MED437
KING SAUD UNIVERSITY

Pharmacology
435 team

Pharmacology
Team 437

Drugs used in management of pain

Objectives:

- Categorize the different classes of drugs used to relieve pain.
- Detail on the mechanism of action,pharmacokinetics and pharmacodynamic effects of morphine and its synthetic derivatives.
- Hints on the properties and clinical uses of morphine antagonists.

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

Editing File

Drugs used in management of pain

What is pain?

- Unpleasant **sensory** & **emotional** experience associated with actual & potential tissue damage, or described in terms of such damage
- The **5th** vital sign suggests that assessment of pain should be as automatic as taking a client's BP and pulse.

Why should we treat pain?

- Pain is a miserable experience
- Pain is the **most common reason patient seek medical advice**
- Impairs the patient functional ability & psychological well being
- Pain increases sympathetic output → Increases myocardial oxygen demand (may lead to Myocardial infarction) and Increases BP, HR
- Pain limits mobility
- Increases risk for DVT (Deep vein thrombosis) and PE (Pulmonary embolism)

Drugs used in management of pain:

Adjuvant drugs

- Primarily indicated for clinical conditions other than pain
- May modify the perception of pain & **remove the concomitants of pain** such as anxiety, fear, depression
- Useful in neuropathic pain
- e.g. Anxiolytics, Neuroleptics,Antidepressants Antiepileptics

Opioids

- Used to relief severe pain
- Opium is derived from the juice of the opium poppy, Papaver somniferum
- The **natural products** include **morphine**, **codeine**, **papaverine** and **thebaine** (the first two are the most widely used)
- Opiates are drugs derived from opium and semisynthetic and synthetic derivatives
- Endogenous opioid peptides, e.g. Endorphins, enkephalins , dynorphins & b- endorphin (These are not enough in severe pain.)

NSAIDs

- Generally the **first class** of drugs used for controlling pain.
- Work at site of tissue injury to prevent the formation of the nociceptive mediators (work peripherally)
- Can decrease opioid use by ~30% therefore decreasing opioid-related side effects.
- They **neither cause tolerance** or **dependence**
- Has a ceiling effect to analgesia. (Maximum effect to analgesia, even when we increase the dose the efficacy is still the same)

Mind Map

- **1st** class of drugs used.
- Prevent the formation of the nociceptive mediators.
- Decrease opioid use by 30%.
- **Neither cause tolerance or dependence**.
- Has a ceiling effect to analgesia.

NSAIDs

Drugs used in management of pain

Anxiolytics

Neuroleptic

Antidepressants

Antiepileptics

modify the perception of pain and remove the concomitants of pain such as anxiety, fear, depression.

Adjuvant drugs

Opioids

RECEPTORS (G-protein coupled r.)

1. **Mu (μ).**
2. **Kappa (κ).**
3. **Delta (δ).**
4. **ORL-1.**

Classification (according to)

Their source

1. **Natural** → Morphine
2. **Semisynthetic** → Heroin
3. **Synthetic** → Pethidine, Methadone, Tramadol & Fentanyl

agonistic/ antagonistic actions

Agonists
Morphine, Codeine, Pethidine, Methadone

Mixed
Pentazocine
Acts as an analgesic if given alone.If a patient has already taken morphine then we give him Pentazocine then it acts as an antagonist of morphine.

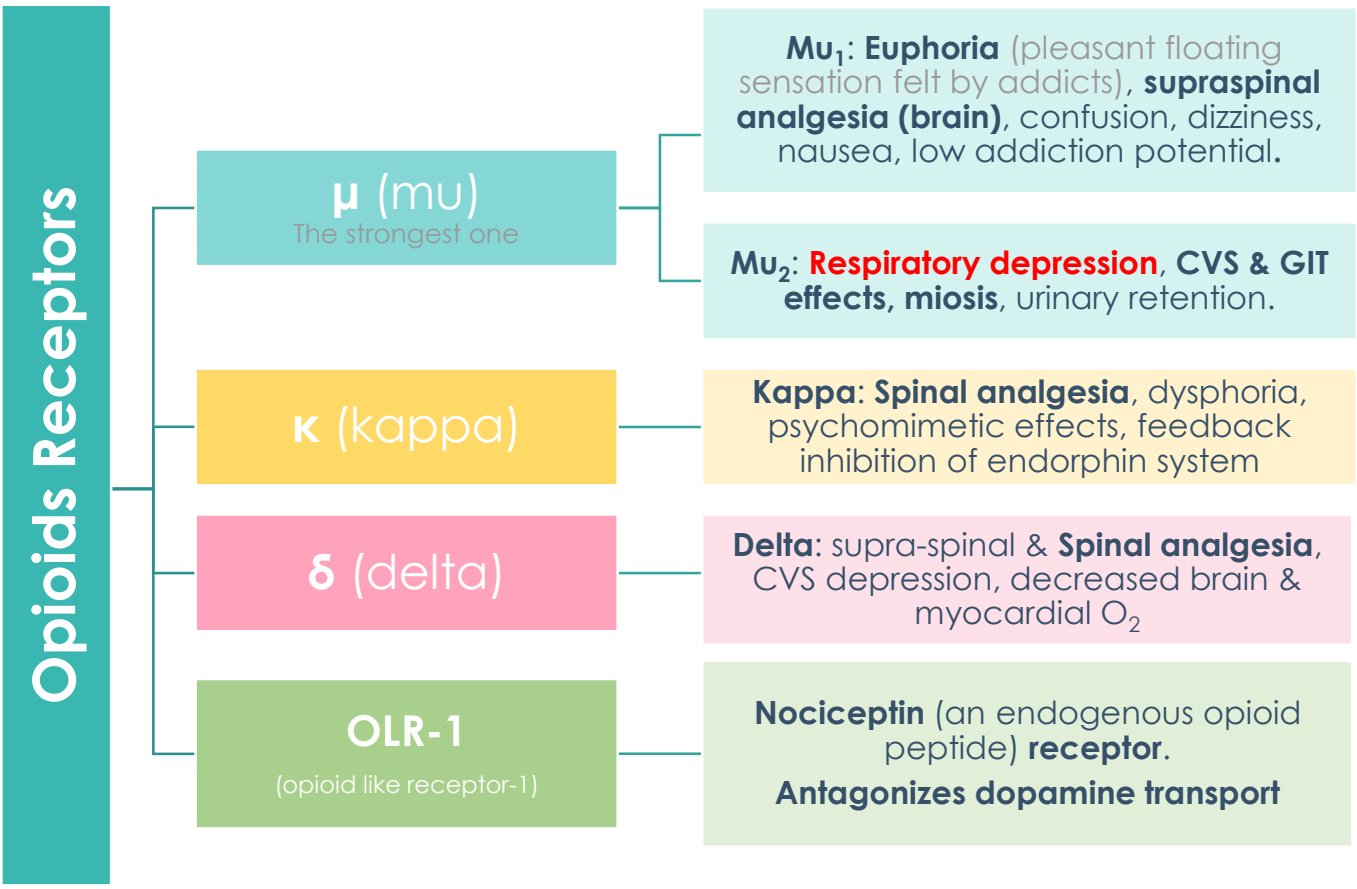
Antagonist
Nalaxone, Naltraxone
Only block opioid receptors, used as antidotes in addicts

Their specificity of action on receptors

- **μ r. agonists** → Morphine, codeine, heroin
- **agonist at k r. & antagonist at μ r.** → Pentazocine

Opioids

- **Opioids exert their pharmacological receptors through 4 types of receptors:**



- All of the 4 receptors are typical G-protein coupled receptors

Opioids

Mechanism of Action of opioids "morphine"

1. Binding to **pre**synaptic opioid receptors coupled to **Gi** (inhibitory G protein) → ↓ **AC** (adenylate cyclase) & **cAMP** → ↓ **voltage-gated Ca^{2+} channels** (inhibit influx of Ca^{2+}, → reduce release of neurotransmitter) → ↓ **excitatory** transmitter.
2. Binding to **post**synaptic receptors → ↑ **opening of K+ channels** (hyperpolarization) → ↓ neuronal excitability.

Simple pic from Lippincotts explain its action.

Pharmacodynamic Actions "morphine"

1. Analgesia [in acute & chronic pain]
2. Euphoria and sedation
3. **Respiratory depression** → By reduction of the sensitivity of respiratory center neurons to carbon dioxide.
4. Depression of **cough reflexes** → Some of the opioid drugs can be added to cough syrup (codeine and not morphine because morphine is strong)
5. Nausea & vomiting → ↑ excitation **CRTZ** (chemoreceptor trigger zone)
6. **Pin point pupil (Miosis)**→ How? It excites the EWN → enhance parasympathetic effect → constrict pupil.
7. Releases **histamine** from mast cells → Causing: itching of skin, hypotension, bronchoconstriction → **contraindicated w\ asthmatic pts.**
8. Effects on **GIT**:-
   - ↑ in tone, ↓ motility of intestine by reducing release of Ach → severe **constipation**
   - ↑biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter→ **contraindicated in biliary colic.**
   - depress renal function and contract gallbladder.

Tolerance **Vs** Dependence "morphine"

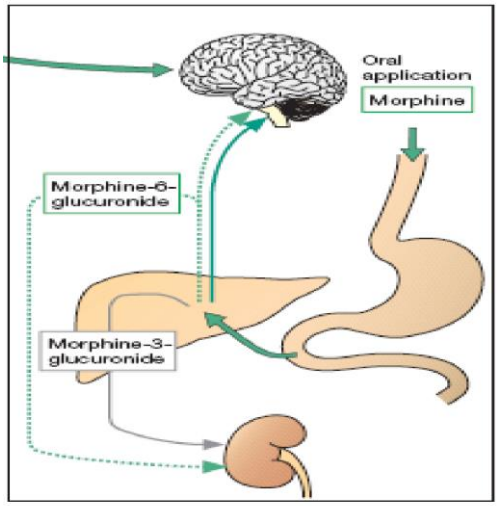
Tolerance	Dependence
Tolerance occurs when the person takes a **higher dose** of the drug to achieve **the same level of response** achieved initially	Dependence develops when the neurons **adapt to the repeated drug** exposure and **only function normally** in the **presence of the drug**
• Occurs **rapidly** with opioids (e.g. **morphine** 12–24 hours) • Develops to **respiratory depression**, analgesia, euphoria and sedation • Miosis doesn't get affected by tolerance, so addicts' pupils will still be constricted, which means that it can be an advantage in detecting addicts	• **Physical** dependence(abstinence) → withdrawal manifestations develop upon stoppage. • Addiction symptoms might appear after giving an antidote • Lasts for a few days (8-10 days) in form of ↑ body ache, insomnia, diarrhea, goose flesh, lacrimation. • **Psychological dependence** lasting for months / years → **craving.**

Opioids

Pharmacokinetics "morphine" :

1:49 min

- T ½ is 2-3 h
- It is slowly and erratically absorbed **orally** (bioavailability 20-40%) → Given **SC**, **IM**, or **IV** injection.
- Metabolized by **conjugation** with **glucuronic acid**
- Undergoes **enterohepatic recycling** →
  - Crosses BBB.
  - Crosses Placenta



C. Metabolism of morphine

Clinical Indications "morphine" :

*Because it causes venodilation

Pain Control

Acute Pulmonary Edema*

Myocardial Ischemia*

Stress Relief
e.g. heart failure (non painful conditions)

Pre-anesthetic medication

cancer pain, severe burns, trauma, Severe visceral pain
(not renal colics/biliary colics (because it constricts the sphincters) , acute pancreatitis)

Adverse Effects "morphine" :

Itching

Constricted Pupil

Sedation
Useful sometimes in preanesthesia

I
Punched
Simon's
Nose
Repeatedly
Crack
Crack

Nausea /Vomiting

Respiratory Depression

Constipation

CVS: **Decrease BP, systole, diastole**

Opioids

Contraindications "morphine":

- Head Injury → bc morphine depresses respiration → retention of CO_2 → dilatation of BV → **increase intracranial pressure** → patient may have hemorrhage.
- Bronchial asthma or Impaired Pulmonary Function → bc it causes respiratory depression & bronchoconstriction due to histamine.

- **pancreatic pain and Biliary colic** → bc it causes constriction of the sphincters
- Elderly (more sensitive due to → ↓ Metabolism, lean body mass and Renal function)
- Pts taking **MAOIs** (enzyme inhibitors) → increase morphine bioavailability and side effects.

- **Infants, neonates, or during childbirth** → ↓ **conjugating capacity** → accumulate → ↓ respiratory level. → Because morphine gets metabolized by conjugation with glucuronic acid which is still not active in infants and neonates, so the morphine will accumulate and cause respiratory depression.

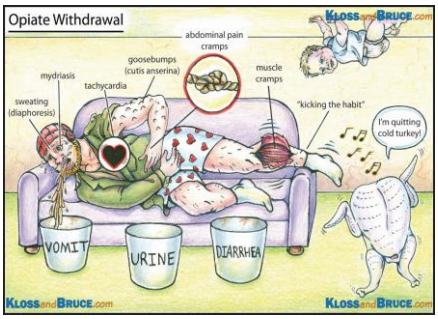
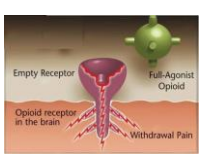
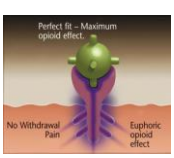
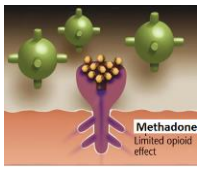
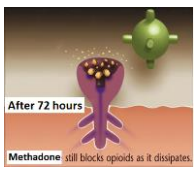
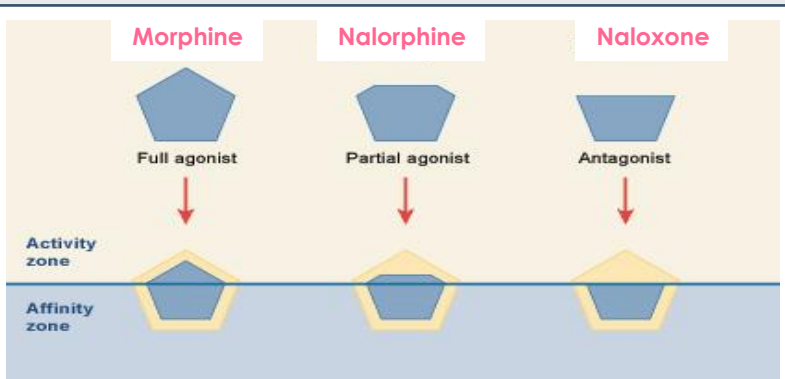
Opioid drugs:

- **codeine**, **Tramadol**, **Pethidine** (mepridine), **Fentanyl**

Drug	**Codiene**
Characteristics	• **μ** Agonist • Natural opioid • Dependence **< morphine**
Indication	• Used in mild & moderate pain (systemic) • cough • Diarrhea

Opioid agonists

Drug	TRAMADOL	PETHIDINE (mepridine)	FENTANYL
Mechanism of action	- Synthetic, **μ (mu)** agonist and less potent than Morphine. → so it is weak Analgesic. - Inhibits **NE** and **5HT** (serotonin) **reuptake**.	Synthetic, more effective **k (kappa)** agonist. **Pharmacodynamics** - Works on k which isn't as strong is μ so LESS. - **Less** analgesic, constipating, depressant on fetal respiration than morphine. - **No** cough suppressant effect. - **Has atropine-like action** (smooth muscle relaxant)	Synthetic, μ (mu) agonist, **more potent** than **Pethidine** and **Morphine** About 100 times stronger than morphine, we can use very low dose of Fentanyl and get the same action as morphine.
P.K	- Can be given **orally** → more **oral bioavailability**.	-	-
Indications	- Mild to moderate acute and chronic visceral pain. **- During labor** because it's metabolized by alkylation	- As in Morphine but **not in cough** and **diarrhea**. - **Better** → **preanaesthetic medication**. - Used in **obstetric analgesia (no decrease in respiration) can be used during labor** - **Used in severe visceral pain; renal and biliary colics (smooth muscles relaxant).**	- Analgesic supplement during anesthesia (**IV** or intrathecal = injection into the spinal canal). - Induce and maintain anesthesia in poor-risk pts (stabilizing heart) - Used in combination with Droperidol (antipsychotic) as **NEUROLEPTANALGESIA**. - In **cancer pain** and **severe postoperative pain**; (transdermal patch changed every 72 hrs) - As an anesthetic in hunting, they cover the arrow tip with it.
ADRs	**- Seizures (not use w\ epileptics)** - Nausea - Dry mouth - Dizziness - Sedation - Less ADRs on respiratory and CVS	- Tremors, **convulsions**, hyperthermia, hypotension. - Blurred vision, dry mouth, urine retention (atropine-like effects) - Tolerance and addiction.	**- Respiratory depression** (most serious) أقوى من المورفين - CV effects are less. - **Bradycardia** may still occur. so we have to monitor the patient

Drug	Opioid agonist	Opioid Antagonists	
	METHADONE	NALOXONE	NALTREXONE
M.O.A	- Weaker synthetic **μ** agonist. - antagonist of the N-methyl- D-aspartate (**NMDA**) receptor.	Pure opioid antagonist	Very similar to **Naloxone**
		(Antidotes) Competitive **antagonists** that bind to the **opioid** receptors with higher affinity than agonists but do not activate the receptors. This effectively blocks the receptor, preventing the body from responding to **opioids.**	
P.D	In non-addicts, it causes **tolerance and dependence** but not as severe as that of **Morphine**.	-	-
P.K	T1/2 = 55 hrs	Effects lasts only for 2-4 hrs.	**Longer** duration of action. T1/2 = 10hrs
Indications	Used to treat and control **opioid withdrawal** (as patches) **It occupies the receptors وتشغلها so there won't be pain and craving** 	- Used to treat and reverse **respiratory depression** caused by opioid overdose. - Reverse the effect of analgesia on the respiration of the **new born baby.** - Precipitates withdrawal syndrome in addicts.	-
	With addiction of opioid:   With mehadone:  	**OPIOID ANTAGONISTS** 	

Boy's slide
Not important!

At-121

- Experimental analgesic, 100 times more potent than morphine
- A bifunctional analgesic, acting as an agonist at both the **μ opioid receptor and the nociceptin receptor**
- **the interaction with the nociceptin receptor blocks the abuse and dependence-related side effects**

Summary

Morphine (natural)

M.O.A	μ receptor agonist. Binds to presynaptic opioid receptors to ↓ excitatory transmitter. and to postsynaptic receptors to ↓ neuronal excitability.
P.D	Analgesia (in acute & chronic pain). - Euphoria & sedation Respiratory depression - Depression of cough reflexes Nausea & vomiting increase → ↑CRTZ - Pin point pupil (Miosis) Releases histamine from mast cells Effects on GIT: ↓ motility → severe constipation. Constriction of biliary sphincter → ↑pressure in the biliary tract & biliary colic. Depress renal function & contract gallbladder
Disadvantage	Tolerance. - Psychological dependence
P.K	It's slowly & erratically - crosses BBB & placenta Given by SC, IM or IV injection Metabolized by conjugation with glucuronic acid Undergoes enterohepatic recycling
Uses	Control pain; cancer pain, severe burns, trauma, Severe visceral pain Acute pulmonary edema (due to venodilation) Myocardial ischemia (due to venodilation) Non painful conditions e.g. heart failure (to relieve distress) Preanesthetic medication.
S.E	Constipation - Itching (due to histamine) Respiratory depression - miosis Nauseia, vomiting - Sedation CVS: ↓ blood pressure, (↓ both diastolic and systolic)
C. I	-Head injury (↑ ICP) -With MAOIs -Bronchial asthma & impaired pulmonary function . -Elderly -Renal/Biliary colic & pancreatic pain. - infants, neonates or during child birth

Opioid antagonists

	Naloxone	Naltrexone
M.O.A	Pure opioid antagonist	
P.D	Effect lasts only for 2-4 hours	Very similar to naloxone but with longer duration of action [t½=10h].
Uses	●Treatment of respiratory depression caused by opioid overdose. ●To reverse the effect of analgesia on the respiration of the new born baby.	-
S.E	Precipitates withdrawal syndrome in addicts.	-

Summary

Opioid Agonist

Drug	M.O.A	P.D	USES	S.E	C. I
Codeine	Natural opioid μ agonist	Less dependence than morphine	In mild & moderate pain, cough, diarrhea.		
Tramadol	Synthetic μ agonist. less potent than morphine	Inhibits also NE & 5HT reuptake Can be given orally; more oral bioavailability	●Mild - moderate acute & chronic visceral pain ●During labor	●Seizures ●Nausea, Dry mouth. ●Dizziness, Sedation ●Less adverse effects on respiratory & C.V.S	Epilepti cs
Pethidine (mepridine)	Synthetic, more effective k agonist	●LESS analgesic, constipating, depressant on fetal respiration than morphine ●No cough suppressant effect ●Has atropine – like action (Smooth muscle relaxant)	●As in morphine but not in cough & diarrhea ●Preanaesthetic medication (better) ●Used in obstetric analgesia. ●Used in severe visceral pain; renal & biliary colics (sm. relaxant). ●Delivery	●Tremor ●Convulsions ●Hyperthermia ●Hypotension ●Blurred vision ●Dry mouth ●Urine retention ●Tolerance & Addiction	
Fentanyl	Synthetic, μ agonist. More potent than pethidine & morphine		●Analgesic supplement during anesthesia ●To induce & maintain anesthesia in poor-risk patients (stabilizing heart) ●In combination with droperidol as neuroleptanalgesia ●In cancer pain & severe postoperative pain (transdermal patch changed every 72 hrs).	●Respiratory depression (most serious) ●CV effects are less bradycardia may still occur.	
Methadon e	Weaker synthetic μ agonist	t½ 55 h (Note that it is long)	Used to treat opioid withdrawal	In non addicts, it causes tolerance & dependence but not as severe as that of morphine	

Questions

MCQs

1-which of the following can be used to treat Opioid withdrawal symptoms?

a)Naloxone .
b) Methadone.
c) Naltrexone.
d) Fentanyl.

2- which of the following opioids can be used during labor?

a) Tramadol.
b) Fentanyl .
c) Methadone .
d) Naltrexone.

3-Mohammed underwent a surgery but suffered from severe postoperative pain. He was given transdermal patches of Fentanyl. which of the following is MOST LIKELY to develop?

a) respiratory depression.
b) biliary colic.
c) dry mouth.
d) seizures.

4-During labor , a patient was given pethidine. the new born suffered from Respiratory depression from the analgesia. which of the following can be given to REVERSE the effect of analgesia on the respiration of the new born baby?

a) Methadone.
b) Fentanyl.
c) Naloxone.
d) Tramadol.

5-which opioid is contraindicated in patients with epilepsy?

a) Fentanyl.
b) Morphine.
c) Codeine.
d) Tramadol.

MCQs answers :

1) b
2) a
3) a
4) c
5) d

Questions

MCQs

6- all of the following are opioid receptor agonists except :

a) morphine.
b) codeine.
c) naloxone.
d) methadone.

7- which combination is best used as neuroleptanalgesia ?

a) Droperidol + Fentanyl.
b) Haloperidol + methadone.
c) Droperidol + pethidine.
d) Haloperidol + Fentanyl.

8-which of the following best describes Pethidine ?

a) Mu receptor agonist.
b) effective in treating cough and diarrhea.
c) k (kappa) receptor agonist.
d) more potent than morphine.

MCQs answers :

6) c
7) a
8) c

SAQ

1- Khalid suffered from severe burns while playing with fireworks. he was rushed to the hospital and was given morphine intravenously. what is morphine's mechanism of action in alleviating the pain?

1. Binding to **pre**synaptic opioid receptors coupled to **Gi** (inhibitory G protein) → ↓ **AC** (adenylate cyclase) & **cAMP** → ↓ **voltage-gated Ca^{2+} channels** (inhibit influx of Ca^{2+}, → reduce release of neurotransmitter) → ↓ **excitatory** transmitter.
2. Binding to **post**synaptic receptors → ↑ **opening of K+ channels** (hyperpolarization) → ↓ neuronal excitability.

2- List 3 common side effects of opioid drugs like morphine?

- constipation
- Respiratory depression
- constricted pupil.

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References:

- Doctors' slides and notes.
- Pharmacology Team 435.

Special thank for team 435 ❤

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