Drugs Used in Chronic Pain

Opioids

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The first two pages are EXTRA INFO but found in slides.

*** PAIN:** Unpleasant sensory & emotional experience associated with actual or potential tissue damage which if uncontrolled decreases the quality of life.

-The intensity of pain may be the same, but some people's perception may be different.

e.g. you and your friend get punched in by the same guy , you might feel pain and he may feel slight pain.

- Also, the nature of pain may differ, pain in the heart is somewhat described as stabbing pain and visceral pain is described as aching.

*** Chronic pain** is divided into :

1- Nocioceptive: activation of pain receptors and is superficial (skin) or deep (muscle and viscera)

e.g. Post Operative, Crush Injuries, Ischemic, Inflammation, Distention

2- Neuropathic: problems or malfunction of the nervous system (PNS or CNS)

e.g. low back pain , cancer pain , diabetic neuropathy , post herpetic neuralgia , post amputation.

- Now let us talk about the pain pathway briefly, so we can know where drugs used in chronic pain work:

*** T**here are main delay centers for pain:

a- Peripheral : nocioceptors

transmitters are : prostaglandin , bradykinin ,5HT , Glutamate, Histamine, ionas, etc…

b- Spinal: dorsal root ganglia or dorsal horn

transmitters are: enkephalin , GABA , Adenosine, NE.

c- Supra spinal : periaqueductal grey (PAG) , thalamus , somatosensory cortex

transmitters are : 5HT , dopamine , GABA

- It is important to know the type of transmitters, so we can find the optimum way of dealing with the pain.

- Peripheral pain we can use: aspirin, NSAID , local anesthetics , capsaicin , anticonvulsants .

- Spinal: for Dorsal root ganglia we can use: local anesthetics , a_2 AD agonists , and NMDA Receptor antagonist

NMDA : refers to glutamate and aspartate , so when we use receptor antagonist we block the action of glutamate and aspartate.

- Descending pain pathway (physiological modulation of pain) we can use: *opioids* , anti depressants and anticonvulsants for **enhancing the effect of pain inhibition** (meaning it helps reduce the pain)

- Supraspinal : we can use *Opioids*, a_2 AD agonists, anti depressants, Anesthetics

- NB. opioids are used in the treatment of chronic pain regardless of the site of pain transmission.

- Now for preferences of which drug to use in case of chronic pain we should know exactly where the pain is originating from:

*** Use of other drugs than analgesics (adjunctive):**

Main drugs for treatment of pain: NSAID and OPIOIDS (analgesics)

1. Anticonvulsants: decrease nerve firing by blocking sodium and calcium channels → thus augmenting the effect of GABA.

   e.g. used in treatment of trigeminal neuralgia(Carbamazepine) , post herpes infection pain (gababentin)

2. Antidepressant drugs: effective if of mixed-receptor type and acting on reducing the affective component of pain and perception of pain.

   e.g. Mirtazapine : headache and migrane

3. Steroids : decrease inflammation and swelling.
4. NMDA receptor antagonist: potentiate the effect of opioids and decrease neuro excitability via blocking glutamate receptors.
5. Capsaicin : block release of substance P (local)
6. Local anaesthetics : block conduction via blocking of sodium channels (patches , spray)

- NSAID:

  - moderate to mild pain
  - Most effective + least side effects
  - Added to opioids to reduce the dose of opioids

OPIOIDS

 Derived from the juice of opium poppy (***Papaver somniferum)***
 Opioids are natural or synthetic compounds that produce the same effect of morphine in the body, so we can say the mimic the action of endogenous opioids.

 You should know that all drugs in this category act by binding to specific *opioid receptors*

What are the ***opioid receptors***?

Opioid receptors are very specific receptors found in certain cells of the CNS, nerve terminals of the periphery and cells of the GIT.

And they are of four types of them:

1. **μ** (mu) **receptors :** when stimulated causes**:**
   a. **Supraspinal** analgesia
   b. Respiratory depression
   c. Euphoria
   d. Physical dependence [it is a state where stopping the drug can cause physical effects in the patient – type of addiction-]

2. **δ** (delta) **receptors :** when stimulated causes**:**
   a. **Spinal** analgesia (so found in spinal cord)
   b. Respiratory depression
   c. Decreased GIT motility
      * enkaphelin works better on these receptors

3. **K** (kappa) **receptors :** when stimulated cause:
   a. **Spinal** analgesia
   b. Sedation >> due to release of histamine
   c. Pupil constriction
   d. Dysphoria

state of feeling unwell or unhappy (opposite of euphoria)

4. **σ** (sigma) **receptors:** when stimulated cause:
   a. Dysphoria
   b. Hallucination
      * *It is not a true opioid receptor, as it binds psychotomimetic drugs. Exceptionally of opioids only benzomorphans binds to it.*

Opioids cellular mechanism of action

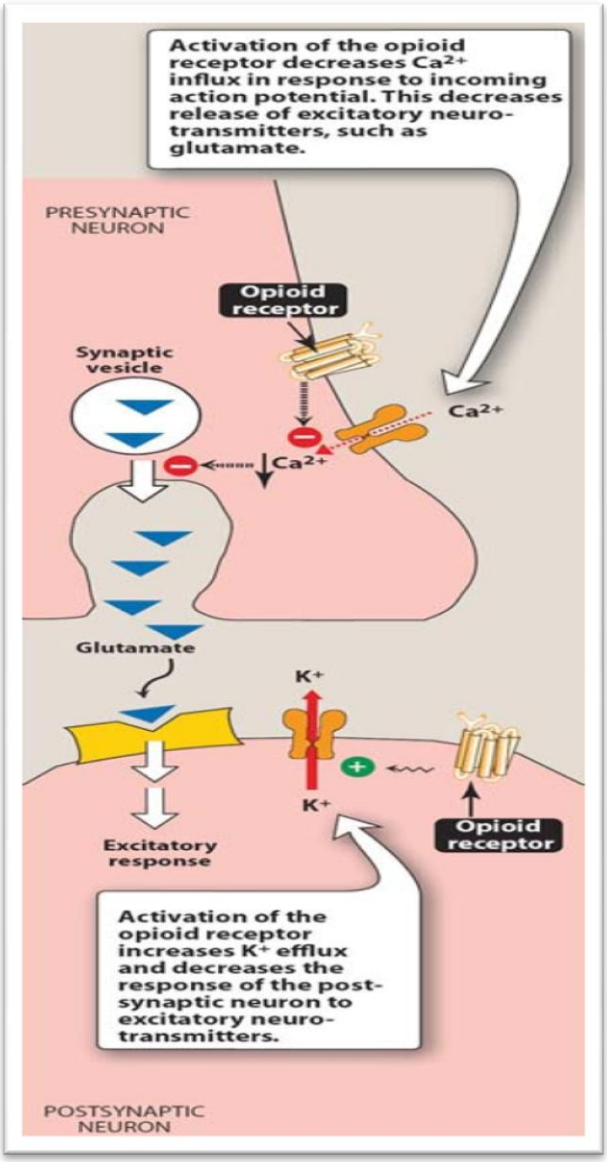
(in Dorsal horn , Periaqueductal gray 'PAG' , periphery) [check figure]

All these receptors are G-protein coupled receptors and how the work is this**:**

- The pre synaptic form of action.

They inhibit adenylyl cylase enzyme, which in turn inhibits the entrance of Ca++ >>> ↓ response to incoming action potential >> ↓ neurotransmitter released

- **The post synaptic form of action** is by increasing the K+ ion efflux out of the cell by opening more gated channels, so decreasing the excitability of the cell



So in PAG the overall picture is :

↓ firing of nociceptive pathways (neurons) converging at Periaqueductal GM ➔to allow for inhibitory firing along the descending pathway returning to dorsal horn➔↓ pain

And in dorsal horn:

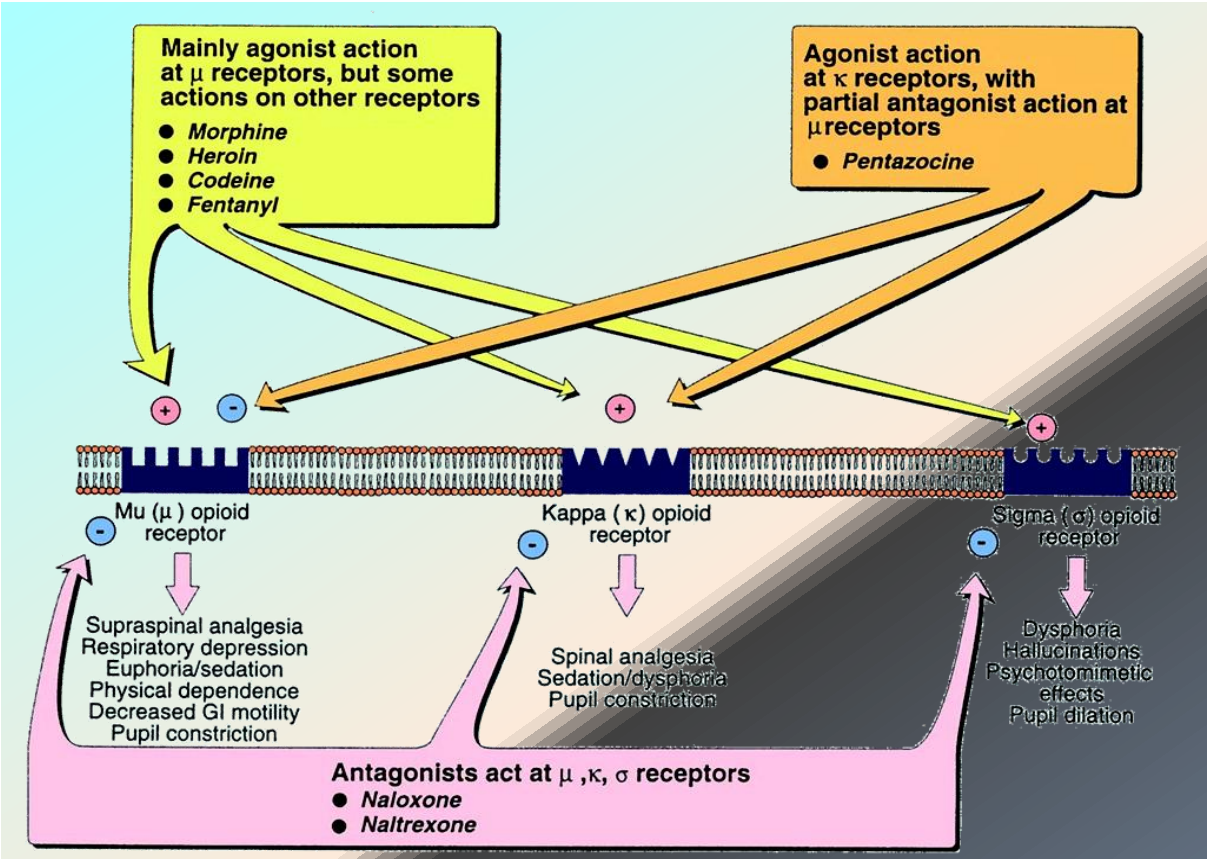
Also inhibit pain transmission by acting directly on the dorsal horn, and by ↓ excitation of peripheral nociceptive afferent neurones.

Classification of opioids:

- **According to source :**
  - ✓ **Natural** : **Morphine**
  - ✓ **Semi synthetic** : **Codeine**
  - ✓ **Synthetic:** **Mepiridine**, **Methadone**, Fentanyl, Tramadol.

- **According to action on receptor:**
  - ✓ **Agonists**:
    - **Morphine**
    - **Codeine**
    - **Methadone**
    - **Heroin**
    - **Tramadol**
  - ✓ **Pure antagonist**:
    - **Nalaxone**
    - **Naltraxone**
  - ✓ **Mixed agonist/antagonist**:
    - Pentazosine

- **According to their specificity of actions on the receptor** [see following figure]:
  - ✓ **Agonist** on μ
  - ✓ **Antagonist** on all receptors
  - ✓ **Agonist** on K and **antagonist** on μ



Examples of opioids:

1st: Morphine:

- Θ is the prototype of agonist opioids
- Θ **HIGH** affinity for μ receptors**.**
- Θ Reminder .. *again!* : Opioids exert their major effects by interacting with opioid receptors in the CNS and in other anatomic structures, such as the gastrointestinal tract and the urinary bladder. Opioids cause hyper polarization of nerve cells, inhibition of nerve firing, and pre synaptic inhibition of transmitter release.

- Θ **Pharmacokinetics:**
  - T ½ is 2-3h.[relatively short]
  - Converts to active morphine 6-glucuronide & an inactive morphine 3-glucuronide metabolite.
  - Administered medically IM and IV.
  - Not given oral, why? Slow absorption! Codeine on the other hand is absorbed well orally.
  - Slow release preparation is used in chronic pain.
  - Crosses **bbb** < *duh?* And placenta
  - Excreted in urine

- Θ **Pharmacological actions of morphine**: 9 actions :]

1) Analgesia in acute and chronic pain, patient stays coconscious

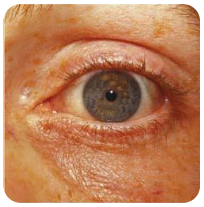
2) Euphoria: It's a powerful sense of contentment & well being

3) Respiratory depression →↑pCO2
   ↳ large dose causes failure and death

4) Depression of cough reflexes (can be used for dry cough)

5) Pin point pupil: results from stimulation of **μ** and **κ** receptors.
Morphine excites the Edinger-Westphal nucleus of the oculomotor nerve, which causes enhanced parasympathetic stimulation to the eye causing miosis

Clinical note:



- Pin point pupil is characteristic of *morphine* use,
- This is important in diagnosing morphine abusers,
  why? because constriction of pupil due to morphine doesn't undergo tolerance .. so in abusers we can find this sign.
- Another effect which doesn't undergo tolerance is convulsions & constipation.

7) Effects on GIT: **a)** ↑ in smooth muscle tone & ↓ motility → severe constipation

b) ↑ pressure in the biliary tract → contraction of gall bladder & constriction of biliary sphincter => morphine is **contraindicated** in patients with biliary colics

8) Release of histamine from mast cells: (not given to patients with asthma)

9) Endocrinal effects: ↓ **LH, FSH, ACTH, testosterone**
↑ **Prolactin, GH, ADH**
↳ **urine retention**

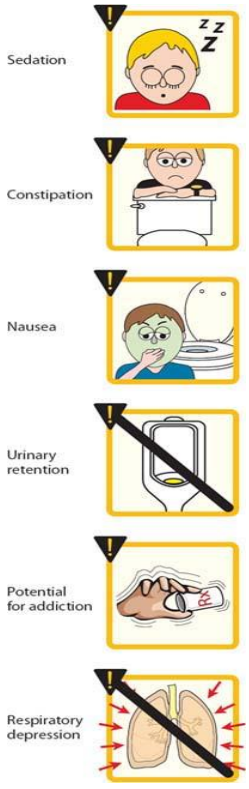
Note: understand the pharmacological actions very well it will help you understand the USE and ADR's.

Θ Clinical indication [therapeutic use]:

1. Control of pain [cancer , burns , trauma , severe visceral pain **except** renal or billiary colics]
2. Myocardial ischemia [analgesic use]
3. Used as a pre-anaesthetic medication
4. Heart Failure to relief stress
5. Diarrhoea [morphine causes constipation]
6. Cough [morphine depresses cough reflex]
7. Acute pulmonary edema [reliefs edema through vasodilatation]

Θ ADR's:

1. Sedation [due to histamine release]
2. Respiratory depression.
3. Constipation.
4. Nausea and vomiting.
5. Itching [due to histamine release].
6. Tolerance , except to: miosis , constipation and convulsions
7. Dependence
8. Euphoria



Θ Contradictions:

1. Head injury.
2. Pregnancy.
3. Bronchial asthma or impaired pulmonary function.
4. Liver and kidney diseases: renal and billiary colics.
5. Endocrine disease: (myxedema & adrenal insufficiency).

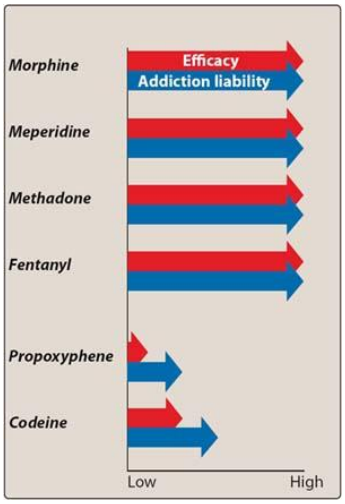
6. Elderly are more sensitive (because of ↓ metabolism, lean body mass & renal function)
7. Not given with MAO inhibitors.
8. Not given to infants, neonates or women during child birth

Risk of resp. depression

Θ Tolerance and physical dependence :

- It is a characteristic about morphine and develops rapidly.
- Withdrawal symptoms appear on stoppage.
- Dependence comprises both:
  - Physical dependence: lasting for a few days in form of body ache, insomnia, diarrhoea, goose flesh, and lacrimation.
  - Psychological dependence: lasting for months / years → craving

*Now we will list some differences between morphine and other opioid which are of **agonist** class:*



Heroin:

- μ agonist
- Crosses BBB
- Converted to morphine
- No medical use
- Strong addicting drug

Codeine:

- μ agonist
- Given orally [morphine not given orally]
- Less efficacy than morphine [less potent]
- Less addicting than morphine
- 10% converted to morphine
- Used in mild & moderate pain, cough, & diarrhoea.

2nd: Merepidine:

- Synthetic
- Strong agonist opioid structurally unrelated to morphine.
- More effective on K receptors than morphine.
- Used for acute pain.

Pharmacokinetics:

- Well absorbed orally **[high oral bioavailability]**
- Given also by IMI
- Short half life
- Gives an active metabolite which has CNS stimulant effect
- Excreted in urine

Pharmacological actions:

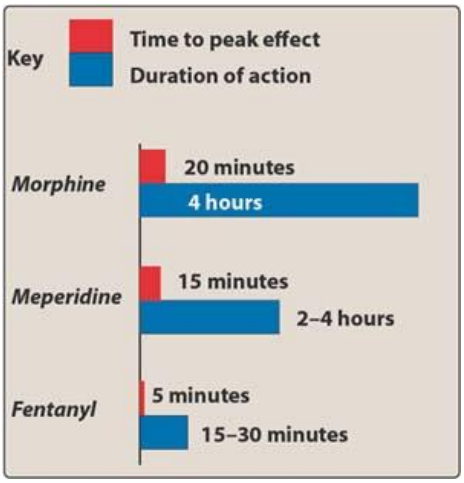
1. Less analgesic , less constipating , less respiratory depressant morphine.
2. Has Atropine-like action
3. Smooth muscle relaxant effect
4. No cough suppressant effect

Clinical indication [therapeutic use]:

1. Same as morphine , but not for cough or diarrhoea ...*why? Look up!*
2. Severe visceral pain

   Including renal and billiary colics
   [cause it relaxes smooth muscle cells]

3. Obstetric analgesia [less resp. depression]
4. Pre-anaesthetic medication [better than morphine due to less addictive effect and faster in peak - see figure]



ADR's:

1. Tremors
2. Convulsions
3. Hyperthermia
4. Tolerance and addiction < less than morphine
5. Hypotension
6. Blurred vision
7. Urine retention
8. Dry mouth

Anticholinergic side effects due to the Atropine-like effect of the drug

3rd: Tramadol :

- Synthetic
- μ agonist
- Its analgesia is also due to inhibition of nor epinephrine and serotonin reuptake.
- Less potent analgesic than morphine

- **Pharmacokinetics:**
  - Given orally or by different other routes and undergoes extensive metabolism.

- **Clinical indication [therapeutic use]:**
  1. Mild to moderate acute & chronic visceral pain.
  2. During labour (child birth) .

- **ADR's :**
  1. Seizures → **contraindicated** to patients who have a history of epilepsy
  2. Nausea
  3. Dry mouth
  4. Dizziness
  5. Sedation
  6. Less adverse effects on respiratory & C.V.S.

3rd: Methadone :

- Synthetic
- μ weaker agonist
- **Used to** control withdrawal symptoms from heroin and morphine abusers.

*How? By this **mechanism:***

When the drug binds strongly to the receptor that decreases the desire for other opioid intake.

Producing less effect (cause it's a weak agonist) → stopping withdrawal manifestations

With time addicts improve by ↓ craving

- Half life is **55** hours... so stays in the body for a long time, reducing the persons craving for other opioids.
- Induces less euphoria.
- In non addicts, it causes tolerance & dependence but not as severe as that of morphine.

*The last 2 drugs are **PURE ANTAGONISTS**.*

Naloxone and **Naltrexone**.

They are the same but has one difference, that is **Naltrexone** has a longer half life = 10 hours

4th: Naloxone:

- **Used to** reverse completely the coma and respiratory depression of opioid overdose & to reverse the effect of analgesia on the respiration of the new born baby.
- It has little effect on pain threshold (reverses incompletely) but can cause hyperalgesia under conditions of stress or inflammation, when endogenous opioids are produced.
- Rapid onset.
- Precipitates (induces) withdrawal syndrome in addicts.