



# Opioids

Pharmacology and Toxicology  
Central Nervous System Module  
Third Year Medical Students

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The Hashemite University

Textbook: pp. 180-193



# Pain

- “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



# Pain

## Pain rating scale





# Pain

## 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**



# Definitions

**Hyperalgesia**: abnormally increased sensitivity to pain

**Allodynia**: pain resulting from an originally non-painful stimulus

**Hypoalgesia**: decreased sensitivity to painful stimuli

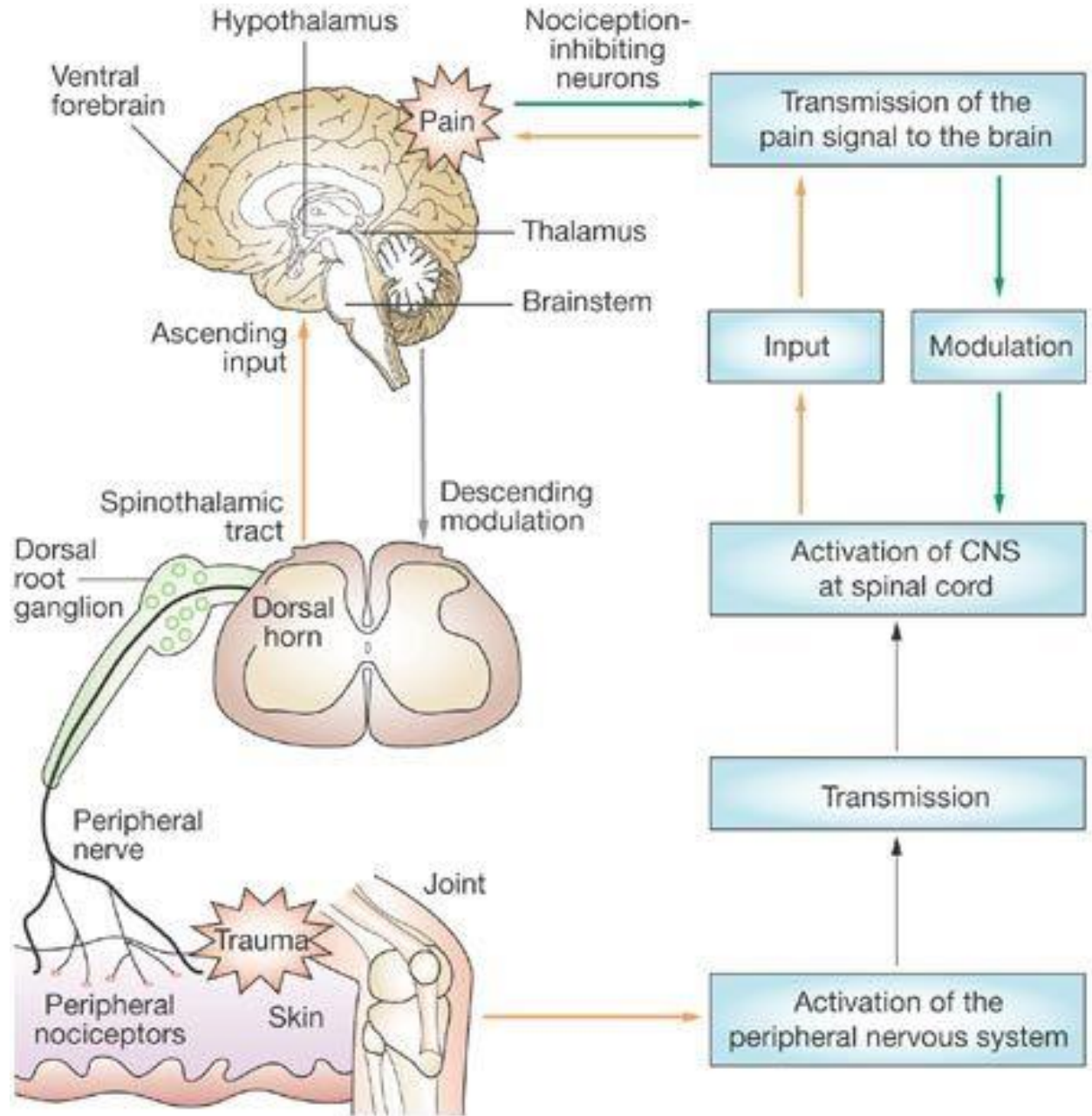
**Analgesia**: reduction or relief of pain sensation without affecting other sensations

**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

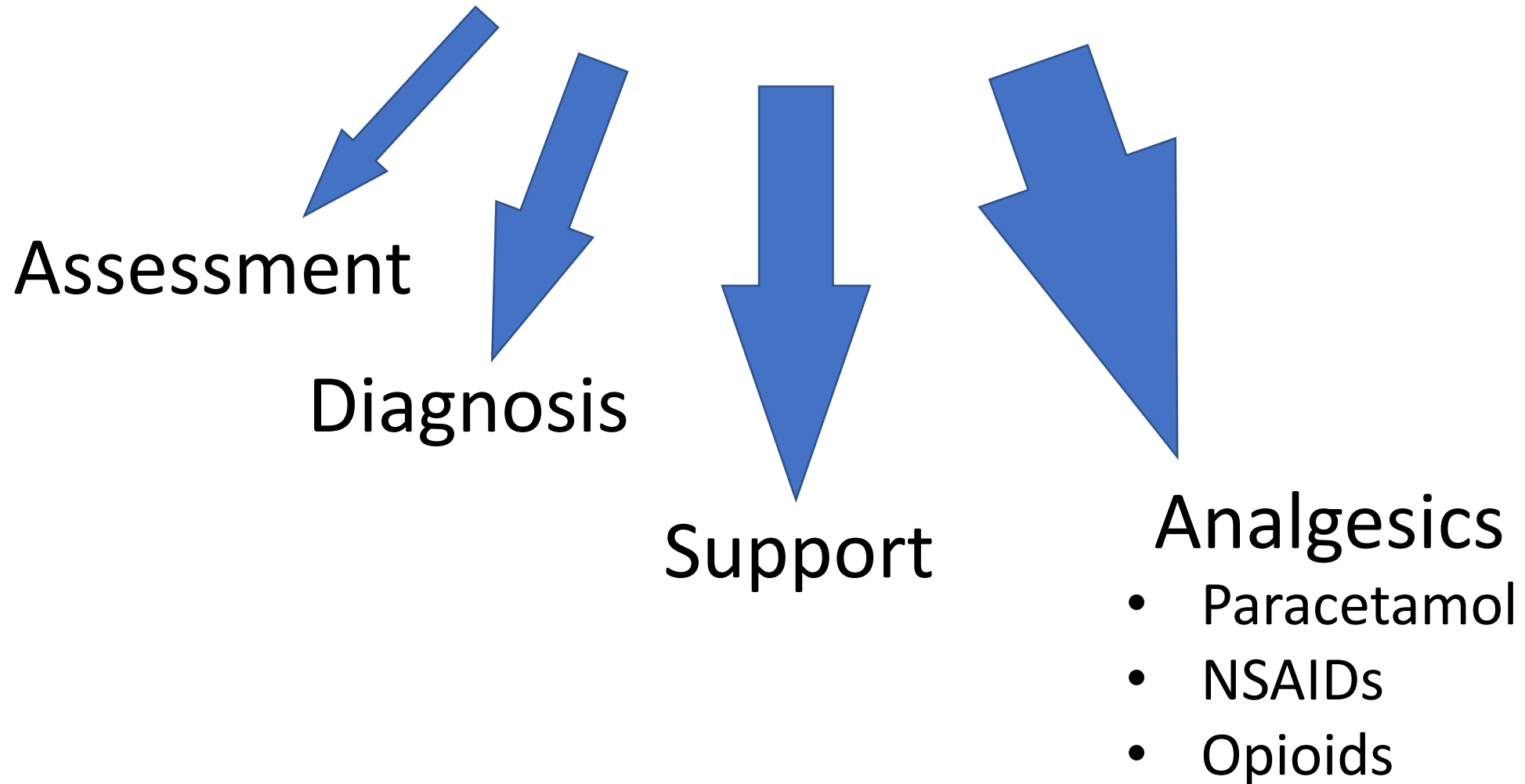
**Paresthesia**: abnormal or altered sensation of the body (numbness, tingling, or burning)



# The Pain Pathway



# How to manage pain?





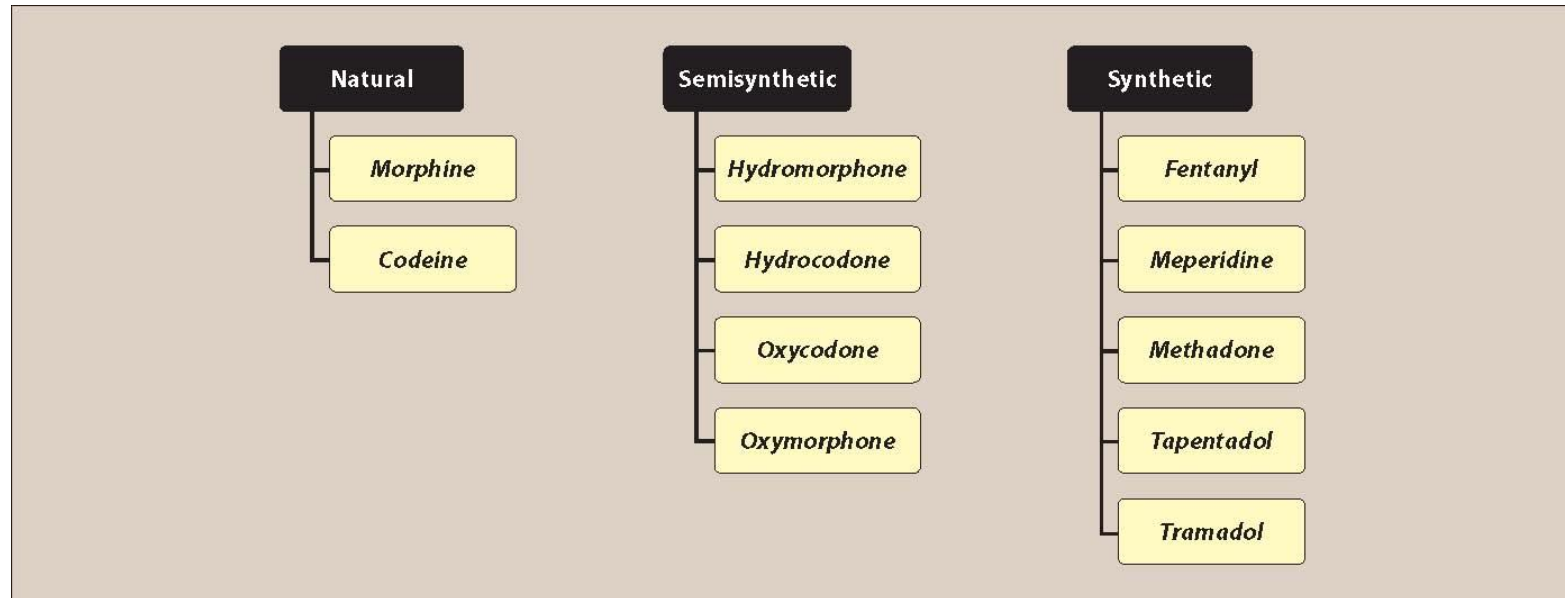
# Can you tell the difference between these terms:

- 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



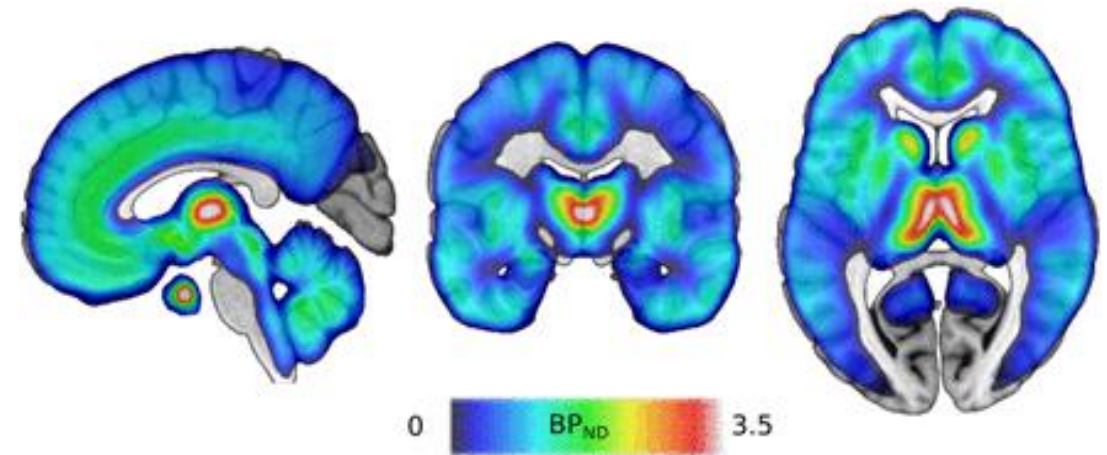
# Opioid Receptors

- Distributed throughout the CNS

- Nucleus of tractus solitaries
- PAG
- Cerebral cortex
- Thalamus
- Spinal cord

But also....

- Gut
- Bladder



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

# Opioid Receptors

## Opioid Receptor



Endogenous opioid

*Endorphins*

*Enkephalins*

*Dynorphins*

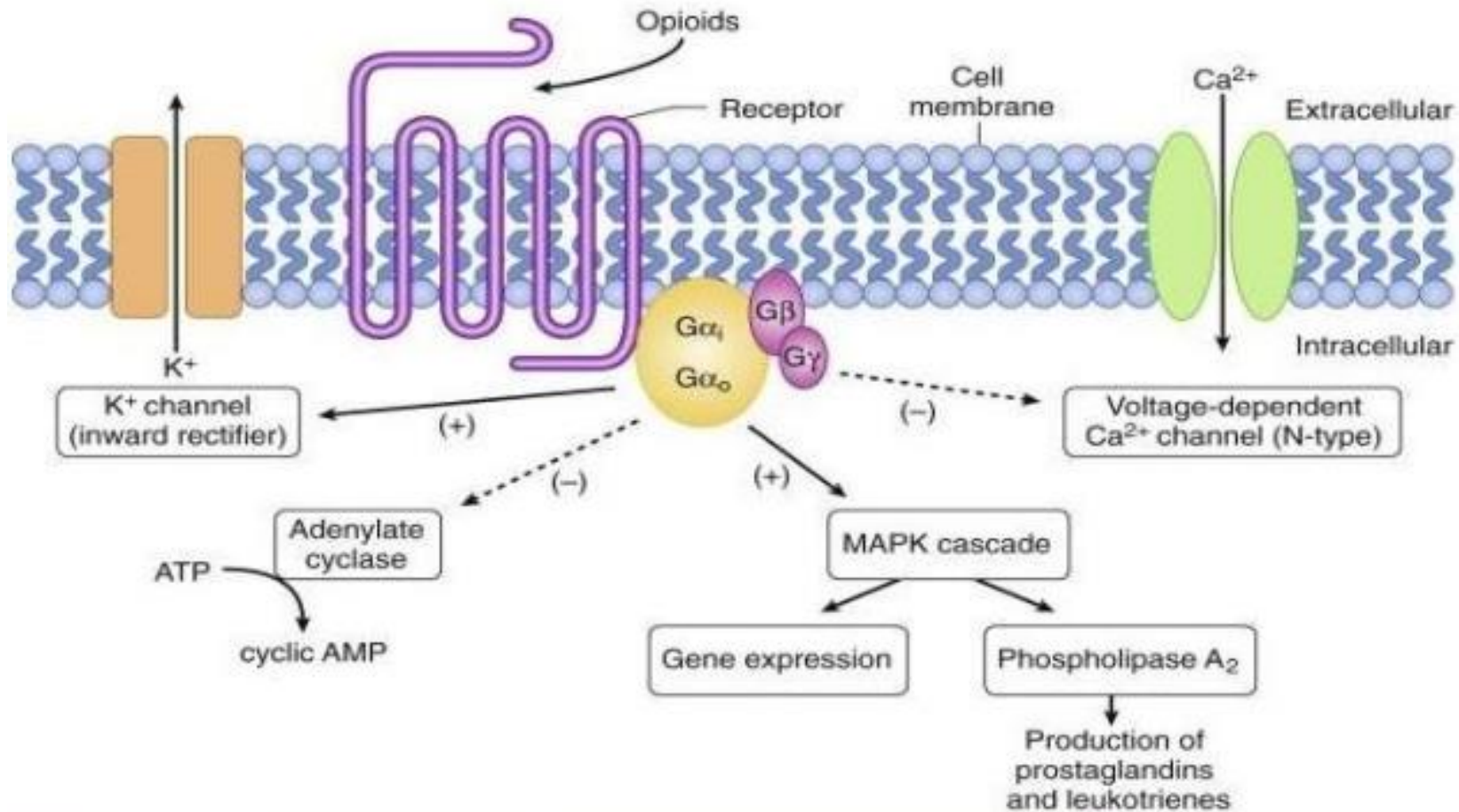
Effect

Analgesia, euphoria,  
respiratory depression,  
constipation, sedation,  
meiosis

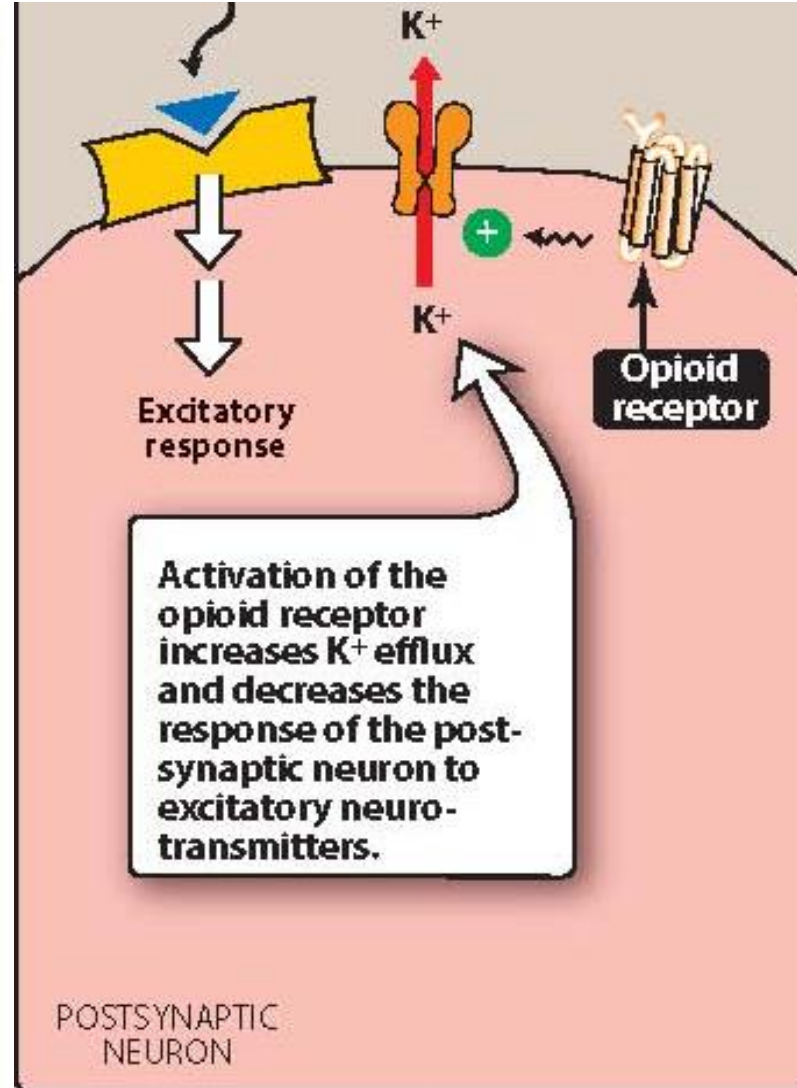
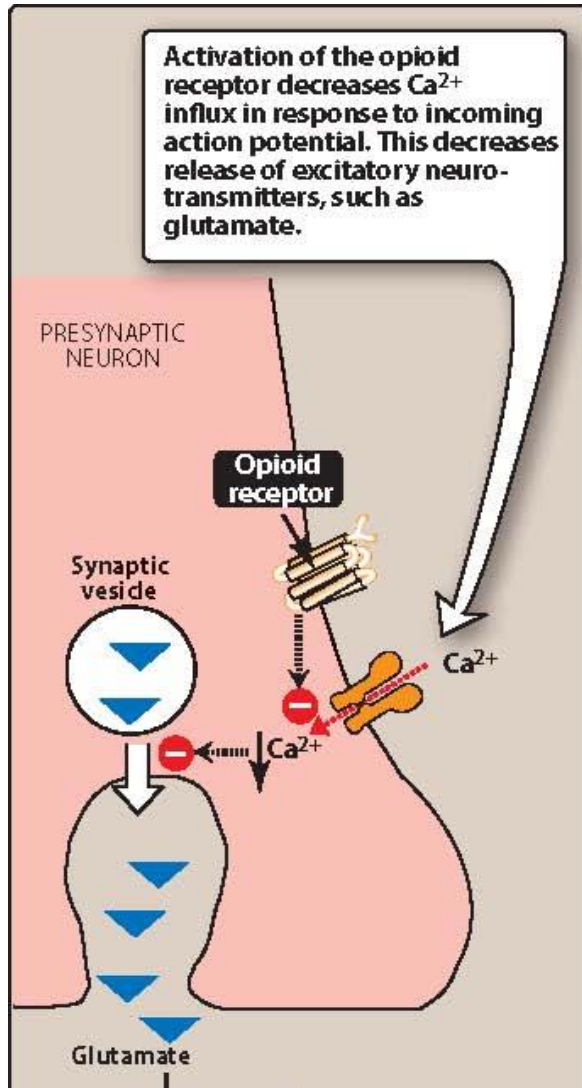
Seizures, analgesia?

Dysphoria, analgesia?

# Opioids: Mechanism of Action



# Opioids: Mechanism of Action



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

Inhibit adenylyl cyclase

Increase *postsynaptic*  $K^{+}$  efflux

Reduce *presynaptic*  $Ca^{++}$  influx



# Opioids

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

Benzmorphans	
<i>Pentazocine</i>	Mixed Agonist/Antagonist
Phenylpiperidines	
<i>Fentanyl</i>	Agonist
<i>Alfentanil</i>	Agonist
<i>Sufentanil</i>	Agonist
<i>Meperidine</i>	Agonist
Diphenylheptane	
<i>Methadone</i>	Agonist





# Opioid Agonists

- Morphine
- Codeine
- Oxycodone
- Oxymorphone
- Hydrocodone
- Fentanyl
- Methadone
- Meperidine

# Morphine

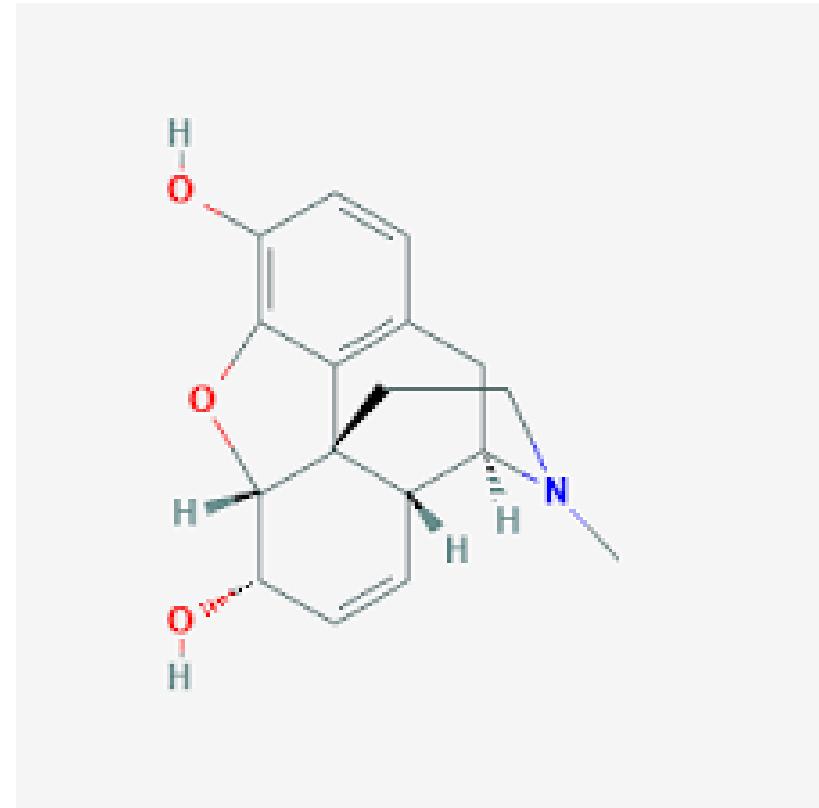
- Natural
- Derived from *papaver somniferum*
- After the Greek god of dreams  
“Morpheus”



# Morphine

## Mechanism of action

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



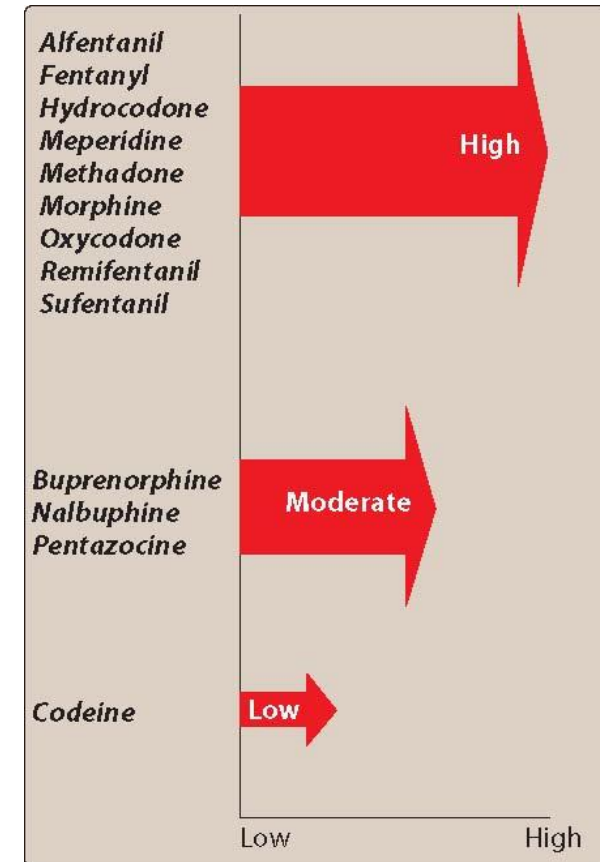
Morphine

# Morphine

## Actions:

- **Analgesia**

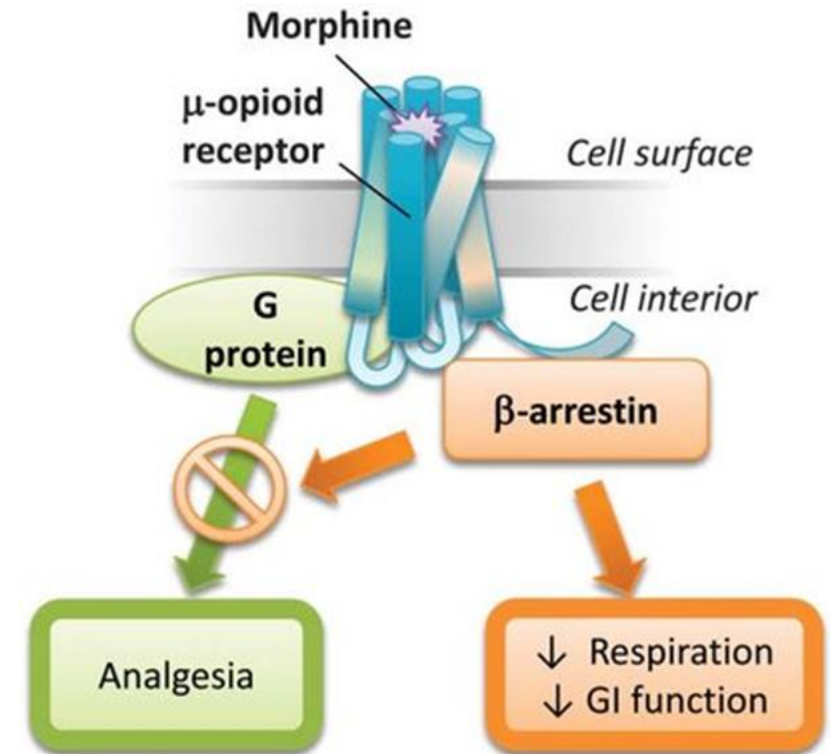
- without loss of consciousness
- raises pain threshold (spinal cord)
- alters perception of pain (brain)
  - ❖ still aware of pain, but not unpleasant
- nociceptive >>> neuropathic



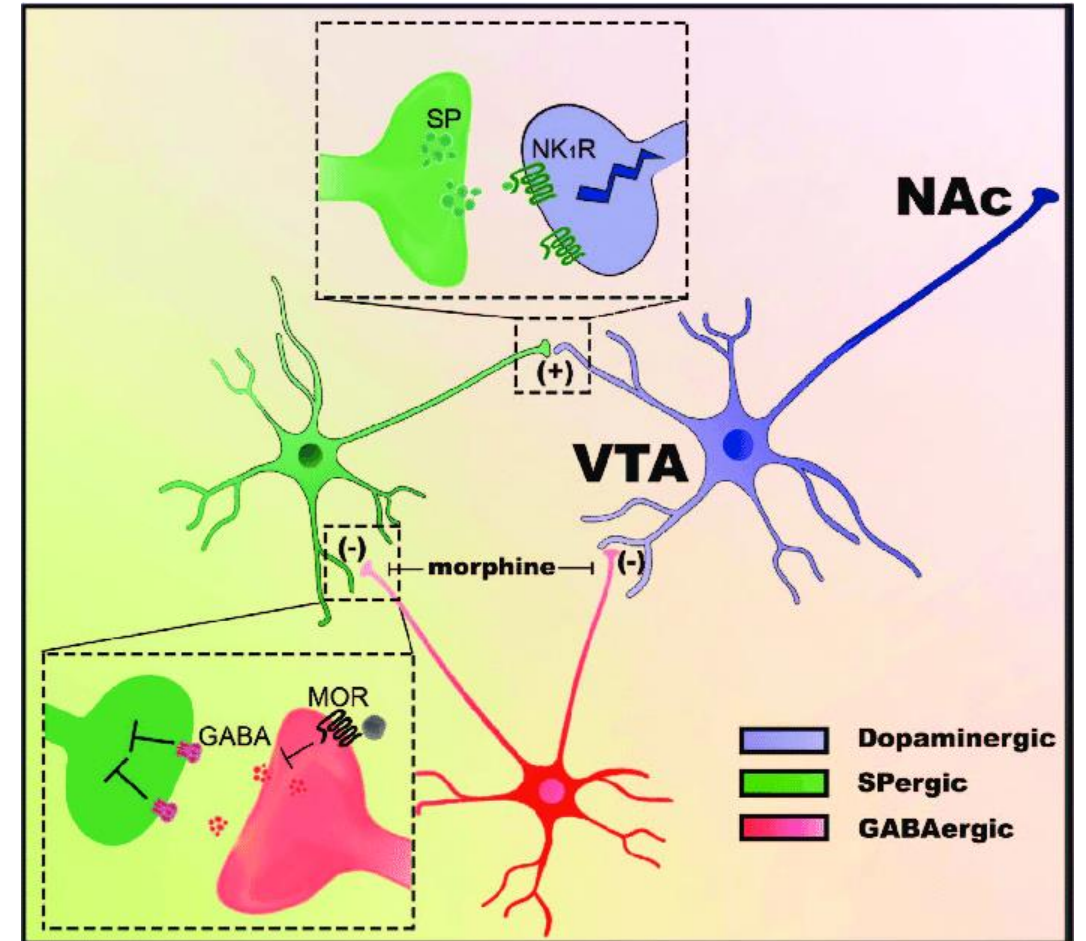
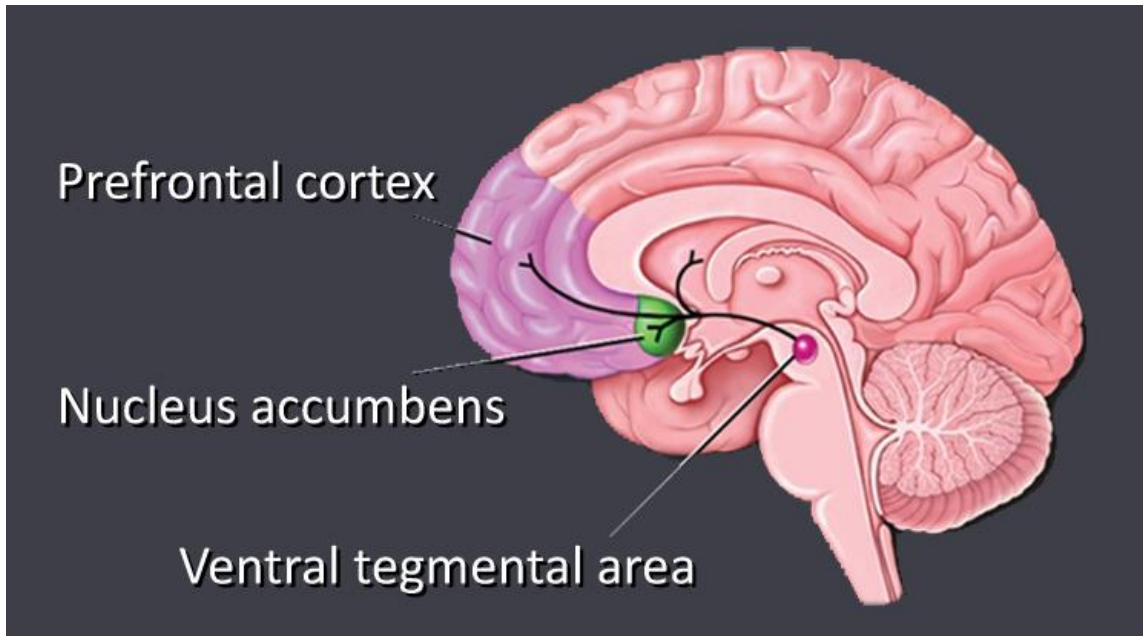
# Morphine

## 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<sub>2</sub>
  - most common cause of **death** from opioid overdose.
  - Tolerance develops quickly



# Morphine and the Reward Pathway

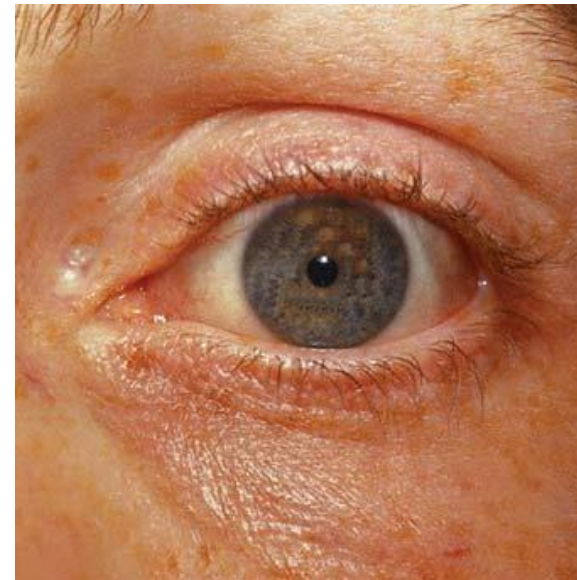




# Morphine

## Actions:

- ↓ cough reflex
  - both morphine and codeine have *antitussive* effect.
- **Miosis**
  - *pinpoint pupil*
  - results from  $\mu$  and  $\kappa$  receptors
  - no tolerance to this effect



miosis

# Morphine

## Actions:

### • Emesis

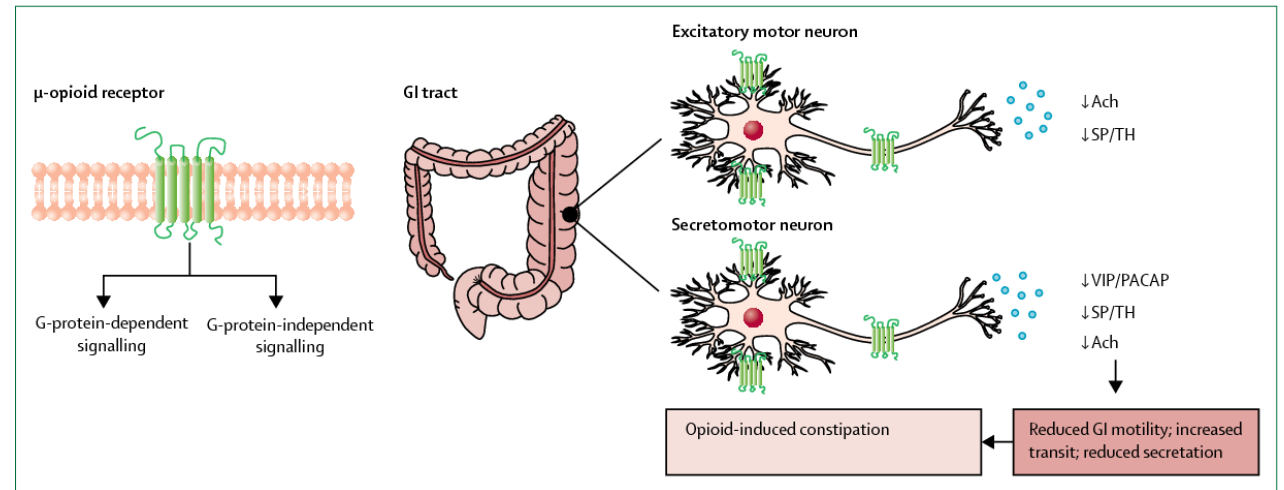
- stimulates the chemoreceptor trigger zone in area postrema → vomiting

### • GI tract

- ↓ gut motility ↑ intestinal smooth muscle tone ↑ anal sphincter tone

- constipation

- **little tolerance to this effect**





# Morphine

## Actions:

- **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.

# Morphine

## Actions:

- **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?

## "MORPHINE"

<b>M</b>	<b>MYOSIS</b>
<b>O</b>	<b>OUT OF IT</b> (SEDATION)
<b>R</b>	<b>RESPIRATORY DEPRESSION</b>
<b>P</b>	<b>PNEUMONIA</b> (ASPIRATION)
<b>H</b>	<b>HYPOTENSION</b>
<b>I</b>	<b>INFREQUENCY</b> (CONSTIPATION, URINARY RETENTION)
<b>N</b>	<b>NAUSEA</b>
<b>E</b>	<b>EMESIS</b>

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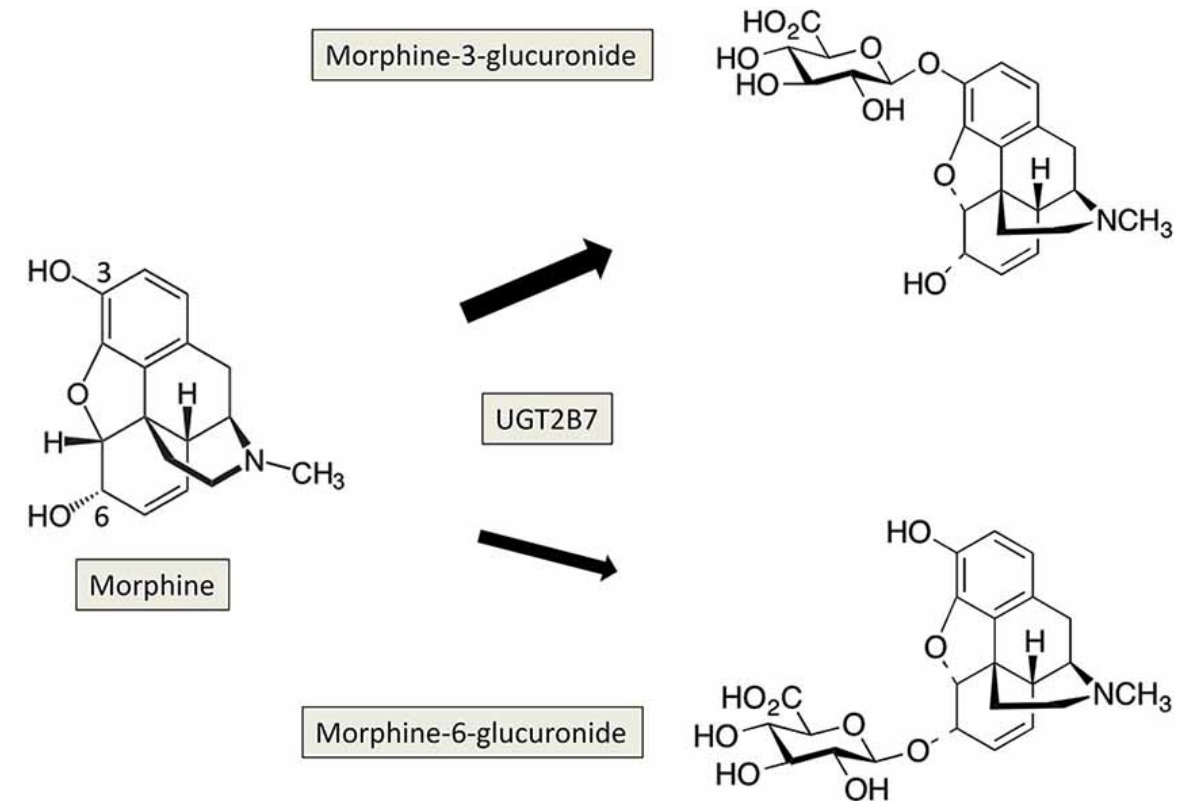


Morphine is used with  
caution/**contraindicated**  
in patients with  
bronchial asthma. WHY?

# Morphine

## 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.





# Morphine

## Analgesia

- Postoperative pain
- Renal colic
- Cancer-associated pain

## MI, Acute Pulmonary Edema (LFV)

- To decrease preload
- Pain

## Preanesthetic

## Therapeutic Uses

## Antitussive?

- Codeine is better

Can you use morphine as antidiarrheal?



# Summary of Morphine's Therapeutic Uses

Therapeutic Use	Comments
<b>Analgesia</b>	<i>Morphine</i> is the prototype opioid agonist. Opioids are used for pain in trauma, cancer, and other types of severe pain.
<b>Treatment of diarrhea</b>	Opioids decrease the motility and increase the tone of intestinal circular smooth muscle. [Note: Agents commonly used include <i>diphenoxylate</i> and <i>loperamide</i> (see Chapter 31).]
<b>Relief of cough</b>	<i>Morphine</i> does suppress the cough reflex, but <i>codeine</i> and <i>dextromethorphan</i> are more commonly used.

<b>Treatment of acute pulmonary edema</b>	Intravenous <i>morphine</i> dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure, possibly via the vasodilatory effect. This, in effect, decreases cardiac preload and afterload, as well as anxiety experienced by the patient.
<b>Anesthesia</b>	Opioids are used as pre-anesthetic medications, for systemic and spinal anesthesia, and for postoperative analgesia.



# Morphine

## Tolerance:

- Happens to analgesic + respiratory depressant + euphoric + sedative effects
- Not to miotic or constipating effects (problem?)
- Cross tolerance develops between opioids

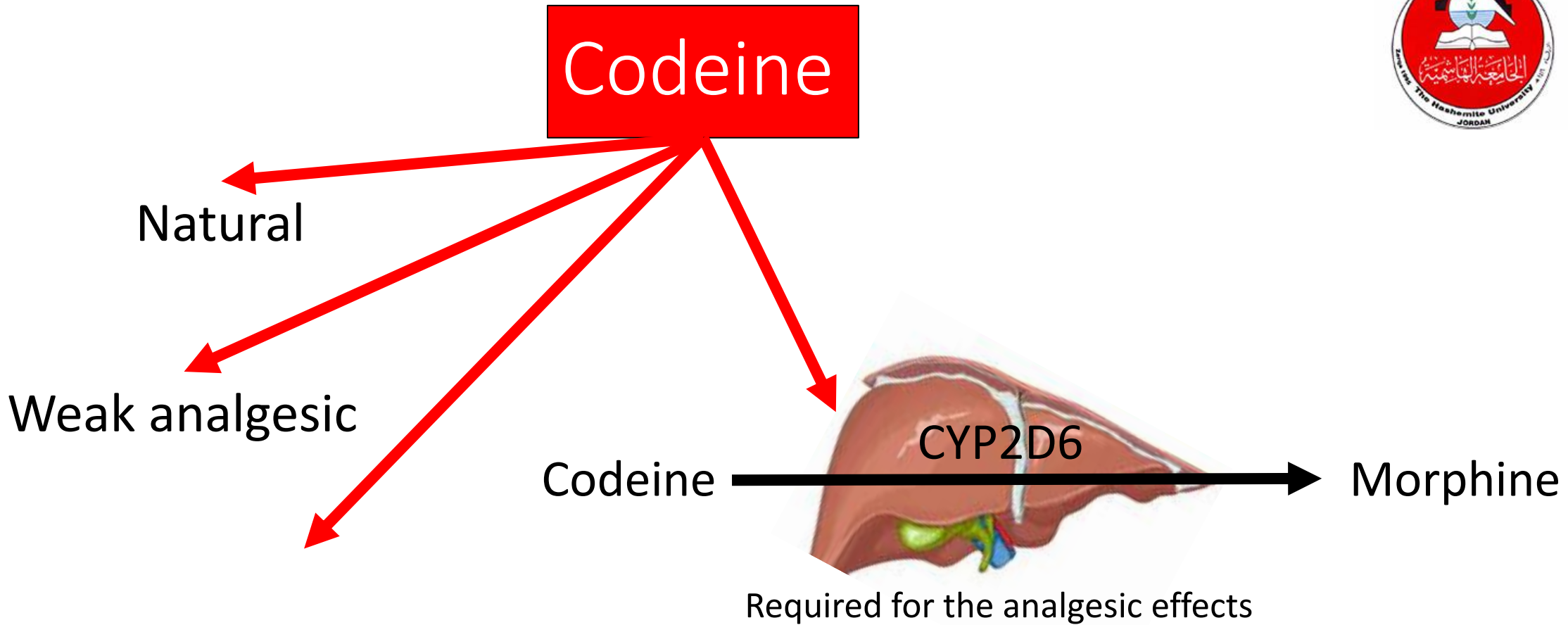
## Dependence

- Physical
- Psychological



# Opioid Agonists

- Morphine
- Codeine
- Oxycodone
- Oxymorphone
- Hydrocodone
- Fentanyl
- Methadone
- Meperidine



**Uses:**

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

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



# Opioid Agonists

- Morphine
- Codeine
- Oxycodone
- Oxymorphone
- Hydrocodone
- Fentanyl
- Methadone
- Meperidine

Oxycodone



oxymorphone

>>>>>>>>>>

morphine  
(parenterally)

highly abused

semisynthetic

oxycodone >>  
morphine (orally)

oxymorphone  
>>> morphine  
(orally)

semisynthetic

Oxymorphone





# Opioid Agonists

- Morphine
- Codeine
- Oxycodone
- Oxymorphone
- Hydrocodone
- Fentanyl
- Methadone
- Meperidine

# Hydrocodone

semisynthetic

Hydrocodone=morphine  
(orally)

## Uses

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





# Opioid Agonists

- Morphine
- Codeine
- Oxycodone
- Oxymorphone
- Hydrocodone
- Fentanyl
- Methadone
- Meperidine

# Fentanyl

Synthetic

Contraindicated  
in opioid-naïve  
patients

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



# Opioid Agonists

- Morphine
- Codeine
- Oxycodone
- Oxymorphone
- Hydrocodone
- Fentanyl
- Methadone
- Meperidine

# Methadone

Synthetic

- Methadone  $\neq$  morphine
- $\mu$  agonist
- NMDA antagonist
- SNRI

## Uses

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





# Opioid Agonists

- Morphine
- Codeine
- Oxycodone
- Oxymorphone
- Hydrocodone
- Fentanyl
- Methadone
- Meperidine

# Meperidine (Pethidine)

Synthetic

- $\kappa$  agonist
- Some  $\mu$  agonist activity
- anticholinergic

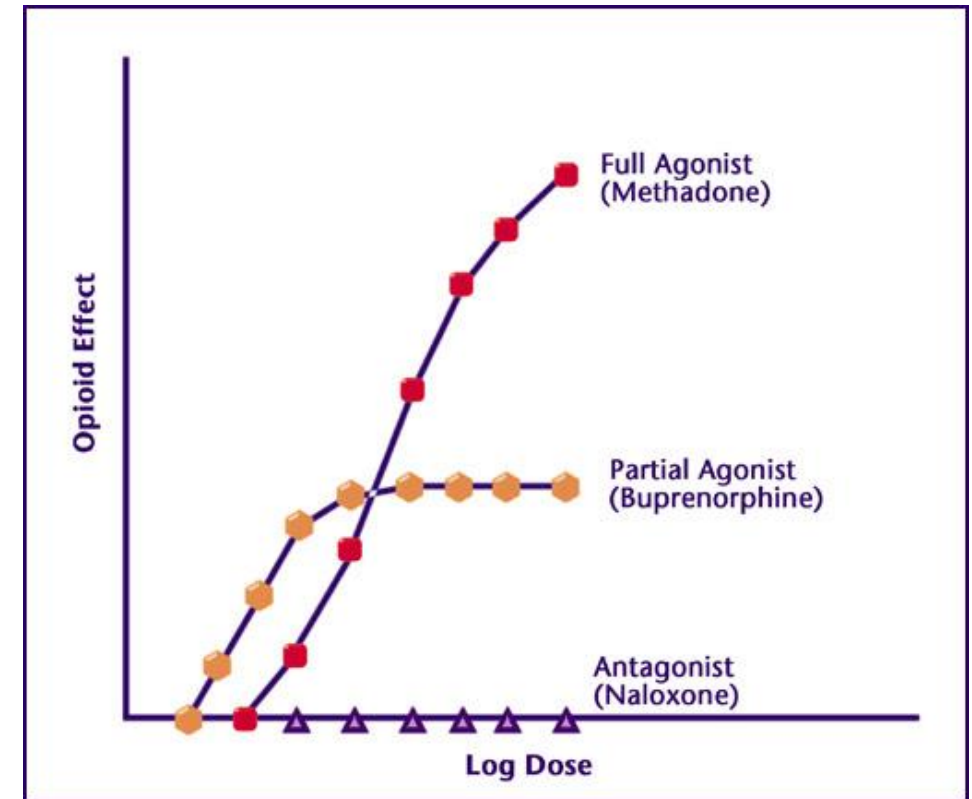
## Uses

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

# 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

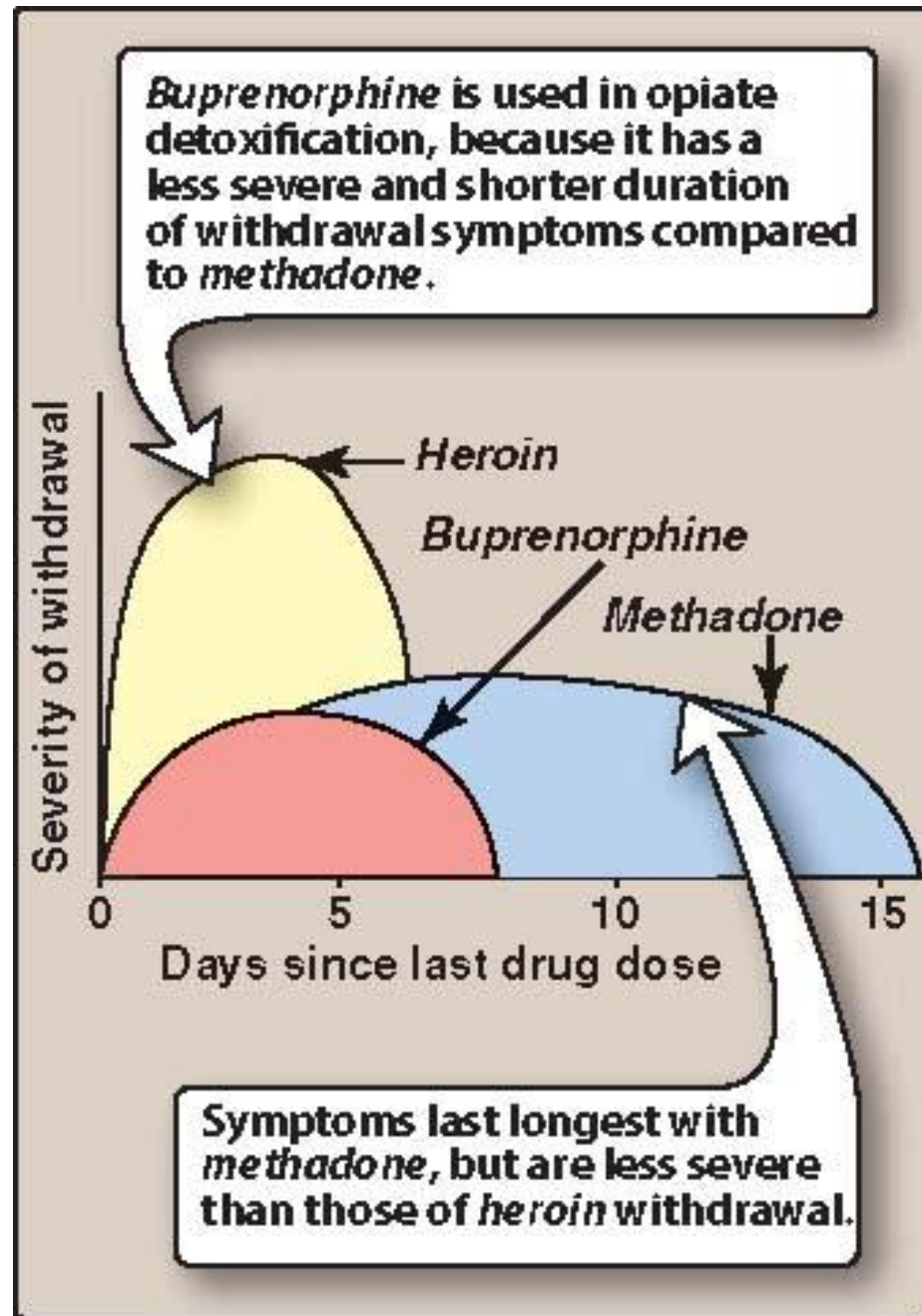
Partial agonist  
at  $\mu$   
Antagonist at  $\kappa$

Little sedation,  
respiratory depression,  
hypotension

Combined with  
naloxone  
(antagonist). Why?

## Uses

- Used for opioid detoxication
- Moderate to severe pain





# Opioid Partial Agonists

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



# Pentazocine

Partial agonist at  $\kappa$   
Antagonist at  $\mu$   
and  $\delta$

Less euphoria

Contraindicated in patients with coronary artery disease

## Uses

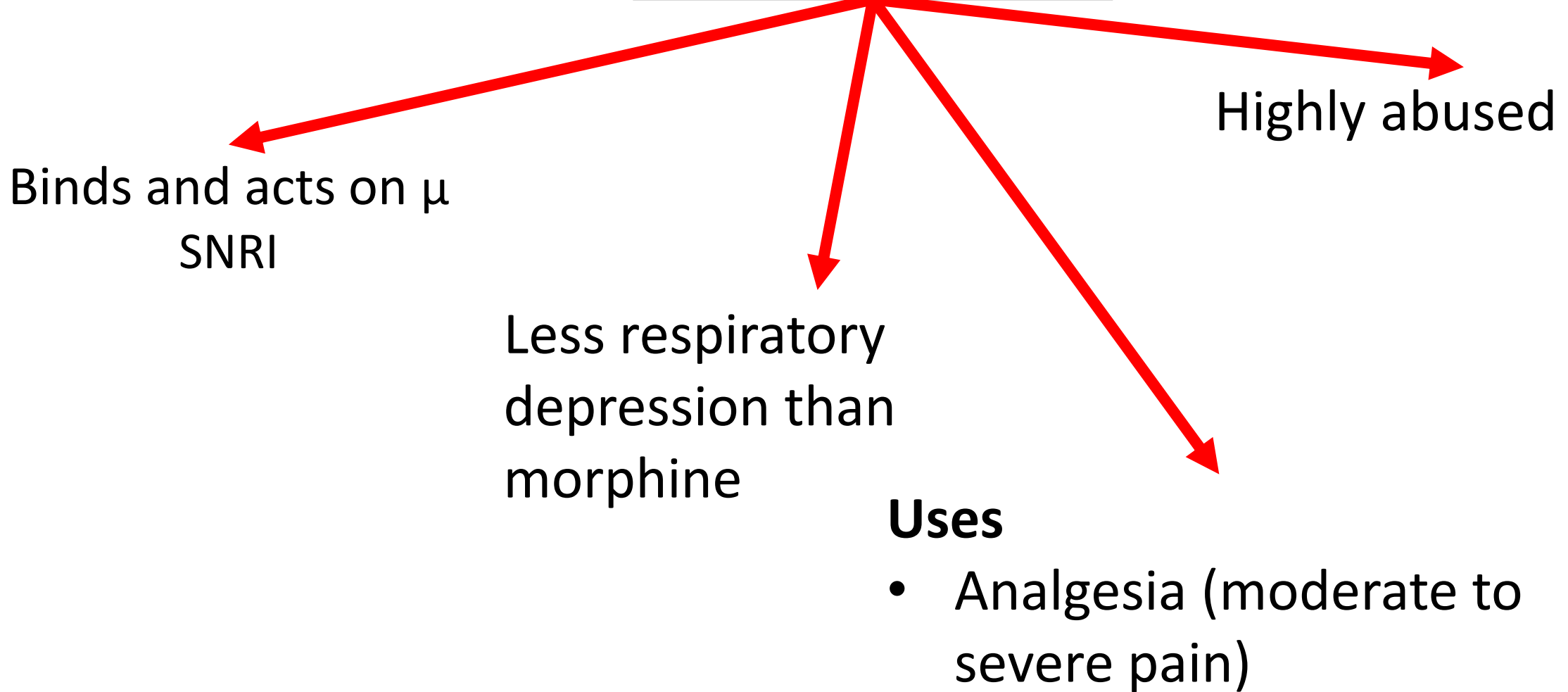
- Analgesia (limited use because of side effects)



# Other Analgesics

- Tapentadol
- Tramadol

# Tramadol





# Opioid Antagonists

- Naloxone
- Naltrexone

# Naloxone

Competitive  
antagonist at  $\mu$ ,  $\kappa$   
and  $\delta$

Administered IV  
Half-life: 30-81 minutes

Can precipitate  
withdrawal

## Uses

- Used to reverse coma and respiratory depression of opioid overdose



# Opioid Antagonists

- Naloxone
- Naltrexone



# Naltrexone

Longer duration of action  
than naloxone  
Oral

## Uses

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



## High-Yield Terms to Learn

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



Activation of  $\mu$  opioid receptors by morphine can result in which of the following effects?

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



Morphine is an 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



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

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