Narcotic analgesics

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By the end of this lecture, the student will be able to:

Lecture outline:

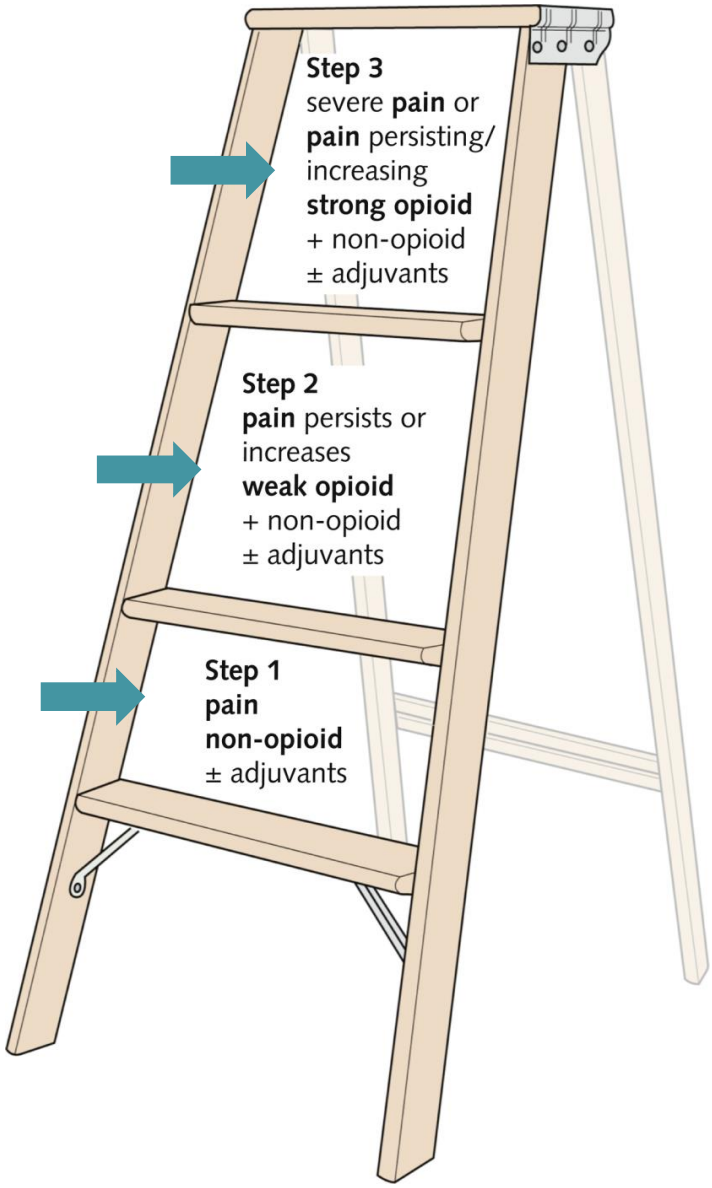
Basic concepts

Pain, which may be **acute or chronic**, is defined as an unpleasant **sensory and emotional** experience associated with actual or potential tissue damage.

Pain is **a subjective** experience.

An analgesic drug is one that effectively **removes (or at least lessens) the sensation of pain.**

Analgesics should be use of **in accordance with the analgesic ladder** (patients with pain should be treated with the least potent analgesic that will control their pain)



Pain perception

Pain perception is simply a three-stage process:

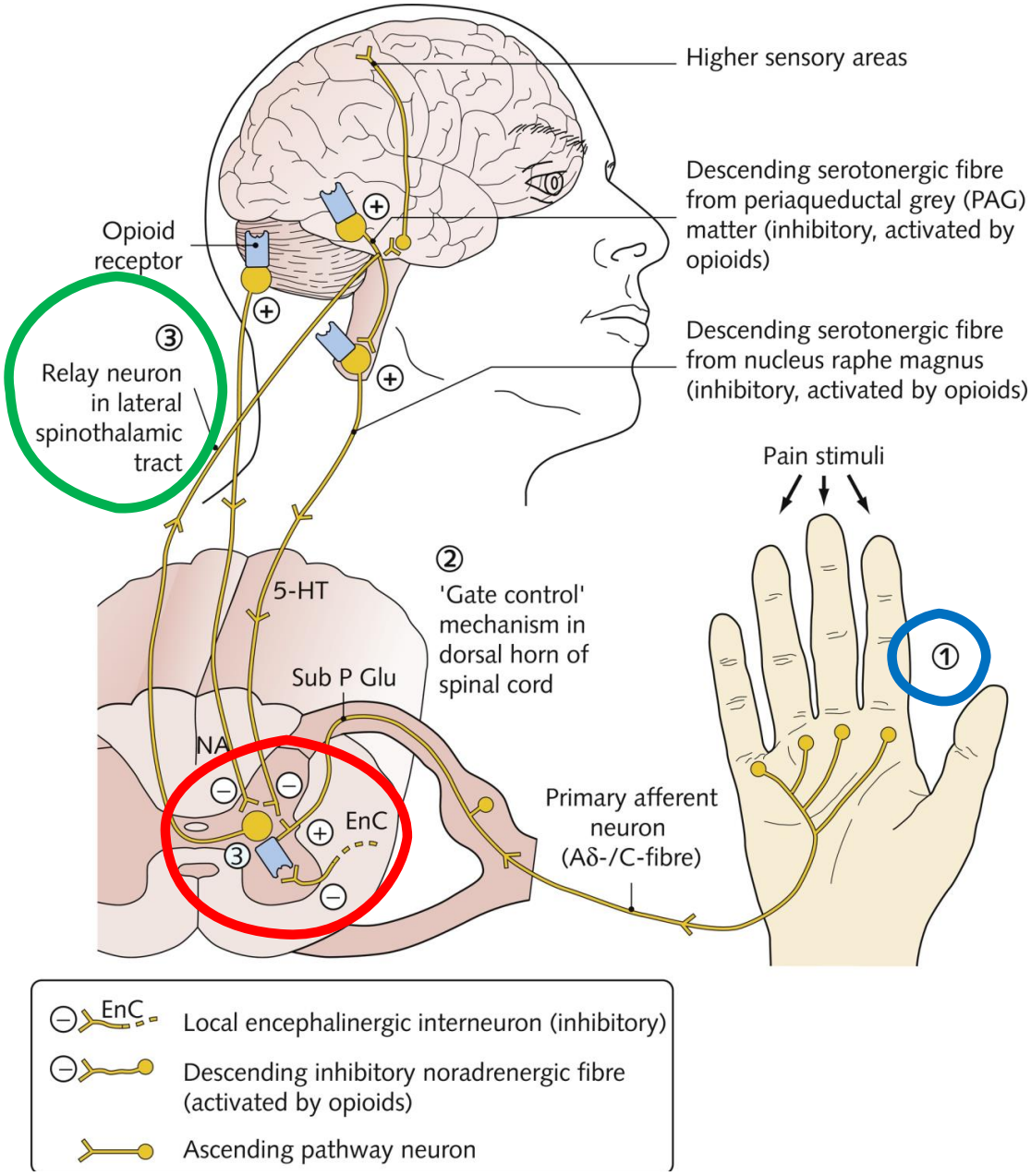
1. Activation of nociceptors (pain-specific receptors) in the peripheral tissues.

2. Transmission of pain information from the periphery to the dorsal horn of the spinal cord

   Pain signals in the spinal dorsal horn are modulated by descending inhibitory noradrenergic/serotonergic tracts from higher brain centers. → "gate-control mechanism".

   Theses inhibitory tracts are activated by endogenous opioids.

3. Upward passage of pain information via the spinothalamic tract, to the higher centers of the brain.



Opioid (narcotic) analgesics

MOA:

Natural or synthetic opioid analgesics relieve moderate to severe visceral or somatic pain by activating (agonists) a specific family of receptors known as **opioid receptors.**

Gold standard for strong pain relief

Opioid receptors

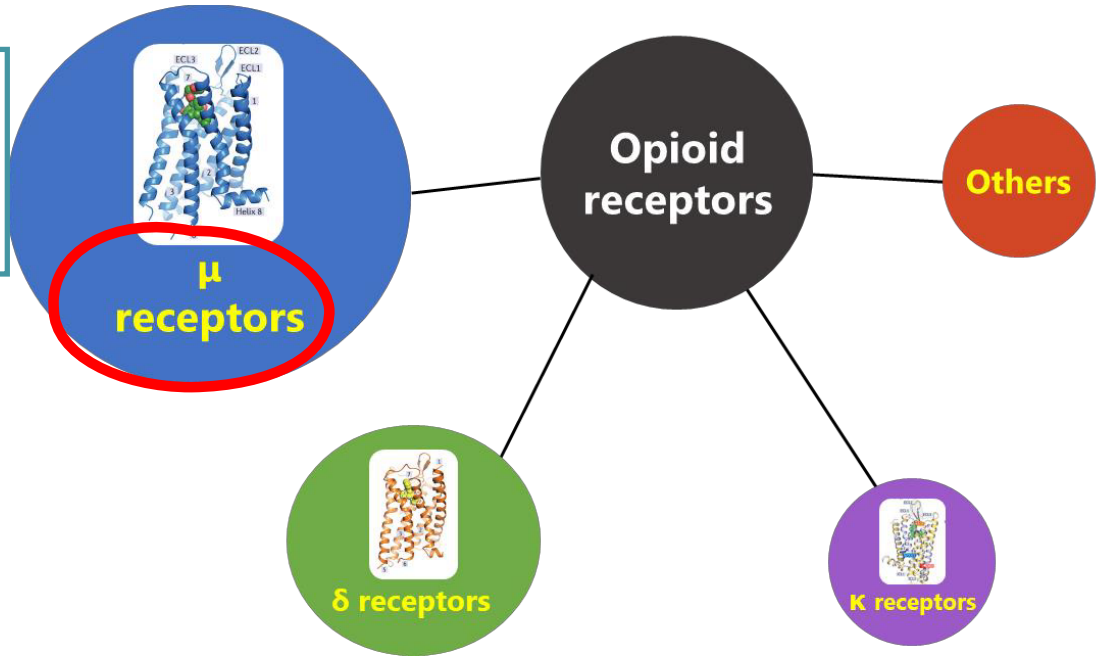
There are **three** major opioid receptor subtypes: μ (MOP), δ (DOP) and κ (KOP).

- μ receptors → responsible for most of the analgesic effects of opioids & for the major adverse effects e.g., respiratory depression
- δ receptors
- κ receptors → contribute to analgesia at the spinal level

Opioid analgesics are μ receptor agonists.

either full agonists, partial agonists/mixed agonist-antagonists (agonists on one opioid receptor but antagonists or partial agonists on another)

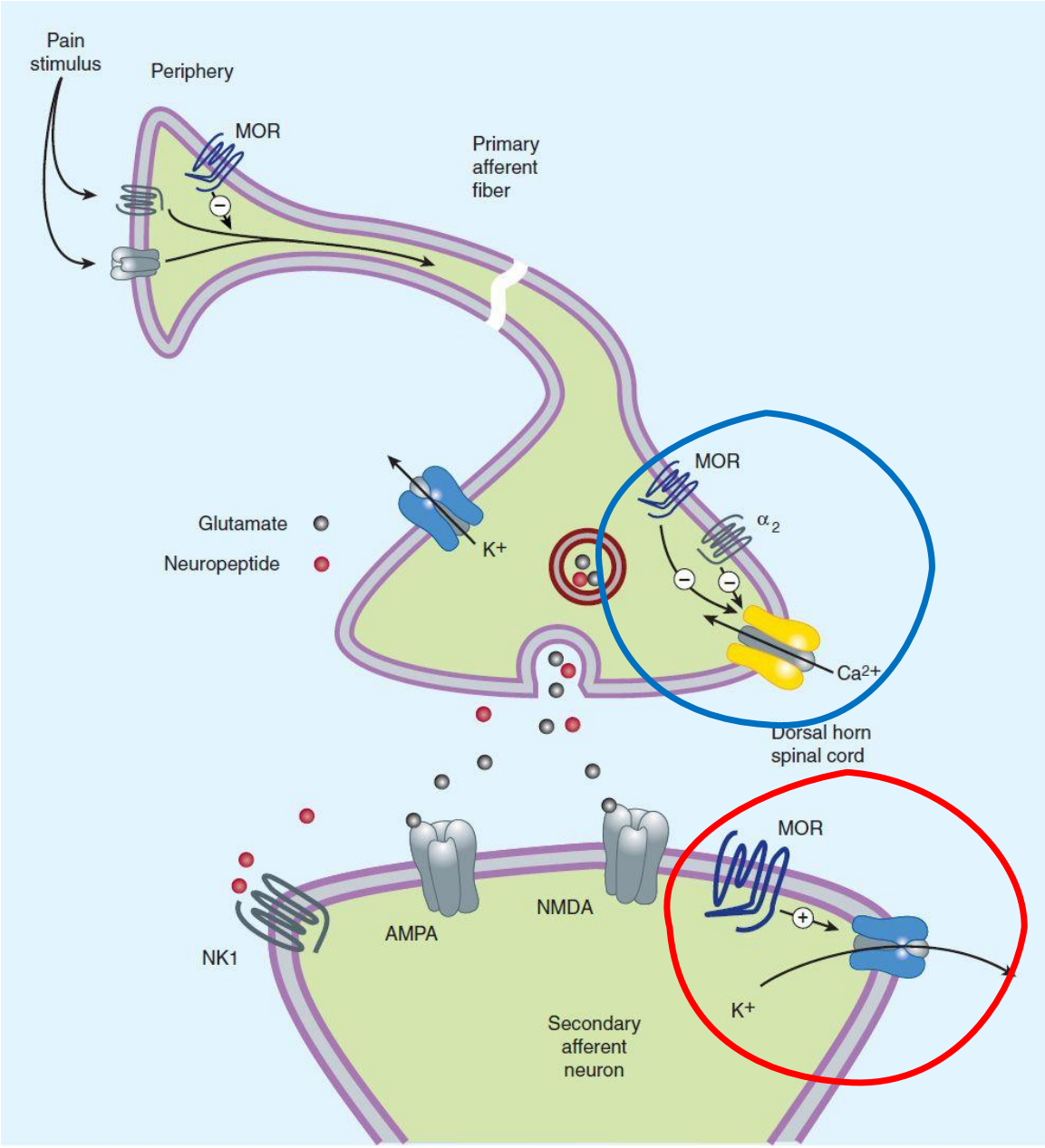
Analgesia
Respiratory depression
Miosis
Constipation
Euphoria
Dependance



Opioid receptors

- Opioid receptors localized at presynaptic neurons ↓ release of pain neurotransmitters (substance P & glutamate) mainly through ↓ in Ca^{++} influx
- Opioid receptors localized at postsynaptic neurons decrease firing through increase in K^+ efflux → hyperpolarization

The net effect of μ receptor activation is to inhibit neuronal activity → so pain transmission is either blocked or diminished



Classification of opioid analgesics

- Opioid analgesics can be classified as full μ agonists, partial μ agonists/mixed agonist-antagonists.
- Based on their analgesic potency, full μ agonists can be further subdivided into strong or weak/moderate agonists.

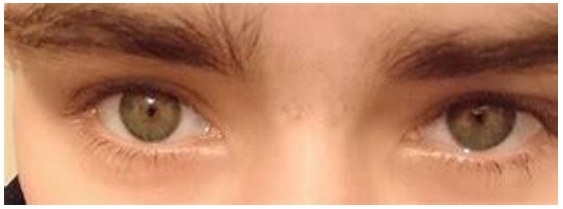
N.B. Pure opioid antagonists have no analgesic effects. They are used to counteract the adverse effects of opioid analgesics taken in overdose and for the treatment of opioid dependence. (e.g., naloxone & naltrexone).

Strong μ agonists	Weak/moderate μ agonists	Partial μ agonists	Mixed agonist-antagonists
▪ Morphine → μ agonist ▪ Meperidine → μ agonist ▪ Methadone → μ agonist ▪ Fentanyl → μ agonist	▪ Codeine → μ agonist ▪ Oxycodone → μ agonist ▪ Hydrocodone → μ agonist	▪ Pentazocine → partial μ agonist & κ agonist ▪ Buprenorphine → partial μ agonist & κ antagonist	▪ Pentazocine → partial μ agonist & κ agonist ▪ Buprenorphine → partial μ agonist & κ antagonist

Pharmacological effects of opioid analgesics

CNS

- Analgesia
- Euphoria
- Inhibition of cough reflex (codeine)
- Tolerance and dependence
- Respiratory depression
- Sedation
- Miosis (pinpoint pupil)



GIT

- Constipation
- Increased biliary sphincter tone and pressure
- Nausea and vomiting

Others

- **CVS**:
  Vasodilation and hypotension
- Flushing & pruritis
- Prolongation of labor (except meperidine)
- Urine retention

Pharmacological effec of opioid analgesics

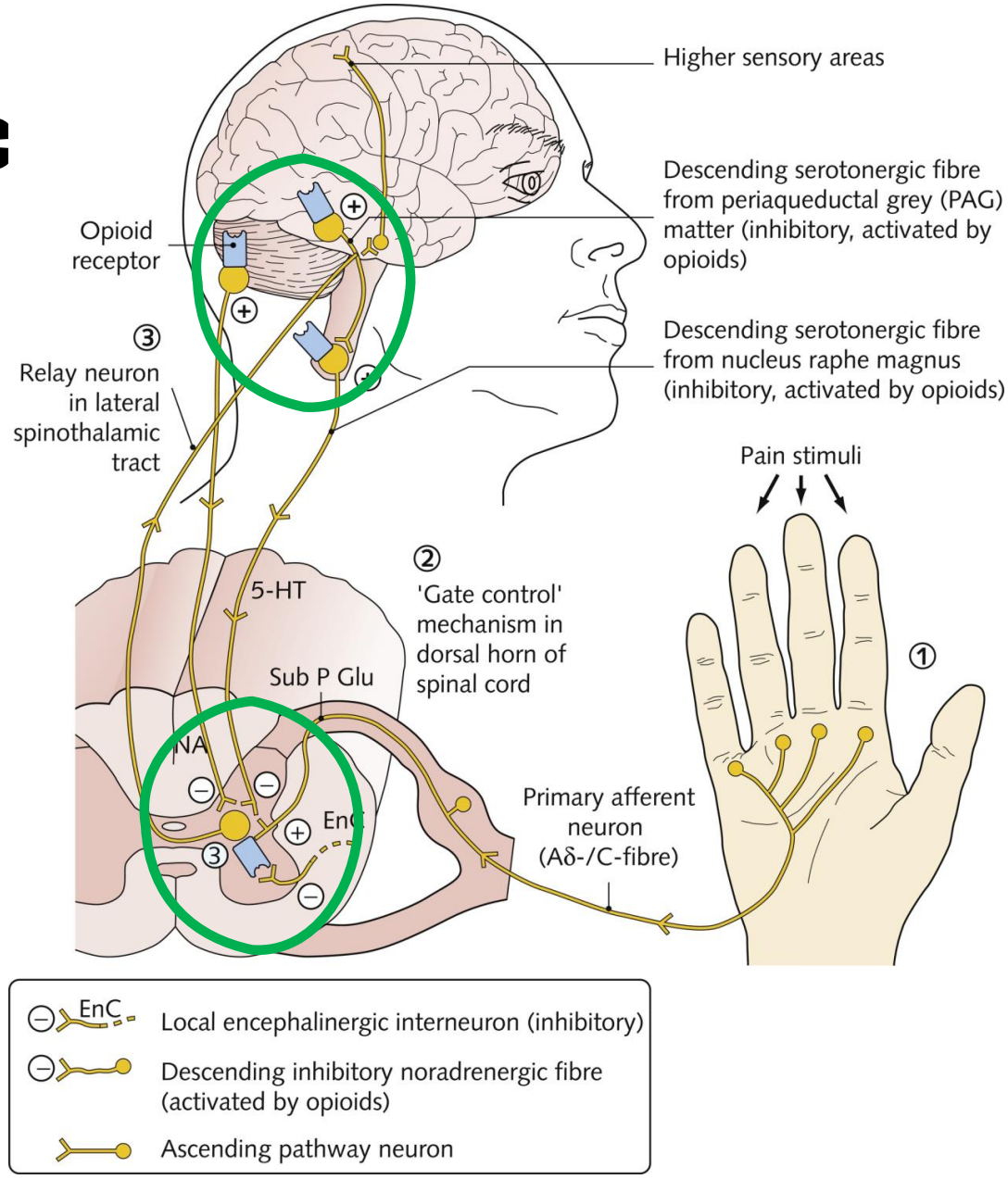
Analgesia

Supra spinal

- Activation of the descending inhibitory tracts

Spinal

- Decrease substance P & glutamate release from presynaptic neuron
- Hyperpolarization of the post synaptic neuron



Uses of opioid analgesics

- Analgesia → Gold standard for strong pain relief

- Anesthesia → as adjunct with general anesthetics
- Antitussive → codeine suppresses cough reflex
- Antidiarrheal → loperamide & diphenoxylate
- Euphoria → major cause of dependence.

Adverse effects of opioid analgesics (Opioid intoxication)

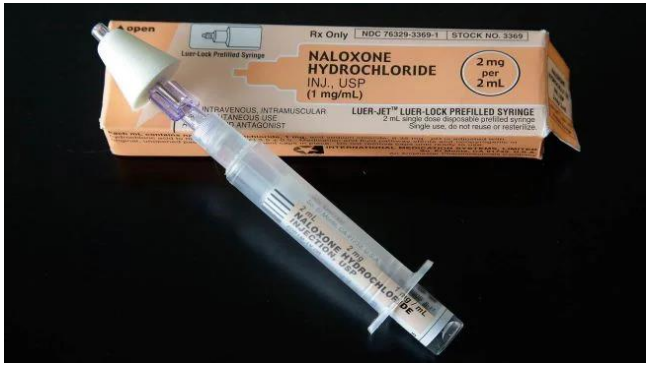
Acute

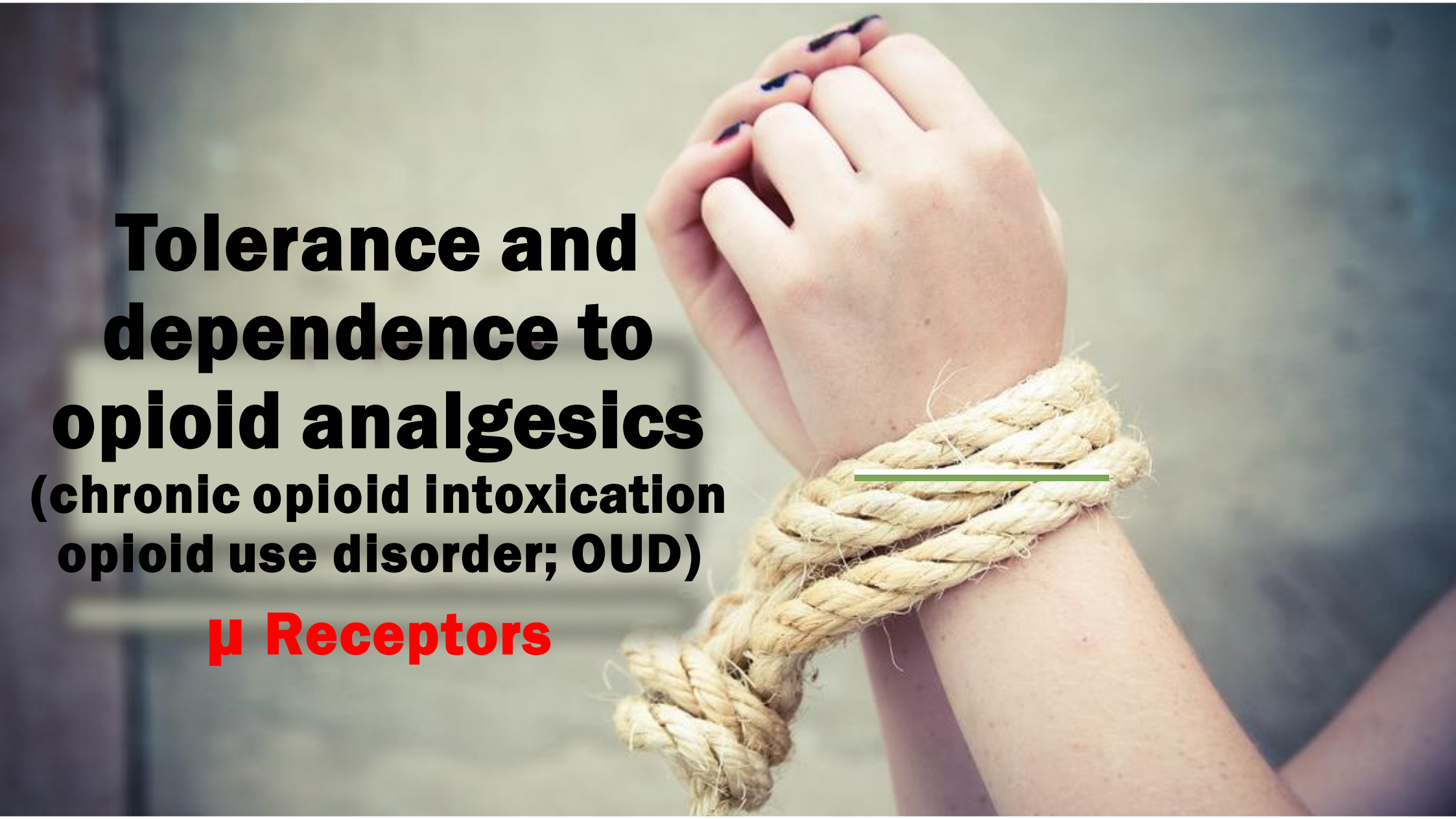
Chronic

- Respiratory depression (as they reduce the hypercapnic drive) → the cause of death in overdose
- ↕ intracranial tension (due to CO_2-induced dilation of in cerebral blood vessels) → CI in patients with closed-head injury
- Nausea and vomiting → direct stimulation of the chemoreceptor trigger zone
- Miosis (pupil constriction) → direct stimulation of the Edinger-Westphal nucleus of the oculomotor nerve.
- Constipation → increase smooth muscle tone & decrease peristalsis
- Exacerbation of pain in patients with biliary dysfunction or a gallbladder attack. Why??
- Pruritis, flushing & bronchospasm → due to histamine release from mast cells
- Tolerance and Dependence

Acute opioid intoxication How can it be reversed

- Due to respiratory depression, cases of opioid overdose need to be rapidly treated.
- Naloxone is a pure competitive antagonist that quickly (in seconds to minutes) displaces opioids already bound to receptors and reverses respiratory depression.




Tolerance and dependence to opioid analgesics
(chronic opioid intoxication opioid use disorder; OUD)
μ Receptors

Tolerance to opioid analgesics

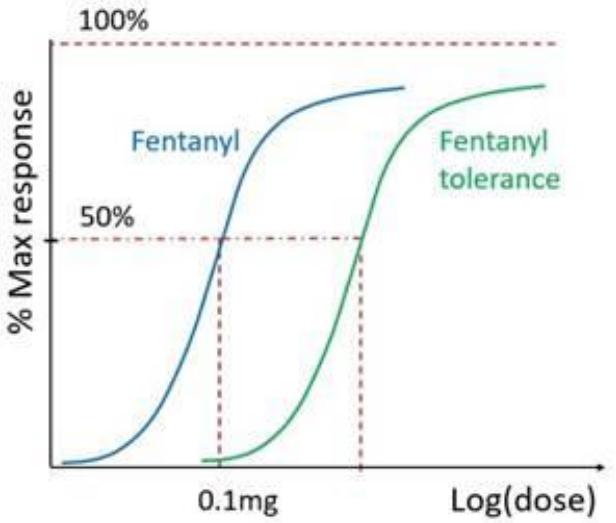
- Tolerance → a decrease in the pharmacologic effect of opioid analgesics observed after chronic/long-term/repeated drug administration.

  Mechanism → pharmacodynamic tolerance to all opioid analgesics (cross-tolerance).

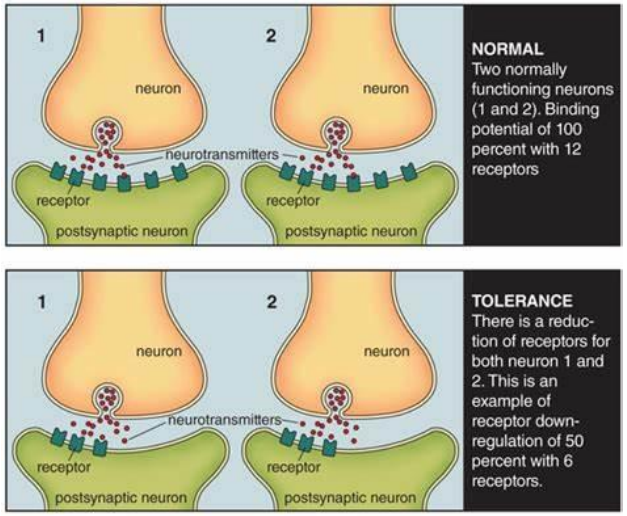
  Primarily results from down-regulation of opioid μ receptors with repeated opioid administration.

Tolerance develops to most of the effects of opioids but not to miosis and constipation.

Tolerance also develops to respiratory depression, still a sufficiently high dose of an opioid analgesic can still be fatal to highly opioid-tolerant individuals.



Note the need for higher Fentanyl doses to achieve the same analgesic effect in tolerant patient compared to normal patients.



Physical dependence on opioid analgesics

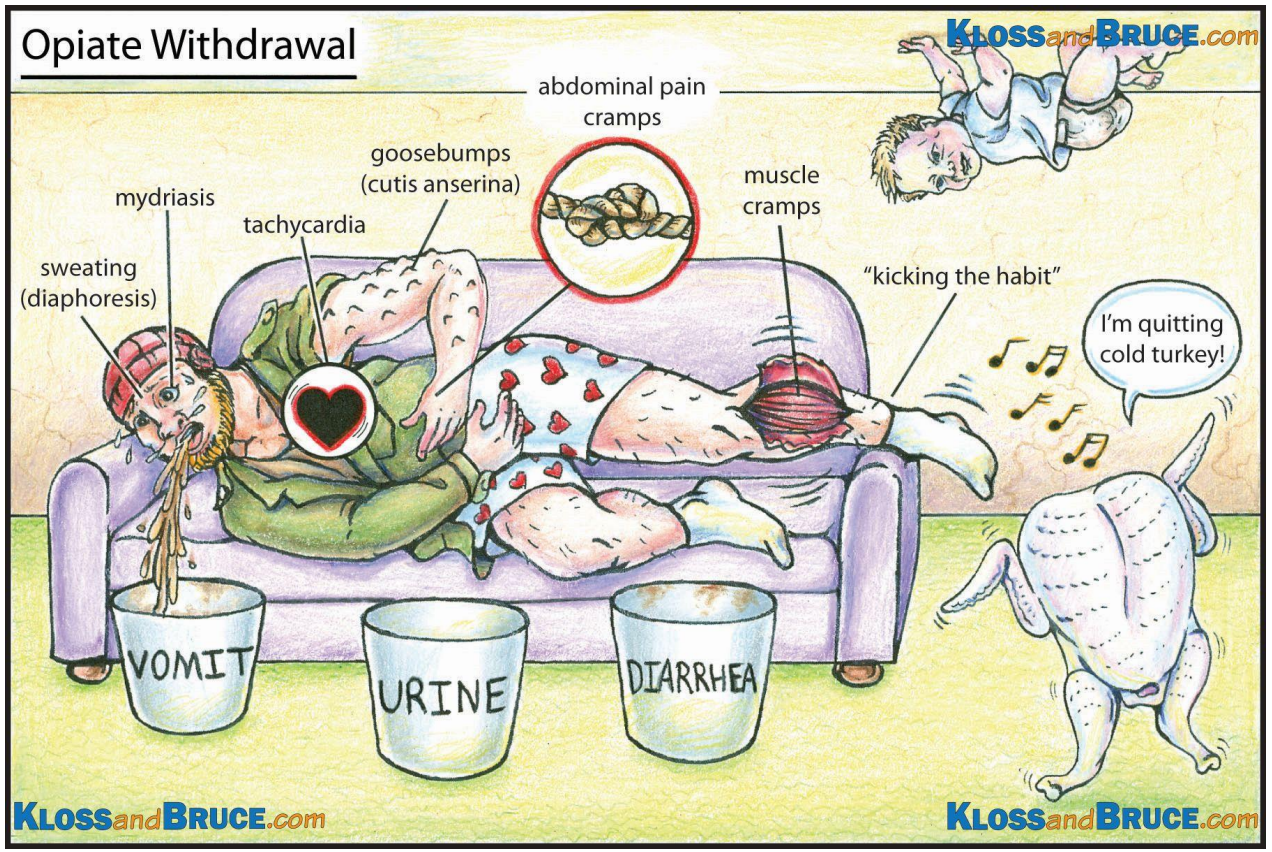
- Opioid tolerance is accompanied by a similar degree of **opioid physical dependence.**
- Physical dependence → **a physiologic state** in which a person's continued use of an opioid analgesic is required for his or her well-being.
- Tolerance and physical dependence represent a newer situation wherein the neuron progressively becomes less responsive to the opioid, and yet requiring continued opioid use to maintain normal functions.
- Opioid withdrawal syndrome → If the chronically used opioid analgesic is abruptly withdrawn (or e.g., after administration of an opioid antagonist), the equilibrium is disturbed and **a rebound hyperexcitability state** occurs

Opioid withdrawal syndrome

A state of **irritable** and sometimes aggressive behavior, plus:

- Fever and sweating
- Tachycardia.
- **Nausea and vomiting**.
- **Pupillary dilation** is an important sign of opioid withdrawal (X opioid intoxication causes pinpoint pupils).
- Piloerection.
- Abdominal cramps and **diarrhea.**

Opioid withdrawal is not life-threatening.



Psychological dependance on opioids

- Drug dependence → a condition in which individual feels **compelled to repeatedly administer** a psychoactive drug (a drug that changes mood or perception).
- When this is done to avoid physical withdrawal symptoms → physical dependence.
- When this is done for a psychological reason (the need for stimulation, feeling high, pleasure, euphoria or to escape reality) → psychological dependence.

Treatment of opioid dependence (OUD)

Aim: help the patient experience **reduced symptoms of opioid withdrawal**, **reduced cravings**, and maintain abstinence from other illicit opioid use.

- *Phase 1 → Medically supervised opioid withdrawal (detoxification)*

  Def: administration of a drug to reduce the severity of withdrawal symptoms.

  Drugs used:

  1. *Longer acting opioid agonists:* methadone and buprenorphine
  2. *Alpha-2 adrenergic agonists:* clonidine.

- *Phase 2 → Opioid replacement, maintenance, or substitution therapy*

  Def: Replacing an opioid with a longer-acting but less euphoric and less addicting opioid.

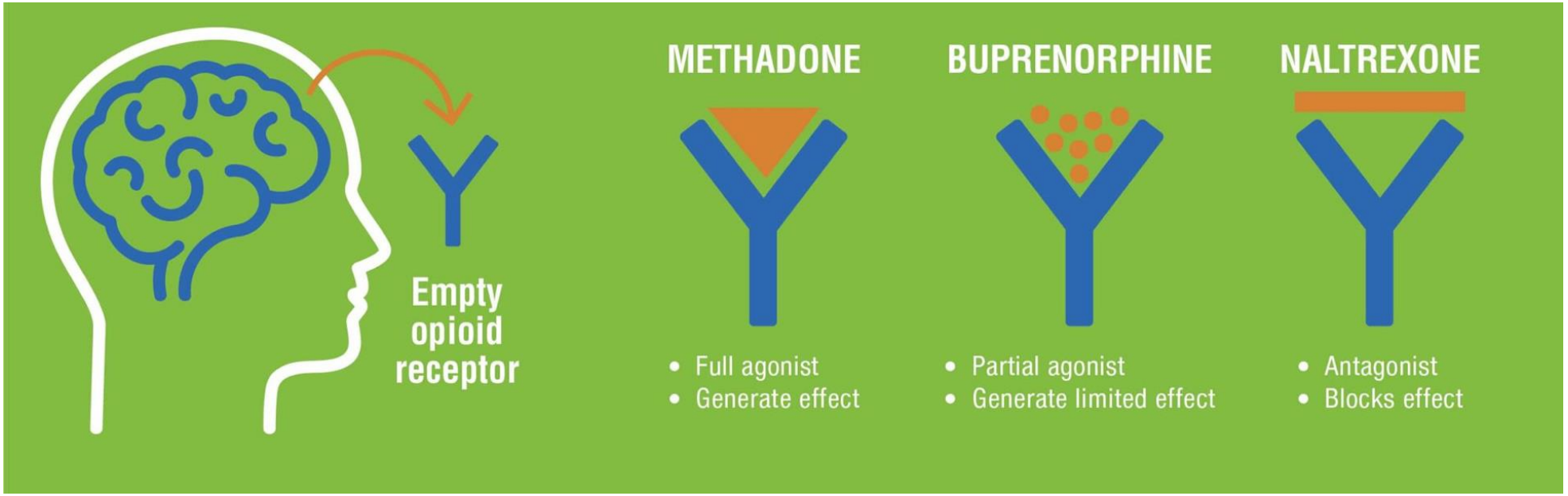
  The commonly used drugs are:

  1. *Agonists:* buprenorphine and methadone.
  2. *Antagonists:* naltrexone (N.B. as opioid antagonists precipitate withdrawal in patients actively using opioids, medically supervised withdrawal is necessary prior to initiation of naltrexone).

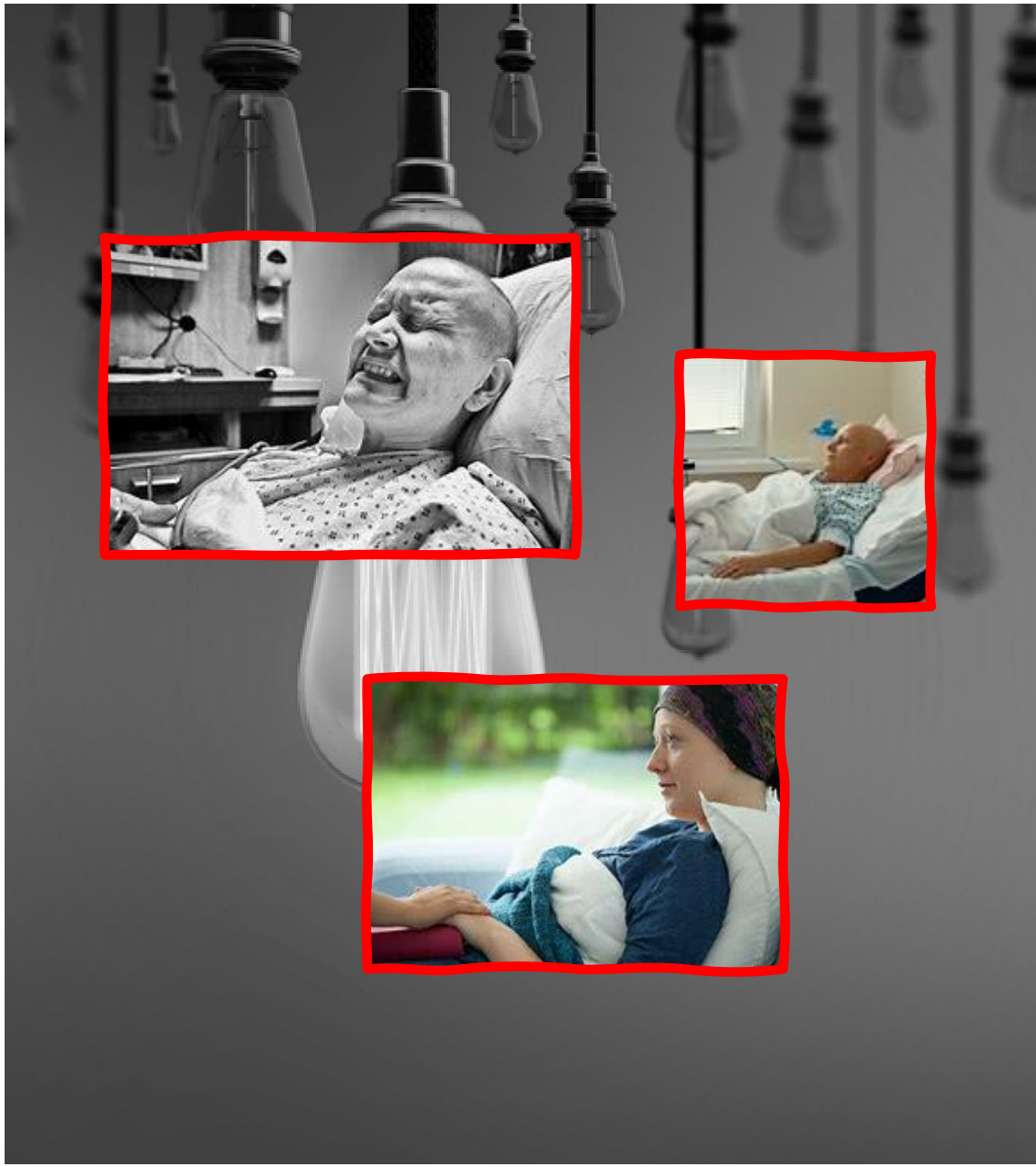
Treatment of opioid dependence (OUD)

- ***Adjunct drugs:***

  1. ***Alpha-2 adrenergic agonists (clonidine)*** → to decrease anxiety associated with opioid withdrawal.
  2. ***Benzodiazepines or other sedating drugs*** → to treat anxiety and insomnia associated with opioid withdrawal
  3. ***Anti diarrheal*** and ***antiemetic drugs***
  4. ***NSAIDs (naproxen)*** → to relieve pain



Would not EARTH look much better without Opioids?



Specific opioid analgesics

1. Morphine

- The standard opioid analgesic.
- It undergoes significant first-pass metabolism in the liver → less effective orally → as larger doses are required when the drug is administered orally.
- The 6-glucuronide active metabolite → is more active and has longer t1/2 than morphine → contributes significantly to the analgesic effectiveness of morphine.
- It is primarily used to treat severe pain associated with trauma, MI and cancer.
- Other use: acute pulmonary edema

Specific opioid analgesics

2. Diamorphine (heroin)

- Twice as potent as morphine
- The most abused illicit opioid drug.
- Highly addictive → as it rapidly enters the brain after injection, and produce an intense euphoric sensation called a rush.

3. Fentanyl and its derivatives

- The most potent opioid agonists available
- A long-acting transdermal skin patch (Duragesic) is available to provide continuous pain relief for patients with severe chronic pain.

4. Pethidine (meperidine)

- Equianalgesic compared with morphine,
- Does not cause constipation or increase biliary pressure → used in pancreatitis.
- Does not prolong labor → used for analgesia in labor.
- Has atropine like action → ↑ HR → used in inferior MI
- Only short courses are allowed → accumulation of a toxic metabolite (normeperidine) might cause seizures in patients with renal failure.

Specific opioid analgesics

5. Methadone

- Longer duration of action and milder withdrawal symptoms
- Administered orally to treat opioid dependence

6. Codeine

- 1/12 of the analgesic potency of morphine → used in mild to moderate pain → Commonly given in combination with aspirin or acetaminophen
- Also used for its antitussive effects.
- The most constipating opioid.
- Less addictive
- Metabolized by CYP2D6 → liable to genetic polymorphism → variable responses in different individuals.

7. Tramadol

- MOA →

1. Agonist at μ receptors
2. Inhibits the neuronal reuptake of 5HT and NE

Used for neuropathic pain

Seizures are the main side effects

Q

P.K. is a well-known drug addict. When he came to your office for his last visit, you noted that he had "pinpoint" pupils and decreased respiration and heart rate. These effects are likely the result of:

a. Morphine-activating μ receptors.
b. Oxycodone-activating κ receptors.
c. Methadone-activating κ receptors.
d. Naloxone-activating μ receptors.
e. Buprenorphine-activating δ receptors.

Q

A 32-year-old homeless woman was found unresponsive with a needle in her arm. The response team quickly administered a dose of naloxone to:

a. Desensitize opioid receptors.
b. Antagonize the ability of opioids to cross the blood-brain barrier.
c. Competitively inhibit opioid-induced respiratory depression.
d. Stimulate the hepatic metabolism of the opioids.
e. Counteract opioid-induced constipation.

References

- https://www.clinicalkey.com/student/content/book/3-s2.0-B9780323758987000237?origin=share&title=Brenner%20and%20Stevens%E2%80%99%20Pharmacology&meta=2023%2C%20Stevens%2C%20Craig%20W.%2C%20PhD&img=https%3A%2F%2Fcdn.clinicalkey.com%2Fck-thumbnails%2FC2019001014X%2Fcov200h.gif
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Thank you