Drugs used in management of pain

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

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

Dr.Foda videos:

Pain

Definition

- **Pain:** an unpleasant **sensory & emotional experience** associated with actual & potential tissue damage, or described in terms of such damage.
- It has been identified as the **5th vital sign** which suggests that the assessment of pain should be as automatic as taking a client's BP, pulse, temperature & respiratory rate.

Why should we treat pain?

- Pain is a miserable experience:
- it is is the most common reason patients seek medical advice
- Impairs the patient's functional ability & psychological well being.
- Increases sympathetic output → ↑ myocardial O_2 demand + ↑ BP + ↑ HR.
- Limits mobility → ↑ risk for deep vein thrombosis (DVT) & pulmonary embolism (PE).

Management of Pain

WHO Pain Ladder

1. **Mild pain** → non-opioid **(Acetaminophen, NSAIDs, Aspirin)** ± adjuvant.
2. **Moderate pain** → mild opioid **(Codeine, Hydrocodone, Oxycodone)** ± non-opioid ± adjuvant.
3. **Severe pain** → strong opioid **(Morphine, Hydromorphone)** ± non-opioid ± adjuvant.

Note that as you go up the ladder, the stronger the analgesia is & the more the ADRs.

Classes of Drugs Used in the Management of Pain

NSAIDs (Non-opioids)

Aspirin - Indomethacin - Diclofenac - Ibuprofen

- Generally the **1st class** of drugs used to control pain.
- **Mechanism:** COX inhibitors; work at site of tissue injury (peripherally) to prevent the formation of nociceptive mediators (PGs, Histamine, Bradykinin).
- **Advantages:**
  - Can decrease opioid use by ~30% → ↓ opioid-related side effects.
  - **They neither cause tolerance or dependence.**
- **Disadvantages:** have a **ceiling effect** (maximum effect) to analgesia (at some point, taking higher doses of NSAIDs will not increase analgesia "hits a ceiling" so they're not effective in severe pain).

Adjuvant drugs

- Primarily indicated for clinical conditions other than pain.
- May modify the perception of pain & remove its concomitants (e.g. anxiety, fear, depression).
- **Examples**
  - **Anxiolytics**
  - **Neuroleptics** (antipsychotics)
  - **Antidepressants**
  - **Antiepileptics**
- Neuropathic pain best responds to anticonvulsants, tricyclic antidepressants, or SNRIs.

Opioids

Focus of lecture

(see next slides)

Note: Opioids suppress both components of pain (sensory + emotional), while NSAIDs suppress the sensory component only.

Opioids

- **Opium:** an alkaloid derived from the juice of the opium poppy (Papaver somniferum).
- **Opiates:** drugs derived from opium & semisynthetic/synthetic derivatives.
- **Opioids:** all compounds that work at opioid receptors (opiates + endogenous opioid peptides).

Opioids Classified based on:

- **Source**
  - **Endogenous** (Opioid Peptides)
    - Endorphins - Enkephalins - Dynorphins
  - **Exogenous**
    - **Natural:** Morphine - Codeine - Papaverine - Thebaine
    - **Semi-synthetic:** Heroin
    - **Synthetic:** Pethidine - Methadone - Tramadol - Fentanyl
- **Agonistic & Antagonistic Actions**
  - **Pure Agonists:** Morphine - Codeine - Pethidine - Methadone
  - **Pure Antagonists:** Naloxone - Naltrexone
  - **Mixed Agonist/Antagonist:** Pentazocine
- **Specificity of Action on Receptors**
  - **μ Agonists:** Morphine - Codeine - Heroin
  - **k Agonist & μ Antagonist:** Pentazocine

Opioid Receptors

- 4 Classes of receptors; all are typical **G-protein-coupled receptors (metabotropic).**
- They are anatomically distributed mostly in the brain, spinal cord & few at the periphery.
- The strongest opioid analgesics act primarily at **μ**, the major analgesic receptor.

Receptors		Analgesic Effect	Side Effects
μ (mu)	μ_1	Supraspinal analgesia (e.g. at periaqueductal grey)	• Euphoria (pleasant floating sensation) • Confusion, dizziness & nausea • ↓ Addiction potential
	μ_2	-	• Respiratory depression • CVS & GI effects • Miosis (except Meperidine → mydriasis) • Urinary retention
K (kappa)		Spinal analgesia (e.g. in the dorsal horn)	• Dysphoria • Psychomimetic effects • Feedback inhibition for Endorphin system
δ (delta)			• CVS depression • ↓ Brain & myocardial O_2 demand
ORL-1	Antagonizes dopamine transport Opioid-receptor-like subtype 1 or *Orphanin*. It is the most recently discovered member. *Nociceptin ligand (recepto)r* , which is structurally similar to *Dynorphin*.		

M.O.A. of Opioids

01

Presynaptic inhibition: binding to presynaptic Gi-coupled opioid receptors → ↓ AC (adenylate cyclase) → ↓ cAMP → ↓ voltage-gated Ca^{2+} channels → ↓ release of excitatory transmitter.

02

Postsynaptic inhibition: binding to postsynaptic receptors → ↑ opening of K^{+} channels → hyperpolarization → ↓neuronal excitability.

Tolerance & Dependence in Morphine

Tolerance	Dependance

• It is gradual loss in effectiveness with repeated doses of the drug.
• Can be overcome by increasing the dose.
• Occurs rapidly with opioids (in 12–24 h with Morphine).
• Develops to all effects (respiratory depression, analgesia, euphoria, sedation) except miosis & constipation.
	1.Physical Dependence (Abstinence):
	• **Withdrawal manifestations** develop upon stoppage:
	  ○ ↑ Body ache
	  ○ Insomnia
	  ○ Diarrhea
	  ○ Goose flesh (bumpy skin)
	  ○ Lacrimation
	• Lasts for a few days (8-10 days).
	2.Psychological Dependence:
	• Lasts for months/years → ***craving***.

Opioid Agonists μ

Morphine

P.K.

- t1/2 = 2 h at low dose every 4h, → disadvantage : frequent dosing for sustained analgesia.
- Slowly & erratically absorbed orally (bioavailability 20-40%) → medically given SC, IM, or IV
Metabolized by conjugation with glucuronic acid.
- Undergoes enterohepatic recycling → ↓ amount of active drug + longer t1/2 & DOA.
- Crosses BBB & placenta → reaches fetus.

★P.D.

1) Analgesia in acute & chronic pain (sensory + emotional analgesia)
2) Euphoria
3) Sedation
4) Respiratory depression
5) Depression of cough reflexes
6) Nausea & vomiting → ↑ CRTZ
7) Pin-point pupil: miosis due to stimulation of oculomotor center.
8) Histamine release from mast cells → flushing & warming of skin.
9) Effects on GIT:
   - ↑ Tone & ↓ motility → severe constipation.
   - Constriction of biliary sphincter → ↑ pressure in biliary tract &biliary colic.
   - Contraction of gallbladder.
10) Depresses renal function

Uses

- **Control pain:** cancer pain, severe burns, trauma, severe visceral pain (thoracic, pelvic, abdominal), but **★NOT in renal/biliary colics or acute pancreatitis** because of constriction.
- **Acute pulmonary edema:** remarkable relief in patients with dyspnea from pulmonary edema associated with left ventricular heart failure.
  - Proposed mechanisms: ↓ anxiety (perception of shortness of breath) + ↓ cardiac preload/afterload.
  - However, if respiratory depression is a problem, Furosemide may be preferred for the treatment of pulmonary edema.

On the other hand, Morphine can be particularly useful when treating painful myocardial ischemia with pulmonary edema.

- **Myocardial ischemia:** ↓ pain + ↓ preload.
- **Non-painful conditions** (e.g. heart failure) to relieve distress
- **Pre-anesthetic medication**

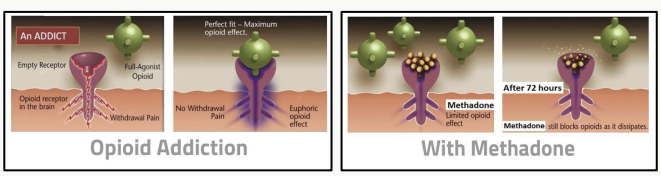
ADRs

- Constipation (↓ GI Motility)
- Respiratory depression
- Itching (histamine)
- Nausea & vomiting (+ CRTZ)
- Constricted pupil
- Sedation
- CVS: hypotension (↓ systolic & diastolic BP) on long-term use (vasodilation)

#★C.I

- Head injury: RESP depression → CO2 retention → cerebral vasodilation → ↑ ICP → bleeding.
- ★Bronchial asthma or impaired pulmonary function
- Pancreatic pain & biliary colic: drug-induced spasm → paradoxical increase in pain.
- Elderly are more sensitive due to ↓ metabolism, lean body mass & ↓ renal function.
- Not given to infants, neonates or during childbirth: they have ↓ conjugating capacity
→ ↓ rate of drug elimination → accumulation → ↓ respiration.
- With MAO inhibitors due to CYP450 enzyme inhibition by the MAOI.

Opioid Agonists μ

P.D.	Uses	ADRs
Codeine		
Natural μ agonist	• Mild & moderate pain • Cough → #RESPA: Dextromethorphan is a synthetic Codeine analog used as a central anti-tussive agent. • Diarrhea	Dependence but < Morphine
Tramadol		
• Synthetic μ agonist that also inhibits NE & 5-HT reuptake • Less potent than Morphine - P.K. : Can be given orally; has more oral bioavailability than Morphine.	• Mild to moderate acute & chronic visceral pain • **During labor** (due to less ADRs on RESP & CVS systems)	•★ **Seizures → not used** in epileptics • Nausea • Dry mouth • Dizziness & sedation • Less ADRs on respiratory & CVS systems
Fentanyl		
• Synthetic μ agonist • More potent than Pethidine & Morphine (x100). • Very strong; small dose can be given encapsulated in an arrow to sedate the animals in hunting.	• Analgesic supplement during anesthesia (IV or intrathecal). • To induce & maintain anesthesia in poor-risk patients (stabilizing heart). • **Neuroleptanalgesia**: in combination with **Droperidol** (neuroleptic/antipsychotic; D2 antagonist). • Cancer pain & severe post-operative pain (transdermal patch changed every 72h).	• **Respiratory depression** (most serious). - Can induce chest wall & laryngeal rigidity, thereby acutely impairing mechanical ventilation. • CVS effects are less, but **bradycardia** may still occur.
Methadone		
Weaker synthetic μ agonist - P.K. : t 1/2 = 55 h (long-acting) → disadvantage : dose difficult to titrate (disproportionate/unpredictable; ↑ in dose can lead to toxicity).	To treat **opioid withdrawal** for addicts (as patches); reduces craving. 	★**In non-addicts, it causes tolerance & dependence but not as severe as that of Morphine.**

Opioid Agonists K

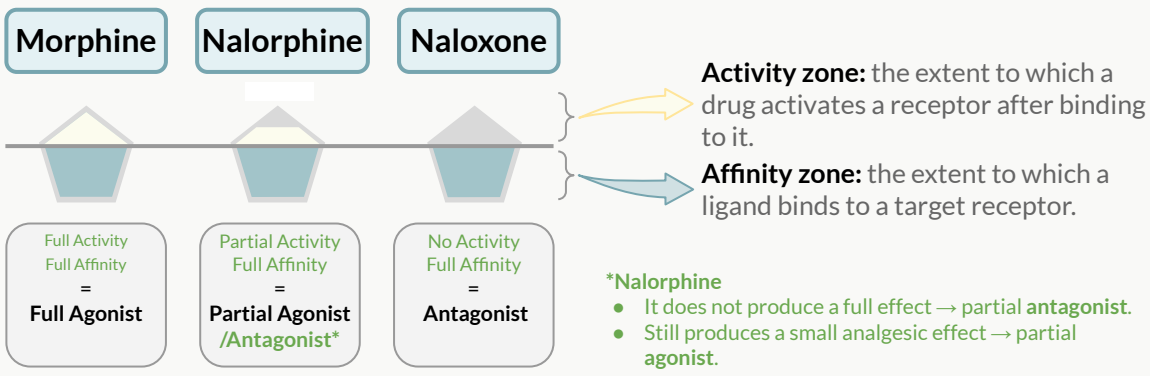
Pethidine (Meperidine)

P.D.	• Synthetic more effective **K agonist** • No action on μ → less analgesic, less constipating, less depressant on fetal respiration than Morphine (Metabolized by alkylation so no respiratory depression in newborn) • No cough suppressant effect • Has Atropine-like action (smooth muscle relaxant) → causes mydriasis instead of miosis.
Uses	• As in Morphine **but not in cough & diarrhea** • Pre-anaesthetic medication (better) • ★**Obstetric analgesia** (no ↓ respiration) unlike Morphine • Severe visceral pain (Including: ★**renal & biliary colics** (smooth muscle relaxant) unlike Morphine)
ADRs	• Tremors • Convulsions • Hyperthermia • Hypotension • Atropine-like effects: blurred vision, dry mouth & urine retention • Tolerance & addiction

Opioid Antagonists

Agent	**Naloxone** (Pure opioid antagonists)	**Naltrexone** (Very similar to Naloxone
P.K.	Effects lasts only for 2-4 h	Longer duration of action (t1/2 = 10 h)
M.O.A.	Opioid receptor antagonists; bind to opioid receptors without activating them.	
Uses	• Used in diagnosis & treatment of opioid overdose (antidote). - Respiratory depression caused by opioid overdose - Reverse the effect of analgesia on the respiration of the newborn baby.	
ADRs	★Precipitate withdrawal syndrome in addicts because they displace opioid agonists from μ receptors.	

Comparing the Activity & Affinity



MCQ

1. A man came to the emergency with weaver respiratory depression caused by morphine. Which drug can manage his condition?			
A. Flumazenil	B.Alcohol	C. Codeine	D. Naloxone
2. When morphine acts presynaptically, it will cause a decrease of which ion influx?			
A. Na+	B. K+	C. Cl-	D. Ca++
3. Which opiate is indicated in treatment if gallbladder colic?			
A. Codeine	B. Morphine	C. Meperidine	D. Oxycodeine
4.which opioid is contraindicated in patients with epilepsy			
A.Morphine	B.Tramadol	C.Fentanyl	D.Codeine
5.: A construction Worker was brought to the ER with head injury after falling down from a height. He is in severe pain. And prone to develop a neurogenic shock. He must receive an opiate analgesic immediately. Which one of these analgesics is prohibited to be given in such case?			
A.Methoxyflurane	B.Meperidine	C.Morphine	D.Tramadol
6.Which of the following statements about fentanyl is correct?			
A.Its withdrawal symptoms can be relieved by naloxone.	B.Fentanyl is 100 times more potent than morphine	C.The active metabolites of fentanyl can cause seizures.	D.It is most effective by oral administration.

1:D ,2:D ,3: C ,4:B ,5:C ,6:B

SAQ

01

A patient develops overdose of an opioid. What medication can you use to treat them and what is the mechanism of action?

Naloxone/Naltrexone. Competitive antagonists that bind to the opioid receptors with higher affinity than agonists but don't activate the receptors. This effectively blocks the receptor, preventing the body from responding to opioids.

02

Mention one special feature for each of the 4 opioid receptors.

μ: euphoria, K: dysphoria, δ: Decreased of brain and myocardial O2 demand, OLR-1: antagonizes dopamine transport.

03

Q1) A 51-year-old woman was seen in the emergency department because of strong abdominal pain for the past hour. Physical examination showed a red-headed, pale-skinned woman in obvious distress, with severe pain and tenderness of the right lank. A presumptive diagnosis of renal colic was made, and the patient was given an IM injection of an opioid drug that is a partial agonist at μ receptors and a full agonist at K receptors. Which drug was most likely administered?

Pethidine

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