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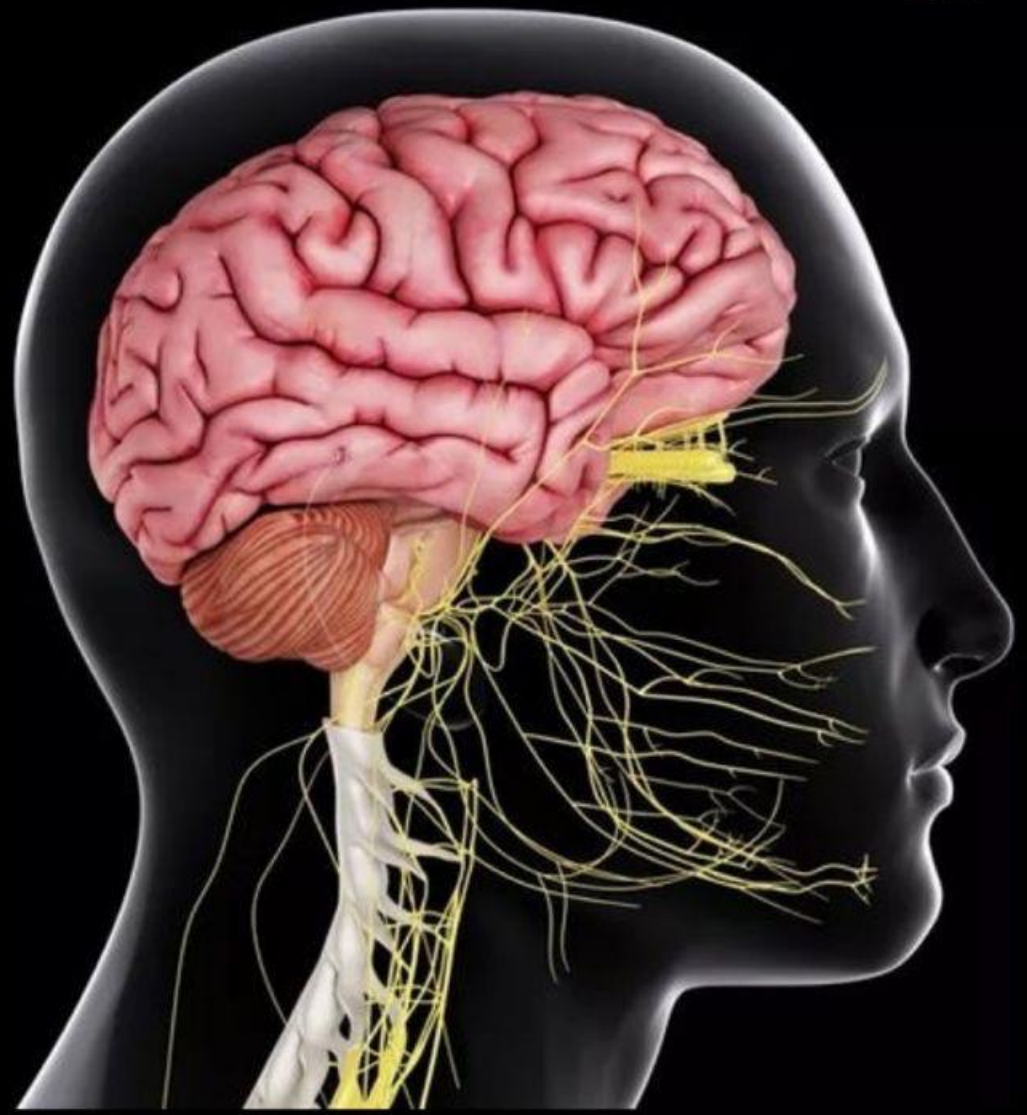

CENTRAL NERVOUS SYSTEM

SUBJECT : Pharmacology

LEC NO. : 2-opioids tables

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http://www.medclubhu.weebly.com/

Pain

Opioids

- "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"
- Acute or chronic
- Consequence of complex neurochemical processes in the peripheral and central nervous systems
- Subjective

Types of pain

- **Nociceptive pain:** pain due to an actual or potentially .tissue-damaging injury that is transduced and transmitted via nociceptors.

Examples: somatic pain, cancer pain, postoperative pain

- **Neuropathic pain**: pain arising as a direct consequence of a lesion or disease of the somatosensory system.

Examples: carpal tunnel syndrome, chemotherapy-induced peripheral neuropathy, postherpetic neuralgia.

- **Others**

Hyperalgesia: abnormally increased sensitivity to pain

Allodynia: pain resulting from an originally non-painful stimulus

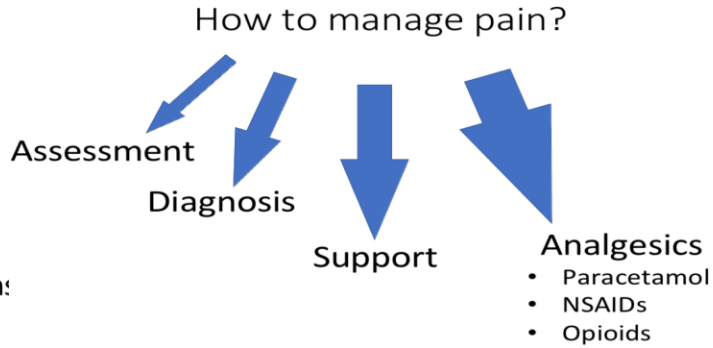
Hypoalgesia: decreased sensitivity to painful stimuli

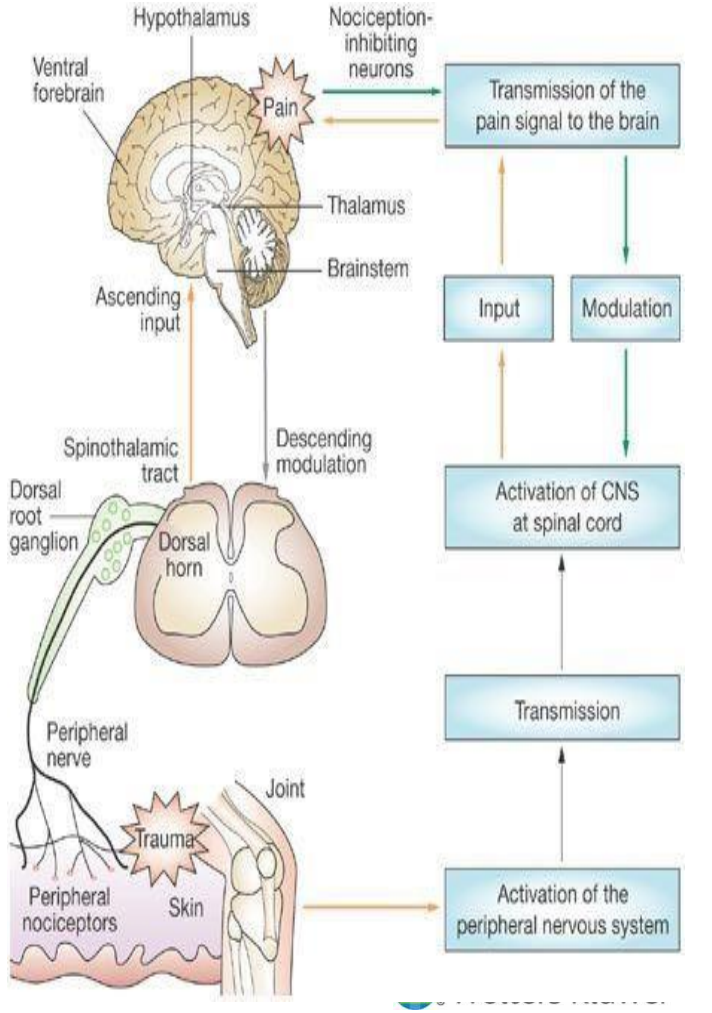
Analgesia: reduction or relief of pain sensation without affecting other sensations

Anesthesia: local or general reduction or absence of all sensations (touch, pain, temperature, …) with or without loss of motor function. This may be accompanied by loss of consciousness

Paresthesia: abnormal or altered sensation of the body (numbness, tingling, or burning)

- Opium?
- Opioid?
- Opiate?
- Narcotic?



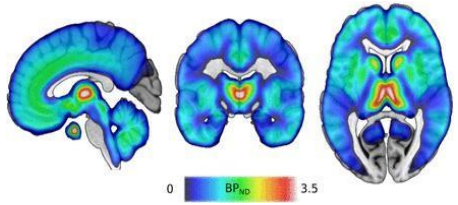


Opioids

- *Opioids* are natural, semi-synthetic or synthetic compounds that bind specifically to opioid receptors and share the properties of one or more of the naturally occurring endogenous opioids

Opioid Receptors

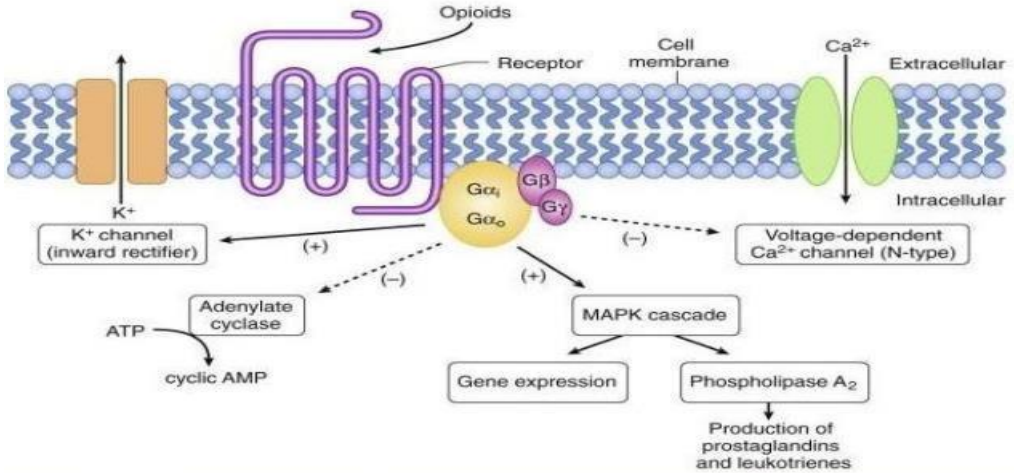
- Distributed throughout the CNS
  - Nucleus of tractus solitaries
  - PAG
  - Cerebral cortex
  - Thalamus
  - Spinal cord But also…. Gut ,, Bladder

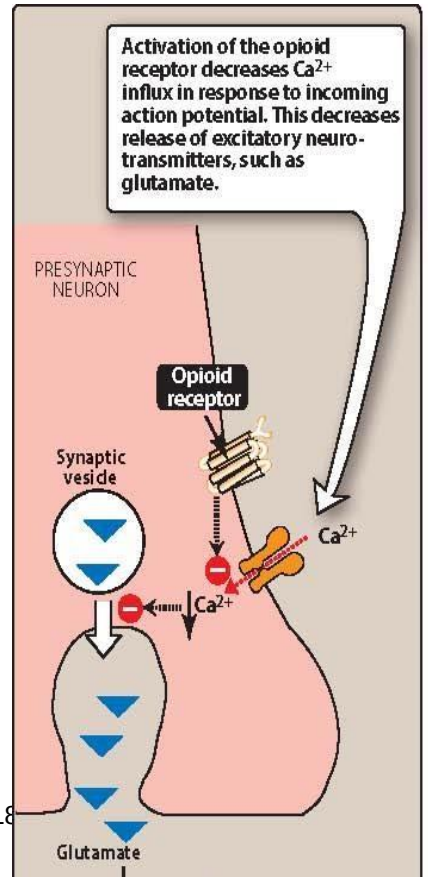


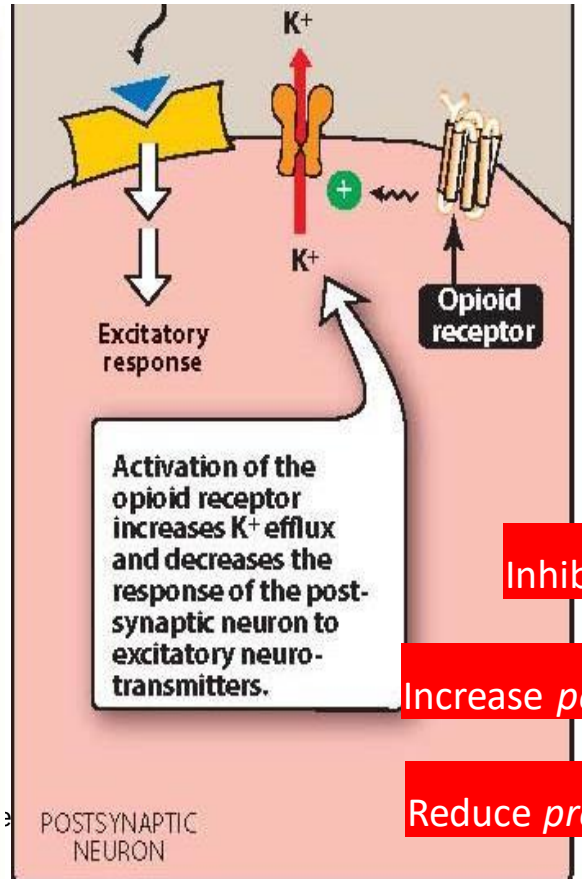
Mean distribution of μ-opioid receptors in the human brain based on the 204 [11C]carfentanil BPND images, *Kantonen et al., 2019*

Opioid Receptor	μ	δ	K
Endogenous opioid	*Endorphins*	*Enkephalins*	*Dynorphins*
Effect	Analgesia, euphoria, respiratory depression, constipation, sedation, meiosis	Seizures, analgesia?	Dysphoria, analgesia?

Mechanism of Action





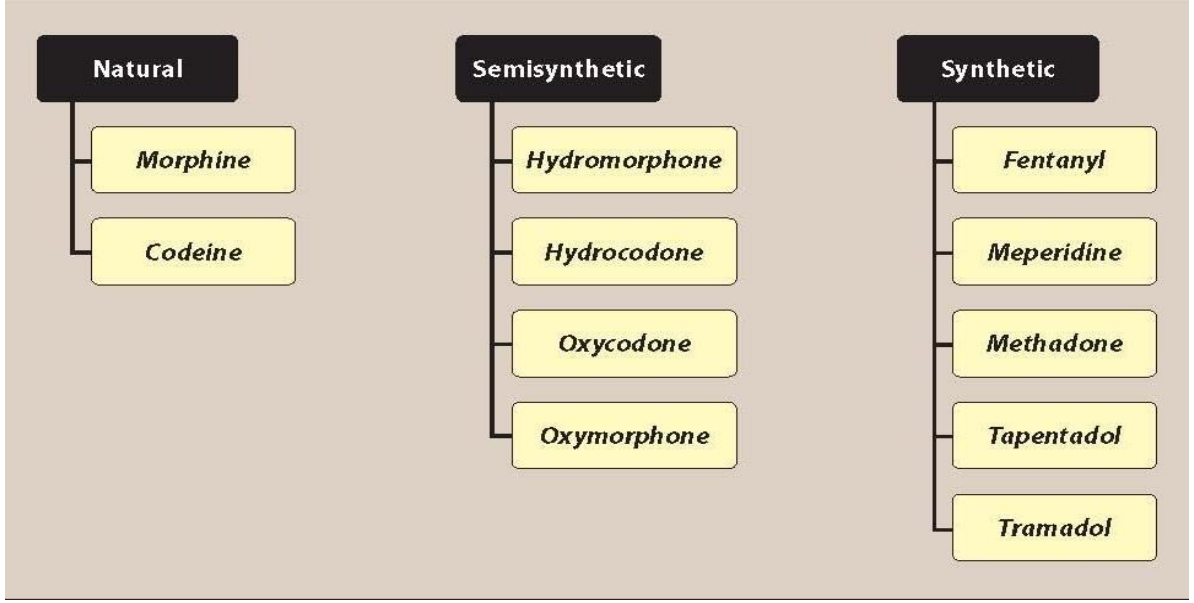


G protein-coupled receptors (GPCRs) [$G_{i/o}$ (inhibitory)]

Inhibit adenylyl cyclase

Increase *postsynaptic* K^+ efflux

Reduce *presynaptic* Ca^{++} influx



Opioid Agonists

1. Morphine
2. Codeine
3. Oxycodone
4. Oxymorphone
5. Hydrocodone
6. Fentanyl
7. Methadone
8. Meperidine

Phenanthrenes	Action on Opioid Receptors
Morphine	Agonist
Codeine	Agonist
Oxycodone	Agonist
Oxymorphone	Agonist
Hydromorphone	Agonist
Hydrocodone	Agonist
Buprenorphine	Partial agonist
Nalbuphine	Mixed Agonist/Antagonist
Butorphanol	Mixed Agonist/Antagonist

Benzmorphan	
Pentazocine	Mixed Agonist/Antagonist
Phenylpiperidines	
Fentanyl	Agonist
Alfentanil	Agonist
Sufentanil	Agonist
Meperidine	Agonist
Diphenylheptane	
Methadone	Agonist

1. Morphine

- Natural
- Derived from *papaver somniferum*
- After the Greek god of dreams

" Morpheus"

Mechanism of action

- Binds to opioid receptors (mainly **μ**)- full agonist
  - CNS, gut, bladder
- Decreases the release of many excitatory transmitters from nerve terminals carrying nociceptive stimuli

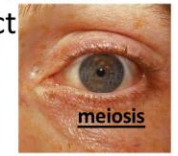
Actions:

- **Analgesia**
  - without loss of consciousness
  - raises pain threshold (spinal cord)
  - alters perception of pain (brain)
    - ❖ still aware of pain, but not unpleasant
  - nociceptive >>> neuropathic

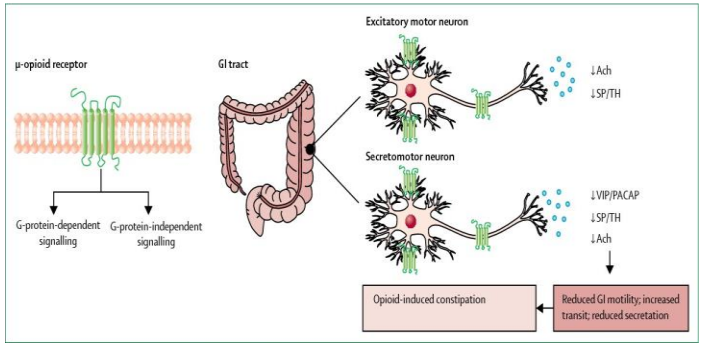
Actions:

- **Euphoria**
  - sense of contentment and well-being
  - caused by the disinhibition of the dopamine-containing neurons of the ventral tegmental area
- **Respiratory depression**
  - reduces the sensitivity of respiratory center to CO_2
  - most common cause of death from opioid overdose.
  - Tolerance develops quickly

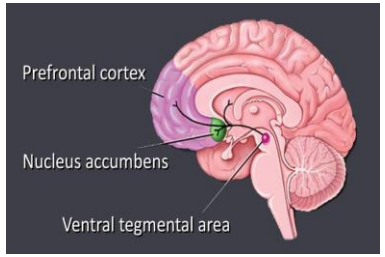
- **↓ cough reflex**
  - both morphine and codeine have *antitussive* effect

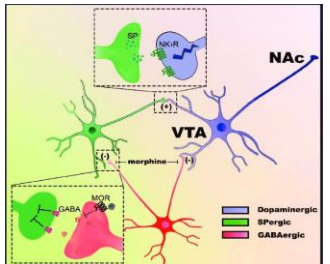


- **Miosis**
  - *pinpoint pupil*
  - results from **μ** and **κ** receptors
  - no tolerance to this effect
- **Emesis**
  - stimulates the chemoreceptor trigger zone in area postrema → vomiting
- **GI tract**
  - ↓ gut motility ↑ intestinal smooth muscle tone ↑ anal sphincter tone
  - constipation
  - little tolerance to this effect

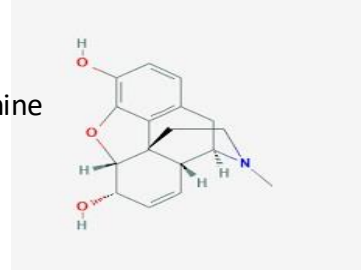


Morphine and the Reward Pathway





- **Cardiovascular**
  - Peripheral vasodilation most prominent effect due to histamine release and decreased adrenergic tone
  - Very high doses may produce bradycardia and hypotension
  - Contraindicated in patients with severe brain/head injury
- **Histamine release**



- Enhance the release of histamine from mast cells, causing urticaria, sweating, and vasodilation.

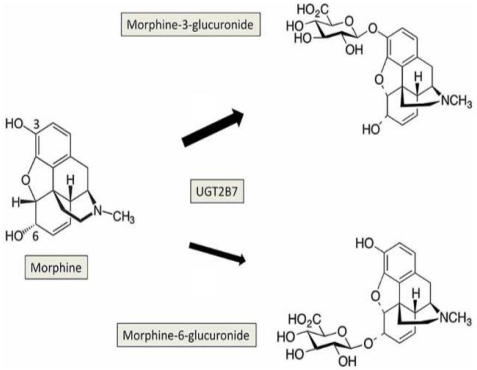
- **Urinary retention:**

- Due to contraction of sphincter, inhibition of reflex of urination and increase ADH.

- **OPIAD: opioid-induced androgen deficiency**
- **Labor. - increases second stage of labor. How?**

Pharmacokinetics

- **Administration:** *IM, IV, SC* – best effect
- **Distribution:** enters all body tissues (including fetus) – contraindicated for analgesia in labor
- **Metabolism**: glucuronidated into 2 metabolites:
  - ❖ Morphine-6-glucuronide: potent analgesic
  - ❖ Morphine-3-glucuronide: not an analgesic
- **Duration of action**: 4-5 h in opioid-naïve patients.



Tolerance: Happens to analgesic + respiratory depressant + euphoric + sedative effects

- Not to miotic or constipating effects (problem?)
- Cross tolerance develops between opioids

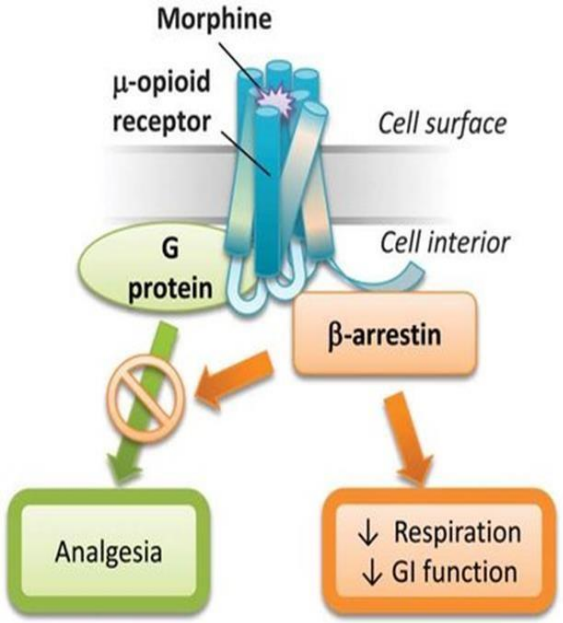
Dependence

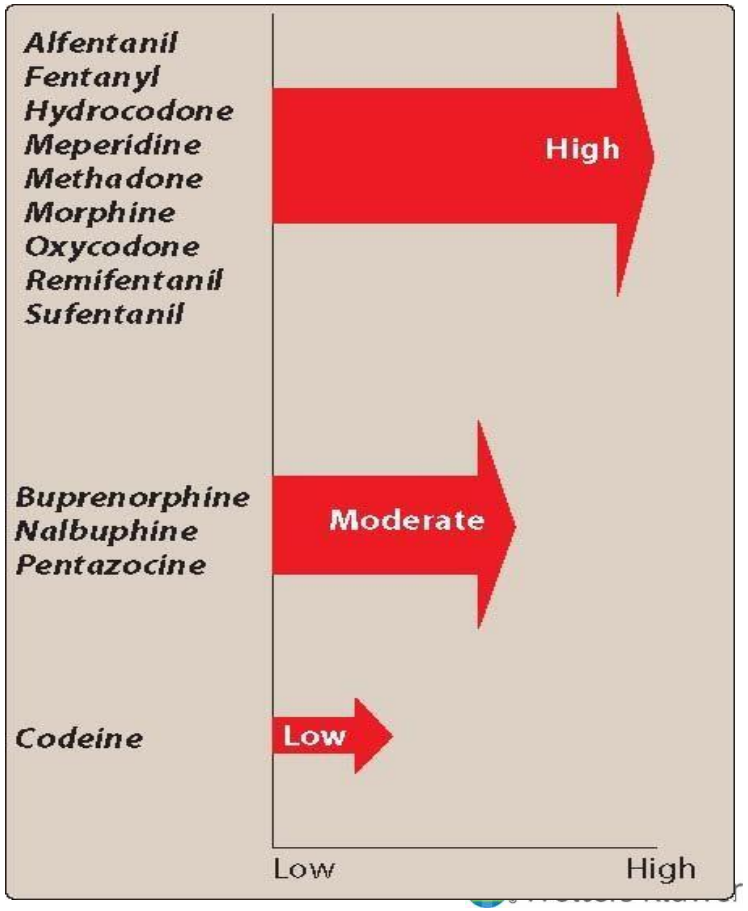
- Physical
- Psychological

Therapeutic Use	Comments
Analgesia	*Morphine* is the prototype opioid agonist. Opioids are used for pain in trauma, cancer, and other types of severe pain.
Treatment of diarrhea	Opioids decrease the motility and increase the tone of intestinal circular smooth muscle. [Note: Agents commonly used include *diphenoxylate* and *loperamide* (see Chapter 31).]
Relief of cough	*Morphine* does suppress the cough reflex, but *codeine* and *dextromethorphan* are more
Treatment of acute pulmonary edema	Intravenous *morphine* dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure, possibly via the vaso-dilatory effect. This, in effect, decreases cardiac preload and afterload, as well as anxiety experienced by the patient.
Anesthesia	Opioids are used as pre-anesthetic medications, for systemic and spinal anesthesia, and for postoperative analgesia.

Tareq Saleh ©

Morphine is used with caution/contraindicated in patients with bronchial asthma. WHY?





Codeine

Natural

Weak analgesic

Codeine → CYP2D6 → Morphine

Required for the analgesic effects

Uses:

- mild/moderate pain (+paracetamol)
- Antitussive (dextromorphan preferred)

-used over-the counter??????

Oxycodone

highly abused

oxycodone >> morphine (orally)

semisynthetic

oxymorphone >>>>>>>>>> morphine (parenterally)

oxymorphone >>> morphine (orally)

semisynthetic

Oxymorphone

Fentanyl

Synthetic

Fentanyl 100-folds > morphine

Uses

- Postoperative pain, epidural analgesia in labor
- Cancer pain
- Anesthesia (sedative)

Kinetics

- Rapid onset of action (15-30 mins)
- Short duration of action

Contraindicated in opioid-naïve patients

Meperidine (Pethidine)

Synthetic

- κ agonist
- Some μ agonist activity
- anticholinergic

Uses

- Used only for short-term analgesia management
- Preferred over morphine during labor

Morphine

Analgesia

- Postoperative pain
- Renal colic
- Cancer-associated pain

MI, Acute Pulmonary Edema (LFV)

- To decrease preload
- Pain

Preanesthetic

Antitussive?

- Codeine is better

Therapeutic Uses

Can you use morphine as antidiarrheal?

Methadone

Synthetic

- Methadone ≠ morphine
- μ agonist
- NMDA antagonist
- SNRI

Uses

- Analgesia (against nociceptive and neuropathic pain)
- Detoxification of opioids and heroin (treatment of opioid abuse)

Hydrocodone

Hydrocodone=morphine (orally)

semisynthetic

Uses

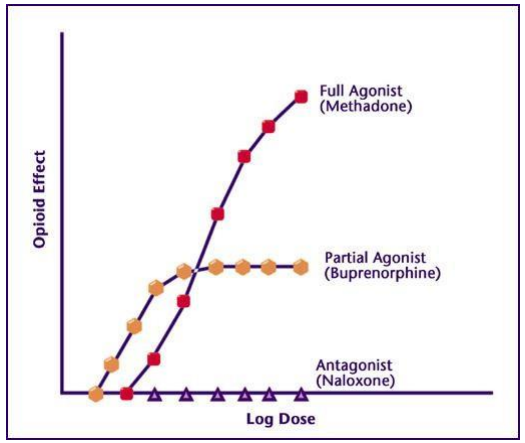
- moderate to severe pain (+ibuprofen or paracetamol)
- antitussive

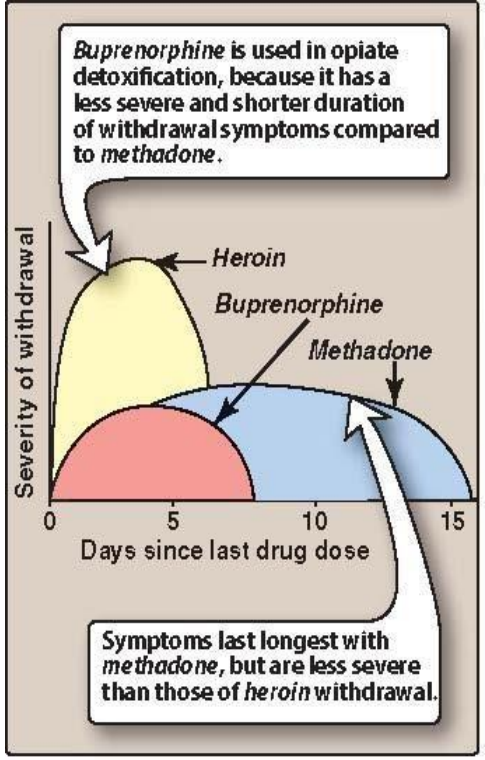
Opioid Agonists

1. **Morphine**
2. **Codeine**
3. **Oxycodone**
4. **Oxymorphone**
5. **Hydrocodone**
6. **Fentanyl**
7. **Methadone**
8. **Meperidine**

Opioid Partial Agonists Mixed Agonist-Antagonist

- **Partial opioid agonists bind to opioid receptors but have only partial efficacy relative to full opioid agonists.**
- **Buprenorphine**
- **Pentazocine**
- **Nalbuphine**





Buprenorphine

- Partial agonist at μ
  Antagonist at κ
- Little sedation, respiratory depression, hypotension
- Combined with naloxone (antagonist). Why?

Uses
- Used for opioid detoxication
- Moderate to severe pain

Pentazocine

- Partial agonist at κ
  Antagonist at μ and δ
- Contraindicated in patients with coronary artery disease
- Less euphoria

Uses
- Analgesia (limited use because of side effects)

Other Analgesics

- **Tapentadol. 2. Tramadol**

Tramadol

- Binds and acts on μ
  SNRI
- Less respiratory depression than morphine
- Highly abused

Uses
- Analgesia (moderate to severe pain)

Opioid Antagonists

- **1 Naloxone. 2 Naltrexone**

Naloxone

- Competitive antagonist at μ, κ and δ
- Can precipitate withdrawal
- Administered IV
  Half-life: 30-81 minutes

Uses
- Used to reverse coma and respiratory depression of opioid overdose

Naltrexone

- Longer duration of action than naloxone
  Oral

Uses
- Used for opioid detoxication (maintenance)
- Used to decrease cravings in patients with alcohol dependence

Morphine is in important component of the treatment of myocardial infarction. The beneficial effect of morphine in the treatment of MI is because of its ability to result in:

A) Decreased venous return (cardiac preload)
B) Increased stroke volume
C) Respiratory depression
D) Reduced peripheral vascular resistance
E) Lowered intracranial pressure

Activation of μ opioid receptors by morphine can result in which of the following effects?

A) Hyperalgesia
B) Arousal
C) Diarrhea
D) Mydriasis
E) Nausea and vomiting

High-Yield Terms to Learn

Opiate	A drug derived from alkaloids of the opium poppy
Opioid	The class of drugs that includes opiates, opiopeptins, and all synthetic and semisynthetic drugs that mimic the actions of the opiates
Opioid peptides	Endogenous peptides that act on opioid receptors
Opioid agonist	A drug that activates some or all opioid receptor subtypes and does not block any
Partial agonist	A drug that can activate an opioid receptor to effect a submaximal response
Opioid antagonist	A drug that blocks some or all opioid receptor subtypes
Mixed agonist-antagonist	A drug that activates some opioid receptor subtypes and blocks other opioid receptor subtypes

The opioid partial agonist that is indicated for the treatment of heroin and opioid dependence is Buprenorphine

The opioid antidote is Naloxone

The opioid agonist used to induce analgesia in labor as a replacement of morphine is Meperidine

Metabolism of Codeine by CYP2D6 to morphine is required to produce its analgesic effects.

Which synthetic full-opioid agonist can be used as during anesthesia? Fentanyl