms together give the drug a different way to deal with pain than other opioids.
- When a patient has severe pain and he's not responding to morphine, we don't have any other choice because morphine is the strongest opioid. Even fentanyl won't be effective because it has same efficacy of morphine. So in this case we use methadone because it has a different mechanism of action that may treat the patient not responding to morphine.
  Why not to use it from the beginning?
  They extensively used methadone for 20 years but then they discovered that methadone caused death to some patients as we've mentioned above so they went back to morphine.

Weak Opioids

- Weak opioids are used **in moderate pain that doesn't respond to NSAIDs**.

Codeine(also called :refacod):

- Moderate pain that doesn't respond to NSAIDs: like toothache that didn't respond 200 mg profen / 3 times a day (maximal load of profen that we can use), we give a drug with a higher E_{max} so you either choose codeine or Tramadol. Dentists in many cases prescribe refacod for their patients. (don't prescribe strong opioids because of their addiction)
- This is not the only application for refacod. It can also be used as an antitussive (treat chronic cough that persists more than two weeks). It's the most important and effective antitussive, but we only use it when other drugs aren't effective **(drug of last resort)**
- The other drug that has an antitussive activity besides codeine is dextromethorphan. It's a synthetic opioid **without** any other CNS activity (no analgesia, no euphoria. Only antitussive), if it doesn't work we use codeine.
- So for chronic cough, at the beginning we use dextromethorphan and if it doesn't work we use the drug of last resort which is codeine despite its CNS activity.

Tramadol/tramal:

- This is an emergency drug. As it works fast.
- When a patient comes to the emergency room with moderate pain, tramal is going to be a good choice.
- Tramadol addiction is a big problem here in Jordan. In 2004 it used to be prescribed on a normal white paper so it became like ملبّس الشعب. nomnom. (Other opioids are prescribed on pink paper, which means that every pill is counted on the doctor and the pharmacist). After that, they needed to find a solution for this problem, but they still thought that it doesn't deserve to be prescribed on pink paper. So they decided to keep prescribing it on the white paper but with a stamp. SO be careful, many people will come to the emergency room to stamp a tramal prescription.
- Tramal produces euphoria if it was taken in very high doses.
- Tramal is considered a weaker opioid. It only causes euphoria at very high doses.

- Method of Action (not fully understood): It weakly binds opioid receptors, hence its weak effect... It is a mild anesthetic.
- Advantages :
  1) Does not cause respiratory depression

2) No nausea/ vomiting/ constipation (constipation is a main side effect of all opioids except this).

3) Rapid Action (useful in emergencies)

4) Lasts long (6 hours)

- Effective in treatment of moderate pain (morphine is reserved for severe pain)

Peripherally acting Opioids

- Because of their constipating effect, opioids can be utilized to reduce the frequency of diarrhea. Loperamide is a famous peripherally acting drug used for this purpose, mainly because it has no absorption from the gut, nor does it cross the BBB (no euphoric effect), so it only acts on μ receptors in the gut, and it can also be used to treat **inflammation induced hyperalgasia** (which is increased sensitivity to pain) in the GI tract.
- Hydromorphone is a morphine substituent (similar to oxycodone) that does not cause glucuronidation (doesn't produce morphine-3-glucuronide, hence no brain toxicity in renal-failure patients).

One last point about opioids: If a patient has been suffering from chronic pain and using one of the opioids for more than six months he will eventually develop tolerance and we solve this problem by opioid rotation which means that we switch the patient to a different opioid every three months giving a better response with an unknown mechanism despite the danger of developing cross tolerance (tolerance for more than one drug).

Also morphine can cause hyperalgesia which is increase sensitivity to pain because it reduces the production of endogenous material and receptor.

Anxiolytics/ Hypnotics

- CNS depressants
- Generally do not have a euphoric activity
- Bind to an allosteric site on GABA receptors > cause entrance of Cl> Hyperpolarizing effect > increase affinity to GABA
- Only causes respiratory depression at very high doses (less risk of respiratory depression than opioids)
- Anxiolytic (anxiety/stress relief) and antidepressant at lower doses, hypnotic (sleep inducing) effect at higher doses, anesthetic at very high doses and we won't use these drugs for this purpose in most of the cases.
- 3 Main groups (Benzodiazepines, Barbiturates, Z- Drugs)

Benzodiazepines (e.g.: Valium)

- 3 types : 1) Short acting (Triazolam).
  2) Intermediate acting (Lorazepam/ Temazepam).
  3) Long acting (Diazepam/ Flurazepam).

- Uses : 1) Anxiolytic
  2) Hypnotic/ Sedative
  3) Anti-seizure effect because they are CNS depressants.
  4) Muscle relaxant (higher doses)
  5) Anterograde Amnesia (short term memory loss -> e.g.: used in endoscopy so patients can forget the procedure)

1) Anxiolytic activity of Benzodiazepines :

(Note: All anxiolytics/hypnotics should not be taken for more than 3 weeks as they can cause tolerance, physical dependence, and addiction.

The dr. believes that they shouldn't be used to deal with the stress of everyday life, only in severe cases and for a short time to limit addiction potential)

- Useful in treatment of severe anxiety that accompanies depression/ schizophrenia
- The anxiolytic effect of benzodiazepines has less potential to cause tolerance than the hypnotic effect (hypnosis requires higher doses -> causes tolerance faster)
- Cross resistance: developing tolerance to one type of drug leads to tolerance of other drugs, since they bind to the same receptors.
- Those drugs shouldn't be used for every day stress.
- The dr reads the following from the slides:

The longer acting benzodiazepines, such as Diazepam, are preferred with anxiety that may require treatment for prolonged periods of time

2) **Hypnotic/ Sedative activity of Benzodiazepines:**

- Hypnotics are widely prescribed around the world to treat insomnia (inability to sleep).
- It is important when prescribing hypnotics to balance between the dose needed to produce the sedative effect required for sleep and to limit the residual hangover after waking up (people waking up after using sleeping pills feel sluggish/fatigued/light-headed -> similar to alcoholic hangover)

The three most commonly prescribed for sleep disorder are longacting Flurazepam, intermediate-acting Temazepam, and short-acting Triazolam.

- Short acting benzodiazepines: no hangover / Long acting: bigger hangover
- Hypnotics should be given for a limited amount of time (less than 2-4 weeks) to prevent addiction
- There are different kinds of sleep disorders :
  1) Inability to fall asleep; we use short acting benzodiazepines (Triazolam) because we only need to initiate sleep

2) Inability to go back to sleep after waking up (2-3 hour sleep) (We use Intermediate Benzodiazepines (Lorazepam/ Temazepam) for a stronger hypnotic effect)

- Long acting benzodiazepines are used to treat insomnia that is accompanied with anxiety (Flurazepam is the drug of choice).
- It is important to prescribe the appropriate drug depending on the kind of sleeping disorder, for eg if you had patient that has a hangover effect from the long acting and a short and disturbance in sleep for the short acting you use the intermediate acting.

Summary

- Strong opioids :
  1. Morphine:
  - ✓ pulmonary edema (when furodemide doesn't work)
  - ✓ severe chronic pain (main drug)
  - ✓ contraindicated in renally compromised patients or it'll cause CNS toxicity (other choices: adjustment of the dose , changing the drug >> either oxycodone / not found in Jordan , or hydromorphine)
  2. Fentanyl :
     - ✓ 100 times more potent than morphine.
     - ✓ Emergency drug.
     - ✓ Used in operations (doesn't stay long in the body, starts working fast).
  3. Meperidine /pethedine:
     - ✓ CNS toxicity (if used more than 3 days/ contraindicated in renal compromised).
     - ✓ drug of labor (least one to produce respiratory stress)
     - ✓ Reduce shivering after operations (most effective in producing hypothermia).
  4. methadone:
     - ✓ linked to death
     - ✓ methadone maintenance clinic for heroin addictive: sustained occupation of the receptors (due to less euphoric activity than heroin and long half life)
     - ✓ mixed mechanism of action (blocking NMDA receptors, inhibiting monoamine oxidase reuptake transporter)>severe pain that doesn't respond to morphine)

- Weak Opioids
  1) Codeine/refacod:
  - ✓ Moderate pain that doesn't respond to NSAIDs (toothache that didn't respond to profen).

- ✓ Antitussive (drug of last resort/ most effective) .other choices before it > dextromethorphan: synthetic opioid without any other CNS activity.

2) Tramadol/tramal:

- ✓ emergency drug (works fast)
- ✓ addiction in Jordan is a big problem
- ✓ Euphoria at very high doses.
- ✓ Does not cause respiratory depression, No nausea/ vomiting/ constipation, lasts long (6 hours).

- Opioids to reduce the frequency of diarrhea: Loperamide > has no absorption from the gut, nor cross the BBB (no euphoric effect).
- Anxiolytics/ Hypnotics:
  - ✓ CNS depressants, no euphoric activity, less risk of respiratory depression than opioids (only at high doses), Anxiolytics at lower doses, hypnotic at higher doses, anesthetic at very high doses.

a) Benzodiazepines (Valium):

- ☒ Short acting (Triazolam), Intermediate acting (Lorazepam/ Temazepam), Long acting (Diazepam/ Flurazepam)
- ☒ Anxiolytics (treat severe anxiety accompanies depression and schizophrenia ,less potential to cause tolerance , lower doses) , Hypnotic/ Sedative(taken for limited time or will be addicted , balance between the dose needed to produce the sedative effect required for sleep and to limit the residual hangover after waking up, short acting > less hangover , inability to fall asleep: use short , Inability to go back to sleep after waking up: use intermediate , insomnia : use long),Anti-seizure, muscle relaxant (higher doses), anterograde amnesia.
- ☒ Not to be taken more than 3 weeks > tolerance, physical dependence and addiction , Cross resistance.

This sheet is dedicated to Raya AlMajali, Yara Anasweh, Layan Attili, Tala Khouri, Hind Motaseb, Saja Bataineh, Dana Suleiman, Mohamed Hindi, Rayman, Loauy w shelet il sooriyeh, my frenemy, Hamzah Mahafzah and HasSan (our loyal lajneh member :P)

Saya suka awak semua rakyat Malaysia <3

#لتسهيل_حياة_طالب_الطب