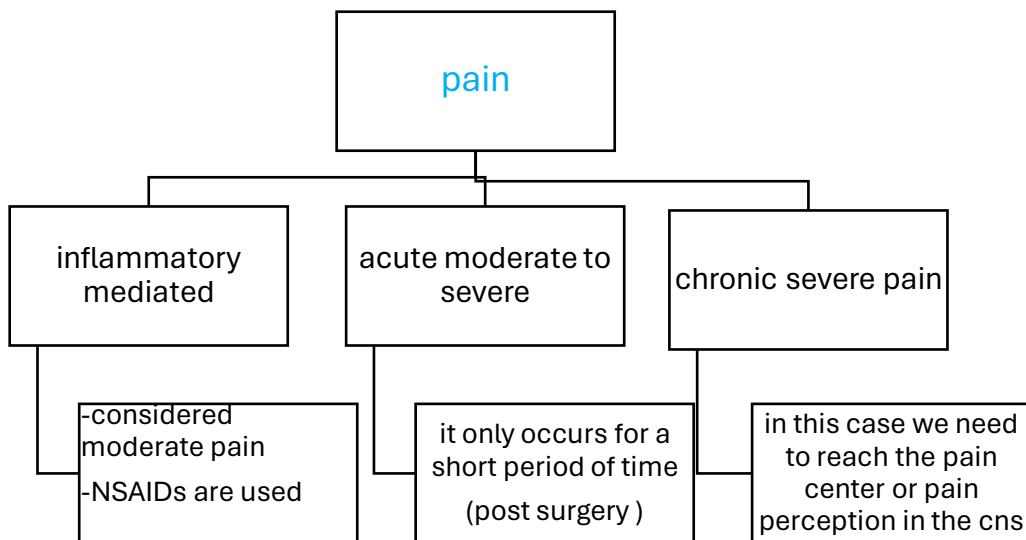


Analgesics and sedatives



Nsaids :

1) these drugs reduce 1. pain 2. inflammation 3. symptoms

2) Diclofenac is the strongest NSAID.

3) NSAIDs have ceiling effect: we use them for moderate pain, but if the pain is moderate to severe or severe [like cancer cases]; they won't work. Even if we give the maximum amount tolerated

4) if the patient didn't respond to NSAIDS (profen for ex) that would be because the pain is higher than its ceiling effect (its max effect)

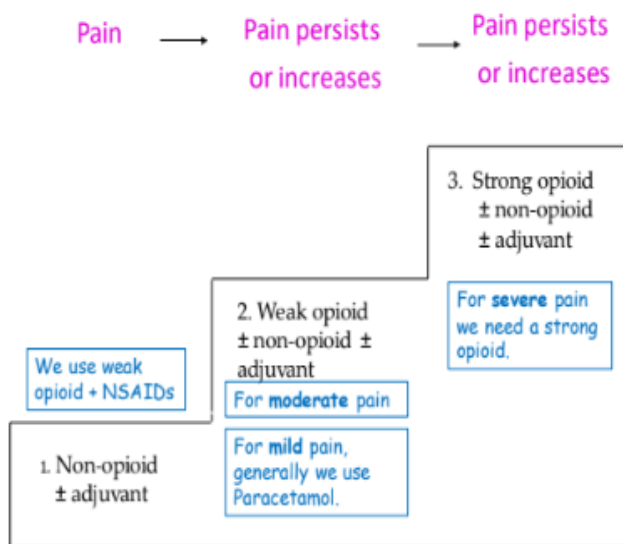
Note: We should know the effect of opioids first dose in first day is different from the effect of 10th dose in 10th day

• Pain is a symptom of a pathologic condition that needs to be taken care of:

– no treatment, pain persists.

– Induced by the release of histamine, serotonin, prostaglandins, bradykinins....(they activate pain signaling).

WHO analgesic ladder



Some historical information:

- In 1804; narcotics [particularly morphine] were extracted from a plant called "opium poppy", as the single effective substance.
- In 1832; aspirin was synthesized, since that time; pharmacology has appeared.
- Before 1832; it was known as plant therapy.
- In plant therapy \Rightarrow plant extraction is given. In pharmacology \Rightarrow drug/medication is given.
- Opioids especially morphine are considered magical drugs...why? Because they have no ceiling effect.

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Important:
management of these drugs depends on severity of pain.

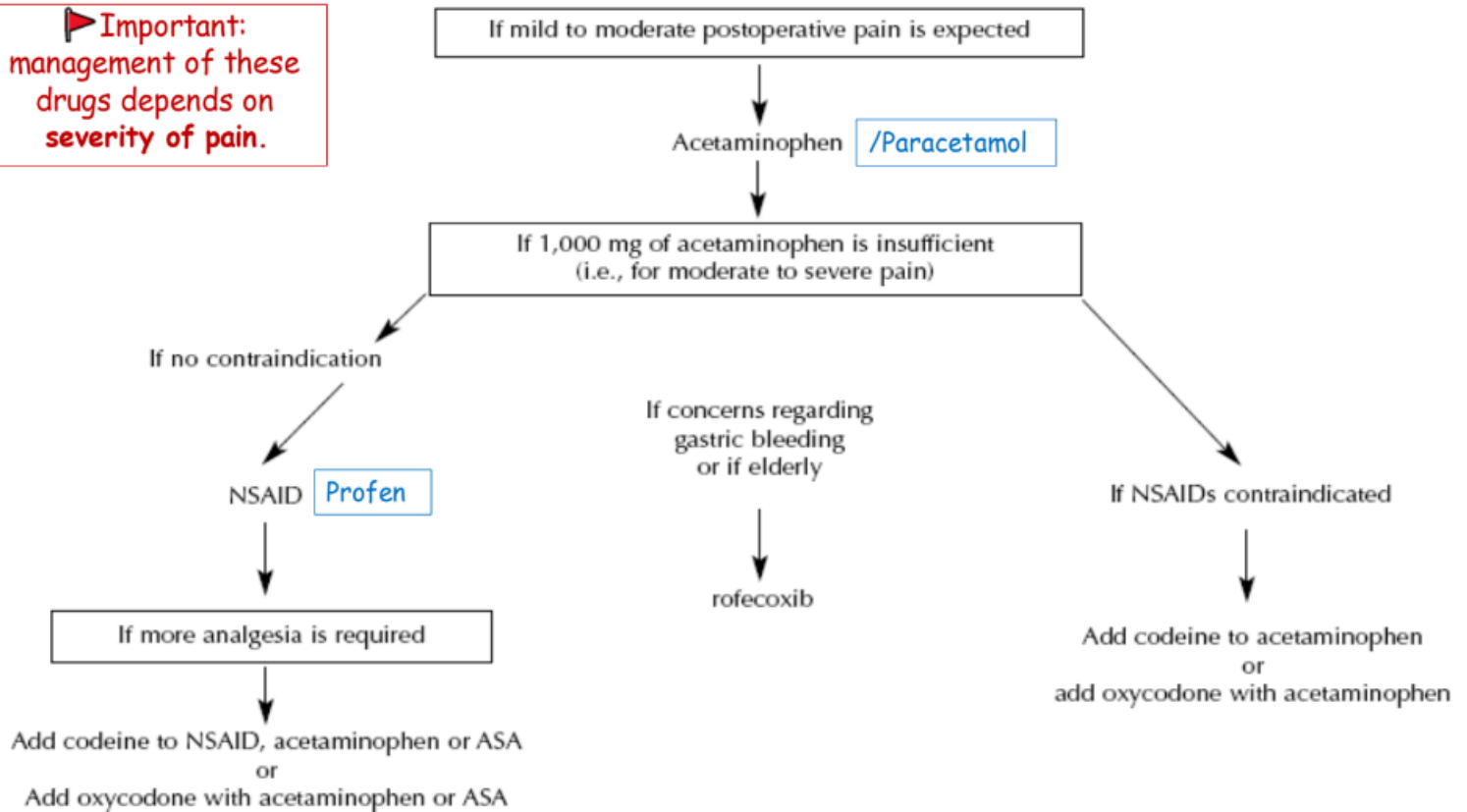


Figure 2: Algorithm for analgesic use. This algorithm should be considered to manage acute postoperative pain in the adult.

Opioids:

- 1) All drugs in this category act by binding to specific Opioid receptors in CNS to produce effects that mimic the action of naturally occurring substances, called endogenous opioid peptides or endorphins (endorphins are responsible for analgesia balance).
- 2) Exert their major effect by interacting with Opioid receptor in the CNS, and in other places such as GI tract and urinary bladder.
- 3) Opioids cause hyperpolarization of nerve cells, inhibiting nerve firing, and presynaptic inhibition of transmitter release. [open K⁺ channels and close Ca⁺⁺ channels],
- 4) Morphine causes analgesia by binding to MU receptors, and patients treated with morphine are still aware of the presence of pain, but the sensation is not unpleasant.
- 5) can cause addiction in 1% of the population.
- 6) On chronic use all opioids cause analgesia, constipation and urinary retention. (because those are side effects of the MU receptors' activation).

In conclusion: Opioids are agonists, they erase the sensation of pain through:

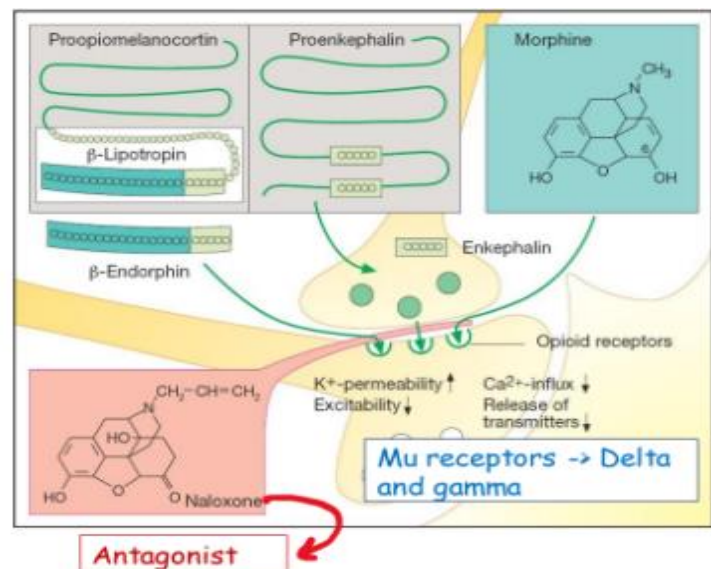
1. Increasing threshold of firing.
2. Decreasing neurotransmitters release.

Main uses of opioids:

- 1) to alleviate moderate to severe pain
- 2) Cough center suppression (antitussive)
- 3) Treatment of diarrhea
- 4) Balanced anesthesia

Mechanism of action of opioids:

- 1) Morphine [exogenous substance], enkephalin and endorphin [endogenous morphine peptides] bind to Mu receptors.
- 2) They decrease excitability, increase the threshold of firing, increase K⁺ permeability [hyperpolarization] and decrease Ca⁺⁺ influx which leads to decreased neurotransmitter release.
- 3) this inhibits the release of glutamate and substance p and as a result we don't feel pain.



opioids

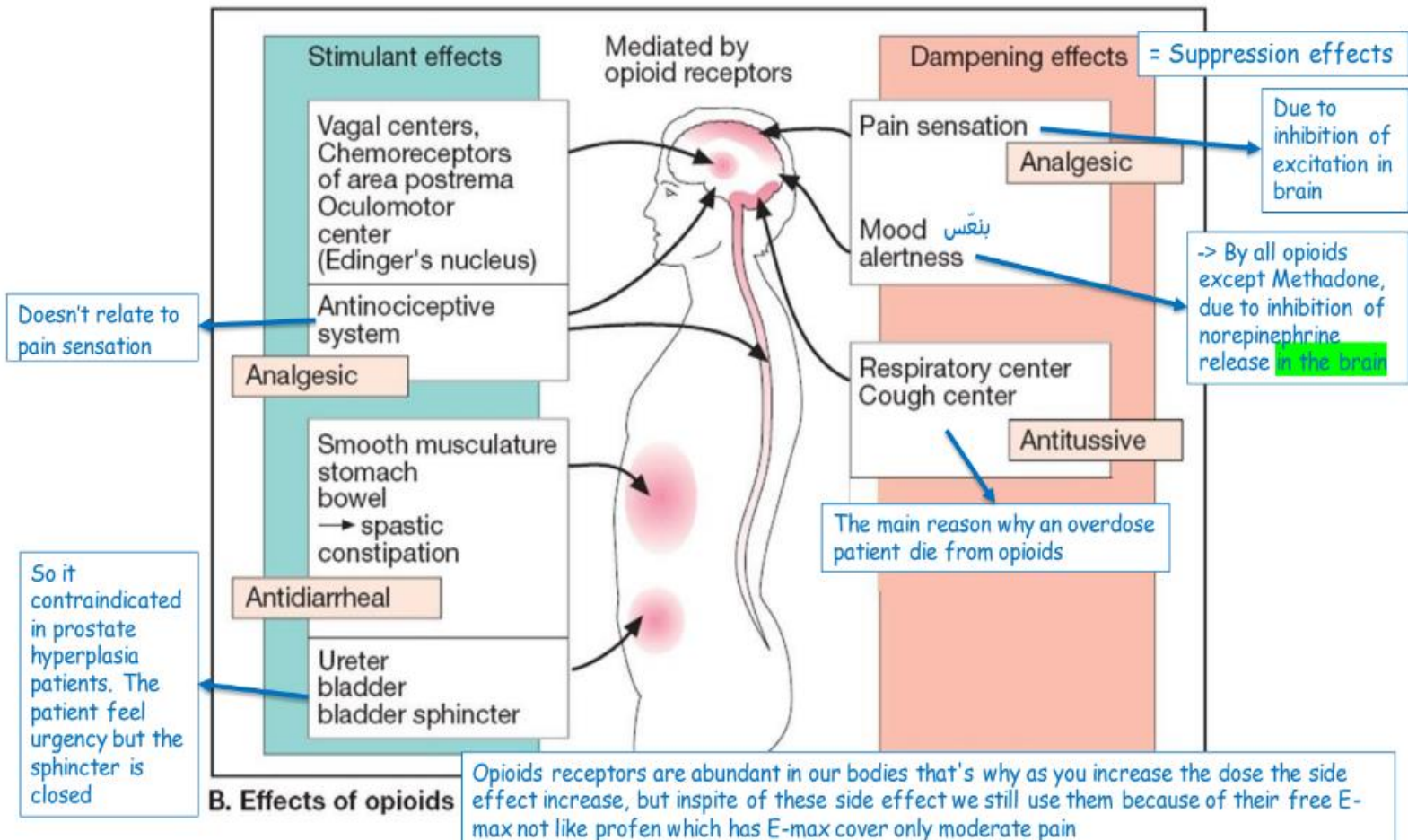
agonists

- 1) Oxycodone (Top seller)
- 2) Oxymorphone
- 3) Hydrocodone
- 4) Hydromorphone (For renal failure) but not included
- 5) Fentanyl
- 6) Morphine
- 7) Methadone

antagonists (antidotes)

naloxone

Effects of opioids



Notes: 1) Codeine is used as an antitussive agent, Because it's a partial agonist, so we avoid addiction.

2) CNS in elderly people is weaker than in young adults, so a normal dose can lead to suppressing the respiratory center

3) Opioids have a sedative (calm the person, decrease activity) not a hypnotic effect (sleep), which something we desire after operations/surgeries.

Opioids' side effects:

1) Euphoria Especially heroin Due to dopamine release Relates to psychological dependence	2) CNS depression decrease motor movements, reduce cognition	3) nausea and vomiting That's why in anesthesia we don't give morphine due to its half life (4 hours) and after the patient wakes up from the operation he feels more nauseous
4) urinary retention	5) diaphoresis and flushing Due to the release of histamine	6) pupil constriction (miosis) PINPOINTED PUPIL
7) respiratory depression	8) constipation and bradycardia Cuz it activates vagal nerve	9) itching Cuz of histamine release

Important points: Contraindications for opioids:

- asthmatic patient due to histamine release
- Prostate hyperplasia patient
- bradycardia patient
- hypotension patient due to histamine

Repeated use of morphine can cause:

- Psychological dependence - Physical dependence - Tolerance
- Withdrawal syndrome - Hyperalgesia

tolerance	dependence	Addiction (abuse)
<p>– Physiologic phenomenon resulting in progressive decline in potency of an opioid with continued use.</p> <p>-always related to agonist</p> <p>-solution: increase the dose</p>	<p>– Physiologic state characterized by withdrawal symptoms upon abrupt discontinuation/ reduction of narcotic therapy.</p> <ul style="list-style-type: none"> • Abstinence syndrome • Independent of tolerance <p>-with time we change something in the patient's body</p> <p>-patient is physically dependent.</p> <p>-Solution: tapering</p>	<p>-Psychological & behavioral syndrome manifested by drug seeking behavior, loss of control of drug use, and continued use despite adverse effects.</p> <p>The patients know that this drug bad for them but still use it.</p>

Note: antagonist drug lead to up regulation. To solve this we give higher doses (you should be careful about patients' respiratory depression while taking opioids and careful of different ages because old patients are more suspected for delirium)

- The only two side effects that don't exhibit tolerance are constipation and Pupil constriction (miosis) even with long terms.