Opioid and Opioid Antagonists

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Analgesic drugs

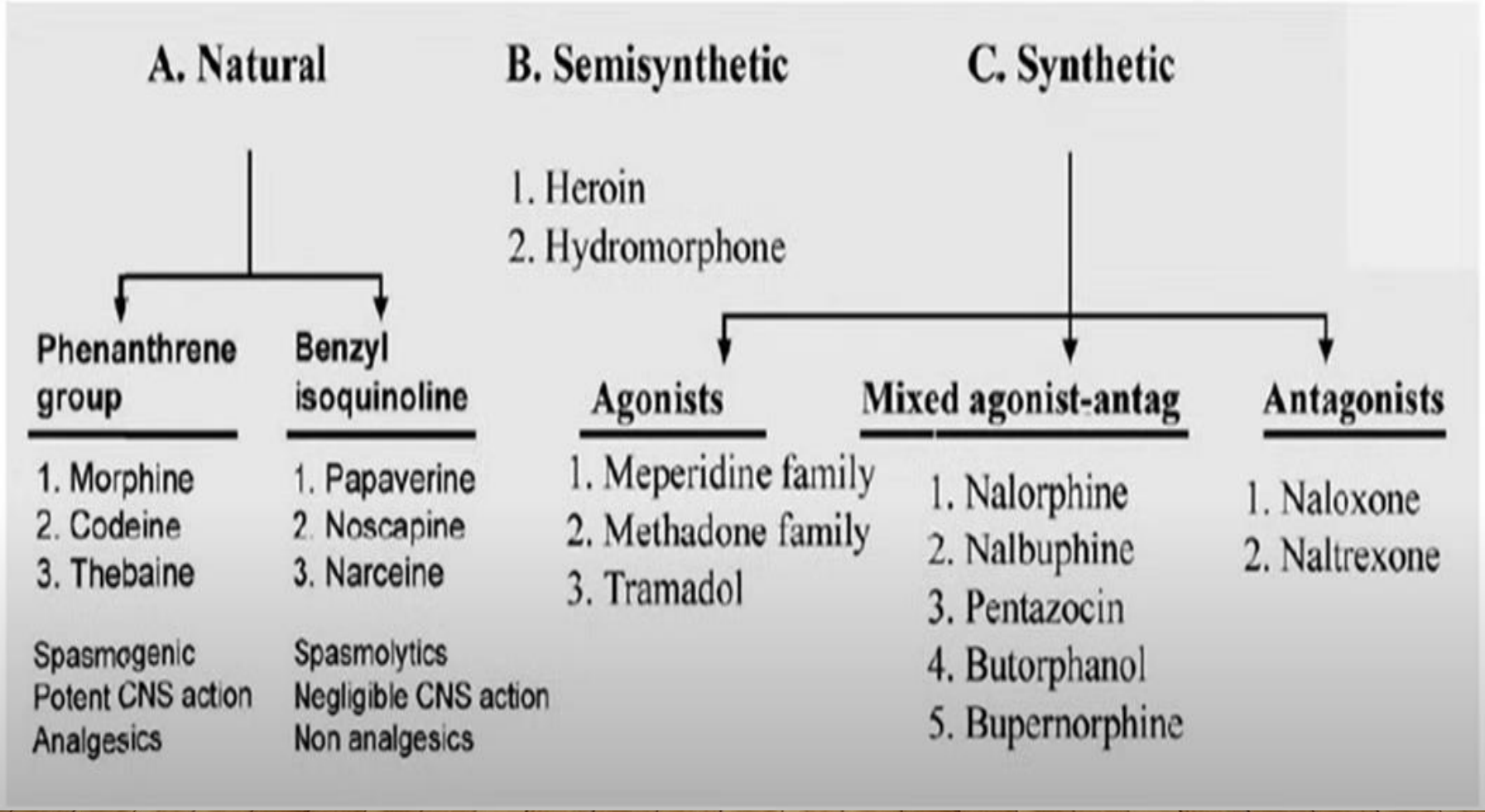
1- Narcotic analgesic (opioid drugs) :relieve pain centrally but in large doses produce drowsiness & prolonged use produces tolerance & dependence

2- NSAIDS

3- Analgesic antipyretic

4- Drugs for neuropathic pain and migraine

Classification of narcotic analgesics



Types of opioid receptors

Receptor subtypes	Effect of stimulation
μ (mu) (1,2,3)	• Supra-spinal and spinal analgesia • Sedation • Inhibition of respiration • Constipation • Modulation of hormone and neurotransmitter release.
κ (Kappa) (1,2)	• Supraspinal and spinal analgesia • Psychotomimetic (hallucinogenic) effects • Constipation
δ (delta) (1,2)	• Supraspinal and spinal analgesia • Modulation of hormone & neurotransmitter release

I- Phenanthrene Opium Alkaloids

Morphine

- Natural phenanthrene opium alkaloid (10% of opium).

Pharmacokinetics:

➲ t½ = (2-3h). ➲ Duration = (6-8h).

Absorption:

- Well absorbed orally, S.C & I.M (but low oral bioavailability 30% only), lozenges escape 1st pass effect.
- In shock, it is used as diluted I.V (not S.C or I.M due to impairment of peripheral circulation).
- By transdermal patch & epidural in anesthesia.
- If taken by nasal insufflations → escape hepatic 1st pass effect (in addiction → non-medical use).

Distribution:

distributed all-over the body.

- It crosses placental barrier:
  a. **During pregnancy** → congenital malformations & fetal addiction.
  b. **During labor** → depresses fetal R.C → neonatal asphyxia (treated by naloxone I.M. to the mother before labor or intra-umblical to the baby after labor).
- Morphine is **less** lipohilic as compared to **heroin** & **fentanyl** which rapidly penetrate brain causing intense rush (highly addictive).

Metabolism:

- Conjugated with glucuronic acid into:
  a. **Morphine-6-glucuronide:** more active than morphine.
  b. **Morphine-3-glucronide:** neuro-excitatory metabolite.
- These metabolites are excreted by kidney,
- These metabolites are relatively polar, so CNS penetration is limited.
- If large doses of morphine were administered or in patients with renal failure, exaggerated response of these metabolites may occur.
- Metabolism is deficient in children & elderly so produces supersensitivity.

Excretion:

In all body secretions: saliva, bile, milk, urine & gastric secretion.

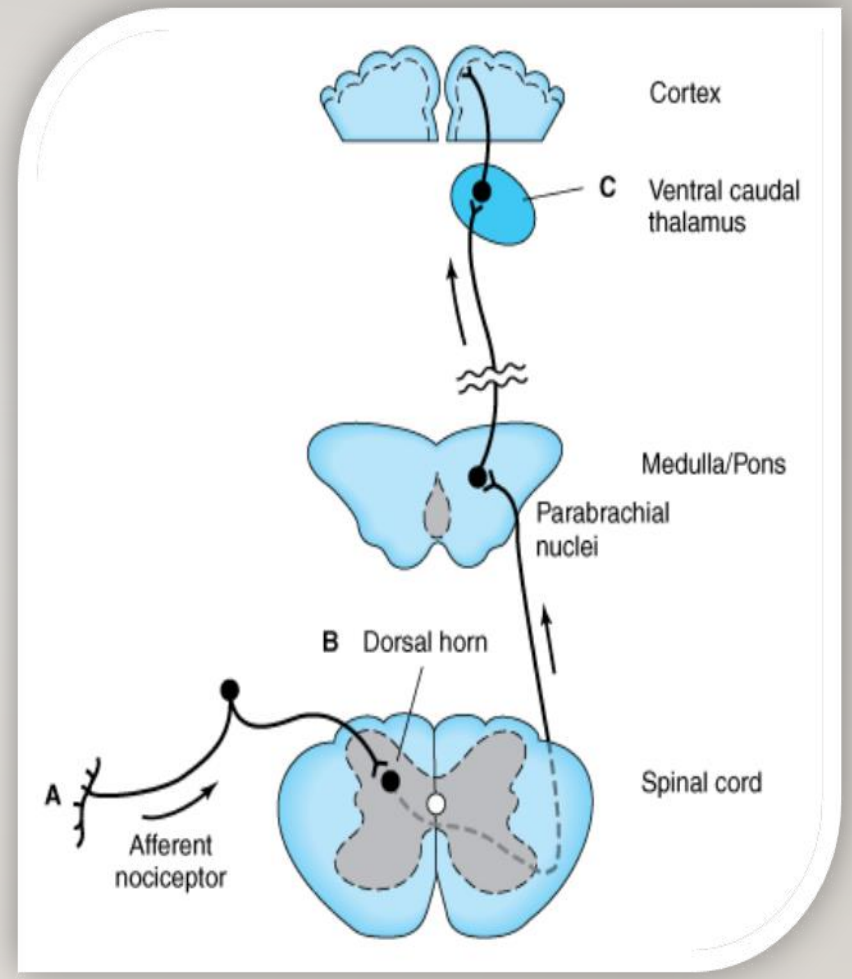
N.B. ***Gastric lavage is essential in all cases of morphine toxicity even not taken orally***

Pharmacodynamics:

Mechanism of action:

Morphine stimulates **opiate receptors** in C.N.S & periphery. These receptors are **G-protein** coupled receptors (G_i).

1. Stimulation of these receptors →inhibit adenyl cyclase → decreases cAMP.
2. **Presynaptically:** block Ca++ channels →decrease release of excitatory chemical transmitters e.g. glutamate, substance P & PG.
3. **Postsynaptically:** open K+ channels → hyperpolarization which produces inhibitory post synaptic potential (IPSP).



Pain pathway & sites of action of opioid analgesics

Pharmacological Actions of morphine

A) CNS: mixed stimulation & depression of certain parts in CNS:

Depressant actions:

a) Analgesic:

- Very effective in deep visceral pain not in itching (↑ histamine release).
- Morphine decreases pain perception (decreases release of substance P & glutamate).

b) Narcosis: Stupor & drowsiness.

c) Depresses R.C, cough center & vasomotor center (V.M.C).

d) Inhibits heat regulating center (H.R.C) (through κ receptors).

e) Decreases release of hormones e.g. ACTH, FSH & LH.

Stimulant effects:

a. Euphoria.
b. Stimulation of Edinger Westpal Nucleus (3^{rd} cranial nerve nucleus) → miosis (PPP).
c. Stimulates cardiac inhibitory center (CIC) → bradycardia.
d. Stimulates chemo-receptor trigger zone (CTZ) → vomiting.
e. Increases ADH release.

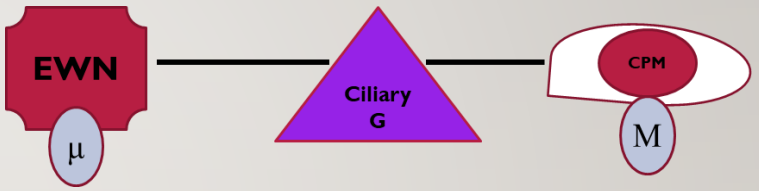
B) Autonomic Nervous System:

- Enhances parasympathetic (bradycardia) & depresses sympathetic (hypotension).

C) Eye:

- Miosis (stimulates {blocks cortical inhibitory neurons to} EWN → activates oculomotor nerve → cilliary nerve → stimulates ciliary muscle & CPM: miosis, accommodation to near vision & ↓ I.O.P)
- **N.B.** Miosis of morphine could be blocked by: *Naloxone* & *atropine*.

D) CVS: (hypotension & bradycardia)



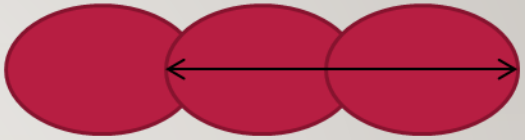
- In normal therapeutic dose → no effect.
- In large dose:
  a. Stimulates CIC: bradycardia.
  b. Hypotension due to:
     - inhibition of VMC
     - direct venodilator (if IV)
     - histamine release.

E) Respiratory system:

- Depresses RC: decrease sensitivity of R.C to CO_2 → hypoventilation & hypoxia.
- Depresses cough center: anti-tussive.
- Histamine release: precipitates attack of bronchospasm in asthmatics.

F) GIT: (spasmogenic → constipation)

1. Decreases all secretion except salivary secretion.
2. Spasmogenic: stimulates segmental (non-propulsive) contraction & inhibits propulsive movement + spasm of sphincter → constipation.
3. Inhibition of defecation reflex.



E) Biliary tract:

- Spasm of sphincter of Oddi & bile duct → increases intra-biliary pressure.
- Also it may aggravate pain in biliary colic (so add atropine).
- It also stimulates pancreatic amylase.

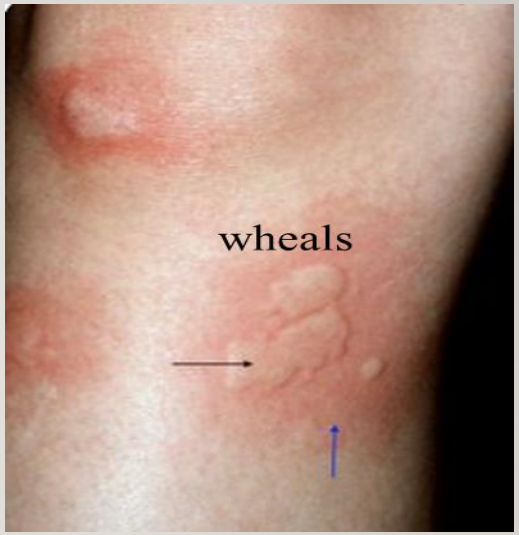
- **N.B.**

The spasmogenic effect of morphine on G.I.T is due to stimulation of μ & δ receptors in GIT So naloxone completely antagonizes spasmogenic effect of morphine on intestine.

G) Renal effect:

1. Urine retention due to:
   - Spasm of the ureteric wall (so not used alone in ureteric colic).
   - Spasm of the sphincter & inhibition of micturation reflex.
2. Oliguria due to:

• Increases ADH. • Hypotension → decreases GFR



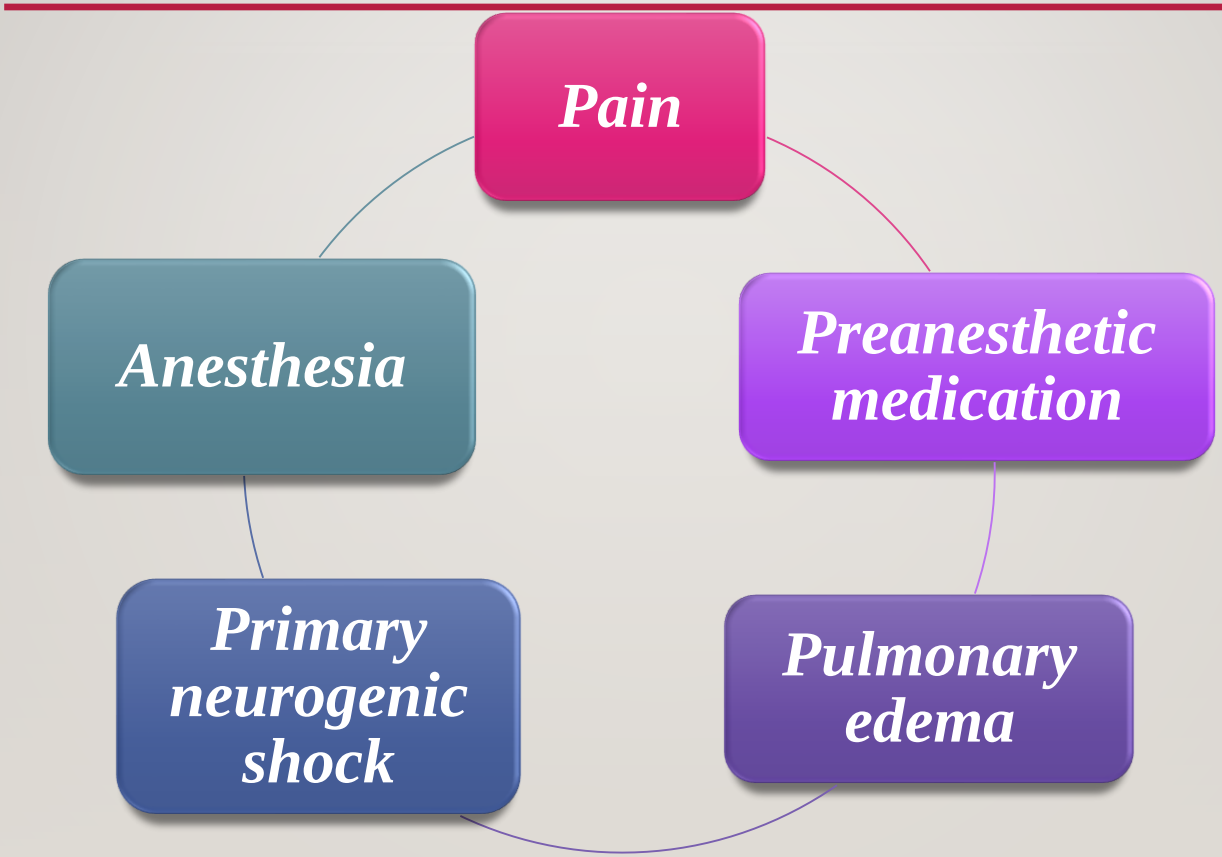
H) Other actions:

1. Spasmogenic effect on smooth muscle.
2. Neonatal asphyxia if taken during labor.
3. Skin: histamine release → VD, itching & wheal formation.

Tolerance to morphine:

- Tolerance to some CNS effects after 10-14 days of continuous use.
- ***No tolerance*** for P.P.P, constipation & excitation.
- ***Cross tolerance*** may occur with other C.N.S depressants.

THERAPEUTIC USES OF MORPHINE



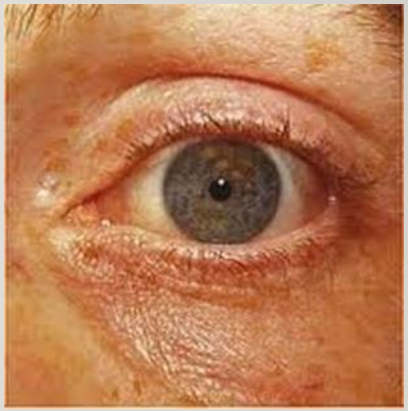
1. Pain: analgesic in severe visceral pain e.g.

a. Cardiac pain e.g. myocardial infarction.
b. Cancer pain in terminal stages.
c. Colic: renal or biliary colic but add atropine.
d. Post-operative: except in cholecystectomy & after eye operations.
e. Fracture: but not in head injuries as it depresses R.C.

2. Preanesthetic medication:

- Morphine is used to provide analgesia, amnesia & sedation but has **disadvantages**:

a. Delay awakening from anesthesia
b. Depresses R.C &VMC.
c. Post-operative urine retention & constipation.
d. Bronchospasm.
e. Miosis (Pin Point Pupil).
f. Vomiting.



3. Pulmonary edema (acute left ventricular failure):

a. Reduce anxiety → decreases after load.
b. Reduce preload by venodilatation.
c. Suppresses the over stimulated R.C & cough center.

4. Primary neurogenic shock:

used by slow I.V route (not S.C or I.M).

- **N.B.** In shock **not** given by S.C as there is delay absorption due to V.C so repeated S.C doses is dangerous as after correction of shock with increasing of blood flow → increase absorption from the injected sites → **toxicity**.

5. Anesthesia: I.V, intrathecal or epidural injections.

Side effects

1. CNS:

➢ Suppress RC & VMC, while stimulating CTZ → vomiting.

➢ Increases intra-cranial pressure (ICP).

1. Respiratory system: bronchoconstriction.
2. GIT: constipation (use laxative).
3. Urinary: urine retention.
4. Allergy.
5. Hypotension.
6. **Dependence**.

Contraindications

1. Extremities of age (very young or very old) → defective metabolism.
2. Head injuries as morphine produces:
    a. Suppresses R.C → CO_2 accumulation → cerebral VD → increase ICP.
    b. Miosis → mask sign of lateralization (diagnosis).
3. Increased intracranial pressure.
4. Impaired pulmonary functions e.g. bronchial asthma & COPD.
5. Impaired liver functions.
6. Alone in biliary or renal colic.
7. Acute abdomen e.g. appendicitis (relieve pain but this will mask the diagnosis).
8. During pregnancy & lactation: neonatal addiction then **withdrawal syndrome** (crying, irritability, diarrhea & convulsions).
5. During labor: supresses RC → neonatal asphyxia and prolong labor.
6. History of allergy & history of addiction.

Morphine toxicity

1)*Acute toxicity:*

- Manifestations:
  - Coma
  - PPP
  - Hypo (hypoxia, hypoventilation, hypotension & hypothermia)
  - then respiratory failure or even death.
- Treatment of acute morphine toxicity:
  a. Artificial respiration& respiratory stimulants e.g. O_2 95% + CO_2 5%.
  b. Stomach wash with permanganate then saline even if given by injection.
  c. Specific antidote: naloxone or nalmefene (longer $t_{1\2}$ = 8-10h).

2) Chronic toxicity (Addiction):

- Tolerance then psychic dependence & physical dependence.
- Chronic constipation & PPP, drug seeking habit (psychological dependence) & slow reaction to stimuli.
- Sudden stop of morphine → **withdrawal symptoms (abstinence syndrome)** which is characterized by (reverse of morphine actions):
  a. C.N.S: pain, muscle spasm, anxiety, insomnia, yawing & mydriasis.
  b. Secretions: increase sweating, lacrimation & rhinorrhea.
  c. Skin: itching.
  d. GIT: vomiting & diarrhea

- **Treatment of morphine addiction (dependence)**:

1. Hospitalization & psychotherapy.
2. Gradual withdrawal of morphine to dose sufficient to prevent withdrawal symptoms.
3. Replacement morphine with methadone (long-acting opiate).

➢ Buprenorphine (partial μ agonist of long duration) can be used.

4. Gradual withdrawal of methadone: methadone is long-acting → less withdrawal symptoms.
5. Clonidine: α_2 agonist.
6. Oral naltrexone (μ antagonist): prevents recurrence.

Used as maintenance therapy to prevent desired effect of morphine.

CODEINE (METHYL MORPHINE)

- Phenanthrene opium alkaloid.
- 10% of codeine → morphine in the body.
- Similar to morphine **but**:
  - *Better oral bioavailability (50%).
  - *Short duration (2-4 h).
  - *Weaker, (1\5 morphine) as analgesic, constipation & addiction.
  - *As potent as morphine as anti-tussive.
- Large doses: excitation, depresses R.C & V.M.C.
- **Therapeutic uses:**
  1. Anti-tussive: in dry dangerous cough as post-operative cough.
  2. Analgesic: in mild or moderate pain and added in paracetamol in same tablet

II- SEMI-SYNTHETIC MORPHINE DERIVATIVE

DI-ACETYL MORPHINE (HEROIN)

- Highly lipid soluble → concentrated in the brain → deacetylated to morphine.
- Short $t_{½}$ = ½ h, less emetic but **highly addictive** (not used for medical purposes).

III- Synthetic Morphine substitutes (Non-Phenantherenes)

Meperidine (Pethidine)

- **Pharmacokinetics:**
  - 50% oral bioavailability.
  - Quick onset & short duration (2-4h).
  - ***Metabolized*** in liver ***into***:

Meperidenic acid: inactive →conjugation with glucuroic acid → urine.

Nor-meperidine: active → excitation & convulsions.

Pharmacodynamics: ***(Morphine like + Atropine like)***

- Less Analgesic (1\10 morphine).
- Less Addiction.
- Less emetic.
- Less inhibition of R.C.
- No Anti-tussive effect.
- No PPP (mydriasis).
- No Constipation.
- No Drowsiness.
- Local anesthetic.
- Increases ADH release.
- Antagonized by naloxone.
- Large dose: excitation (atropine like + nor-meperidine).

- **Uses of meperidine:**

1. ***Pain:*** severe visceral pain eg. Myocardial infarction & alone in colic.
2. ***Preanesthetic medication:*** better than morphine.
3. ***Labor*:** obstetric analgesia.

Fentanyl

- Alfentanyl, Sufentanil & Remifentanil.
- Synthetic narcotic analgesic related to mepridine.
- **Strong μ agonist** → strong analgesic 80 times more than morphine.
- **Highly lipohilic** so quick onset & short duration especially remifentanil.
- not oral due to extensive GIT 1st pass metabolism.
- Used alone or with droperidol as analgesic ± nitrous oxide as anesthetic
- **Side effect:**
  1. Vomiting & marked suppression of R.C.
  2. Increases muscle tone & rigidity → needs muscle relaxant.
- **Uses:** neurosurgery & endoscopies, pain killer as transdermal patch.

Diphenoxylate (Lomotil)

- It has morphine like action on GIT.
- Some lipid solubility → some cross BBB → some C.N.S effect.
- Used to treat diarrhea.
- Combined with atropine.

Loperamide (Imodium)

Actions:

1. Stimulates opiate receptors present in GIT but not pass BBB.
2. Inhibits intestinal motility (as morphine).

- **Uses:** In diarrhea of various etiologies.

Methadone

Actions:

- Narcotic analgesic as potent as morphine with $T_{1\2} > 24h$.
- Oral administration
- Longer than morphine (more tissue binding) & slow release → fewer withdrawal symptoms so less dependence.
- Inhibits RC, cough center, prolonged QT interval constipation & miosis + strong local anesthetic.

- **Uses:**

1. Analgesic in severe pain (not common).
2. Treatment of morphine & heroin dependence.

Dextromethorphan

- Synthetic antitussive.
- **No** (analgesia, addiction & inhibition of R.C).

Mixed Agonist-Antagonists Narcotic Analgesics

- They are agonists at κ receptors & antagonists at μ receptors.
- **Characters:**
  - They are **agonists in the absence of morphine** (no morphine addiction) → κ agonist → analgesic.
  - In the **presence of morphine (addiction) → μ antagonist** → withdrawal symptoms. (*except buprenorphine* : μ partial agonist).
- Mild dependence → mild withdrawal symptoms.
  - **Partial agonist at R.C (low ceiling effect):** With increasing dose → increasing the analgesic effect but no increase in R.C depression, but if respiratory depression occurs it will be resistant to naloxone reversal.
- **Used as** an analgesic & can be used in the diagnosis of opiate addicts.
- **Examples:**

1)Pentazocine 2)Nalbuphin 3) Butorphanol

4)Buprenorphine:

- μ partial agonist, slow dissociation from receptor → long duration.
- Administered orally or better sublingual to bypass 1st pass effect.
- Used in the treatment of opioid & heroin dependence.

Narcotic Antagonists

- **Examples:** - Naloxone& Nalmefene (injection). - Naltrexone (oral).
- **Characters:**
  - Pure opiate antagonist (mainly μ blockers), but also block (κ, δ & sigma).
  - Block all action of opiates.

(1) Naloxone

- Has short $t_{½}$ (1-2h) & used by injection I.V.
- Metabolized by hydroxylation & conjugation with glucuronic acid.
- **Uses:**

1. Treatment of acute morphine poisoning.
2. Neonatal asphyxia:
   a. IM to the mother before labor.
   b. Intra-umbilical to the baby after labor.
3. **Diagnosis of opiate addiction** (SC naloxone → mydriasis" withdrawal manifestations").

- **Side effects:** tachycardia & arrhythmia.

(2) Naltrexone

- Oral administration, Half life = 10hrs.
- Long duration.

Used in addiction (after detoxification).

Side effects: hepatotoxicity, nausea & sedation.

(3) Nalmefene

Derivative of naloxone but with long duration (8-10hrs).

- **Used in** treatment of opioid over dose.

Thank you