Opioids

General

- Weak opioids
  - Tramadol
  - Codeine
- Strong opioids
  - Oxycodone
  - Morphine
  - Methadone
  - Fenatyl — used in operations
  - Mepiridine — used in labor
- Pregnancy and elderly
  - pregnancy
    - if aetaminophen is insufficient, opioids are considered
    - acceptable during pregannncy provided they are given for a short for a duration
    - chronic opioid use can result in fetal dependence, premature delivery and growth retardation
  - elderly
    - opioid analgesics haev an increased likelyhood of mor eprofound adverse effects as well as prolonged durations of action, therefore its best not to select an opioid
      - if its necessary to select an opioid, reduced doses must be utilized

Withdrawl reactions

Remember the stronger the euphoria the harder it is to be treated

- acute action (pt is taking opioid)
  - · Analgesia
  - · Respiratory Depression
  - · Euphoria
  - · Relaxation and sleep
  - · Tranquilization
  - · Decreased blood pressure
  - · Constipation
  - · Pupillary constriction
  - · Hypothermia
  - · Drying of secretions
  - · Flushed and warm skin
- withdrawl sign (within 24-48 hrs after stopping opioids)
  - · Pain and irritability
  - · Hyperventilation
  - · Dysphoria and depression
  - · Restlessness and insomnia
  - · Fearfulness — increase sympathetic activity so increase in NEP
  - Increased blood pressure
  - · Diarrhea
  - · Pupillary dilation
  - · Hyperthermia
  - · Lacrimation, runny nose
  - · Chilliness and "gooseflesh"
- in withdrawl reactions all opioids' action get reversed
  - analgesia-->pain
  - respiratory depression --> hyperventilation
  - euphoria--> dysphoria and depression
  - tranquilization--> fearfulness
- solution for withdrawl syptoms — tampering — process of lessening or reducing the doses

Not all medications that cause physical dependence, cause psychological dependence, as cortisol that let the adrenal gland depends mainly on exogenous cortisol doesn't exhibit psychological dependence, in addition to antidepressant.

Psychological dependence is the most serious problem here , because it depends on the cause of talking opioids.

- When people takes opioids seeking the feeling of Euphoria , addiction might happen from the first dose, due to psychological dependence.
- But when we give cancer patients opioids, we are seeking pain relieve , addiction doesn't happen , only has physical dependence.

Morphine

- MOA
  - Kidney
    - it has 2 metabolites
      - morphine - 6- glucuronide
        - active ingredient
        - function — binds to opioid receptors and is beleived to contribute to the effects of the parent compound
      - morphine - 3 - glucuronide
        - toxic one
        - function
          - does NOT bind to the receptor
          - believed to contribute in some cases to adverse effects
            - myoclonus
            - confusion
      - these metbaolites are considered a clinical issue only when their concentratiosn in the blood are likely to flactuate differently than the concentration of the parent compound — this can occur during renal insufficiency — So, if your patient has renal insufficiency-> the metabolite excretion is weak so this will lead to build up of morphine metabolite —>don't give him morphine, because it's metabolite causing toxicity in the brain. — in this case we give hydromorphone
- side effects
  - hypotension — it opens the peri-capillary (connection between veins and arteries) so this will leads to pooling down of the blood
  - analgesic side effects (like we mentioned earlier)
  - inhibit the respiratory centre (decrease breathing rate and depth)--> hypoxia — due to the decrease in noradernaline
- contradicted
  - in patients who have prostatic hypertrophy
  - pts who have gallbladder stones
  - pts who have bradycardia — since it causes a vagal stimulation causing hear tbloock
  - labor
    - it causes contraction in the uterus so it will delay labor and distress on the fetus
    - instead we use Mepiridine
- addiction — high — due to a high euphoric effect
- features
  - prototype known fro 250-300 yrs
  - no ceiling effect — whenever you increase the dose, the activity is increasing so you should be careful about tolerance , physical dependence and addiction
  - half life
    - 4-6 hrs
    - takes 30 - 60 minutes to start working
  - first pass effect — duration 1-4 hrs — we have to adjust the dose for the pt 4 times a day
  - bioavailability — 40% when given orally
- routes of administration
  - orally
  - injection
  - pumps
- clinical use
  - severe pain
  - induces sleep in clinical situation when pan is present and sleep is necessary
  - it may be used to supplement the sleep-inducing properties of hypnotic agents
  - used in the trx of acute pulmonary edema
  - IV morphine helps in dyspnea which is caused by pulmonary edema assocaited with left ventricular failrue
  - releives diarrhea — by decreasing the motility and increasing the tone of the intestinal smooth muscles

Hydromorphone

- features
  - not available in Jordan
  - may be preferred over morphine for patients with decreased renal clearance, to preempt the potential for toxicity from morphine metabolite accumulatio — It is not excreted in kidney , instead , it is excreted in bile . So No Fluctuations Happened In Renal Insufficiency Patients.
  - looks like fetanyl, but fetanyl is used more frequently than oxycodone

Fentanyl

- features
  - semi-synthesized drug
  - potency — 100 times more potent than morphine
    - so dealing with morphine is easier than fentanyl
    - so for respiratory depression to occur it needs 1/100 of morphine (very toxic drug)
  - first pass metabolism
    - very high
    - when given orally our body only recieves 1-2% of the dose so it wont be given orally — this is in contrast to morphone bioavailabiltiy which is 40%
  - half life
    - lasts for only 1 hr
      - fast
      - in contrast to morphine which lasts for 4-6 hrs
    - 30 minutes to an hour — in contrast to morphine which takes 30-60 minutes
- route of administration
  - injectable — use for acute pain
  - transdermal patch
    - 12 micrograms in the patch that works for 12 hrs
    - used for chronic pain
  - NOT ORALLY — oral tablets are illegal and usually sold by Mexican cartel causing death
- clinical use
  - IV form is used in anasthesia
    - why we don't leave the patient on the analgesic anaesthesia ? Because it makes the patient unconscious and doesn't feel anything so we try to avoid stage 4 anaesthesia which means coma and death
    - We do balance anaesthesia , giving anaesthesia to make the patient unconscious and help it (to stay away from stage 4) by using muscle relaxants(blocking nicotinic receptor to prevent reflexes) and using fentanyl (to prevent the pain)
  - intraoperative use
    - MOST IMPORTANT USE
    - this is because we can titrate it (it has a short half life)
- metabolism and excretion
  - metabolism — in the liver
  - excretion — in pylori — doesnt reach the kidneys so we can use it with patients who have kidney problems

Heroin

- similar potency to fentanyl
- features
  - MOST EUPHORTIC drug so its the most addicitve
  - MOST EXPENSIVE drug
- clinical use
  - used for trx but the euphora it causes is huge

Oxycodone

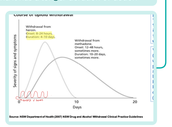
- features
  - no difference — looks like morphine
  - not found in Jordan
  - oral — route of administration

Mepiridine, Pethidine

- this is why it should be given for less than 5 days
  - this accumulation causes
    - CNS hyper-excitability
    - subtle mood changes
    - tremors
    - multifocal myoclonus
    - severe seizures
  - repetitive dosing leads to accumulation of the toxic metabolite normeperidine (fat soluble)
- features
  - e.g 250 mg per day — common with repeated large doses
  - less of a euphoric effect than morphine so less addiction
  - increases the excretin of serotonin in the brain
- contraindication
  - on pts taking antidepressents (SSRIs) or SNRI
    - since antidepressents also increase the levels of serotonin which leads to serotonin syndrome which then leads to death
  - since Naloxone only works on cases related to opioid receptors — we CANT use Naloxone as antidote in this case
- uses
  - since it doesnt cause stress on the baby — obsteric labor
  - shivering — Shivering (hypothermia) is a common situation after labor, both meperidine and epidural anesthesia can be used for pain relief during labor, but they have different effects
- MOA
  - vagal nerve inhibition
  - at the same time activates the MU GABA and Delta Receptors (muscarnic receptors)
- clearance
  - use of meperidine in patients with kidney disease is not recommended — renally clearance

Methadone

- MOA
  - NMDA receptor blocking
    - as methadone blocks the NMDA receptors its MOA is different than morphine we use it when patients develop tolerance (doesnt respond to morphine) this process is called OPIOID ROTATION
      - For more clarification, opioid rotation means we give a drug which differs in structure and MOA such as when patient developed tolerance to morphine we use methadone (for month then we back to morphine)
  - monoaminergic reputake transporters
- clinical uses — treats difficult pain, especially when morphine failed.
- side effects — causes a long QT interval (torsade de pointes) which can cause death before respiratory depression occurs
- features
  - Half of the resultant euphoria from morphine — It causes euphoria but in a lower level .
  - drug of choice for trx of addiction because
    - It has a long half life .
    - So methadone may be accumulated dose , so taking into accounts giving doses that dont reach the point of addiction
    - used because of its long half life and we make the pt satisfied (because they still are at the euphoria leve but in a smaller level)
  - At the beginning we treat the patients from morphine then from methadone (we should pay attention to physical dependence and tolerance) , rather than giving it twice weekly we give it only once weekly, then once every two weeks.
    - We call this steps methadone rehabilitation or rehabilitation of addict which needs 6 months to a year
- difference between heroin and methadone
  - Methdone has a wider and lower peak than heroine this indicates that it needs more time to withdraw (more duration as seen in the diagram), therefore we use it for physical and psychological withdrawl
  - Morphines curve (in hrs not days) (look at the red curve) when we stopped the morphine the patient will go to the withdrawl symptoms, here we treat the patient by methdone because the euphoria here is milder than morphine and heroine and it has a longer duration of action



Codeine

- MOA — pure patial agonist (low EMax and low potency) for Mu receptors for mild – moderate pain (antitussive and dental pain because these pain isnt severe)
- clinical use
  - drug of choice for dental pain to the pt who dont respind to NSAIDs (called revacod) works as morphine but is a parial agonis
  - used as an antitussive
- features — oral codeine has a higher bioavailability than morphine (around 60-70%) but to enter the body , part of them enters as codeine, the rest turns into morphine (not a high amount and we consider it not the basis of MOA) thses conversion occurs due to our problem in jordan which called CYP2D6 which is enzyme in the liver convert the codeine towards morphine in small rate but because of our origin in Jordan we have ultrarapid alleles for CYP2D6 ,around 13% of the community have 3 or more. We call this people ultrarapid metabolisers for CYP2D6 ,more morphine will produce and it may cause toxicity (in youngs not elderly)
  - In contrast, in Sweden 7-8% poor metabolisers, which means the don't have any cope of the CYP2D6 allelel's so they have small amounts of converted morphine (little effect of codeine)
- contraindications — because it may cause respiratory depression — in children

Tramadol

- MOA — inhibition for norepinephrine re uptake and when it increases in the brain it causes feedback inhibition on a2 receptors causes inhibition on of norepinephrine outflow which causes analgesia
- features
  - Analgesic action mechanism
    - Not fully understood
    - Weak affinity for mu-opioid receptor
  - looks like codeine
- routes of administration
  - oral
  - IV
- contraindication — dont use with Mepiridine and SSRIs and MOAI — since it increases NEP so it can lead to serotonin syndrome
- uses
  - combine it with clonidine for pain management
  - for moderate pain treatment — as effective as morphine
  - for severe pain treatment — less effective than morphine
- advanatages
  - Less respiratorpsychomotor recovery depression
  - less nausea
  - less vomittig
  - less constipation
  - Rapid
- disadvantages — can lead to addiction

Loperamide

- features
  - peripheral acting opioid receptor
  - mu receptor agonists
  - doesnt cross teh BBB
  - relieves diarrhea