#5

Drugs used in management of pain

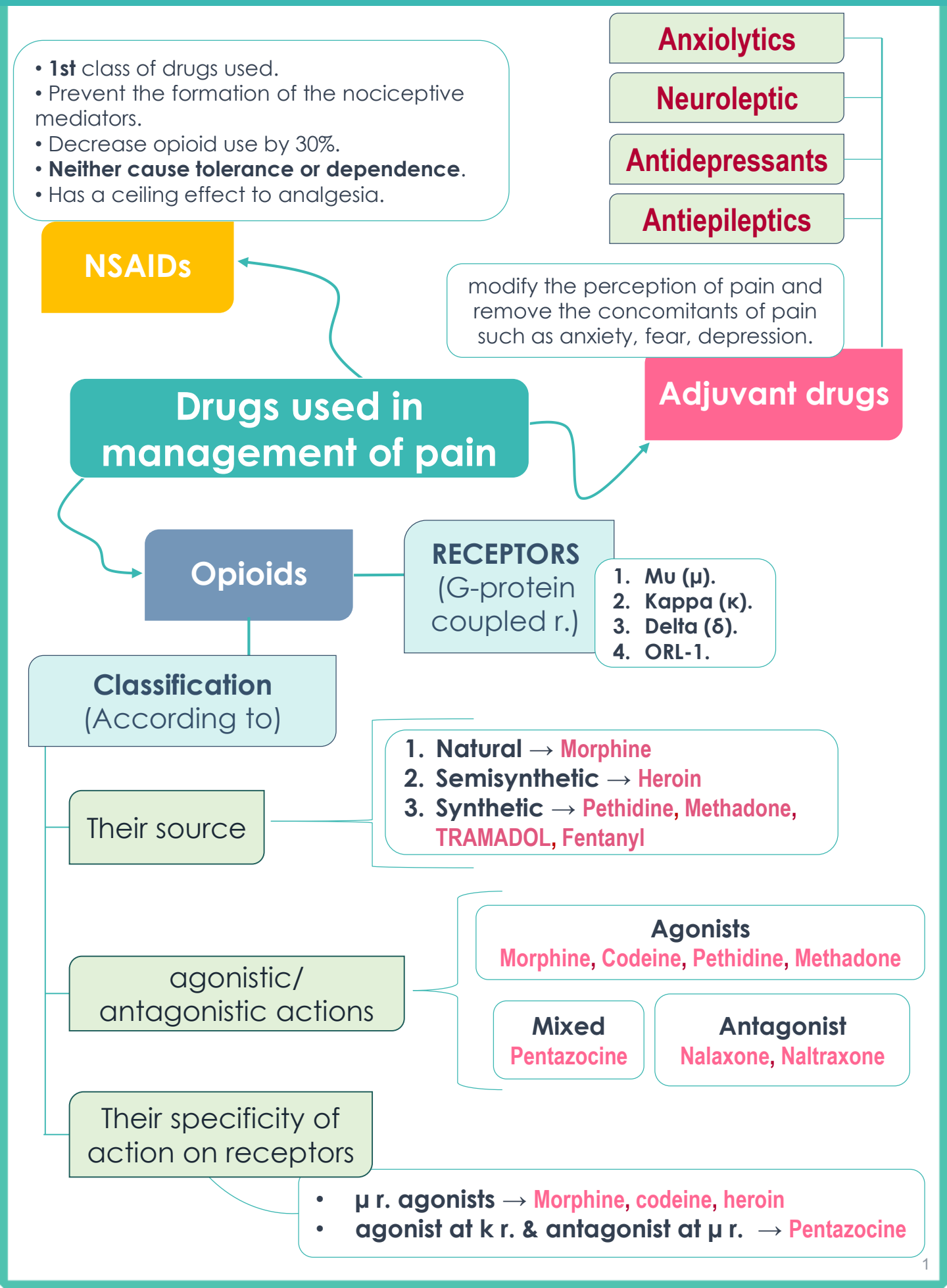
Objectives:

- Revise how pain is perceived and modulated, emphasizing on neurotransmitters, receptors, channels involved.
- Classify drugs used in management of pain.
- Expand on pharmacology of opiates, patterns of classification, mechanism of action, indications, ADR,…etc. detailing on morphine as an example.
- Compare in brief actions and indications of other opiate agonists and antagonists.

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

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
Anxiolytics
Neuroleptic
Antidepressants
Antiepileptics
modify the perception of pain and remove the concomitants of pain such as anxiety, fear, depression.
Adjuvant drugs
Drugs used in management of pain
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
Antagonist
Nalaxone, Naltraxone
Their specificity of action on receptors
• μ r. agonists → Morphine, codeine, heroin
• agonist at k r. & antagonist at μ r. → Pentazocine

Drugs used in management of pain

What is pain?

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 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

- Drugs primarily indicated for clinical conditions other than pain
- May modify the perception of pain (by ↓ AP) and remove the concomitants of pain such as anxiety, fear, depression.
- e.g. Anxiolytics, Neuroleptics, Antidepressants, Antiepileptics
- Useful in neuropathic pain.

Opioids

- Opium is derived from the juice of the opium poppy, *Papaver somniferum*
- The **natural products** include ***morphine***, ***codeine***, ***papaverine*** and ***thebaine***
- *Opiates* are drugs derived from opium and semisynthetic and synthetic derivatives
- Opioids refer to opiates and endogenous opioid peptides, e.g. **beta- endorphin**
- - Opioids are natural, semi- synthetic, or synthetic compounds that produce morphine-like effects.
- - **Uses**: Their primary use is to relieve **intense pain**, whether that pain results from surgery, injury, or chronic disease.

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
- Can decrease opioid use by ~30% therefore decreasing opioid-related side effects.
- They **neither cause tolerance** or **dependence**
- Has a ceiling effect to analgesia.

OPIOIDS

WHO Pain Ladder:

Why do we use more than 1 drug?
→ Combination of drugs lowers the ADRs

Mild pain

Nonopiois ± Adjuvant:
Aspirin, Acetaminophen, NSAIDs…

Moderate pain

Opioid ± Nonopioid (NSAIDs) ± Adjuvant:
Codiene, Hydrocodone, Oxycodone…

Sever pain

Opioid ± Nonopioid ± Adjuvant:
Morphine, Hydromorhone…

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

Opioids Receptors

- **μ (mu)**
  - Mu_1: Euphoria, **supraspinal analgesia (brain)**, confusion, dizziness, nausea, low addiction potential.
  - Mu_2: Respiratory depression, CVS & GIT effects, miosis, urinary retention.
- **κ (kappa)**
  - **Kappa: Spinal analgesia**, dysphoria, psychomimetic effects, feed-back inhibition of endorphin system
- **δ (delta)**
  - **Delta**: supra-spinal & **Spinal analgesia**, CVS depression, decreased brain & myocardia O_2
- **OLR-1** (opioid like receptor-1)
  - **Nociceptin** (an endogenous opioid peptide) receptor
    Antagonizes dopamine transport

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

Classification of Opioids:

A- According to **agonistic/antagonistic** actions:

1- **Agonists**; **Morphine**, **Codeine**, **Pethidine**, **Methadone**

2- **Mixed agonists /antagonists**; **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.

3- **Pure antagonist**; **Nalaxone**, **Naltraxone**

B- According to their **specificity of action** on receptors:

Morphine, **codeine**, **heroin**→ **μ -receptor agonists**

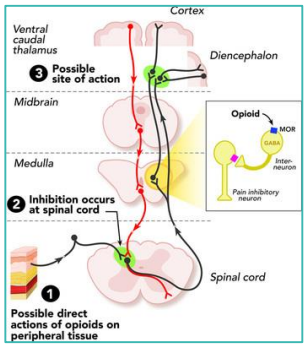
Pentazocine → **agonist at k –receptors**
→ **antagonist at μ-receptors**

C- According to their **source**:

1- **Natural: Morphine.**

2- **Semi-synthetic: Heroin** →
(Diacetylmorphine, synthesized form morphine)

3- **Synthetic: Pethidine**, **Methadone**.



Mechanism of Action of opioids "morphine"

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

Simple pic from Lippincotts explain its action.

Pharmacodynamic Actions "morphine"

1. Analgesia [in acute & chronic pain] more effective on visceral & skeletal pain.
2. Euphoria relieves anxiety of patient. → that's why ppl may addict it.
3. **Respiratory depression** → by reduc- tion of the sensitivity of respiratory center neurons to carbon di- oxide.
4. Depression of **cough reflexes** → treatment of **non**-reproductive cough.
5. Nausea & vomiting → ↑ excitation **CRTZ** (chemoreceptor trigger zoon)
6. **Pin point pupil** → **Diagnostic feature of opioid addiction.**
   How? It excites the EWN → enhance parasympathetic effect → constrict pupil.
7. Releases **histamine** from mast cells → causing: hypotension, bronchoconstriction, itching of skin → contraindicated w\ asthmatic pts.
8. Effects on **GIT**:-
   - ↑ in tone, ↓ motility of intestine → severe **constipation** → In GIT reduces motility (peristalsis) by **reducing release of Ach** → used to treat **diarrhea**.
   - ↑biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter→ **contraindicated** in biliary colic.

Opioids

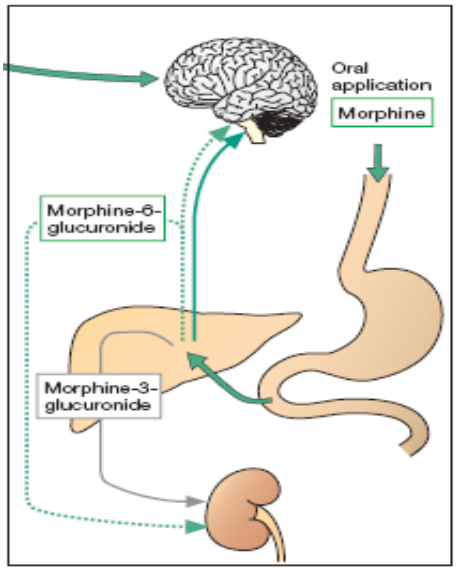
Tolerance **Vs** Dependence

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	• **Physical** dependence → withdrawal manifestations develop upon stoppage. • 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. • Dependence developed mainly w\ morphine.

Pharmacokinetics of opioids:

1:49 min

- T ½ is 2-3 h
- It is slowly and erratically absorbed **orally** (bioavailability 10-40%) → Given **SC**, **IM**, or **IV** injection.
- Metabolized by **conjugation** with **glucuronic acid** → its metabolized is 6 timed potent from morphine.
- Undergoes **enterohepatic recycling** →
  - Crosses BBB.
  - Crosses Placenta → Infants born of addicted mothers show physical dependence on opiates and exhibit withdrawal symptoms if opioids are not administered



C. Metabolism of morphine

Clinical Indications

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 renalcolics** (bc it constricts the ureter) **/biliary colics, acute pancreatitis** (bc the gall bladder & pancreas has similar sphincter constricted by morphine)

Opioids

Adverse Effects

Revise the pharmacodynamics (page 4) to know how these ADRs developed.

Itching	Constricted Pupil	Sedation
Nausea /Vomiting	Respiratory Depression	Constipation

I Punched Simon's Nose Repeatedly *Crack*

Contraindications

- 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.

- **Biliary colic** → it increase the pressure of biliary tract.
- Elderly (more sensitive due to → ↓ Metabolism, lean body mass → Reduce volume of distribution of blood, and Renal function)
- Pts take **MAOIs** (Monoamine oxidase inhibitors) → bc depressant actions of morphine are enhanced

Infants, neonates, or during child birth → ↓ conjugating capacity → accumulate → ↓ respiratory level. → bc they do not have glucuronyl enzyme to degrade it

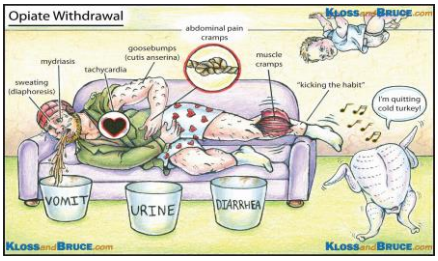
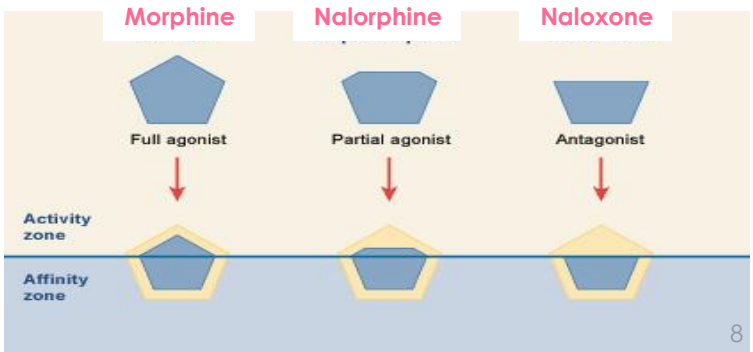
Opioid drugs:

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

Drug	**Codiene**
Characteristics	• μ Agonist • Dependence < **morphine**
Indication	• Used in mild & moderate pain (systemic) • **Dry 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** - **Less** analgesic, constipating, depressant on fetal respiration than morphine. - **No** cough suppressant effect. - **Has atropine-like action** (smooth muscle relaxant) - Does **not** cause **pinpoint pupils** but, rather, causes the pupils to dilate because of an **anticholinergic action**.	Synthetic, μ (mu) agonist, **more potent** than **Pethidine** and **Morphine**
P.K	- Can be given **orally** → more **oral bioavailability**.	-	- Highly lipophilic. - Short Duration.
Indications	- Mild to moderate acute and chronic visceral pain. - **During labor** → because it does not inhibit respiration.	-As in Morphine but **not in cough** and **diarrhea**. -**Better → preanaethetic medication**. -Used in **obstetric analgesia** (no decrease in respiration) - Used in **severe visceral pain; renal and biliary colics** (smooth muscles relaxant). - Used for **acute** pain.	- 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 as **NEUROLEPTANALGESIA**. - In **cancer pain** and **severe postoperative pain**; (transdermal patch changed every 72 hrs)
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) - CV effects are less. - **Bradycardia** may still occur.

Drug	Opioid agonist	Opioid Antagonists	
	METHADONE	NALOXONE	NALTREXONE
MOF	- Weaker synthetic **μ** agonist. - antagonist of the N-methyl- D-aspartate (**NMDA**) receptor.	- Pure opioid antagonist - Competitive antagonist to μ, κ, and δ.	Very similar to **Naloxone**
		antagonists rapidly reverse the effect of agonists, precipitate the symp- toms of opiate withdrawal → used as diagnostic feature in pts dependent on opioids.	
P.D	In non-addicts, it causes **tolerance and dependence** but not as severe as that of **Morphine**.	-	-
P.K	$T_{1/2}$ = 55 hrs	Effects lasts only for 2-4 hrs.	**Longer** duration of action. $T_{1/2}$ = 10hrs
Indications	Used to treat and control **opioid withdrawal** (in people who have become addicted to opiates such as heroin) - neurogenic pain → NMDA antagonist. 	- 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 	

Summary-1

Drug	Morphine
Mech. of action	• **Pre synaptic** (bind to opioid receptors coupled with Gi ➔↓ AC & cAMP ➔↓ voltage-gated Ca^{2+} channels ➔↓ excitatory transmitter). • **Post synaptic** (bind to post synaptic receptors ➔↑ opening of K channels ➔ ↓ neuronal excitability)
P.K	• T ½ short = 2-3h. • Slowly & erratically absorbed orally (bioavailability 20-40%). • Medically given by SC, IM or IV injection. • Metabolized by conjugation with **glucuronic acid**. • Undergoes enterohepatic recycling, • crosses **BBB** & **placenta**.
P.D	• Analgesia (acute & chronic) • Euphoria. • Respiratory depression. • Depression of cough reflexes. • ↑CRTZ → Nausea & vomiting. • Pin point pupil • Releases histamine from mast cells • On GIT:- ↑ in tone ↓ motility ➔ severe constipation ➔↑ pressure in the biliary tract + constriction of biliary sphincter ➔ contraction of **gall bladder**
TOLERANCE & DEPENDENCE	• Tolerance: rapid 12–24h (develops to respiratory depression, analgesia, euphoria and sedation, constipation & pupil size don't develop tolerance) • Dependence: ▪ Withdrawal effects upon stoppage. ▪ Lasting for 8-10d "physiological" ▪ End of months & years "craving"
Indications	• **Control pain** ➔ mostly Visceral. • Acute pulmonary edema. • Myocardial ischemia • Non painful coditions e.g. heart failure (to relieve distress) • Preanesthetic medication.
ADRs	Constipation, Respiratory depression, itching, Nausea & vomiting, Constricted pupil, sedation.
C.I	• **HEAD INJURY** • **BRONCHIAL ASTHMA** • Biliary colic • Elderly. • MAOIs • Infants, neonates or during child birth ➔↓ conjugating capacity ➔ accumulate ➔↓ respiratory (b/c before 15 days of birth glucuronic acid didn't form yet)

Summary-2

Drug	codeine	TRAMADOL	Pethidine (mepridine)	Fentanyl	METHADONE
P.D	• μ Agonist. Causes **less** dependence than **morphine**.	• Synthetic. • μ Agonist. less potent than **morphine**. PO; more oral bioavailability. **Inhibit NE & 5HT reuptake.**	• Synthetic • **more** effective k agonist ○ **Less** analgesic, constipating, depressant on faetal respiration than **morphine**. ○ No cough suppressant effect. ○ **Has atropine like action** (Sm. relaxant)	• Synthetic • μ agonist **more** potent than **pethidine** & **morphine**.	• **Weaker** synthetic. • μ agonist. – **t½ 55 h**
Use	Mild & moderate pain, cough, diarrhea.	Mild - moderate acute & chronic visceral pain, & During labor.	• As in morphine but not in cough & diarrhea. • Preanaesthetic medication (better) • obstetric(pregnant) analgesia (No ↓ resp.) • **In severe visceral pain; renal & biliary colics** (sm. relaxant)	• Analgesic supplement during anesthesia, (IV or intrathecal) **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 72hrs).	**To treat opioid withdrawal**
ADRs	---	• Seizures **(not in epileptics)**, • Nausea, Dry mouth, Dizziness, Sedation • Less adverse effects on respiratory & C.V.S	Tremors, Convulsions, Hyperthermia, Hypotension. Blurred vision, Dry mouth, Urine retention. Tolerance & Addiction.	• **Respiratory depression (most serious)** • **CV** effects are **less**. • Bradycardia may still occur.	In non addicts, it causes tolerance & dependence but not as severe as that of **morphine**.

Opioid antagonists

Drug	Naloxone	Naltrexone
Indications	Used to treat respiratory depression caused by opioid overdose. reverse the effect of analgesia on the respiration of the new born baby.	---
Extra info.	• Pure opioid antagonist • Precipitates withdrawal syndrome in addicts • Effect lasts only for 2-4	Very similar to naloxone but with longer duration of action [t½=10h]

Flash Cards | MCQs | Editing File

You can find all drugs in the flashcards' file.

Thank you for checking our team!

Pharmacology 435

@ pharmacology435

أثير النشوان

أسرار باطرفي
العنود العمير
آية غانم
حصه المزيني
دلال الحزيمي
رغدة قاسم
ريم العقيل
سارا الحسين
ساره الخليفة
لمى الزامل
لولوه الصغيّر
لينا إسماعيل
ملاك اليحيا
نورة البصيص

خالد أبوراس

إبراهيم العسعوس
احمد الخياري
زياد السالم
عبدالعزيز الحماد
فوزان العتيبي
فارس المطيري
قصي عجلان
ماجد العسبلي
محمد ابونيان
محمد السحيباني
يوسف الصامل

Sources:
1- 435's lecture.
2- https://www.drugabuse.gov
3- Pharmacology (Lippincotts Illustrated Reviews Series), 5th edition. Chapter 14.
4- Basic & Clinical Pharmacology by Katzung. Chapter 31, 12th edition

Revised by
هشام الغفيلي & خولة العماري