

# Opioids

## Related use of Morphine

- Dependence - Physical Dependence
  - Physiological state
    - characterized by withdrawal of symptoms upon abrupt discontinuation/ reduction of narcotic therapy
  - Abstinence syndrome
  - Independent of tolerance
  - tapering — solution
- Addiction
  - Physiological and Behavioral syndrome
  - manifested by drug seeking behaviour, loss of control of drug use and continued use despite adverse effect
- Tolerance
  - Physiologic phenomenon resulting in progressive decline in potency of an opioid with continued use.
  - antagonist drugs leads to regulation — always related to agonist
  - example
    - eg ventolin inhaler ( salbutamol)
    - Salbutamol is a beta agonist so if patient used it heavily, tolerance might occur due to receptors' desensitization or down regulation, and this might end up with Hyperalgesia
- Hyperalgesia
  - Hyperalgesia (Need high dose to make effect/happens because even the endogenous Salbutamol (agonist) can't bind to its receptor due to low regulation)
  - increase the dose — solution
- Hyperalgesia (continued)
  - no tolerance
  - no dependence
  - has addiction
  - morphine has all three concepts
- side effects
  - constipation — the only two side effects that dont exhibit tolerance even with long term are
  - pupil constriction ( miosis)

## Contraindications

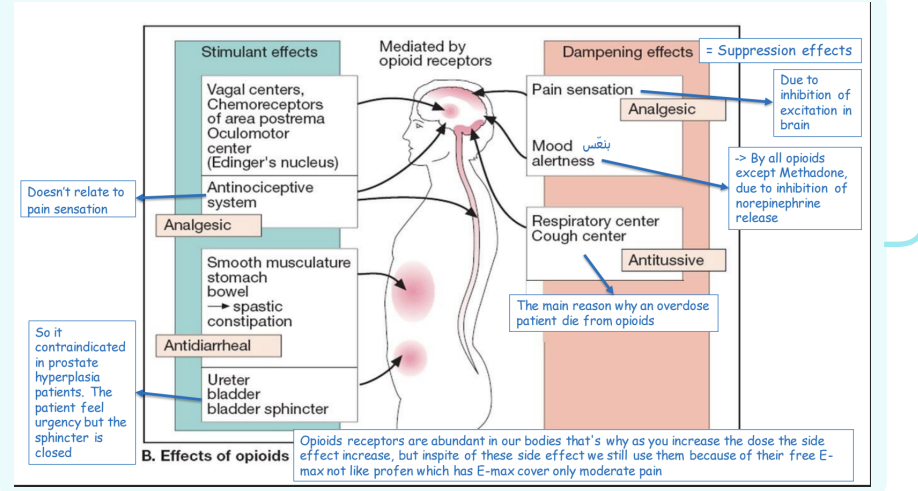
- Prostate hyperplasia
- due to histamine release
- Asthmatic patients
- Bradycardia patient
- due to histamine
- Hypotension patient

## Side effects

- Euphoria
  - high level of pleasure and it relates to PSYCHOLOGICAL dependence
  - related to reward system due to dopamine increase Dopamine pathway related to GABA neurons that are pressing on dopamine receptors/pathway so opioids remove this pressure and dopamine release
- CNS depression
  - so it has sedative effects — decreases motor movements, reducing cognition
- Nausea and vomiting
  - That's why in anesthesia we don't give morphine due to its half life (4 hours) and the patient after wake up from operation feels nauseous and if we give him/her morphine as analgesia will become more
- Respiratory depression
- Urinary retention
- Diaphoresis and flushing
  - due to release of histamines
- VERY IMPORTANT — PINPOINTED PUPILL — Pupil constriction (miosis)
- Constipation
  - activates the vagal nerve
  - give them laxatives
- Itching
  - due to release of histamine
- Bradycardia
  - due to the stimulation of vagal nerve

## Effects of Opioids

- Dampening effects = suppression effects
  - analgesia — Pain sensation
    - due to inhibition of excitation in the brain
  - Mood alertness
    - caused by all opioids except Methadone
    - due to inhibition of NE release
  - antitussive
  - Respiratory centre + Cough centre
    - this is the MAIN reason why an overdose patient may die from opioids
    - has a dapening effect here so overdose leads to inhibition of it causing death
    - for coughing suppression we use Codeine since its a partial agonist, so we avoid addiction
    - CNS in elderly people is weaker than young adults, so normal dose can lead to suppress the respiratory centre.
- Stimulant effects
  - Vagal centres, Chemoreceptors of area postrema, Occulomotor center (Edingers nucleus)
  - Analgesic
  - Antinociceptive system
    - Doesnt relate to pain sensation
  - Antidiarrheal — Smooth musculature stomach bowel -->spastic constipation
  - so its CONTRAINDICATED IN PROSTATE HYPERPLASIA — Ureter, Bladder, Bladder sphincter



## Features

- have a successful effect in relieving pain
- have a sedative not hypnotic effect which is why we use in operations and surgeries
  - sedative — calms the person
  - hypnotic — promotes and maintains sleep
- have a bad side effect in addiction since 1% of the whole population gets addicted to them
- no ceiling effect
  - opioid receptors are abundant in our bodies that why as you increase the dose the side effect increases
  - in spite of these side effects, we still use them because of their free E mac not like profen which has an Emac cover of moderate pain only
- normally giving a drug has types of effects
  - therapeutic — in this case its analgesia
  - side effects
    - constipation — in GI theres a medication cated Libromide which is used as an antidiarrheal agent (its an opioid but it doesnt cross BBB so it wont produce CNS effects)
    - urinary retention
- theyre agonists by erasing the sensation of pain through
  - increasing threshold of firing
  - decreasing neurotransmitter release
- Agonists vs Antagonists examples
  - Agonists
    - Oxycodone — top seller
    - Oxymorphone
    - Hydrocodone
    - Hydromorphone — for renal failure -but not included
    - Fentanyl
    - Morphine
    - Methodone
    - Heroin — has the strongest Side effects
  - Antagonist — Naloxone

## Indications

- Analgesia — to alleviate moderate to severe pain — main use
  - Balanced Anaesthesia
  - Cough centre suppression — antitussive
  - Diarrhea Treatments
- ABCD

## MOA

- all drugs in this category acts by binding to specific opioid receptors in the CNS to produce effects that mimic the action of naturally occurring substances called endogenous opioid peptides or endorphins
    - these endorphins are responsible for the analgesia balance, through binding to their specific receptors.
    - They produce analgesia in an unknown way
    - Mu receptors are the receptors that morphine binds to for exerting their effect but they arent only found in the CNS it can also be found in other systems
  - so they exert their major effect by interacting with opioid receptors in the CNS and in other palces like the GI tract and urinary bladder
    - effect in different systems
      - CNS — analgesia
      - GI — constipation
      - Urinary system — urinary retention — decrease uterus muscle contraction and increase sphincter tone
  - what they do
    - they bind to Mu receptors — technically speaking they dont actually bind to Mu receptors but we assume that they do
    - they cause the K+ channels to open so causing hyperpolarization
    - this hyperpolarization will cause an increase in teh threshold for firing making it harder for an action potential to occur
    - so there is gonna be a decrease in Ca2+ influx
    - so decrease in neurotransmitters released — like substance P and glutamate so this results in not feeling pain
- ON CHRONIC USE ALL OPIOIDS CAUSES ANALGESIA, CONSTIPATION AND URINARY RETENTION

## Types of pain

- Moderate pain
    - Inflammatory mediated pain by PG
    - these drugs reduce — pain, inflammation, symptoms
    - we use NSAIDs for relieving it — Diclofenac is the strongest NSAID
    - they have a ceiling effect
      - refers to the phenomenon in which a drug reaches a maximum effect, so increasing the dosage doesnt increase its effectiveness
      - opioids especially morphine are considered magical drugs since they have NO ceiling effect
  - Acute moderate to severe pain
    - such as post-operative pain
    - its acute — only for a short period of time
  - Chronic severe pain
    - such as cancer pain — 20 million cancer patient per year
    - so in severe pain we need to reach the pain centre or pain reception in the CNS
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- The WHO analgesic ladder diagram shows three steps: 1. Non-opioid analgesics (e.g., paracetamol, NSAIDs), 2. Weak opioids (e.g., codeine, tramadol), and 3. Strong opioids (e.g., morphine, fentanyl). It also includes a box for 'Management of acute moderate to severe pain' which recommends a combination of a non-opioid analgesic and a weak opioid.

## Pain

- definition — pain is a symptoms of a pathological condition that needs to be taken care of
  - no treatment there is still gonna be pain
  - induced by the release of histamines, serotonin and prostaglandins and bradykinin
- historical information
  - 1804 — narcotics (particularly morphine) were extracted from a plant "opium poppy" as the single effective substance
  - 1832 — aspirin was synthesized since that time pharmacology has appeared
  - before 1832 — known as plant therapy
    - in plant therapy --> plant extraction is given
    - in pharmacology --> drug/medication is given
- is what brings patients to doctors
- fear is what can keep the patient from going to the doctor at appropriate times
- treatments are often done on the inflamed, hypersensitive tissue of a patient