Drugs used in chronic pain

opioids

Introduction

Pain: unpleasant sensory and emotional experience with actual or potential tissue damage. Can be acute or chronic.

Pain transmission and processing:

Noxious stimuli

↓

Activation of nociceptors

↓

Transmission of information through dorsal horn of s.cord
(release of stimulatory transmitter peptides like substance P, gultamate, NO)

↓

Onward transmission to higher brain centers

↓

Processing in the higher brain centers

↓

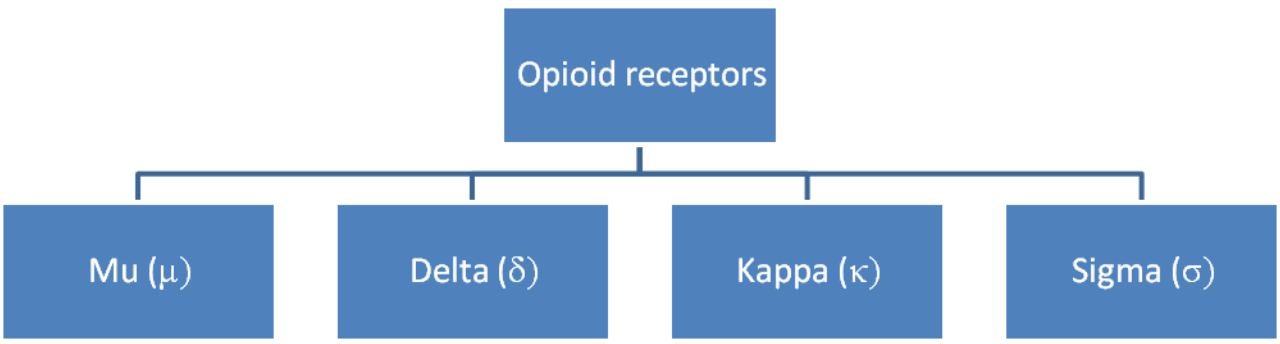
Release of inhibitory trasnsmitters
(endogenous peptides like enkephalins ,endorphins ,dynorphins)

Endogenous opioid transmitters: they constitute pain inhibiting system in the brain and spinal cord.

Analgesia: it is a state in which a painful stimuli are moderated (modulated) , although perceived but felt no more painful.

Opioids

- Derived opium which is obtained from the poppy, *Papaver somniferum* and *P album.*
- Opioids are natural or synthetic compounds that produce the same effect of morphine in the body, so we can say they mimic the action of endogenous opioids.
- They act on opioid receptors.



Mu: when stimulated cause:
1. Supraspinal analgesia.
2. Respiratory depression
3. Euphoria
4. Physical dependence

Delta: when stimulated cause:
1. Spinal analgesia
2. Respiratory depression
3. Decreased GI motility

Kappa: when stimulated cause:
1. Spinal analgesia
2. Sedation
3. Pupil constriction
4. Dysphoria: unpleasant or uncomfortable mood

Sigma: when stimulated cause:
1. Hallucination
2. Dysphoria

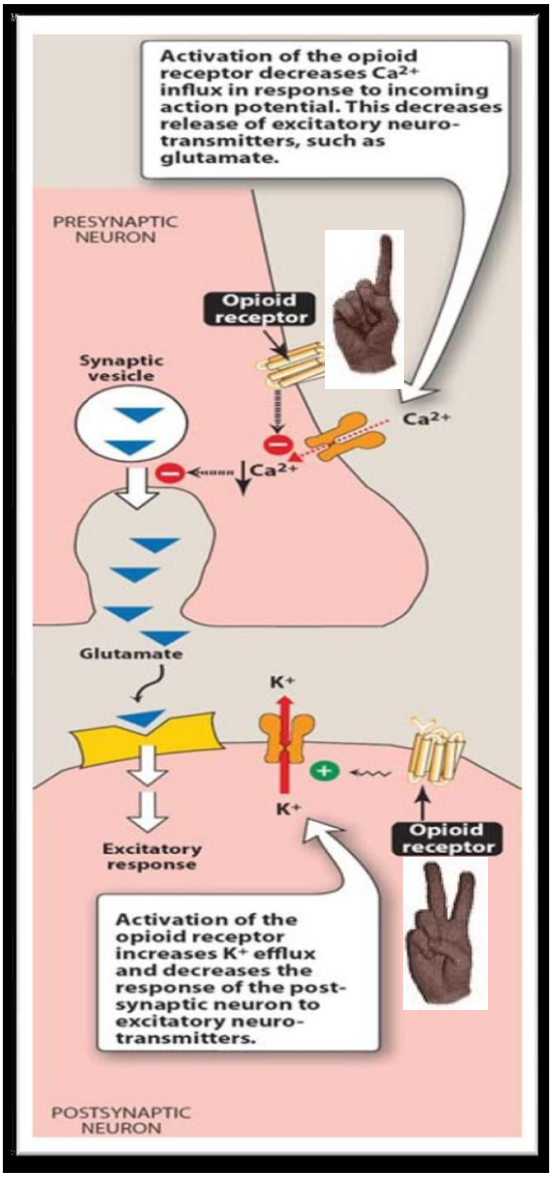
*binds to **psychotomimetic drugs**. Only benzomorphans of opioids binds to it.

- Most of clinically used opioids are relatively selective to **Mu receptors.**
- **Endogenous opioids** are more selective to δ and κ
- All of these receptros are G– protein coupled.

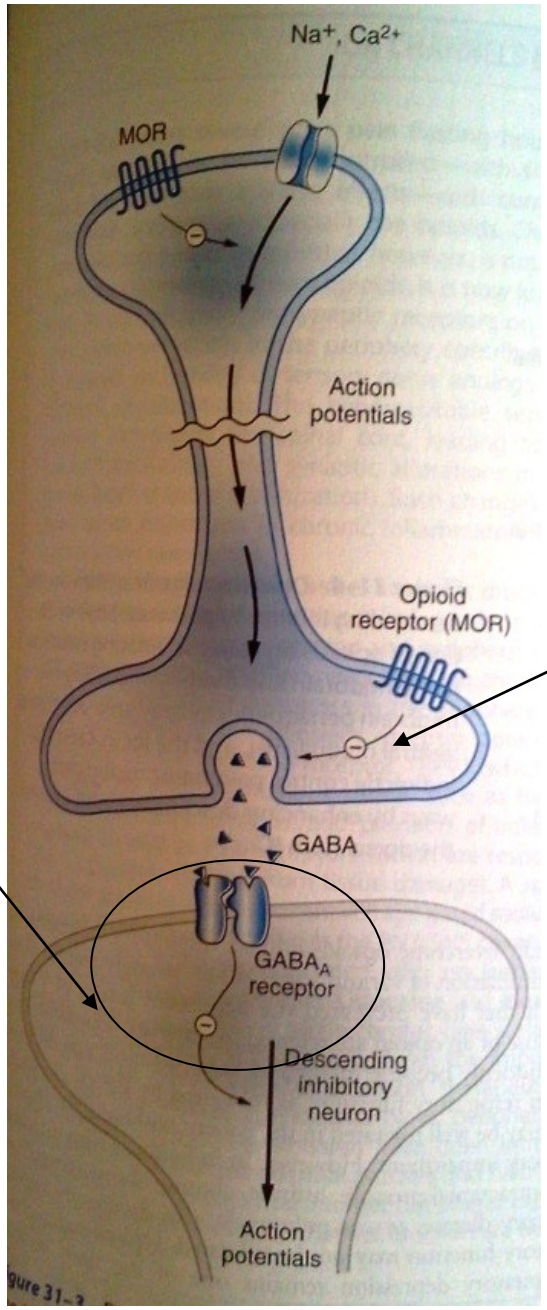
Mechanism of action

The opioids have two well-established actions on neurons:
1. They close voltage-gated Ca^{+2} channels on presynaptic nerve terminal and thereby reduce transmitter release (e.g. glutamate, ACH, norepinepherine, serotonic, and substance P)
2. They hyperpolarize and thus inhibit postsynaptic neurons by opening K^+ channels.

- All three major receptors are present in the dorsal horn of the spinal cord. Both on spinal cord pain transmission neurons (post synaptic) and on the primary afferenets that relay the pain message to them (presynaptic).



Other mechanism of action of descending (inhibitory) pathway:

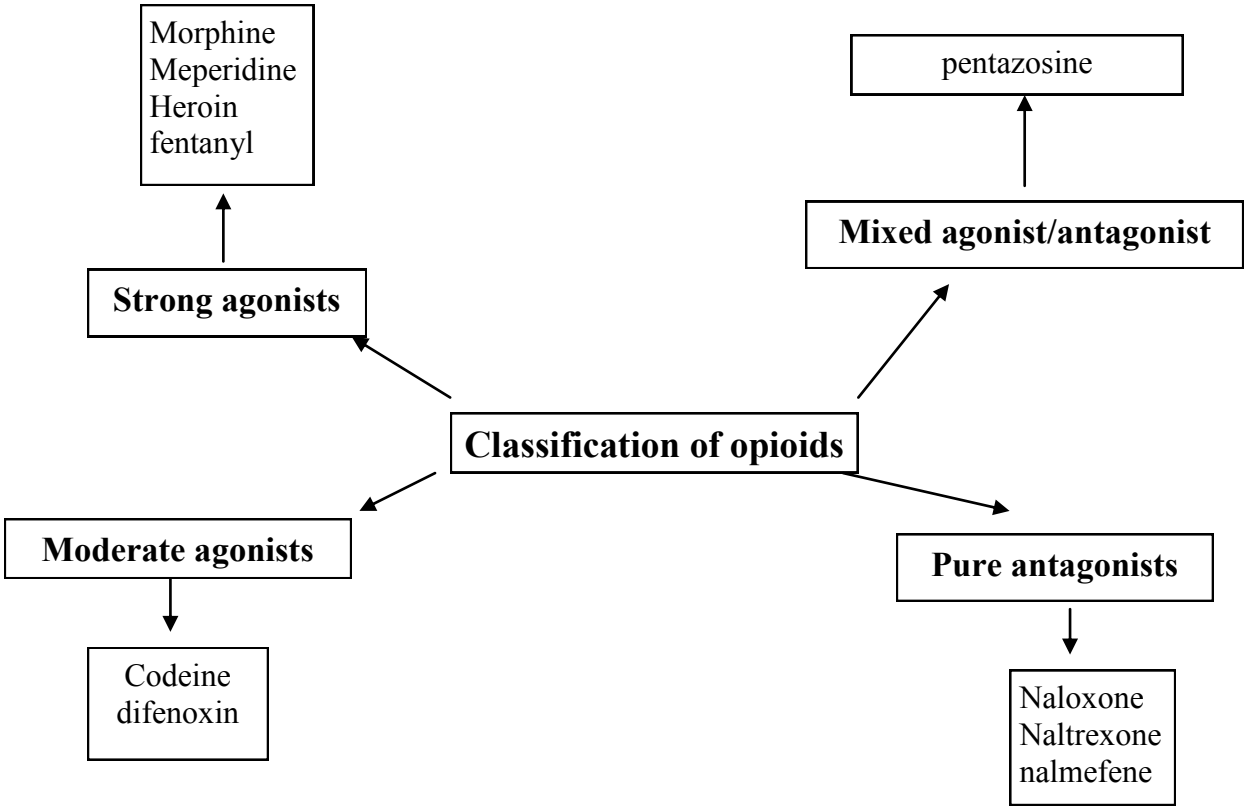


1- This inhibitory neuron (inhibits nociception processing) is inhibited by interneuron

2- Opioids inhibit release of GABA which inhibits the inhibitory neuron

In summary: inhibit the inhibition —> activation

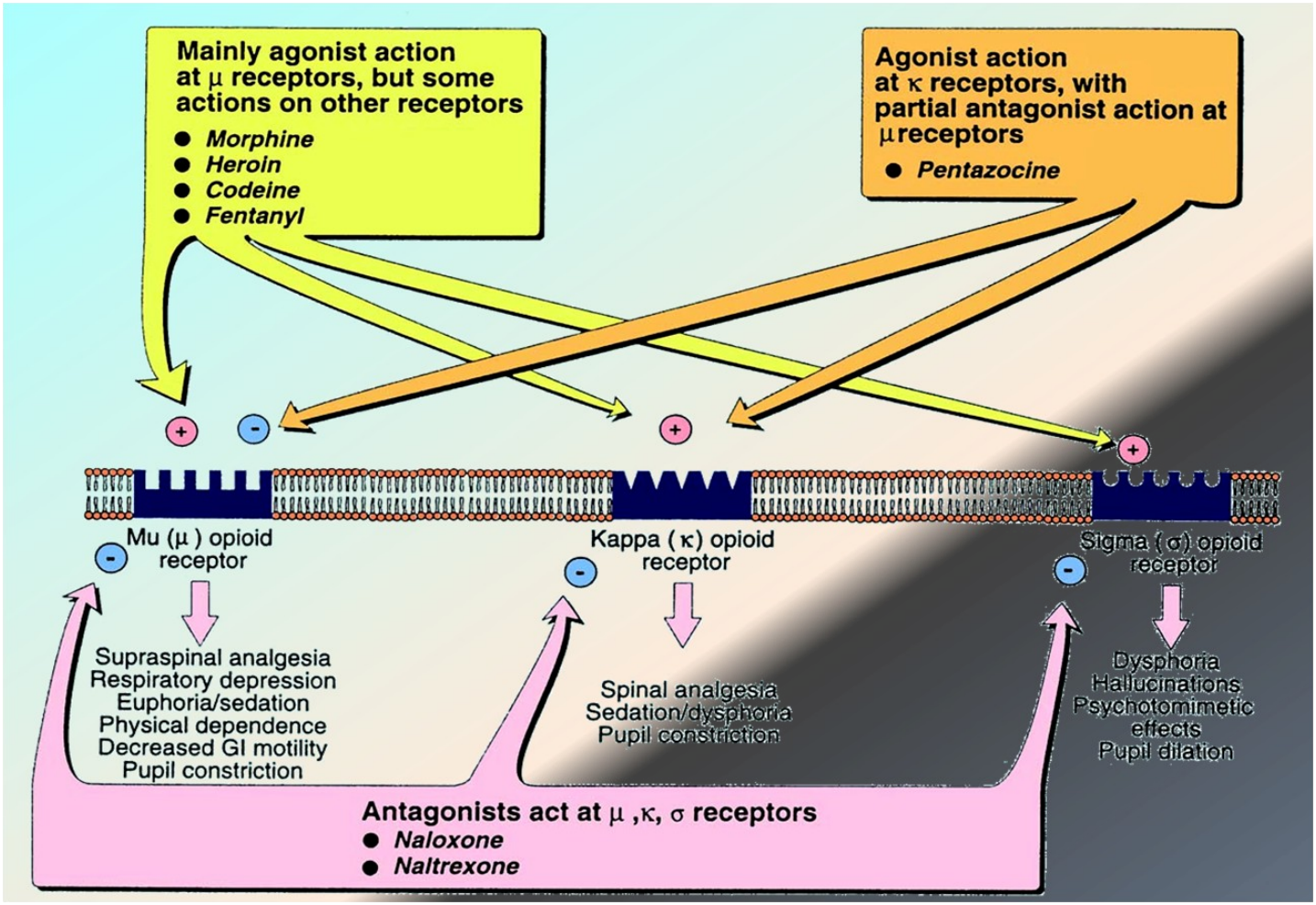
- Exogenous opioid may evoke the release of endogenous opioids that additionally act at κ and δ receptors. Thus, even receptor selective opioid may have an indirect action on other receptors.



Classification according to source:

1. Natural: morphine
2. Semi synthetic: codeine
3. Synthetic: mepridine, methadone, fentanyl, tramadol.

According to their receptor selectivity:



Morphine

- It's the prototype of agonist opioids.

Pharmacokinetics:
Absorption: administered medically as IM or IV but not orally because it has a slow and erratic absorption. Slow released preparation are used in chronic pain.

Distribution: it has duration of action for 4-6 hours but in case of epidural administration, the duration increased due to decreased volume of distribution. All opioids bind to plasma protein with varying affinity. They localize in highly perfused tissues (brain, lungs, liver, kidneys, and spleen). Least opioid that crosses the BBB

Metabolism: Converted to active morphine 6-glucuronide & much less active morphine 3-glucuronide metabolite.

Exretion: conjugates of morphine are excreted in urine mainly and a little amount in bile.

Pharmacological action of morphine:

1) Analgesia in acute and chronic pain, by raising pain threshold at spinal cord level and by altering the brain perception for pain. patient stays conscious
2) Euphoria: It's a powerful sense of contentment & well being by stimulation of ventral tegmentum
3) Respiratory depression : Respiratory depression by reducing sensitivity of respiratory center neurons to CO2. This effect is dose dependant and large doses may lead to respiratory cessation and death.(most common cause of death in acute Opioid over dose)
4) Depression of cough reflexes (antitussive effect). However, suppression may allow accumulation of secretions and thus lead to airway obstruction and atelectasis (codeine is superior in cough depression)
5) Pin point pupil (miosis): results from stimulation of **μ and κ receptors.**
6) sedation: there is no amnesia. In a standard analgesic doses, disruption of normal REM and non REM sleep occurs.
7) truncal rigidity: an intensification of tone in the large trunk muscles has been noted. It reduces thoracic compliance and interferes with ventilation.

8) Effects on GIT: a) ↑in smooth muscle tone & ↓ motility —>constipation
b) ↑ pressure in the biliary tract—> contraction of gall bladder & constriction of biliary sphincter
C) hydrochloric acid is decreased

8) Release of histamine from mast cells —> urticaria (when administered parenterally) , sweating ,vasodilatation, it can cause bronchoconstriction (not given to patients with asthma)

9) Endocrinal effects: ↓ LH, FSH, ACTH, testosterone
↑ Prolactin, GH, (by diminishing dopaminergic inhibition.) ↑ ADH (↑ in ADH leads to urinary retention)

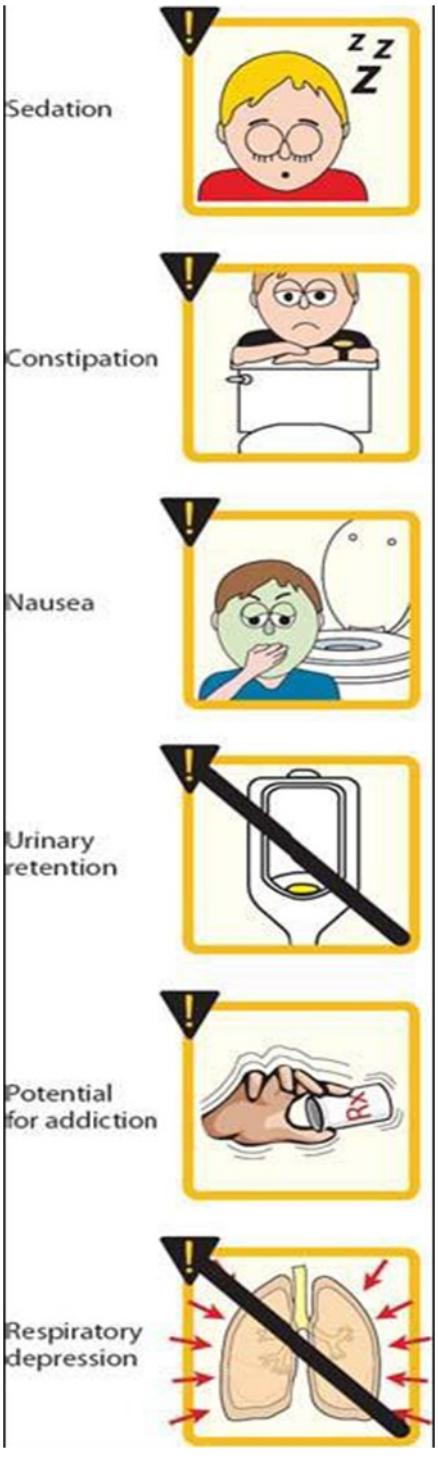
10) Emesis: vomiting due to stimulation of CTZ in area postrema, but sensations produced are not unpleasant.

11) temperature: μ agonists produce hyperthermia. Kappa produce hypothermia.

12) bradycardia

13) renal: renal function is depressed by to actions: decreased renal plasma flow and antidiuretic effects of opioids.

14) uterus: opioids prolong labor in an unknown mechanism.



Uses:

1. Control of pain (severe constant pain is relieved) [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] (codeine and dextrmoethorphan are superioir)
7. Acute pulmonary edema [IV administration, reliefs edema through possibly by vasodilation]
8. Reduce shivering (mepridine)

Adverse effects:

Sedation, respiratory depression, constipation, nausea & vomiting, tolerance & dependence, dysphoria & euphoria, increased intracranial pressure, and postural hypotension.

Contraindications:
Head injury, pregnancy, impaired pulmonary function, impaired hepatic or renal function, endocrine diseases (myxedema & adrenal insufficiency), elderly are more sensitive.

Drug interactions:
Opioids are not given with MAO inhibitors, sedative-hypnotics, antipsychotic tranquilizers.

Tolerance and dependence

Tolerance: gradual loss of effectiveness with frequent doses. Clinically manifest after 2-3 weeks of frequent exposure. Tolerance does not develop to miosis, constipation, and convulsion. Also, does not develop to mixed agents and antagonists.

Dependence: a characteristic withdrawal or abstinence syndrome when a drug is stopped or an antagonist is administered. Physical dependence symptoms lasts for days and they are: rhinorrhea, lacrimation, yawning, chills, gooseflesh (piloerection), hyperventilation, hyperthermia, mydriasis, vomiting, diarrhea, anxiety, hostility. Psychological dependence (craving for opioids) may last for months/years.

Strong agonists
Meperidine (pethidine)

- Structurally unrelated to morphine
- More effective on K receptors than morphine, But primarily binds to μ receptors

Pharmacokinetics:
Well absorbed orally. Mostly given as IM. Half life= 2-4hr. metabolized in liver by N-methylation to normepridine which has CNS stimulant effect. Excreted in urine.

Pharmacological actions:
1. Less analgesic , less constipating, less respiratory depressant than morphine, & less urinary retention effect
2. Has Atropine-like action
3. Smooth muscle relaxant effect
4. No cough suppressant effect
5. Dilates cerebral vessels like morphine. ↑CSF pressure and contracts smooth muscles (but less than morphine)
6. No significant CVS action when given orally. On IV administration it cause ↓in PVR, ↑peripheral blood flow and ↑ cardiac rate.
7. now a days it is not recommended for chronic pain and chronic use.

Uses:

1. *Same as morphine , but not for cough or diarrhoea*
2. Severe visceral pain Including renal and billiary colics [cause it relaxes smooth muscle cells]
3. Obstetric analgesia. due to its shorter duration of action ,and is less depressant on fetal respiration.
4. Pre-anaesthetic medication [better than morphine due to less addictive effect and faster in peak
5. May Cause dependence , and can be substitute for heroin and morphine dependant person.

Adverse effects:

1. Tremors
2. Little Convulsions
3. Tolerance and addiction (less than morphine)
4. Sever Hypotension
5. Blurred vision (mydriasis)
6. Urine retention
7. Dry mouth
8. If given with neuroleptics provokes severe reactions such as convulsion , hyperthermia.
9. May Cause dependence, and can be substitute for heroin and morphine dependant person.
10. Produce partial tolerance to other opiates.
11. Dependence

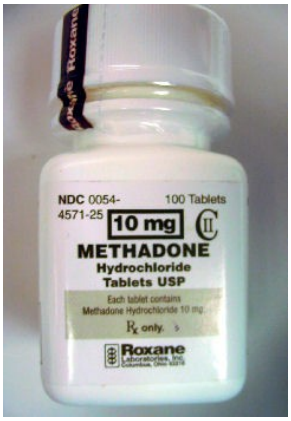
Heroin

- synthetic μ agonist
- Lipophilic, Crosses BBB
- Converted to morphine & its effect last half long
- No medical use
- Strong addicting drug
- Cause exaggerated euphoria when taken by injection

Codeine

- μ moderate agonist
- Given orally [morphine not given orally]
- Less efficacy than morphine [less potent]
- Less addicting, euphoria & dependence than morphine
- 10% converted to morphine
- Used in mild & moderate pain, cough, & diarrhoea.
- It is often used in combination with Acetaminophen/Aspirin
- Good antitussive at doses that does not cause analgesia.

Methadone



- Equal analgesic potency to morphine but with longer duration of action and less euphoria.

Pharmacokinetics

- well absorbed orally, fat soluble and readily penetrates into brain.
- Can be administered rectally, subcutaneously, spinally and IV
- It has a half life of 24 hrs.
- It accumulates in tissues ,and then slowly released.
- Biotransformed in liver and excreted in urine as active metabolites.

Mechanism of action:

It's a μ receptor agonist and block both NMDA receptors and monoaminergic reuptake transporters.

Uses:

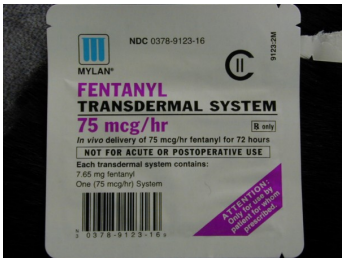
1. Relieve difficult-to-treat pain (neuropathic, cancer pain)
2. Treatment of opioid abuse by:

- Binding strongly to opioid receptors therefore decreasing desire for other opioid.
- Producing less effects
- Decrease craving
- It causes mild but prolong withdrawal syndrome.

Adverse effects:

its miotic and respiratory depressant effects lasts for 24 hrs. It increases billiary pressure and produce constipation like morphine.

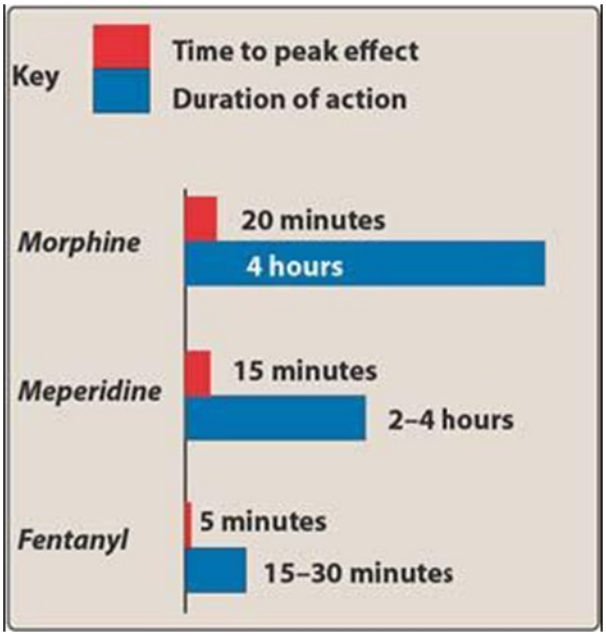
Fentanyl



- Chemically related to meperidine
- Has 100 fold analgesic potency as morphine

Pharmacokinetics:

- highly lipid soluble and crosses BBB readily.
- Has rapid onset and short duration of action (15-30 min)
- Injected usually IV or intrathecally.
- It can be administered transmucosally and transderml patch (contraindicated in hypoventilated patients) in cancer patients, which may be effective for 72 hours.
- It is metabolized to inactive metabolites by P450 3A4 and drugs that inhibit this isoenzyme can potentiate its effect
- Eliminated through urine

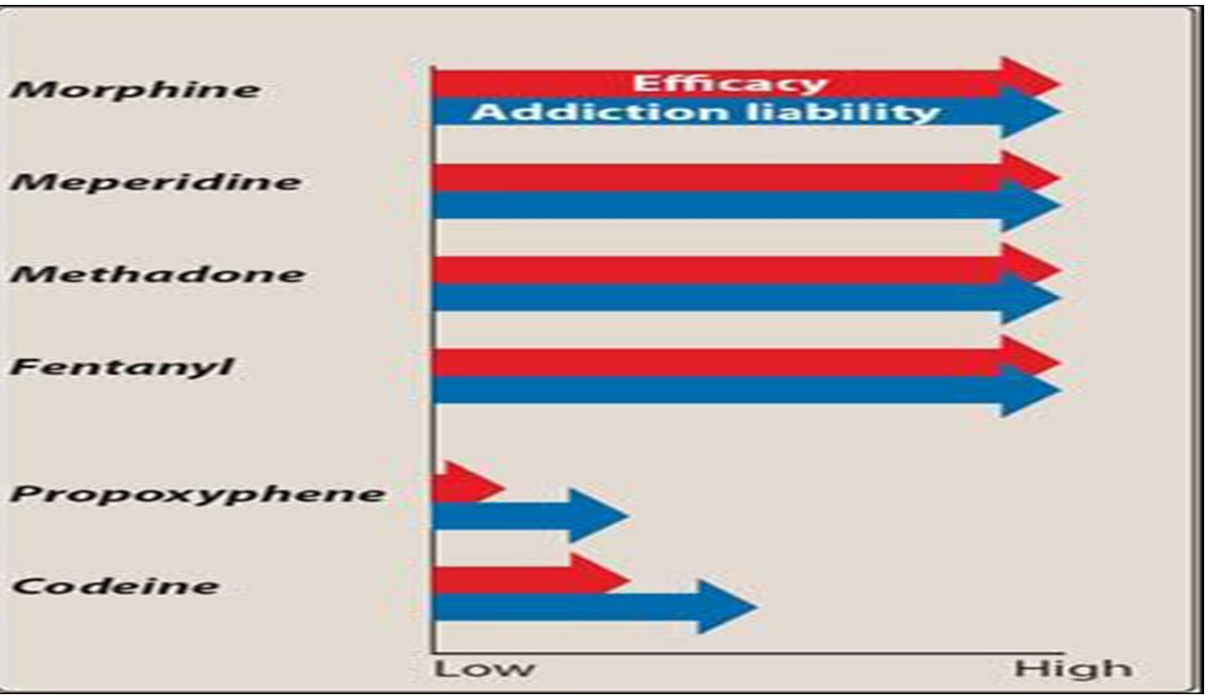


Uses:
Epidural fentanyl analgesia postoperatively and during labor.

Adverse effects:
Same as other μ agonists

Sufentanyl, alfentanil, and remifentanil:

- These are related to Fentanil
- Sufentanil is more potent to fentanil
- Other two are less potent and much short acting



Opioids with mixed receptor actions

- Drugs that stimulate one receptor and block other are termed as mixed agonist-antagonists.
- Their effects depend on previous exposure to Opioid agonists
- In individual who have not received opioids , these drugs show agonist activity and are used to relieve pain
- In opioid dependent patients, these drugs may show primarily blocking effects. That is, they produce withdrawal symptoms

- It has agonist action on kappa receptors, and weak antagonist on mu and delta receptors.
- It produces analgesia by activating receptors in spinal cord and used to relieve moderate pain
- It is administered orally or parenterally ,has shorter duration of action
- Subcutaneous administration is not recommended.
- It produces less euphoria as compared to morphine
- In higher doses causes respiratory depression and decreased activity of GIT.

Adverse effects:

- High doses ↑ BP and cause hallucination, nightmares, tachycardia, dizziness.
- In patient suffering from angina it ↑ mean arterial pressure, pulmonary artery pressure and thus ↑ work of heart.
- It ↓ renal blood flow.
- Despite its antagonist effect it does not antagonizes respiratory depression of morphine but can precipitate a withdrawal syndrome in morphine abusers.
- Tolerance and dependence develop on repeated use.

Contraindication:

It is contraindicated in epilepsy, co-administration with morphine and cardio vascular diseases

Buprenorphine

Pharmacokinetics:

- It is a partial agonist on mu receptors, with long duration of action, poor oral bioavailability
- Administered sublinguallym parenterally, or as spray.
- It is metabolized in liver and excreted via bile and urine

Uses:

Its major use is in opiate detoxification, because it has a less sever and short duration of withdrawal symptoms compared to methadone.

Adverse effects:

Respiratory depression that cannot be reversed by naloxone. ↓ or rarely ↑ B.P ,nausea ,dizziness.

Miscellaneous drugs
Tramadol

- Synthetic, μ agonist, centrally acting
- Its analgesia is also due to inhibition of norepinephrine and serotonin reuptake.
- Less potent analgesic than morphine

Pharmacokinetics:
- It is administered orally
- It undergoes extensive metabolism

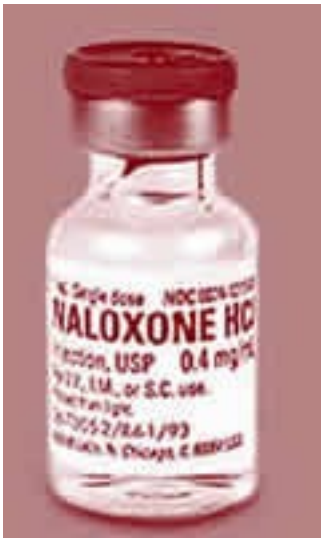
Actions:
- It is used to manage moderate to moderately severe pain usually used for treament of chronic pains
- Its respiratory depressive effect is less pronounced than morphine
- Naloxone can only partially reverse analgesia produced y tramadol or its active metabolites

Adverse effects:
nausea, vomiting, dry mouth, dizziness, sedation , It may cause anaphylaxis, seizures (especially patients taking TCA, or SSRI)

Contraindication:
In patients with history of epilepsy.

Antagonists

- In normal individual Opioid antagonists do not produce any effect.
- They rapidly reverse the effect of agonists. will normalize respiration, level of consciousness, pupil size an bowel activity.
- They precipitate the opiate withdrawal symptoms.
- they have a relatively high affinity for μ receptors but they can also reverse the agonists at δ and κ receptors.



Naloxone

- Used to reverse the respiratory depression and coma due to Opioid over dose

- It rapidly displaces all receptor bound Opioid molecule and in this way reverse the effects of opioid overdose.
- The effect is very fast ,withn 30 seconds of IV administration
- It has little effect on pain threshold (reverses incompletely) but can cause hyperalgesia under conditions of stress or inflammation, when endogenous opioids are produced.
- Patients get revived and alert.
- It has a half life of 1–2 hours
- It has 10 times more affinity for μreceptors than for K

Naltrexone

- It is well absorbed orally
- Undergoes rapid 1st pass metabolism
- It has a half life of 10 hours.
- A single dose of drug can block the opioid effect for 48 hours.
- Due to long duration of action it is proposed for maintenance for opioid addicts.
- It has been observed that naltrexone decreases craving for alcohol in chronic alcoholics