ANALGESICS, ANTI-PYRETICS & ANTI-INFLAMMATORY DRUGS

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What Is Pain?

- The word "pain" comes from the Latin "poena" meaning a fine, a penalty.

- An unpleasant sensation that can range from mild, localized discomfort to agony. Pain has both physical and emotional components.Physical pain is associated with actual or potential tissue damage. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. It is unquestionably a sensation in a part of the body, but it is also unpleasant, and therefore also an emotional experience. Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons.

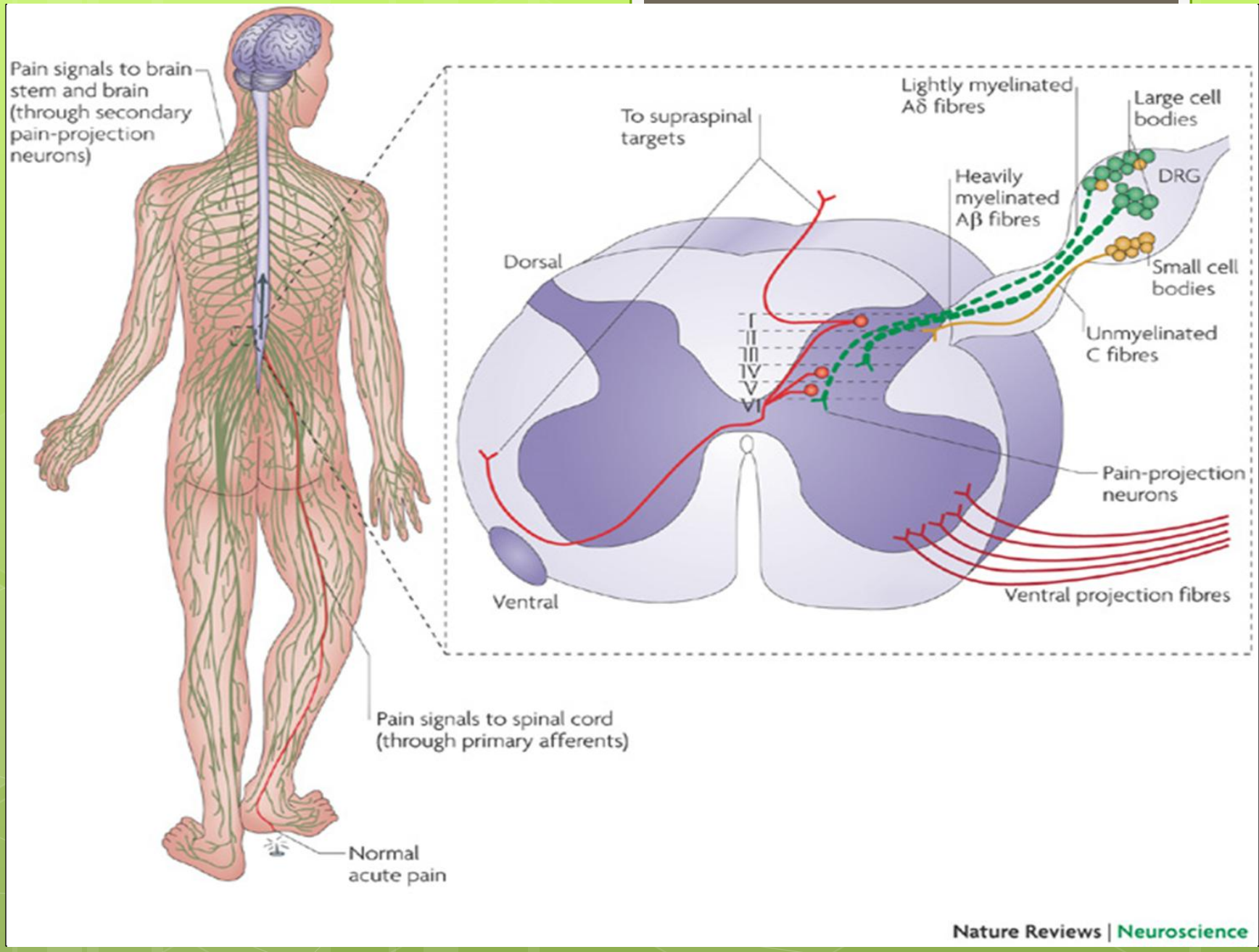
Physiology of Pain

- **Acute pain** sharp, pricking, well defined, (defined as < 3 months duration) transmitted principally by fast conducting myelin A-delta fibers.

(**Aδ fibers-A delta fibers found in the skin and muscle, myelinated, respond to mechanical stimuli. Produce intermittent pain**.)

- It has major nociceptive input (physical trauma, pleurisy, myocardial infarction, perforated peptic ulcer).

- The narcotic (opioid) and sometimes non-narcotic analgesics are used for treatment of acute pain.


Pain signals to brain stem and brain (through secondary pain-projection neurons)
To supraspinal targets
Lightly myelinated Aδ fibres
Large cell bodies
Heavily myelinated Aβ fibres
DRG
Dorsal
Small cell bodies
Unmyelinated C fibres
I
II
III
IV
V
VI
Pain-projection neurons
Ventral
Ventral projection fibres
Pain signals to spinal cord (through primary afferents)
Normal acute pain
Nature Reviews | Neuroscience

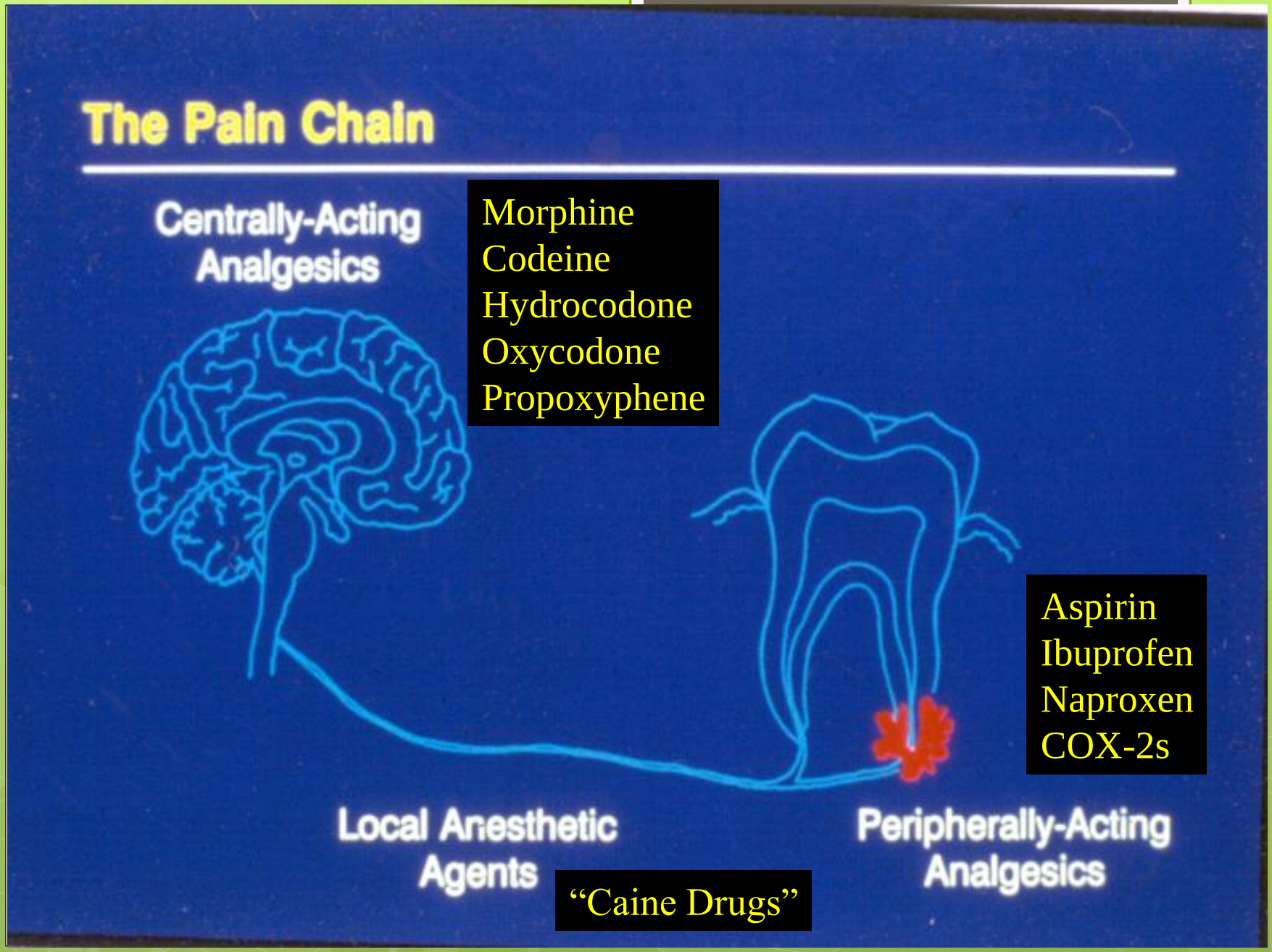
Physiology of Pain

- **Chronic pain:** dull, aching, poorly localized, (defined as > 3 months duration) is transmitted principally by slow conducting non-myelinated C fibers. It is better regarded as a syndrome rather than a symptom. It is depressing to the patient who sees no prospect for relieving the suffering. Analgesics alone are often insufficient and adjuvant drugs (antidepressants or neuroleptics) as well as non-drug therapy (including psychotherapy) have increasing importance.

  (C fibers-C fibers distributed in the muscle as well as the periosteum and the viscera. These fibers are unmyelinated, conduct thermal, chemical and strong mechanical stimuli. Produce persistent pain.)

- **Types and reasons**

  Neuropathic pain
  Inflammatory pain
  Bone cancer pain
  Fibromyalgia
  Migraine
  Psychogenic pain

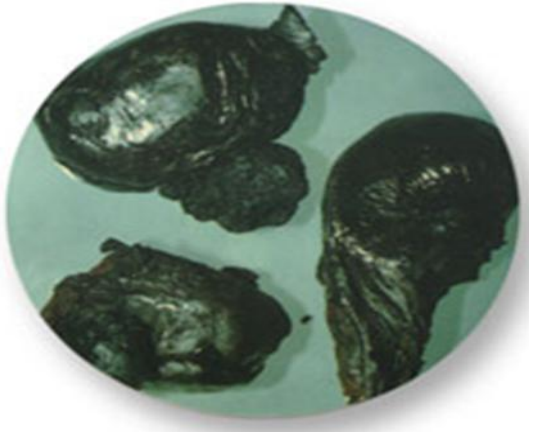

The Pain Chain
Centrally-Acting Analgesics
Morphine
Codeine
Hydrocodone
Oxycodone
Propoxyphene
Aspirin
Ibuprofen
Naproxen
COX-2s
Local Anesthetic Agents
"Caine Drugs"
Peripherally-Acting Analgesics

Analgesics (pain killer)

- Opiates and morphinomimetics
- NSAIDs and other anti-inflammatory drugs
- Some tricyclic antidepressants
- Local anesthetics
- Some antiepileptic drugs
- Others: ketamine, mexiletine, etc

Opioid analgesics

Opium flowers



Crude opium

Collecting resin
of opium poppy

Seeds of
opium poppy

Classification of opiates

- Natural opiates: morphine, codeine, papaverine and thebaine;
- Semi-synthetic opiates: hydromorphone, hydrocodone, oxycodone, oxymorphone, desomorphine, diacetylmorphine (Heroin), nicomorphine, dipropanoylmorphine, benzylmorphine and ethylmorphine;
- Fully synthetic opioids: fentanyl, pethidine, methadone, tramadol and propoxyphene;
- Endogenous opioid peptides: endorphins, enkephalins, dynorphins and endomorphins.

MOA OF OPIATES

- In general, opioids act upon mu-, delta-, and kappa-receptors on CNS neurons producing:

  Analgesia via decreased neuronal transmitter release and decreased nociceptive impulse propagation

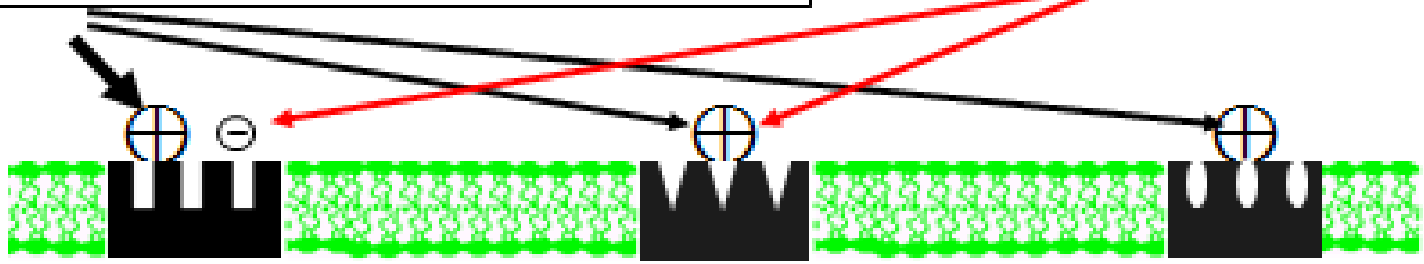
- Appears to work by elevating the pain threshold, thus decreasing the brain's awareness of pain

Receptor type	Location	Effects
μ	Brain, spinal cord	Analgesia, respiratory depression, euphoria, addiction, ALL pain messages blocked
κ	Brain, spinal cord	Analgesia, sedation, all non-thermal pain messages blocked
δ	Brain	Analgesia, antidepression, dependence

opioid agonists and antagonists

Mainly agonist action atμreceptors,
but some actions on other receptors
- Morphine
- Heroin
- Codeine
- Fentanyl

Agonist action at κreceptors,
with partial antagonist action
at μ receptors
- Pentazocine



μ opioid receptor

Analgesia
Respiratory depression
Euphoria/sedation
Physical dependence
Decreased GI motility
Pupil constriction

κ opioid receptor

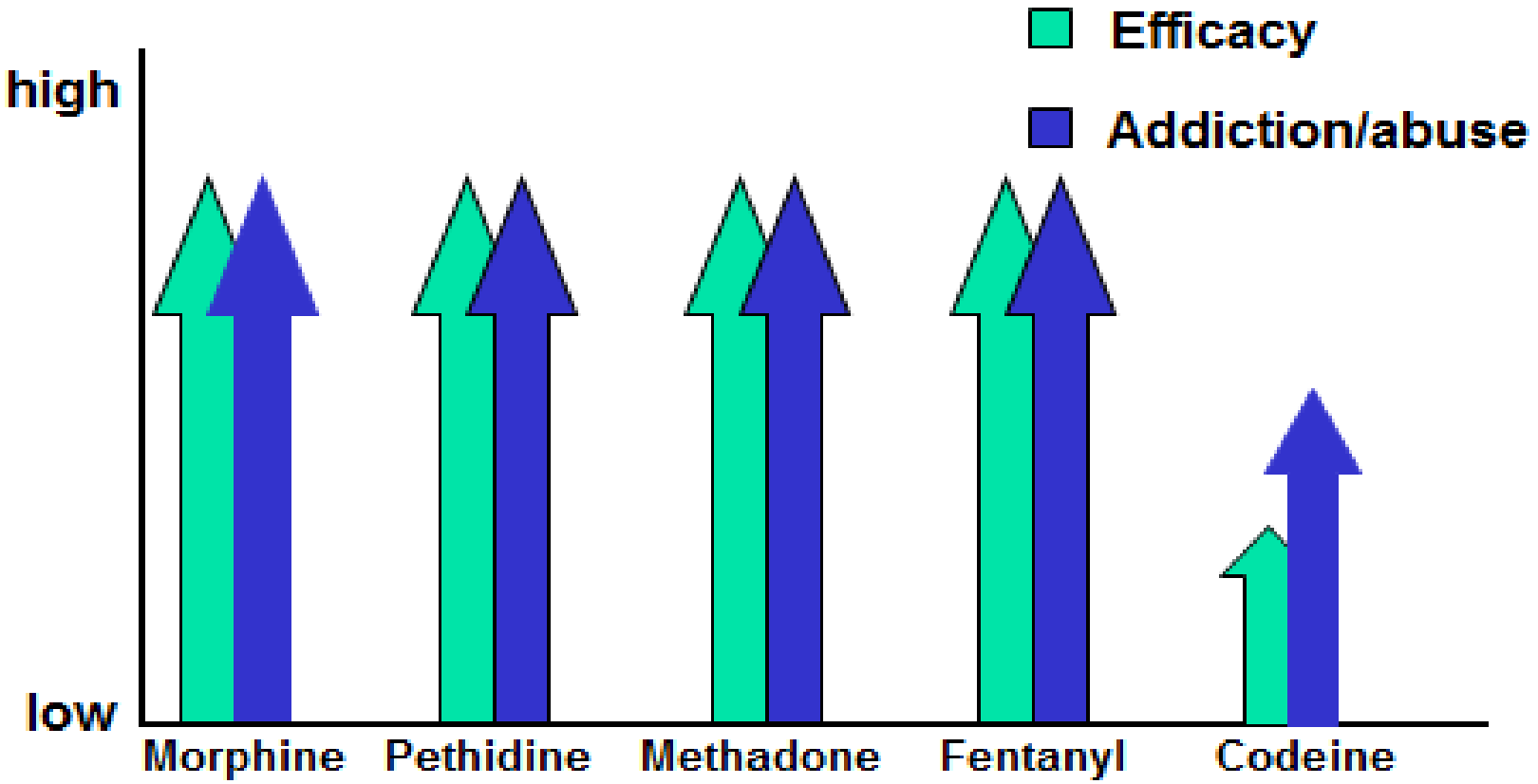
Analgesia
Sedation/dysphoria
Pupil constriction

δ opioid receptor

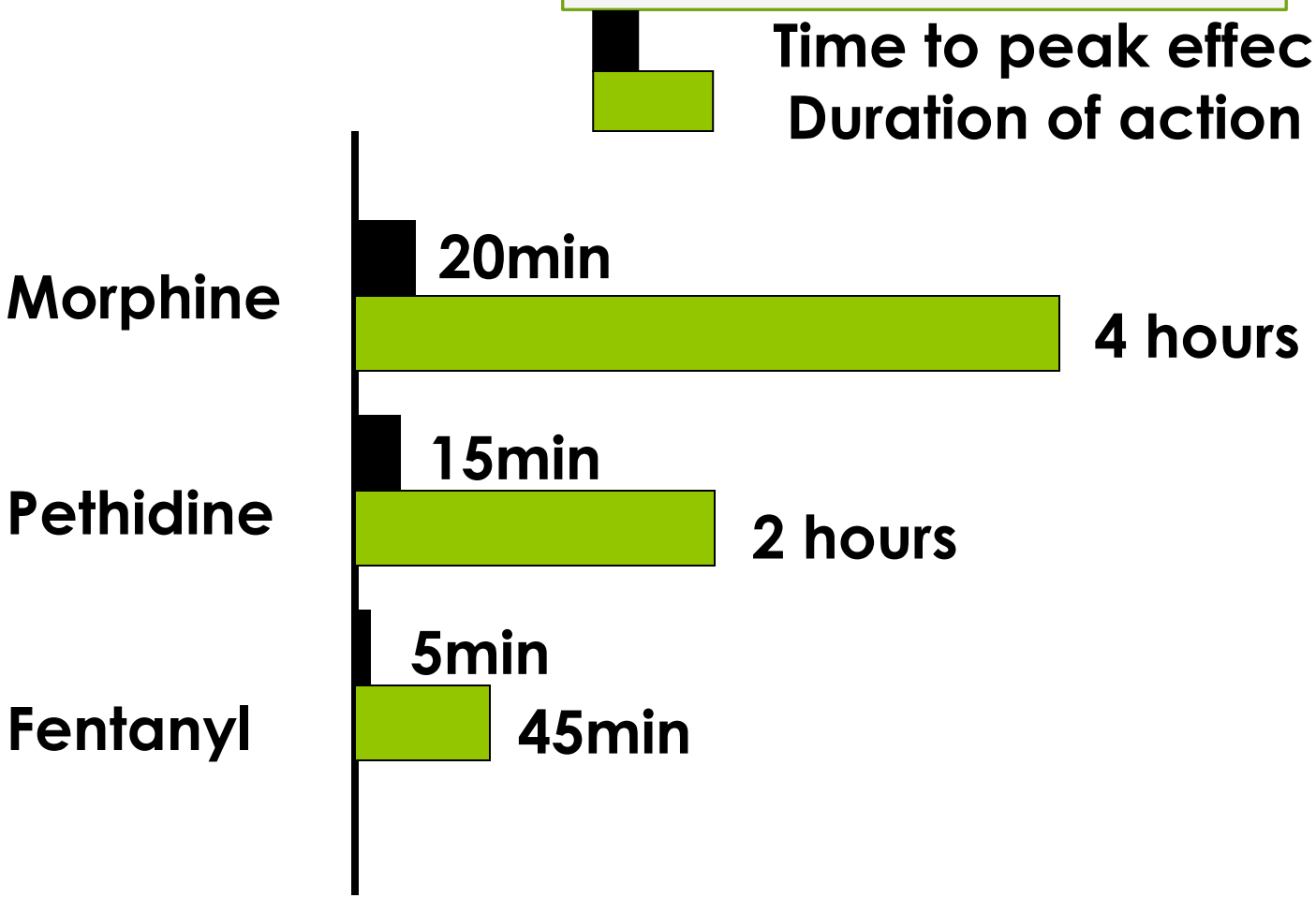
Analgesia

Antagonist act at μ, κ, δ receptors
- Naloxone
- Naltrexone

Efficacy Vs Addiction/abuse



A comparison of the maximum efficacy and addiction/abuse liability of commonly used narcotic analgesics



Time to peak effect and duration of action of several opioids administered intravenously

Morphine

1 Pharmacological effects:

A Analgesia:

- Raises the pain threshold at the spinal cord level, alters nociception in the brain.
- Relieves anxiety and fear

B Euphoria:

- Produces a powerful sense of contentment and well-being by stimulation of the ventral tegmentum.

C Respiration:

- Causes respiration depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide.

D Depression of cough reflex:

- May allow accumulation of secretions and thus lead to airway obstruction and atelectasis.
- Replaced by other safer antitussives .

Morphine

E Miosis:

- The pinpoint pupil is the characteristic of morphine use, little tolerance.

F Emesis:

- Causes vomiting by stimulating the CTZ in the medulla but with no unpleasant sensations.

G Sedation:

- Causes drowsiness and clouding of mentation, even disrupting sleep

H Gastrointestinal effect:

- Decreases motility of smooth muscle and increases tone, which causes constipation and increases pressure in the biliary tract (worsens abdominal colic, eg. Sphincter oddi contraction).

Morphine

I Cardiovascular :

- Has no major effects on the cardiovascular system.
- Is usually contraindicated in individuals with severe brain injury (because that increased PCO_2 induced by respiration depression leads to cerebral vasodilation and consequential increase in cerebral blood flow and intracranial pressure).
- Causes postural hypotension sometimes.

Morphine

J Histamine release:

- Causes pruritus, urticaria, sweating, vasodilation and bronchoconstriction.

K Hormonal actions:

- Inhibits release of LH.
- Increases GRH, ADH, PRL

M Immune depression

Morphine

2 Therapeutic uses:

A Analgesia:

- Used for various pain, especially acute, obstinate constant pain (e.g. burn, cancer pain);
- Fixed interval of administration reduces tolerance and dependence;
- Severe pain of renal and biliary colic + MR blockers.

Morphine

2 Therapeutic uses:

B Cardiac asthma:

- **Acute left ventricular heart failure induces pulmonary edema**
- **Reduces anxiety, cardiac preload and afterload.**
- **Particularly useful for painful myocardial ischemia with pulmonary edema.**

C Treatment of diarrhea: synthetic surrogates.

Morphine

2 Therapeutic uses:

D **Relief of cough:** synthetic antitussives

E **Premeditate drugs before anesthesia :**

sedative, anxiolytic, and analgesic properties. For high-risk surgery administered systemically; for local (epidural) anesthesia.

Caution: respiratory suppression

Morphine

3 Adverse effects:

- **Respiratory depression**
- Vomiting, constipation, biliary colic
- Dysphoria
- Allergy-enhanced or postural hypotensive effects
- Urinary retention (prostatic hypertrophy)
- Elevation of intracranial pressure (head injury)
- Immune depression

Morphine

3 Adverse effects:

- **Tolerance and Physical Dependence**
- Repeated use produces tolerance to the respiratory depression, analgesic, euphoric and sedative effects, but not to pupil-constricting and constipating effects.
- Physical and psychologic dependence readily occur for strong μagonists, especially used on necessities.

Morphine

3 Adverse effects:

- **Tolerance and Physical Dependence**
- Withdrawal symptoms: a series of autonomic, motor and psychological response that incapacitate the individual (rhinorrhea, lacrimation, yawning, chills, gooseflesh, hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhea, anxiety, and hostility).

Morphine

4 Contraindications:

- Women during labor or lactation
- New-born infants
- Chronic obstructive pulmonary disease (COPD)
- Asthma

Pethidine (meperidine)

1 Actions and mechanisms:

- Binds to opioid receptors, particularly μ receptor.
- Actions similar to but less potent than morphine.

----Transient decrease of gastro-intestinal motility and increase of the tone

---- Indistinctly central depression of cough reflex.

Pethidine (meperidine)

2 Therapeutic uses:

- **Analgesia: various severe pain, including during obstetric labor (less depression of respiration in newborn infants)**
- **Cardiac asthma**
- **Administration before anesthesia and artificial hibernation, combined with chlorpromazine and promethazine**

Pentazocine

- An <u>agonist on κ receptor</u>,

but a weak antagonist

at μ and δ receptors

(partial agonist).

- Actions (less potent compared with morphine): analgesia and respiratory depression, indistinct euphoria and dependence. Dysphoria, hallucinations and hypertension in high dose
- Used for moderate or chronic pain.

TRAMADOL

- Tramadol provides moderate pain relief.
- Because of its **dual actions** as a μ-agonist and monoamine transport inhibitor, it produces less respiratory depression for a given analgesic effect.
- Tramadol is a weak **agonist at μ-receptors**. *Its major metabolites are more potent agonists at μ-receptors*.
- Tramadol also **inhibits monoamine transporters** (principally **NA and 5-HT**) which is thought to produce analgesia synergistically with μ-agonism.

FENTANYL

- About 80 times more potent

Than morphine in analgesia

- Actions similar to morphine
- Main use is in anaesthesia,

used in conjunction with

droperidol, a neuroleptic, producing

neuroleptanalgesia

METHADONE

Similar actions to morphine

Longer duration of action

($t_{1/2}$ 37 h)

Less problems with withdrawal

Can be used to wean heroin and morphine addicts off the drug

DEXTROPROPOXYPHENE

- **Dextropropoxyphene** ($t_{1/2}$ 5 h) is structurally similar

to methadone and differs in that it is less analgesic and

less dependence producing. It is weak μ/κ/δ-agonist.

- Analgesics usefulness approximates to that of codeine, but its duration of action is longer.

Naloxone

- **Competitive blocker of opioid receptor, with ten-fold higher affinity for μ receptor than for κ.**
- **Actions:**

  --- precipitates withdrawal symptoms;

  ---reverses the coma and respiratory depression of opioid overdose (short action duration! Naltrexone with much longer action duration);

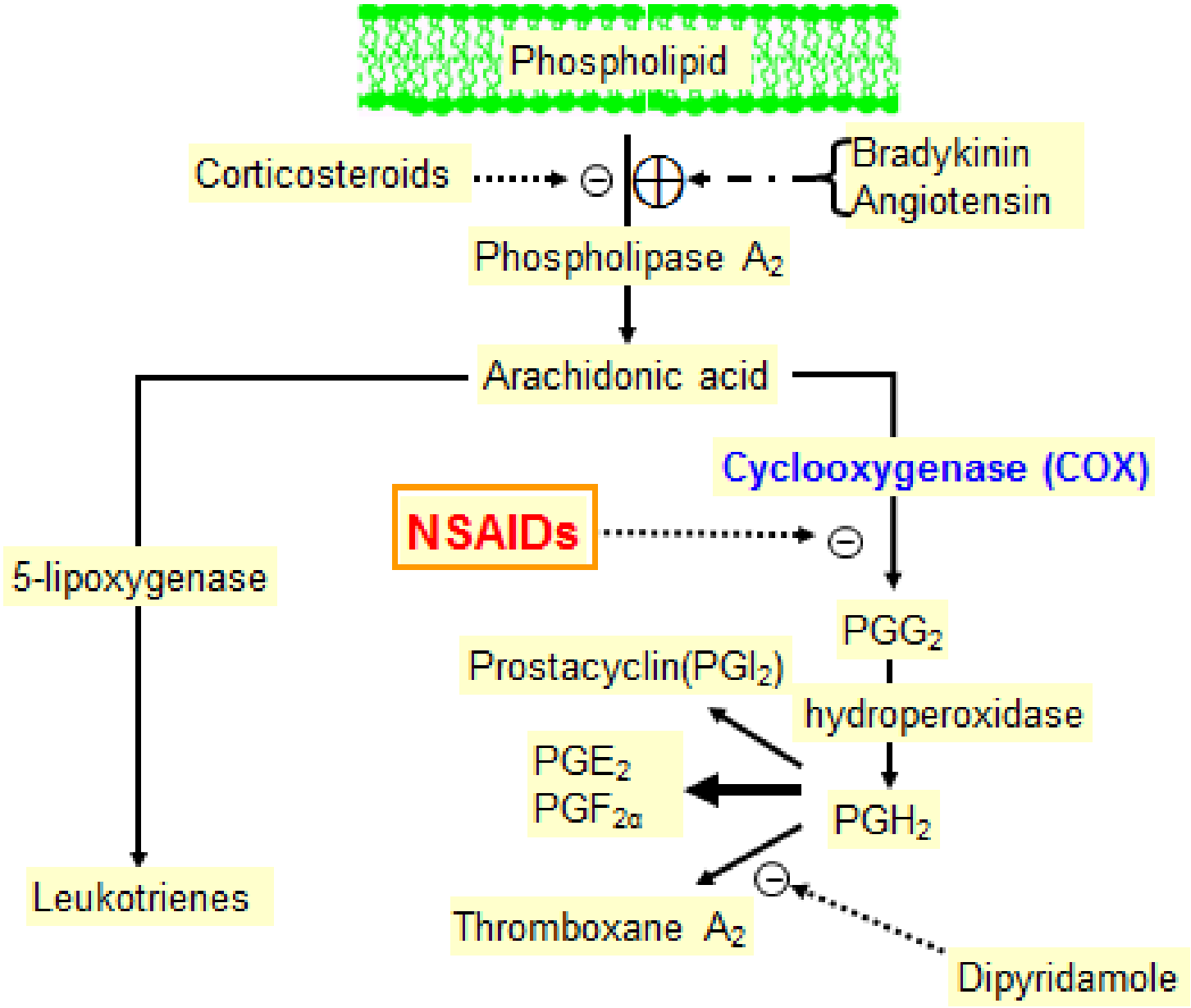
  --- eliminates some adverse effects with opioids

Other analgesics

- **Tramadol: weak μ receptor agonist, inhibits uptake of NA and 5-HT, effective on moderate to severe acute and chronic pain.**
- **Tetrahydropalmatine : effective on persistent blunt pain**

Non-steroidal anti-inflammatory drugs, NSAIDs

MOA OF NSAIDs



MOA OF NSAIDs

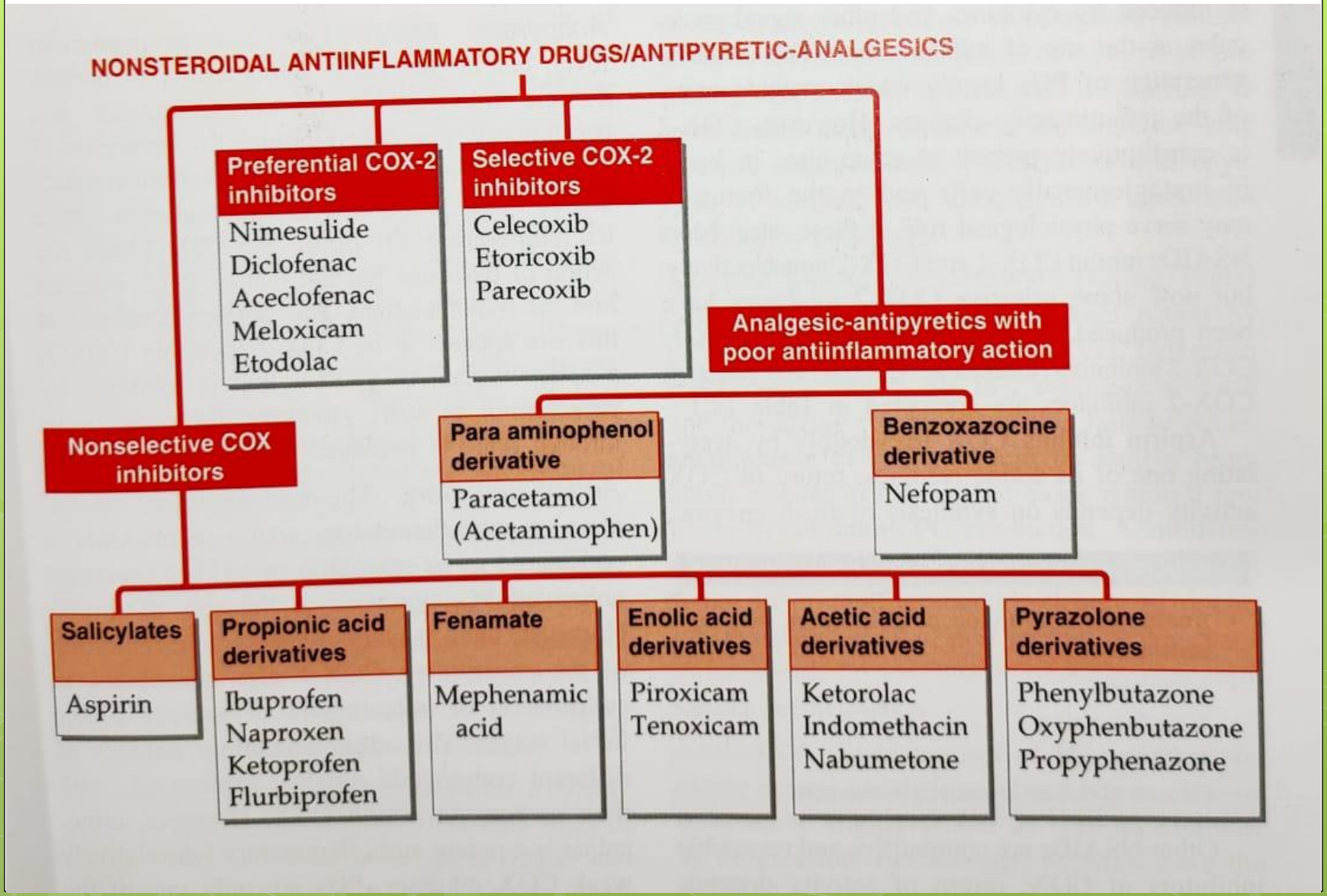
- Mechanism of action—inactivate cyclo-oxygenases, enzymes required for the production of prostaglandins
- **ASA and traditional NSAIDs inhibit both COX 1 and COX 2**
- **COX 1 is present in all tissues esp. GI, kidneys, endothelial cells and in platelets**

Prostaglandins important in:

1. **Protection of kidneys and stomach**
2. **Regulate vascular tone and platelets in CV system**

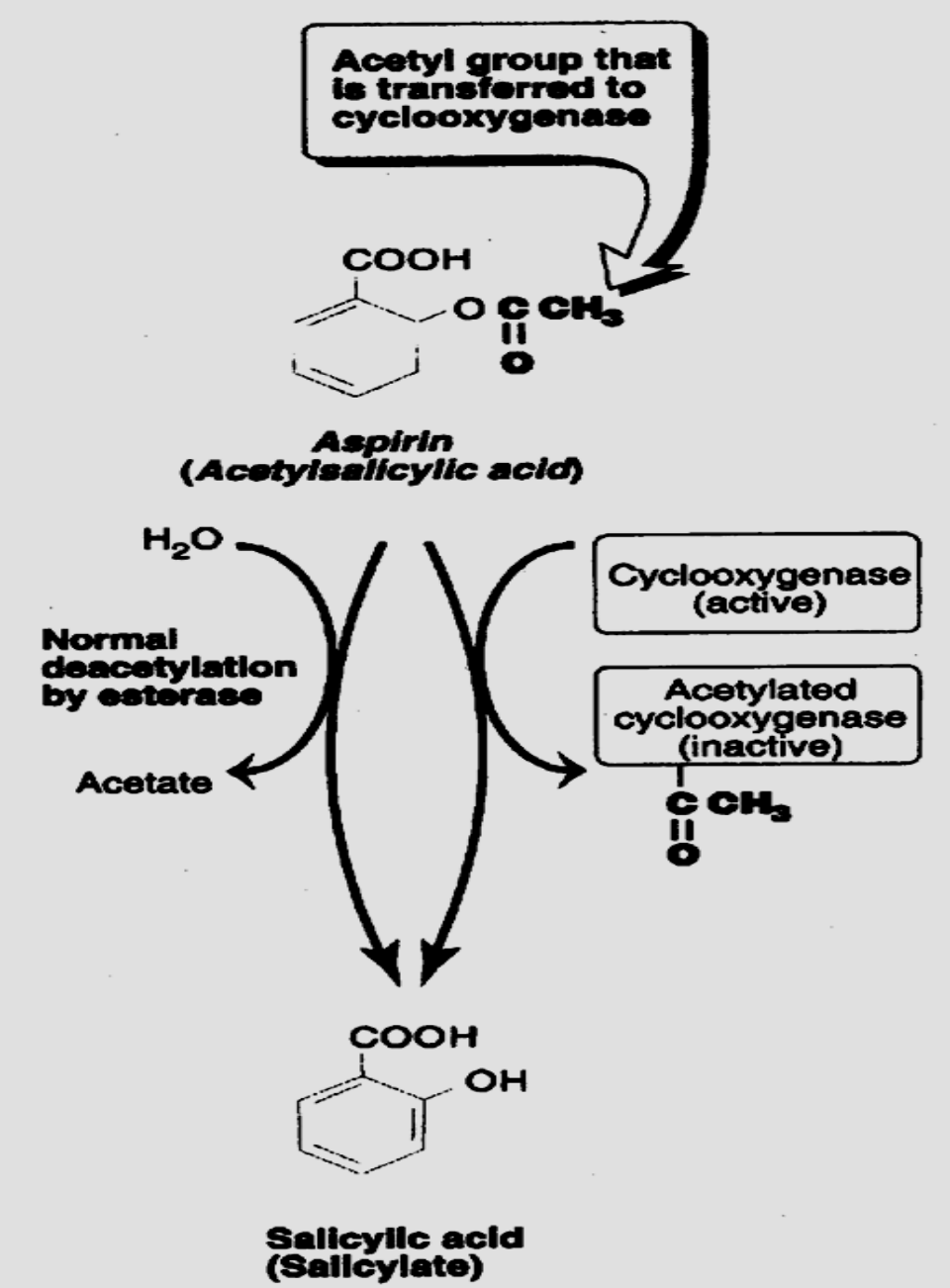
- **COX 2 is Found in brain, bone, kidneys, GI tract, and the female reproductive system**
- **Overall, prostaglandins produced by COX 2 are associated with pain and inflammation**

Classification of NSAIDs



Aspirin

- **MOA:** acetylating **COX** enzyme <u>irreversibly.</u>



Aspirin

Actions and therapeutic uses:

A **Antipyretic and analgesic & anti-inflammatory actions:**

- **Act on hypothalamus to decrease response to pyrogens and resets the thermostat toward normal and lowers the body temperature by increasing heat dissipation.**
- **Prevent prostaglandins from increasing the pain and inflammation produced by other substances released by damaged cells.**

Aspirin

B **Anti-rheumatic actions:** at large dose (4-6 g/d).

C **Anti-aggregation of platelets and vasoconstriction:** at small dose (~100 mg/d), irreversibly inhibits thromboxane production in platelets without markedly affecting PGI_2 in the endothelial cells of the blood vessel.

Adverse effects:

Prolonged bleeding time

Excessive ventilation: respiratory alkalosis

Salicylism: Toxicity in the CNS (headache, dizziness, nausea, vomiting, tinnitus)

Contraindicated in Reye's syndrome: liver and brain injury in children with virus infection

Acetaminophen

- Slow and prolonged antipyretic and analgesic effects
- No obvious anti-inflammation effect
- Less stimulation to gastrointestinal tract
- Damage of liver and kidney if used for a long time and at high dose

Indomethacin

- One of the most potent inhibitors of COX
- High potency of anti-inflammatory, analgesic, and antipyretic activity
- Used for ankylosing spondylitis (SA), Osteoarthritis (OA) and gout
- Effective in treating patent ductus arteriosus
- High incidence of adverse effects like:
  - central nervous system effect
  - gastrointestinal complaints
  - allergic reactions
  - hematopoietic reactions

Sulindac and Etodolac are less toxic and used for OA, RA, SA and acute gout.

Propionic acid derivatives

- Anti-inflammatory, analgesic and antipyretic activity
- Less gastrointestinal effects
- Change platelet function and prolong bleeding time
- Used for the treatment of various arthritis and dysmenorrhea

Inhibitors of TNF-α

- TNF-α is the predominant factor in inflammatory reaction.
- Include infliximab, adalimumab and IgG1
- Used for the treatment of rheumatoid arthritis, spondylitis ankylosans and other autoimmune diseases.

THANKS
FOR A PATIENT LEARNING