Clinical pharmacology of analgesic and anti-inflammatory drugs.

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Plan of lecture:

Analgesic drugs

- Opioid analgesics
- Non-opioid analgesics

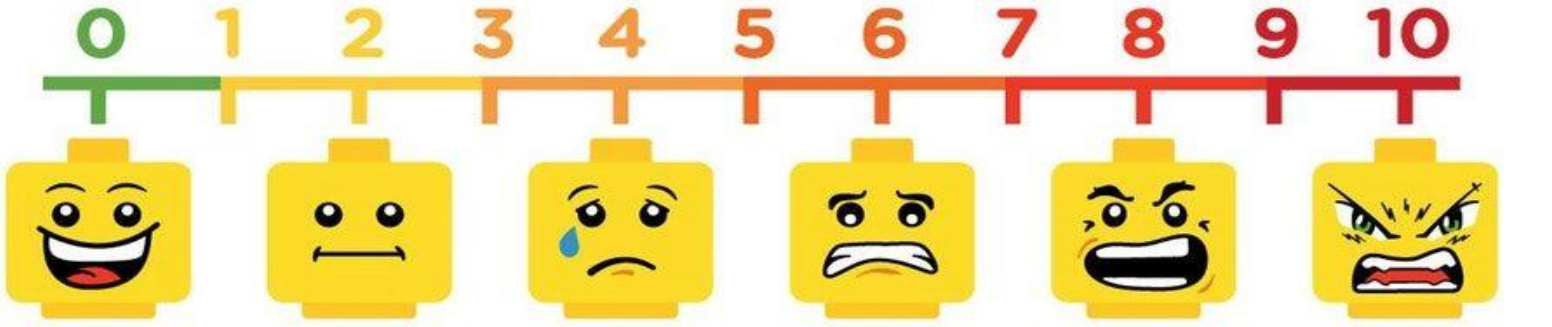
Antiinflammatory drugs

- NSAIDs
- Non-selective NSAIDs
- Selective NSAIDs
- Antirheumatic drugs

Pain Definition:

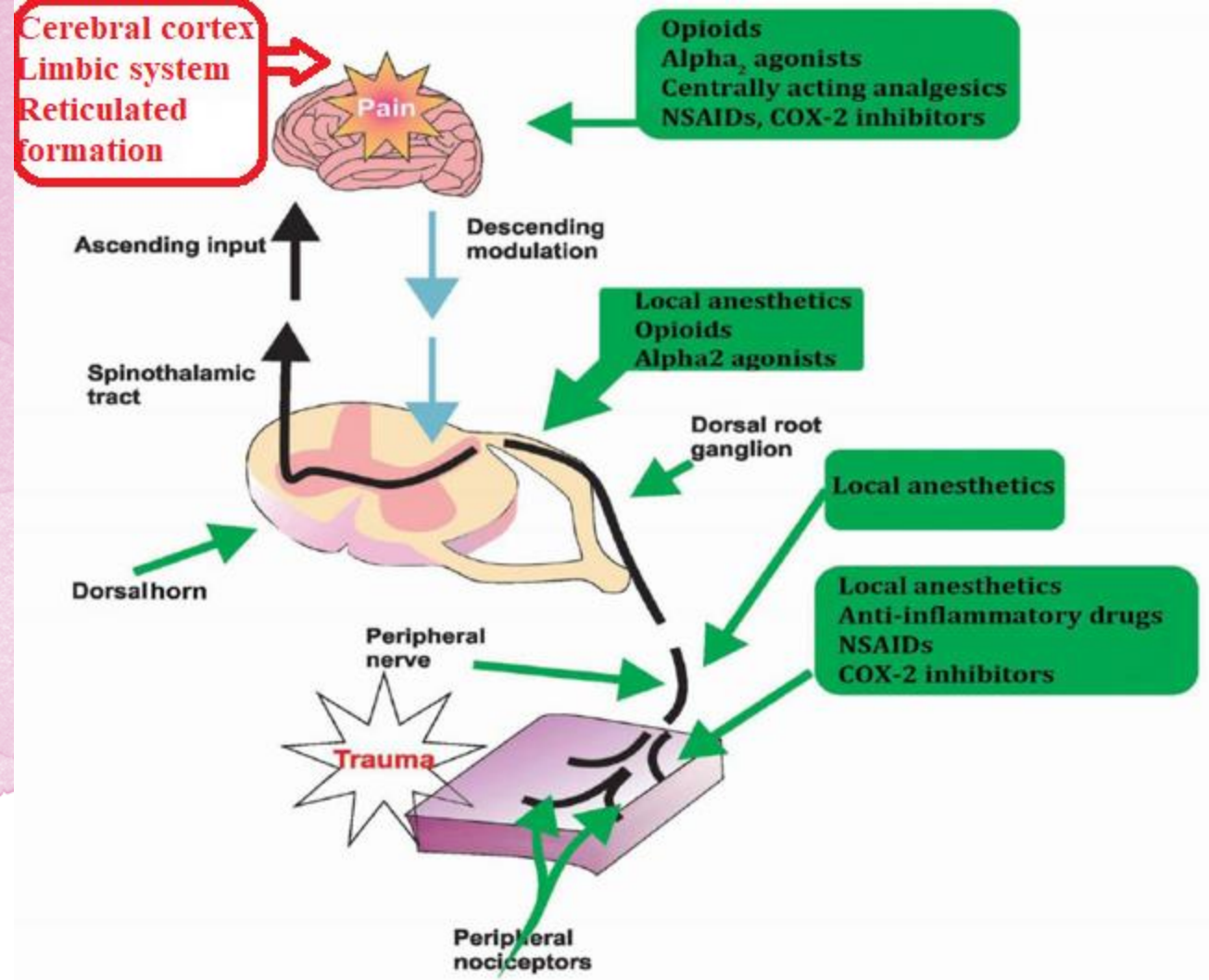
- *An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*
- ***(Source:** International Association for the Study of Pain)*

PAIN ASSESSMENT CHART



NO PAIN	MILD PAIN	MODERATE PAIN	SERIOUS PAIN	SEVERE PAIN	WORST PAIN POSSIBLE
No Pain	Can Be Ignored	Interferes With Daily Tasks	Interferes With Concentration	Interferes With Basic Needs	Bed Rest Required
+ Alert + Smiling	+ Flat + No Humor + Serious	+ Frown + Sad Eyebrows + Single Tear	+ Grimace + Intense Stare	+ Bulged Eyes + Palpable Fear + Audible Screams	+ Agonizing Screams + Face Distorted Beyond Recognition

Nociceptive pathway:



Analgesics

Proper analgesics

- **With central action**
- ✓ Opioid analgesics
- ✓ Non-opioid analgesics
- ✓ Mixt analgesics
- **With peripheral action**
- ✓ Antipyretic analgesics

Co-analgesics

- ✓ Tricyclic antidepressants;
- ✓ Neuroleptics;
- ✓ Muscle relaxants;
- ✓ Anticonvulsants;
- ✓ Calcium channel blockers
- ✓ Calcitonin;

Para-analgesics

- ✓ Glucocorticoids
- ✓ Nitrates
- ✓ Antacids
- ✓ Triptans
- ✓ Acetazolamide

Classification:

Drugs with predominant central action:

- Opioid analgesics: morphine, trimeperidine, meperidine, fentanyl,sufentanil, alfentanil, remifentanil, methadone, dextromoramide, dextropropoxyphene, butorphanol, buprenorphine, pentazocine, pyritramide, etc.
- Non-opioid analgesics

1. Paraaminophenol derivatives or antipyretic analgesics: paracetamol, phenacetin and combined drugs (citramon,solpadein, coldrex, saridon, panadol etc.).
2. Drugs from various groups: clonidine, amitriptyline, imipramine, ketamine, carbamazepine, sodium valproate, baclofen,somatostatin, diphenhydramine.

- Mixed-acting analgesics: tramadol

Drugs with predominant peripheral action:

- Salicylic acid derivatives: acetylsalicylic acid, salicylamide, methylsalicylate.
- Pyrazolone derivatives: metamizole and combination preparations (baralgin,spasmalgon, plenalginine, etc.), phenylbutazone, etc.
- Acetic acid derivatives: ketorolac.
- Various groups: ketoprofen, dexketoprofen, nefopan.
- Non-steroidal anti-inflammatory drugs:

non-selective: diclofenac, ibuprofen, indomethacin, acid niflumic, piroxicam etc.;

selective: nimesulide, celecoxib etc.

Opioid analgesics. Duration of action:

The parenteral way of administration:

- short (20-45 min) - fentanyl, alfentanil, sufentanil
- medium (3-5 hours) - - morphine, tramadol, trimeperidine, dextromoramide, butorphanol, pentazocine, pethidine, methadone
- long (6-8 hours) - buprenorphine

The enteral way of administration:

- Short (3-4 hours) - trimeperidine, pethidine, pentazocine, tramadol
- medium (4-6 hours) - morphine, methadone, dextromoramide, dextropropoxyphene, pyritramide
- long (6-8 hours) - buprenorphine, morphine retard

Opioid analgesics. Clinical activity:

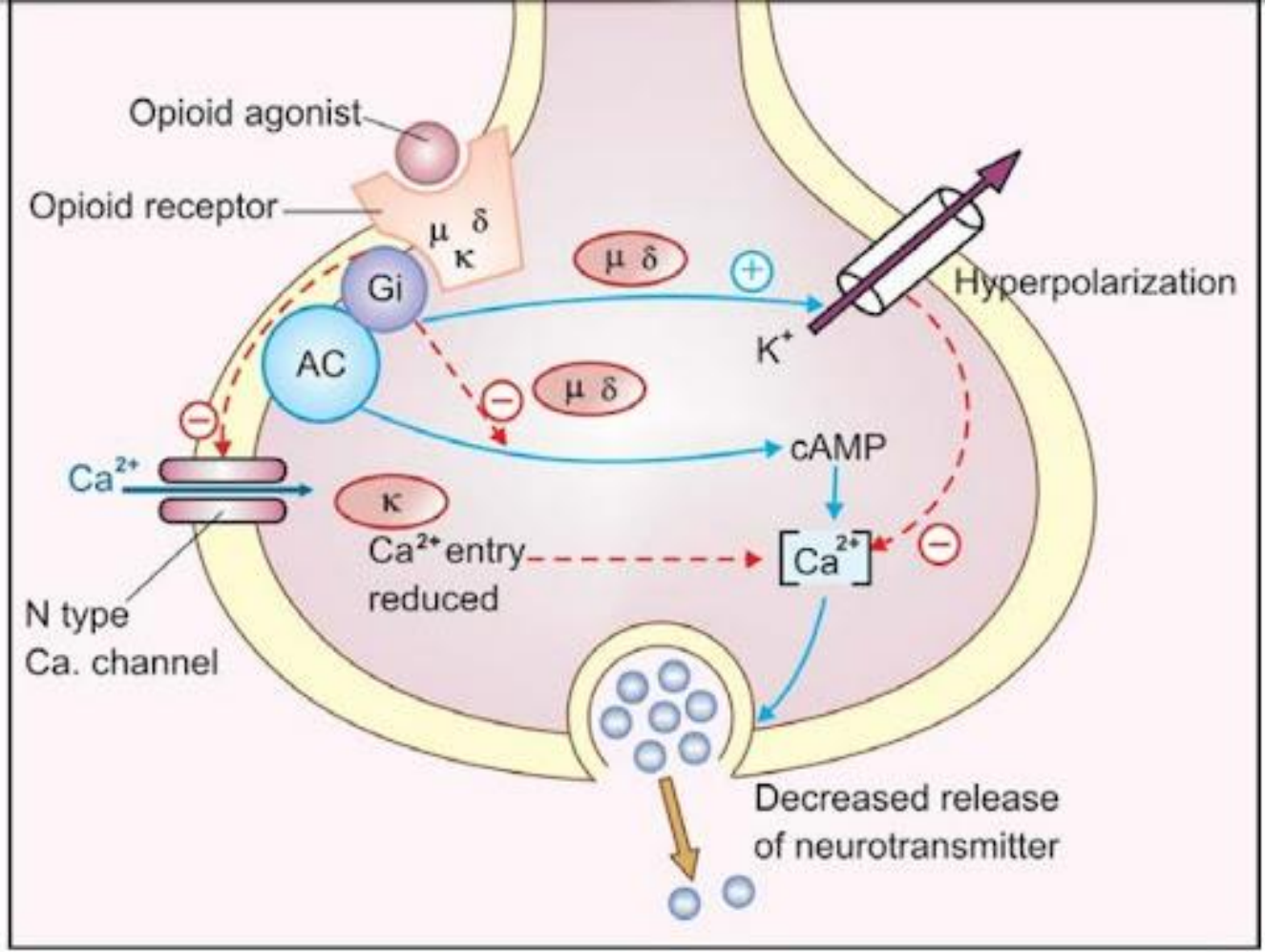
Parenteral way of administration:

- weakly active 30-100 mg - trimeperidine, pentazocine, tramadol, pethidine, codeine, tilidine
- active 5-10 mg - morphine, methadone, pyritramide, dextramoramide, nalbuphine
- very active 0.01-4 mg - fentanyl, sufentanil, lofentanil, alfentanil,butorphanol, buprenorphine, levorphananol

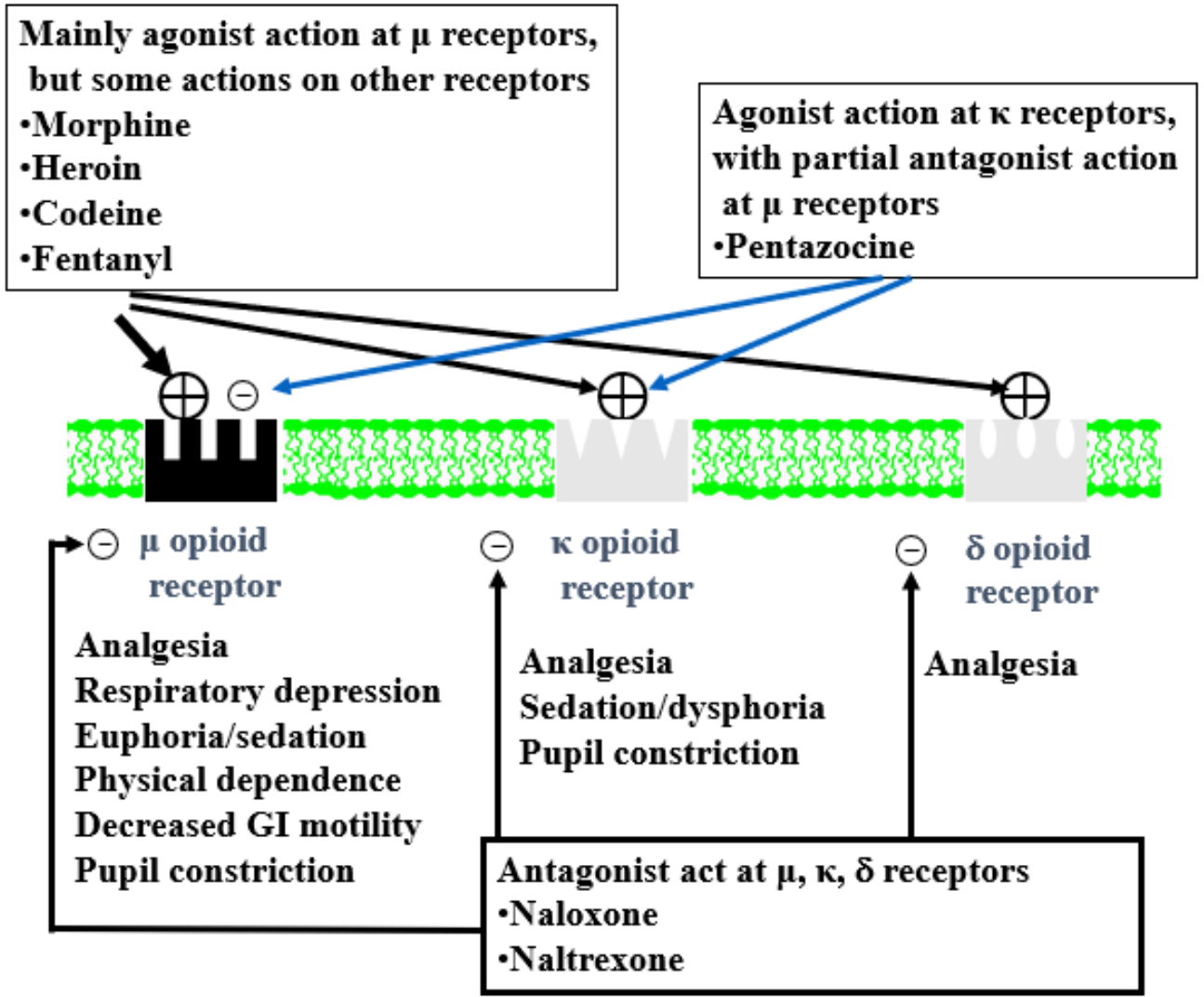
Enteral way of administration:

- weakly active 180-300 mg - trimeperidine, pentazocine, pethidine
- active 50-100 mg - morphine, dextropropoxyphene, tramadol, tilidine
- very active 5-20 mg - methadone, dextromoramide, buprenorphine, pyritramide

Opioid analgesics Analgesic effect



Opioid analgesics



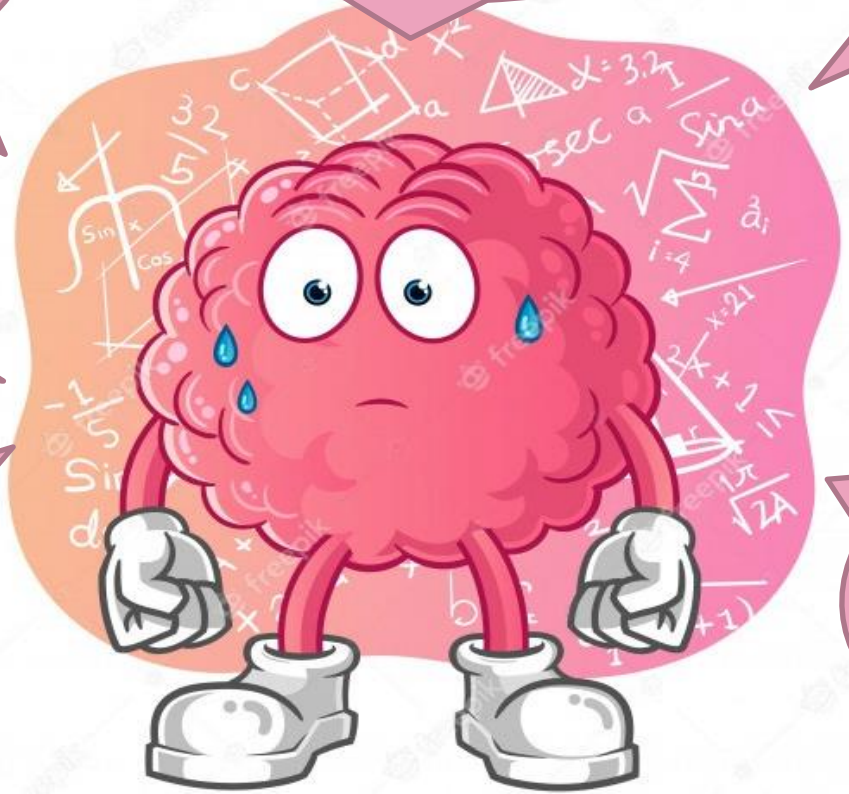
Opioid analgesics on CNS:

I. morphine euphoria; in non-drug addicts it is less pronounced and of shorter duration;
II. morphine sleep: in non-drug addicts it is more pronounced.
III. morphine abstinence: it can be erased or even absent in non-drug addicts and has a serious character in morphine addicts; it manifests itself by exacerbating the sensation of pain, restoring the feeling of fear and anxiety, negative emotions, the appearance of unwanted vegetative deviations (heart rhythm disorder, frequent - tachycardia, nausea, etc.)

The optic nerve center – stimulation (miosis).

Hypothalamic-pituitary system – ✖ gonadoliberin corticoliberin ➡ FSH, LH, ACTH, testosterone, estrogen and cortisol

Respiratory center - inhibition



Vomiting center – emmetic effect

Cough center – inhibition (antitussive effect)

The center of the vagus nerve – stimulation

Thermoregulatory center – inhibition (hypothermia)

Blood

- Abusing opioids through injections can cause veins to collapse or clog blood vessels.
- The chemicals produced by the disintegration of muscle tissue caused by opioid abuse move through the bloodstream, damaging organs, to extents such as kidney failure and heart attacks.

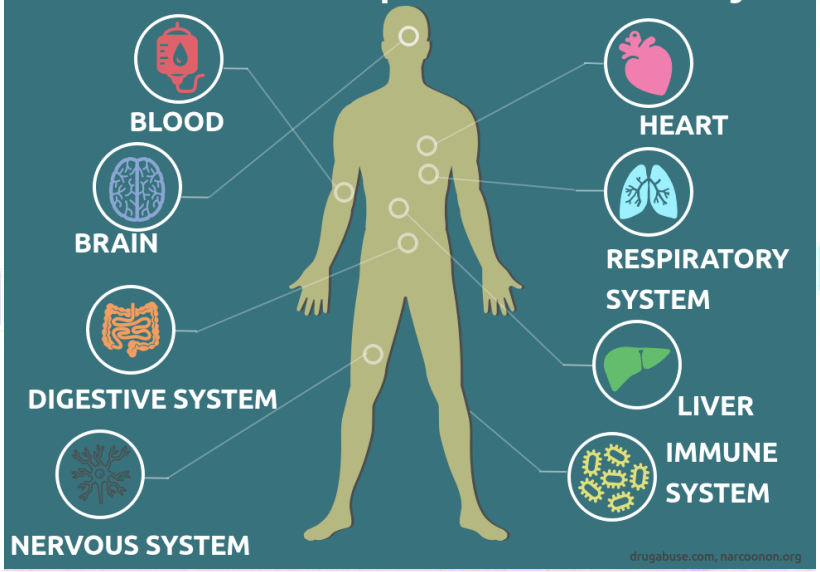
Brain

- Opioid abuse can cause daytime sedation, drowsiness, sleepiness and increased accounts of "nodding off."
- Long term users are also at risk of developing depression.

Digestive System

- Opioid abuse affects the muscles of the digestive system, leading to constipation, bowel obstruction, perforation and resultant periodontitis.
- Frequent opioid use can cause nausea and sudden, uncontrollable vomiting.

The Effects of Opioids on the Body



Nervous System

- Increased sensitivity to pain and hyperalgesia are effects of opioid abuse.
- Opioid abuse can cause an overall slowing of physical movement, loss of coordination and muscle tissue to break down.

Immune System

- Opioid abuse can inhibit immune responses, increasing susceptibility to infections.
- Abusing opioids through injection and sharing needles causes risk of HIV and Hepatitis C.

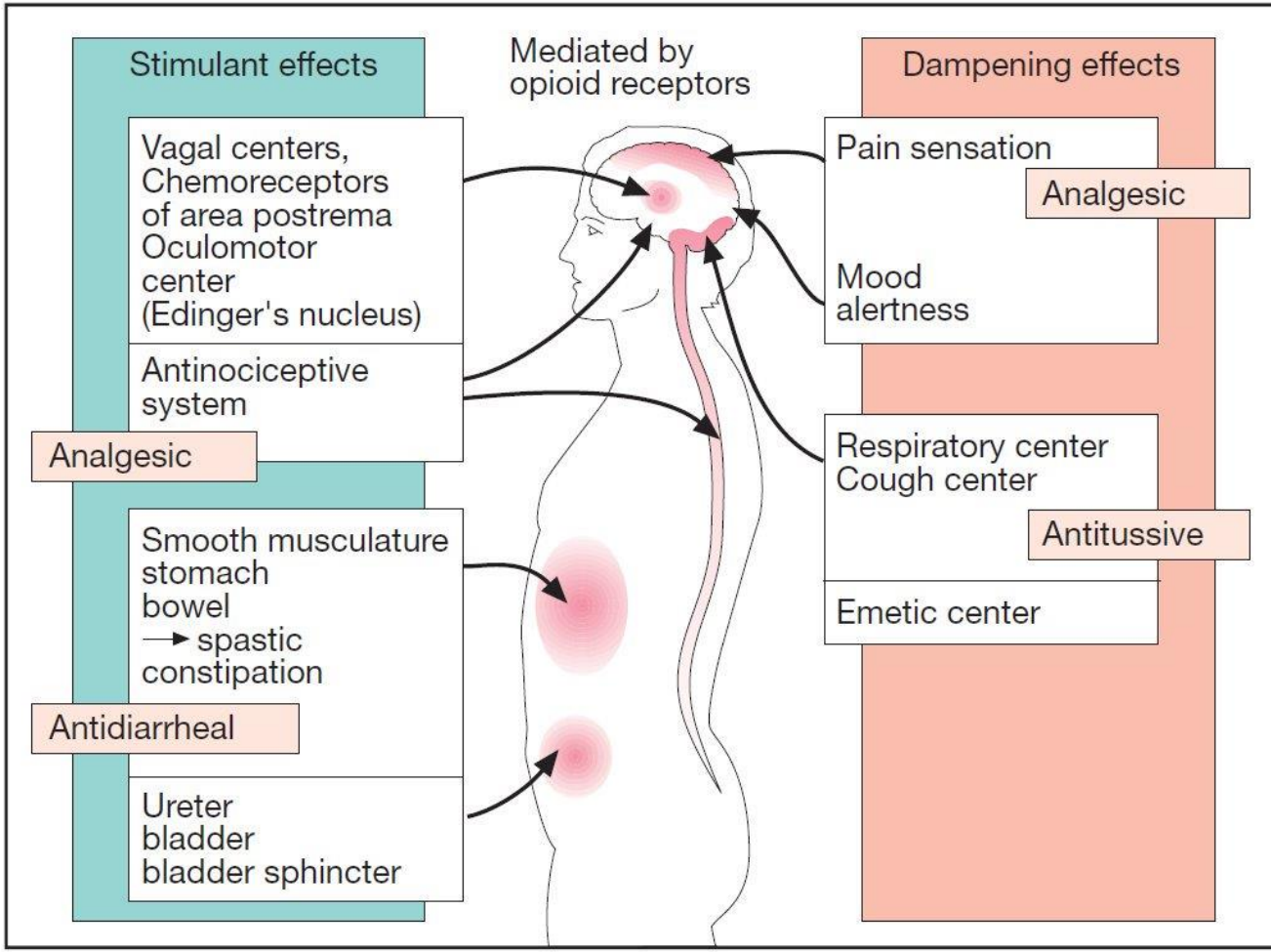
Heart

- Opioid abuse can cause endocardities, an infection of the heart lining due to contaminents.

Respiratory System

- Opioids can cause respitory depression which slows breathing and can deprive the brain and body tissue of oxygen, severely damaging organs.
- Conditions linked from opioid abuse include septic pulminory embolisms, interstitial lung disease and tuberculosis infections.

Opioid analgesics. Pharmaco dynamics:



Effects of opioids

Source : Color Atlas of Pharmacology 2nd Ed (Thieme,2000)

Opioid analgesics. Pharmakokinetics:

Absorption: - parenterally (injectable) it is high (s.c., i.m.) and very high spinal (epidural, intrathecal)

In internal, sublingual, transnasal and transcutaneous administration, absorption depends on the degree of lipophilicity of analgesics.

Internal path: For example. morphine, with the lowest lipophilicity, is absorbed p.o. slow and varied so that the effective dose ratio p.o./s.c is 60/10 mg morphine via p.o. It is used in the form of retard preparations (morfilong) used in chronic pain.

The effect of the first hepatic passage is relatively strong for most opioid analgesics. That is why the doses are much higher in the administration of p.o. compared to the parenteral route.

The effect of the first hepatic passage is weaker in some opioid analgesics: codeine, oxycodone, methadone, levorphananol and consequently the relative potency of the pathway p.o. compared to the parenteral route is higher (about 60%)

Opioid analgesics. Pharmako kinetics:

- The sublingual pathway, due to the very small absorption surface, imposes two conditions: high lipophility and high potency (low active doses)
- These conditions are achieved by fentanyl, methadone, buprenorphine
- Sublingual bioavailability is better (and without large interindividual variations) compared to the internal route. Due to the avoidance of the first hepatic passage (eg buprenorphine has a bioavailability of 50% sublingually, compared to 15% p.o., therefore buprenorphine is frequently used sublingually. Intrarectal bioavailability is higher (50-70%) compared to the p.o. pathway, also due to the possible avoidance of the first hepatic passage.

Distribution:

Opioid analgesics bind insignificantly to plasma proteins (most - 33-70%) except methadone (90%).The drugs are distributed in the parenchymal organs - lungs, liver, kidneys, spleen. The accumulation of highly lipophilic drugs (fentanyl) in adipose tissue slows down their metabolism. Penetration through the blood-brain barrier depends on the degree of lipophilicity. Thus, opioid analgesics with low lipophilicity penetrate more difficult, and when epidural administration achieves a deep and lasting analgesia (12-24 hours). The blood-brain barrier is missing in newborns, so the use of opioids for analgesia at birth can inhibit the child's respiratory center.

Metabolism:

Opioid analgesics containing hydroxyl groups (morphine, hydromorphone, oxymorphone, levorphanol) are conjugated to glucuronic acid. Ethers (meperidine) are hydrolyzed by tissue esterases. However, it turned out that these metabolites have a more pronounced analgesic activity than the initial drug. In patients with renal impairment, the accumulation of these metabolites produces stronger and more lasting analgesia.

Some opioid analgesics undergo O-desalkylation (codeine, oxycodone, hydrocodone) or oxidation (pentazocine, etc.) with subsequent glucuronidation in the second stage. A number of drugs are metabolised by N-desalkylation: pethidine to norpetidine (toxic metabolite), proproxyfen to norpropoxyphene (active metabolite).

Ways of administration:

Currently, along with the traditional ways of administration (internal, s / c, i / m,) are used: prolonged forms (morfilong etc.), rectal suppositories (with morphine and hydromorphone), transdermal patches (fentanyl, buprenorphine, etc.), intranasal aerosol (butorphanol), scheduled infusion systems, epidural and intrathecal introduction of opioid analgesics, especially in patients with chronic pain.

Opioid analgesics. Indications:

- very intense acute pain syndrome (postoperative, posttraumatic.);
- acute myocardial infarction;
- unoperable cancer;
- biliary, renal, intestinal colic;
- chronic pain;
- neuroleptanalgesics;
- obstetric analgesia;
- dyspnea from acute pulmonary edema;
- diarrhea;
- intravenous anesthesia.

Opioid analgesics. Side effects:

Miosis

Orthostatic hypotension

Respiratory depression

Pain suppression/**P**ruritus

Histamine release/**H**ormon release

Increased intracranial pressure

Nausea

Euphoria

Sedation

Morphine:

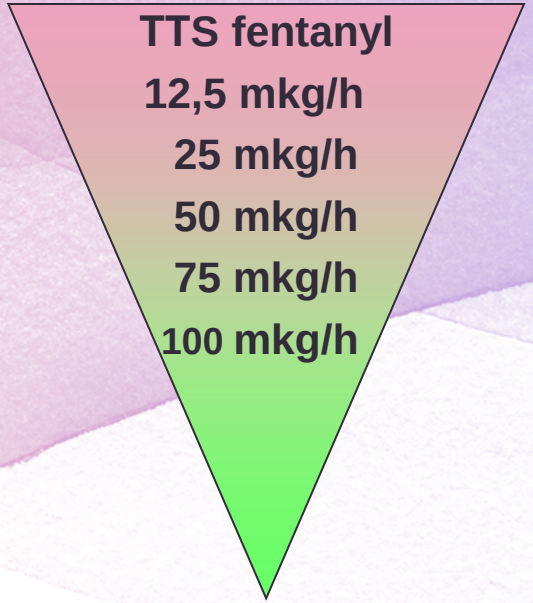
- Morphine activates opiate receptor to produce analgesic effect like endogenous opiate peptides.
- high affinity for μ receptors
- varying affinities for δ and κ receptors
- low affinity for σ receptors in CNS and gastrointestinal tract.

Fentanyl

Benefits :

- The most powerful opioid
- Stable pain control (72 hours)
- There is no limit to the dose of painkillers
- The addictive effect is weaker
- Inactive metabolites
- Less commonly causes intestinal dysfunction (St. Oddi's spasm, constipation)
- Large therapeutic range

Agonist of μ receptor



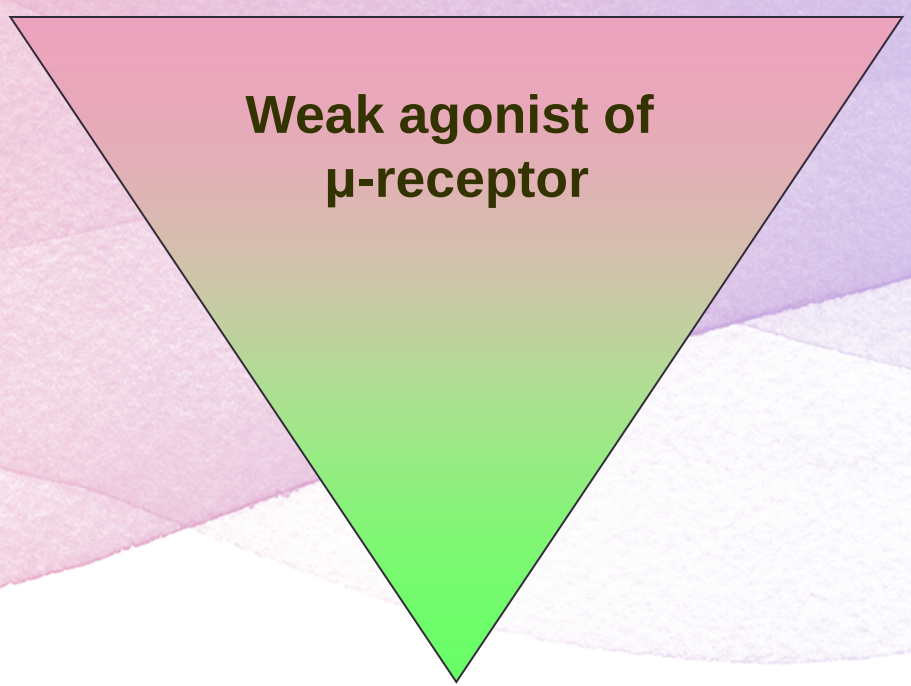
Disadvantages:

- Long-term titration of doses, which is possible by the presence of several dosage forms
- Not to be used in case of hyperthermia, hyperhidrosis
- Contact dermatitis is possible

Tramadol:

Benefits:

- **Side effects are poorly started: nausea, constipation,**
- **does not inhibit respiration,**
- **does not cause drug dependence**
- **Effective in mild to moderate pain**



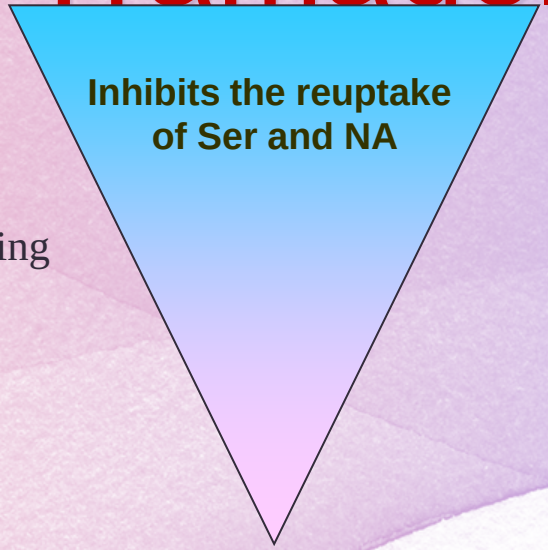
Disadvantages:

- **Effective in moderate pain**
- **Maximum dose 400-600 mg / day.**
- **Analgesic potential 0.05-0.1**

Tramadol:

Benefits :

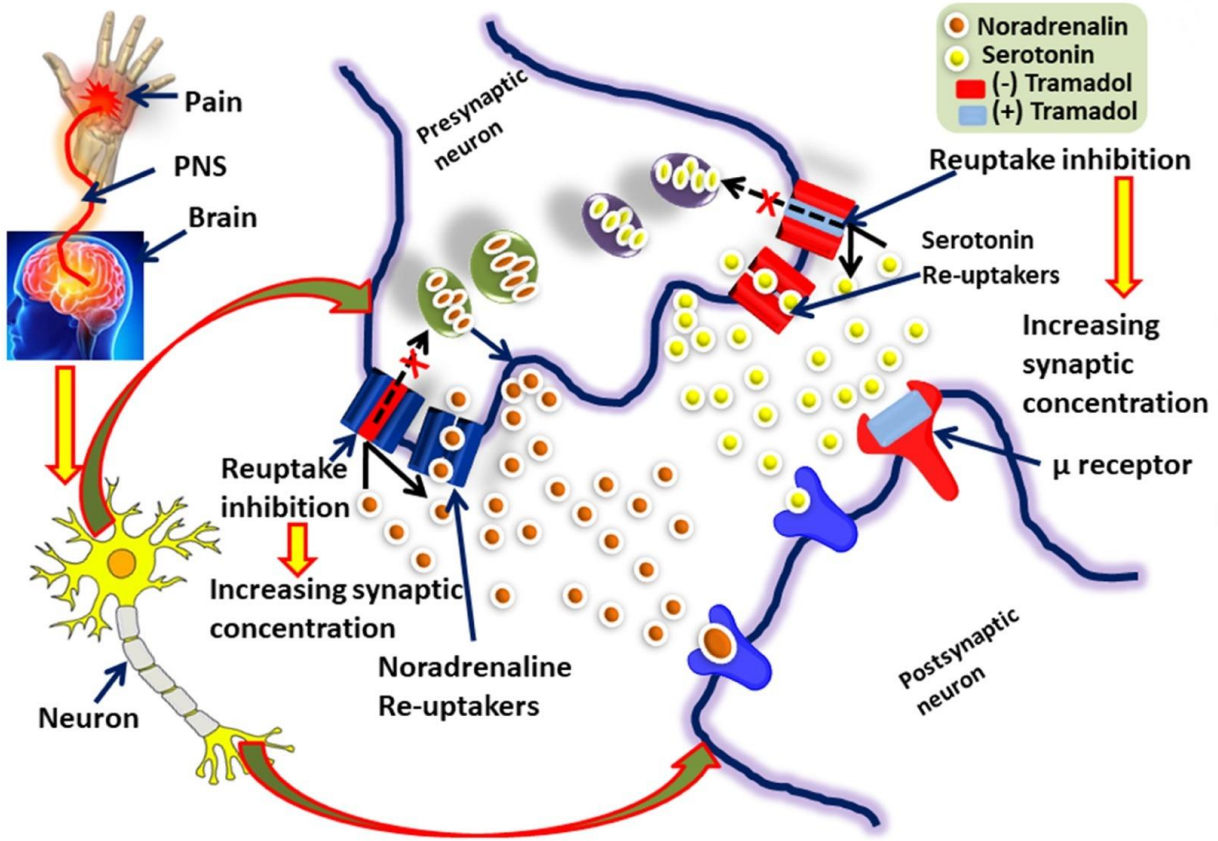
- Stimulating action;
- Low opioid potential;
- Double mechanism by potentiating the antinociceptive system and inhibiting the nociceptive one



Disadvantages:

- Increased anxiety;
- Tachycardia, ↑ TA, tremor;
- Mood swings (improvement, less often - dysphoria);
- Change in activity (decrease, less often - increase);
- Epileptic seizures (especially in combination with tricyclic antidepressants and IRSS and NA);
- Agitation, arousal, nervousness, insomnia, hyperkinesia
- Naloxone ineffective at overdose

“TRAMADOL


Noradrenalin
Serotonin
(-) Tramadol
(+) Tramadol
Pain
PNS
Brain
Presynaptic neuron
Reuptake inhibition
Serotonin Re-uptakers
Increasing synaptic concentration
μ receptor
Reuptake inhibition
Increasing synaptic concentration
Noradrenaline Re-uptakers
Neuron
Postsynaptic neuron

Tramadol:

Indications:

- moderate and acute and chronic pain,
- in diagnostic procedures,
- malignant neoplasms,
- acute myocardial infarction,
- neuralgia,
- trauma in patients who do not respond to non-opioid analgesics.

- Tramadol is prescribed to adults and adolescents 50 mg (tablets or capsules) or 20 drops per mouth with little liquid or sugar, 1 suppository or 100 mg S / c., I / m. su I / v. slowly or in infusion.
- The daily dose should not exceed 400 mg. In children 2-14 years 1-2 mg / kg. Drops will be preferred in oral administration. Long-term treatment can result in mental and physical dependence on the patient.

Tramadol:

Contraindications and precautions:

- acute alcohol intoxication, hypnotics, analgesics and other CNS inhibitors,
- hypersensitivity to the preparation,
- age under 2 years.
- It is used with caution in chronic respiratory diseases, pregnancy.

Side effects

- sweating, dizziness, fatigue,
- nausea, vomiting,
- dry mouth, palpitations,
- postural hypotension, collapse,
- convulsions, respiratory depression,
- alergic reactions.

Agonist – Antagonist:

- Not the first choice
- For patients with opioid withdrawal syndrome
- moderate analgesic effect
- Psychotomimetic side effects
- Potential for the development of low drug abuse

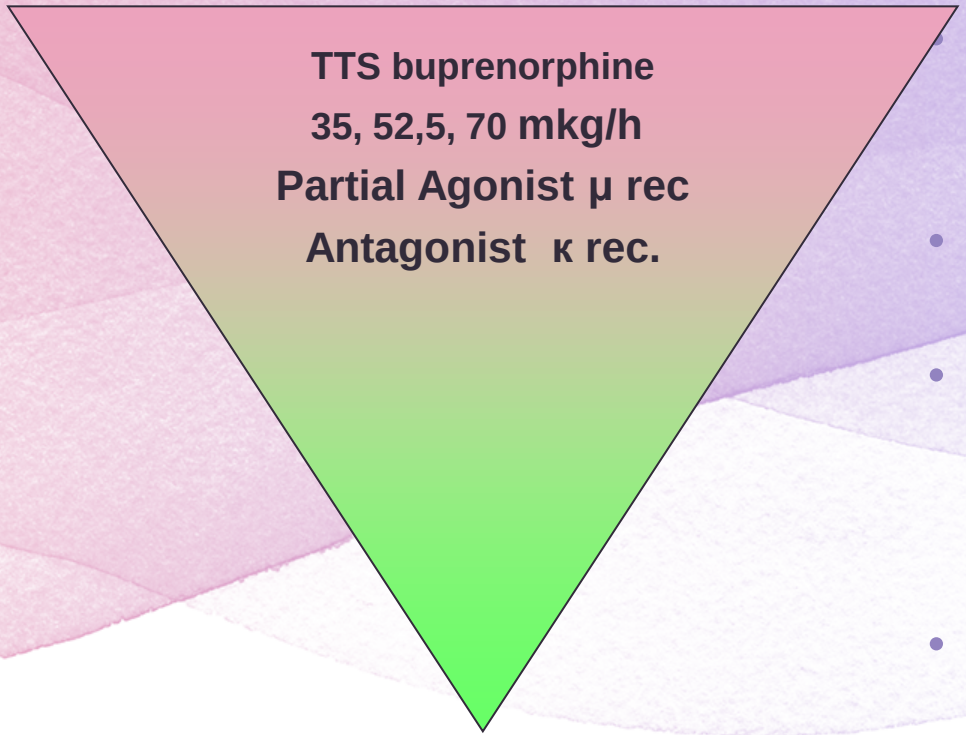
Example:

- Butorphanol (Stadol)
- Pentazocine (Talwin, Talwin NX)
- Buprenorphine (Buprenex)

Buprenorphine:

Benefits

- **Strong opioid and universal**
- **Duration of action of TTS- 72 hours**
- **lower dependency potential**
- **Less commonly causes intestinal dysfunction (St. Oddi's spasm, constipation)**



Disadvantages:

- **Moderate-severe pain therapy: "saturation effect" - 3.2 mg / day**
- **Contraindicated liver failure**
- **Do not administer in case of hyperthermia, hyperhidrosis, Contact dermatitis**
- **Long-term dose**

Recommended step medication for the treatment of neuropathic pain

First line:

- Tricyclic antidepressants: Amitriptyline
- Selective serotonin reuptake inhibitors: Duloxetine, Venlafaxine
- A-δ calcium channel ligands: Gabapentin, Pregabalin
- Local anesthetics - Lidocaine (5% plaster)

Second line:

- Mixed analgesics: Tramadol,
- Opioid analgesics

Third line:

- Some antidepressants: Bupropion, Paroxetine
- Some antiepileptics: Carbamazepine, Valproic Acid
- Capsaicin applied topically in low concentration (plaster)
- NMDA receptor antagonists: Dextromethorphan
- Antiarrhythmics: sodium channel blockers: Mexiletine

Analgesic drugs with predominant peripheral action:

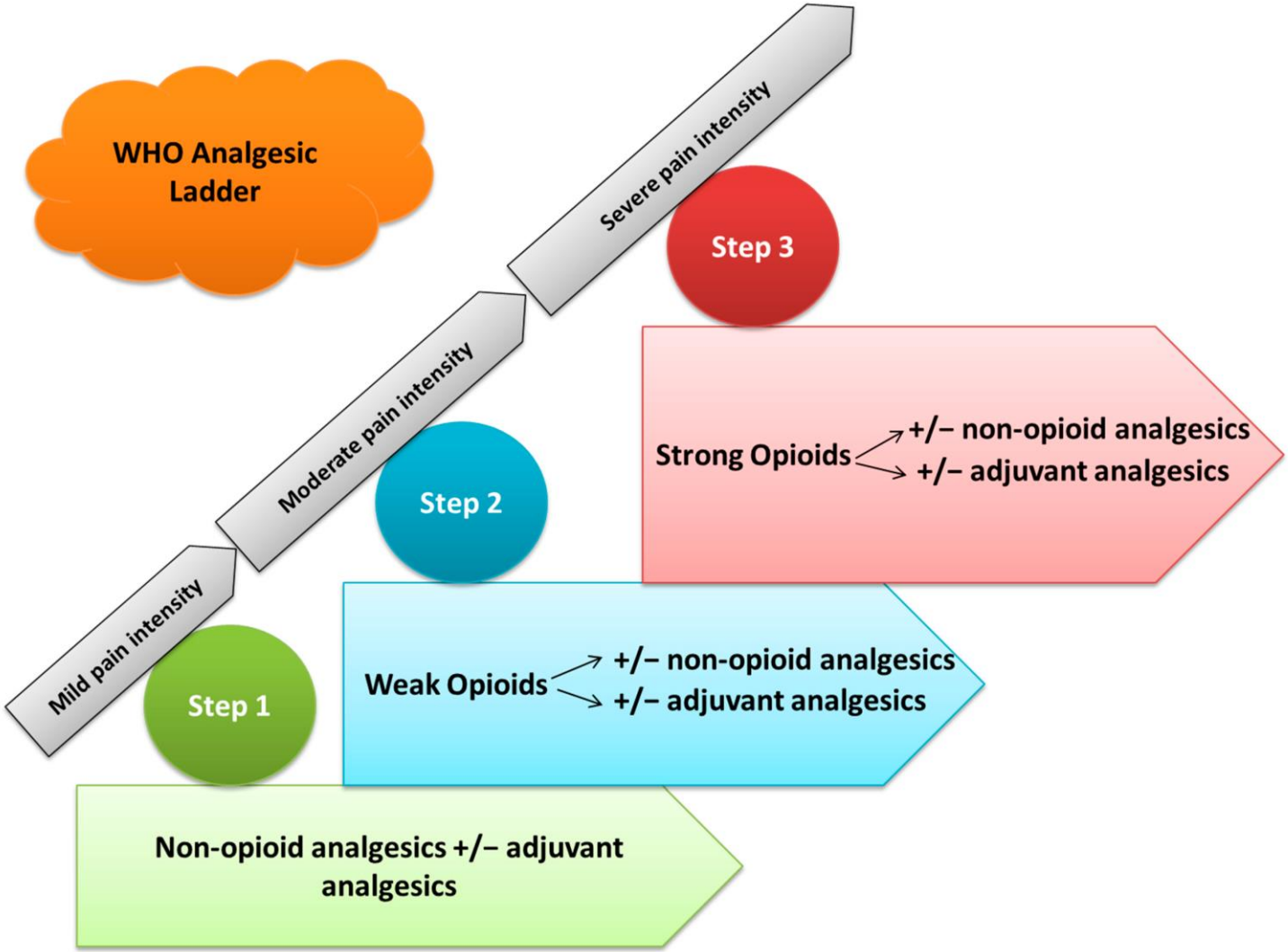
A. Acetylsalicylic acid derivatives: - acetylsalicylic acid, salicylamide, methylsalicylic acid.
B. Pyrazolone derivatives: - metamizole and combined preparations (baralgin, spasmalgon, plenalgin, etc.), phenylbutazone, etc.
C. Heteroacrylacetic derivatives: ketorolac
D. Various groups: ketoporofen, dexketoprofen, nefopan
E. Non-steroidal anti-inflammatory drugs:
    1. non-selective: diclofenac, ibuprofen, indomethacin, niflumic acid, piroxicam, etc.
    2. selective: nimesulide, celecoxib etc.

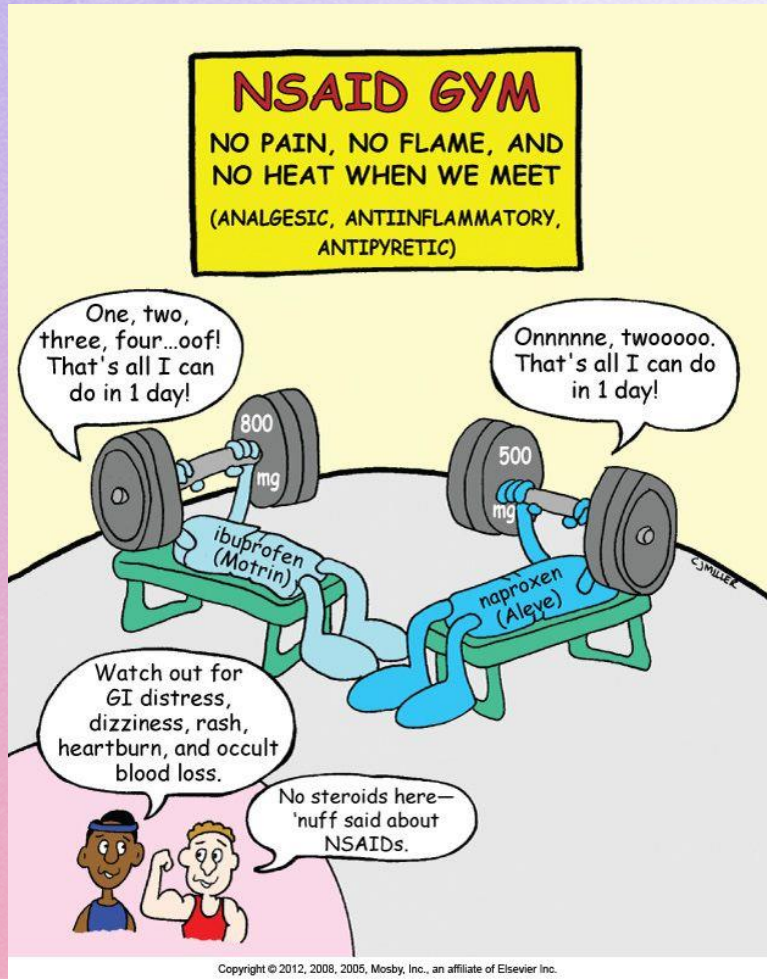
Non-opioid analgesics with predominant peripheral action

Peripheral and central mechanism:

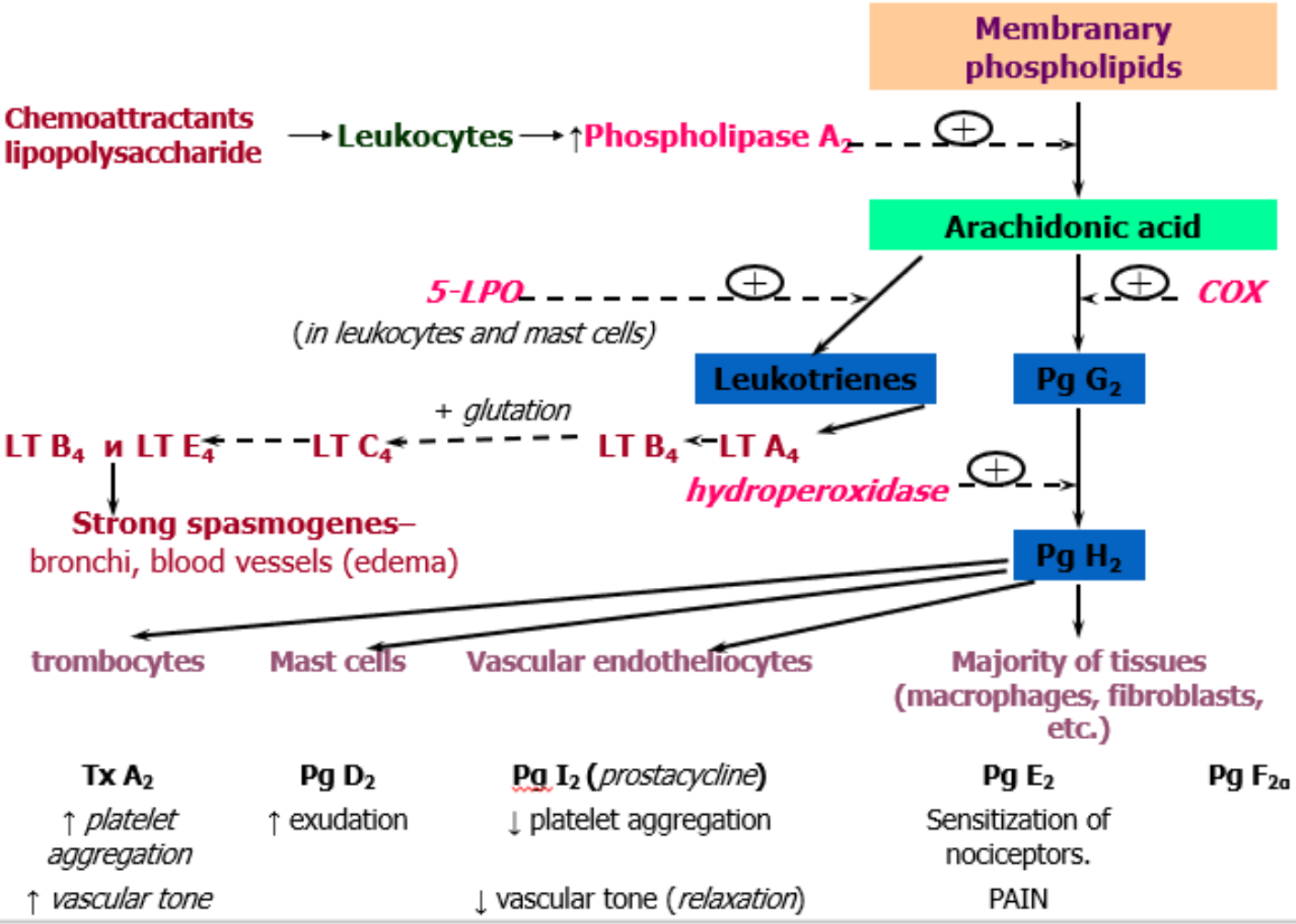
I. The main component of the analgesic action is the peripheral one due to: that it inhibits COX by decreasing prostaglandin formation, PGs have a hyperalgesic role, sensitizing nociceptive endings to the action of algogenic substances (bradykinin, 5-HT), prostaglandins (PGE2 and PGI2) increase the sensitivity of nociceptive nerve endings (nociceptors) as well as the release of substance P, causing hyperalgesia

II. The central component is made by: inhibition of prostaglandin synthesis in the CNS by blocking COX. It influences the transmission of painful impulses on the afferent pathways at level I (posterior horns of the spinal cord) and II (reticulated formation, limbic system, hypothalamus, etc.), and at the thalamus increases the threshold of pain perception.In the spinal cord, inhibition of prostaglandin synthesis decreases the release of substance P and suppresses hyperalgesia.


WHO Analgesic Ladder
Severe pain intensity
Moderate pain intensity
Mild pain intensity
Step 3
Step 2
Step 1
Strong Opioids
+/− non-opioid analgesics
+/− adjuvant analgesics
Weak Opioids
+/− non-opioid analgesics
+/− adjuvant analgesics
Non-opioid analgesics +/− adjuvant analgesics



Arachidonic acid metabolism



COX – 1 VS COX - 2

COX – 1

- Intrinsic synthesis
- Physiological functions:
  - gastrointestinal protection
  - platelet aggregation
  - Vascular resistance regulation
  - Renal blood flow regulation

COX – 2

- Induced
- Physiological:
  production of PG - elevated during pregnancy
- pathological:
  producing proteinase, PG, and other inflammatory mediators

Classification:

Nonselective COX inhibitors(traditional NSAIDs)

- Salicylates-aspirin/acetylsalycilic acid
- Propionic acid derivatives-Ibuprofen, naproxen, ketoprofen, flurbiprofen
- Fenamates - Mephanemic acid
- Aryl-acetic acid derivatives-diclofenac, aceclofenac
- Oxicam derivatives-Piroxicam, tenoxicam
- pyrrolo-pyrrole derivative- ketorolac
- Indole derivatives-indomethacin
- Pyrazolon derivatives-Phenybutazone, Oxyphenbutazone
- Para-aminophenol derivatives (acetoaminophen)-Paracetamol

Selective COX-2 inhibitors-Celecoxib, parecoxib,Nimesulide, meloxicam

SAIDs–Steroidal anti-inflammatory drugs–GCS–Prednisolon, Dexamethasone

Pathogens or toxins

↓(+)

PMNs

↓

pyrogen release

↓(+)

hypothalamus

↓

PG E_2 synthesis and release

↓(+)

body temperature-regulating center in hypothalamus

↓

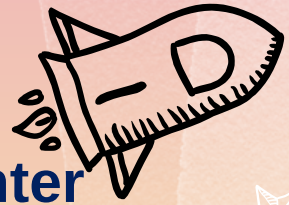
set point for body temperature↑

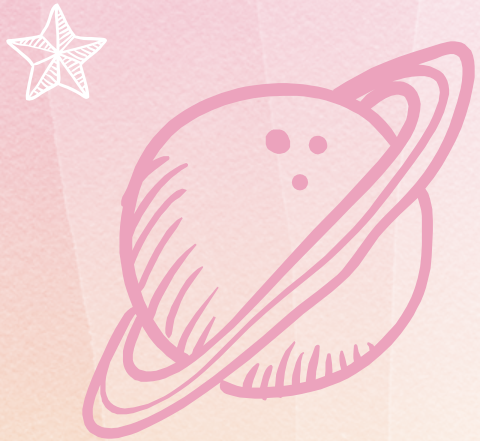
↓

heat production↑and heat dissipation↓

↓

body temperature↑(fever)





Acetylsalicylic acid (ASA, aspirin)

Pharmacokinetics:

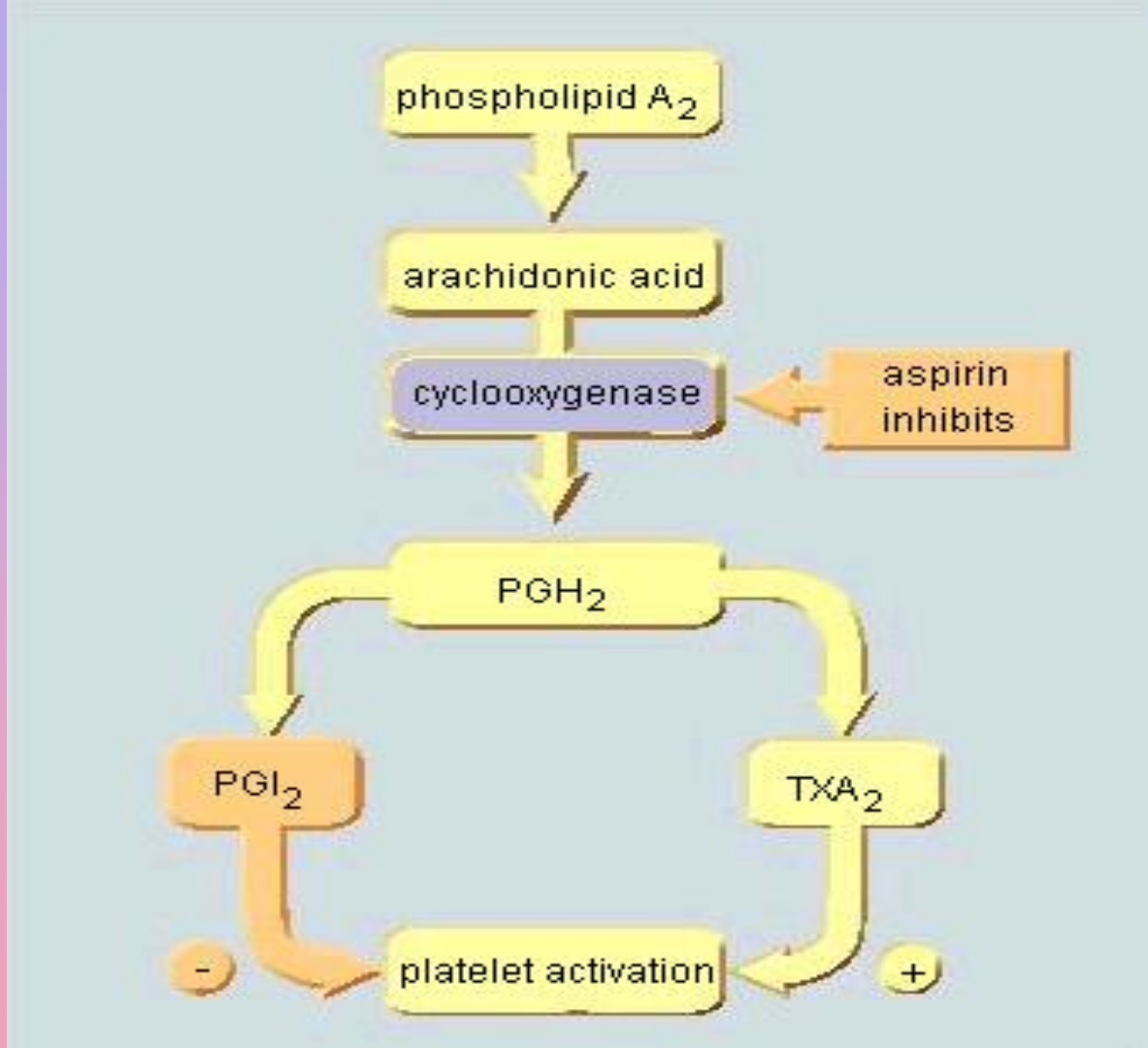
- metabolized in liver by the hydrolyzation to salicylate and acetic acid by esterases .
- in oral small dose, metabolized in first-order kinetics and half life is 3.5 h,
- in large dose (1g/time,>4g/day), metabolized in zero-order kinetics because hepatic metablic pathway becomes saturated, which prolong $t_{1/2}$ of aspirin to 15 h or more to lead to toxication.

Pharmacodynamics:

1. antipyretic action: rapid and moderate in potency.
2. analgesic effects: effective for mild, moderate dull pain.
3. antiinflammatory effects: to treat rheumatoid and
4. rheumatic arthritis, symptomatic relief.
5. antiplatelet effects: to inhibit platelet aggregation and
6. secondary release of ADP from activated platelets by inhibition of TXA_2 production.

Other effects:

- increasing alveolar ventilation
- increasing gastric acid secretion and diminishing mucus protection to cause epigastric distress, ulceration,
- Hemorrhage
- retention of sodium and water to cause edema and hyperkalemia.

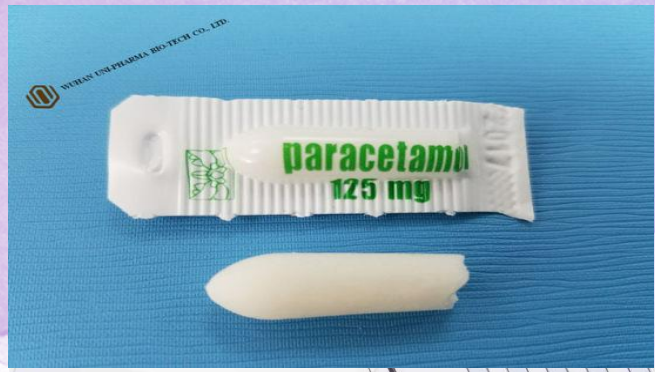


Side effects:

- gastrointestinal reaction: epigastric distress, nausea, vomiting, gastric ulceration.
- hepatic damage: mild, reversible.
- prolonging bleeding time due to inhibition of platelet functions in small dose and reduction of plasma prothrombin level in large dose
- large dose of aspirin uncouples oxidative phosphorylation. Energy normally used for production of ATP is dissipated as heat, which explains hyperthermia caused by salicylates when taken in toxic quantities.
- Reye's syndrome: seen during viral infections fatal -->fulminating hepatitis with cerebral edema.
- Salicylate toxication (salicylism):
  - mild intoxication: headache, mental confusion, drowsiness, difficulty in hearing, vomiting
  - severe intoxication: hyperventilation, severe CNS disturbulance, respiration depression and marked alteration in acid-base balance
  - Medication: discontinuation of salicylates, gastric lavage, relieving symptoms, intravenous infusion of $NaHCO_3$ and dialysis.

Acetaminophen = Paracetamol

- inhibits prostaglandin synthesis in CNS, but less effect on peripheral cyclooxygenase.
- antipyretic and analgesic effects are similar to aspirin in potency
- no anti-inflammatory activity.
- Use: dull pain and hyperpyrexia., choice for children with viral infections or chicken pox.
- Adverse effects: skin rash and drug fever, hypoglycemic coma, renal tubular necrosis and renal failure in long-term administration, acute hepatic necrosis in large dose.



How it works?

- ✓ inhibition of prostaglandin synthesis in the CNS (does not influence peripheral synthesis);
- ✓ systemic inhibition of sensitization and central hyperalgesia can be obtained;
- ✓ Inhibition of COX-3 in the bone marrow -->reducing the synthesis of prostanoids - one of the hyperexcitability factors;
- ✓ influence on serotonergic system -- > increased serotonin concentration
- ✓ ↑↑↑ in combination with acetylsalicylic acid, metamizole sodium
- ✓ ✚ spasmolytics and cholinoblockers, can remove some moderate spastic pain
- ✓ Don’t cause physical dependence.

When?

- Headache, migraine, toothache, muscle aches
- Postoperatory pain
- Arthritis
- Neuralgia,
- Fever,
- Pain in dysmenorrhea.
- In Europe, is used as first-line analgesic in the postoperative period.

How?

- internally, 0.2–0.4 g 2–3 times daily, 0.5 g 3 times daily in adults,
- 10 mg / kg body weight - 3-4 times a day in children.
- The analgesic effect of paracetamol, at a dose of 500 mg, in mild to moderate pain is equivalent to that of acetylsalicylic acid (500 mg) or ibuprofen (200 mg).

According to WHO recommendations, the harmless doses of paracetamol are 4g / day for adults and 60 mg / kg / day for children.

Side effects?

- hemoglobinuria, hematuria, cyanosis;
- allergic rashes, rashes, hives;
- drowsiness, collapse;
- nervous excitement, convulsions;
- methemoglobinemia, anemia, thrombocytopenia, agranulocytosis;
- general weakness, profuse sweating;
- in case of prolonged use - nephritis.

Paracetamol, unlike other NSAIDs, does not cause damage to the gastrointestinal mucosa, does not affect platelet aggregation

Indomethacin:

Pharmacodynamics:

- anti-inflammatory, analgesic and antipyretic effects
- more potent than aspirin as an anti-inflammatory agent
- inferior to the salisylates at dose tolerated by patients with rheumatoid arthritis.
- Used in rheumatoid and rheumatic arthritis, not routinely for analgesia and antipyresis because of its toxicity and side effects.

Side effects:

- 35%-50% of patients report some adverse effects and most adverse effects are dose-related.
- gastrointestinal complains.
- CNS effects: frontal headache, dizziness, vertigo, mental confusion etc.
- hematologic effects: neutropenia, thrombocytopenia, inpaired platelet functions, rare aplastic anemia.
- contraindication: in pregnancy, patients with psychiatric disorders, epilepsy, parkinsonism, renal diseases, peptic ulcers.

Ibuprofen:

- anti-inflammatory, analgesic and antipyretic activity.
- chronic treatment of rheumatoid and osteoarthritis.
- less intense of gastrointestinal effects than that of aspirin.
- Dose for children: 10mg/kg, every 6-8 hours. Maximum single dose is 400 mg/dose, and maximum daily dose is 40 mg/kg/day up to 1200 mg/day
- Dose for adults: 200 – 400 mg/dose, every 6-8 hours. Maximum dose: 3200 mg/day (prescription strength); 1200 mg/day

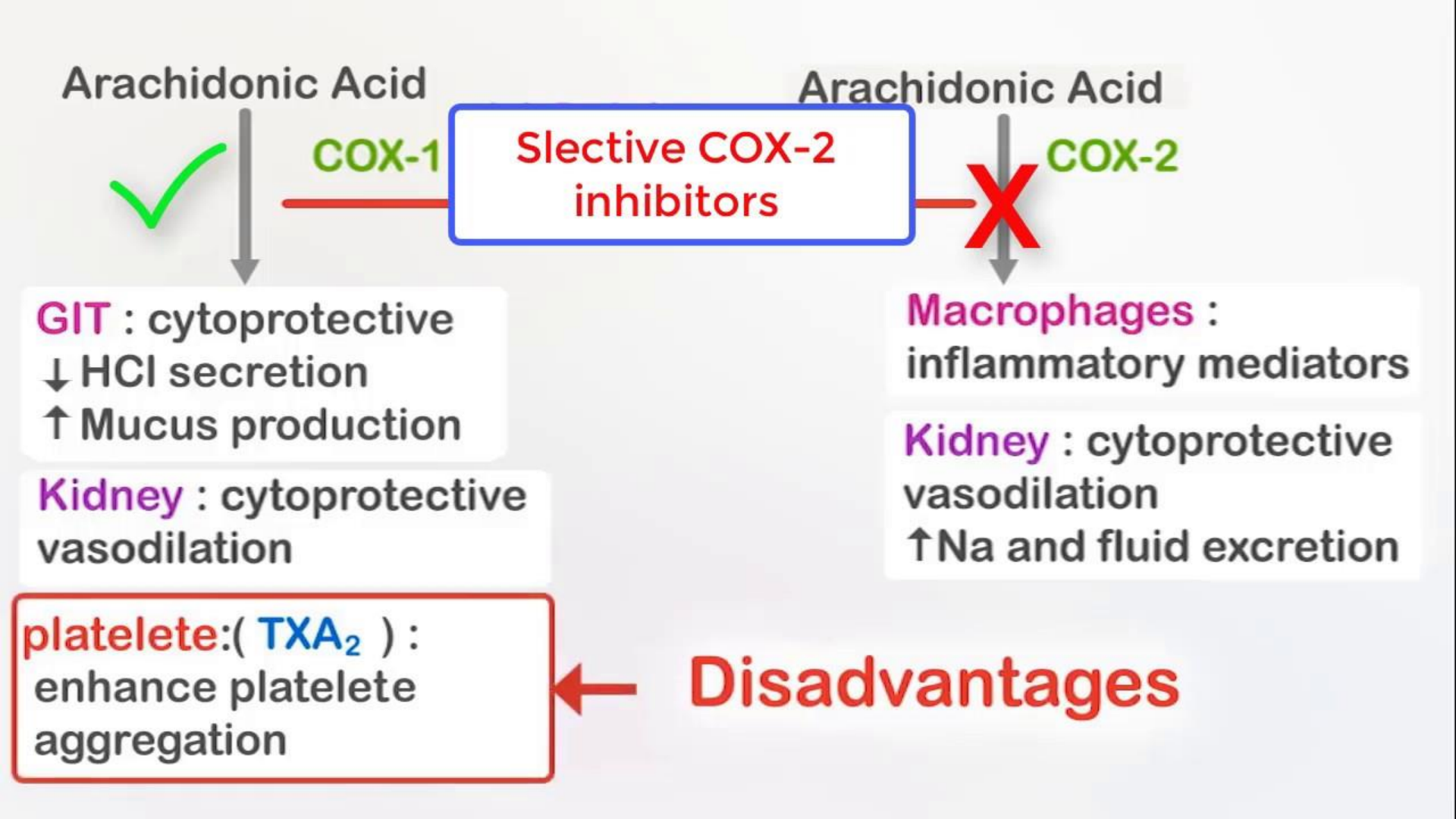
Indications:

ANALGESICS (PAINKILLERS)

RELIEVE PAIN

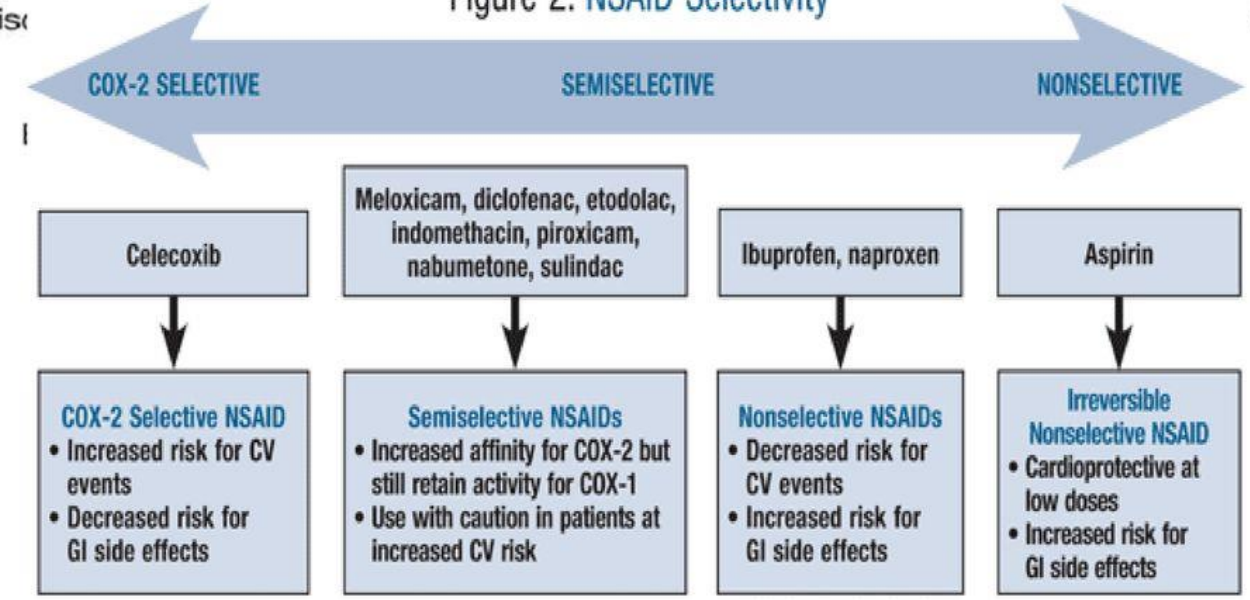






Arachidonic Acid
COX-1
Slective COX-2 inhibitors
Arachidonic Acid
COX-2
GIT : cytoprotective
↓HCl secretion
↑Mucus production
Kidney : cytoprotective
vasodilation
platelete:(TXA2) :
enhance platelete
aggregation
Macrophages :
inflammatory mediators
Kidney : cytoprotective
vasodilation
↑Na and fluid excretion
Disadvantages

NSAIDs Selectivity

Figure 2. NSAID Selectivity



COX: cyclooxygenase; CV: cardiovascular; GI: gastrointestinal; NSAID: nonsteroidal anti-inflammatory drug. Source: References 3, 17.

Selective COX – 2 inhibitors:

- Anti-inflammatory with less adverse effects, especially GI events.
- Potential toxicities: kidney and platelets - ? increased risk of thrombotic events.
- Assoc with MI and stroke because they do not inhibit platelet aggregation.
- Thus,.. should not be given to patients with CV disease
- Role in Cancer prevention
- Role in Alzheimer's disease

Effects of NSAIDs:

- ✓ Anti – inflammatory
- ✓ Antipyretic
- ✓ Analgesic
- ✓ Antiplatelet
- ✓ Closure of ductus arteriosus in newborn

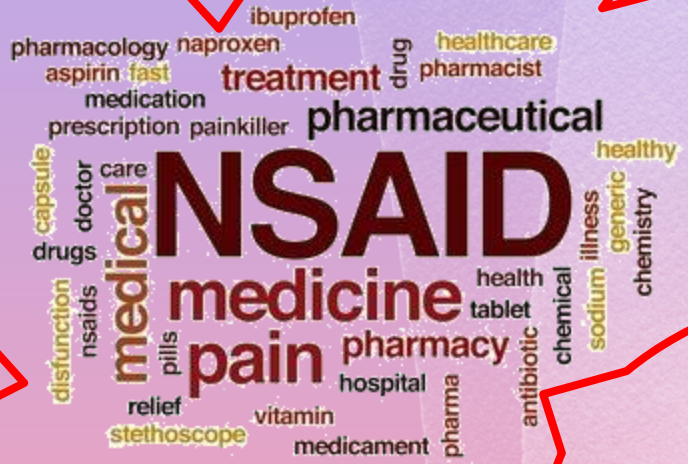
Indications:

- Rheumatoid arthritis.
- Osteoarthritis, deforming osteoarthritis.
- Collagenosis.
- Ankylosing spondylitis.
- Lumbago.
- Inflammatory disorders of the peripheral nerves.
- Acute periarticular diseases (bursitis, tendonitis,synovitis etc.).
- Inflammatory disorders of the connective tissue, of muscles.
- Moderate pain syndrome (headache,dental pain, arthralgia, myalgia, neuralgia).
- Pain and inflammatory syndrome in infections, after surgery and trauma.
- Primary dysmenorrhea.
- Gout.
- Fever.
- Thrombosis prophylaxis

Medular toxicity
Allergic reactions

GIT tract:
Dyspepsia
Gastroduodenal ulcer
GI bleeding and perforation

Kidney:
Electrolyte imbalance
Sodium retention
Edema
Reduces GFR
Nephrotic sdr
Acute interstitial nephritis
Renal papillary necrosis
Chronic kidney disease



Cardiovascular system:
Edema
Hypertension
Congestive heart failure
Myocardial infarction
Stroke and other thrombotic events

Synthesis

Beneficial effects of inhibition of prostaglandin synthesis by NSAIDs (remember of 5 A's)

Analgesia
Antipyretic
Anti-inflammatory
Antithrombotic
Arteriosus (NSAIDs for closure of patent ductus arteriosus)

Contraindications to NSAIDs (remember of BARS)

Bleeding
Asthma (10% of asthmatics are sensitive to non-steroidals)
Renal disease (hypovolaemia)
Stomach (peptic ulcer or gastritis)

NSAIDs-classification (remember of Painted By SOFIA).

Propionic acid derivates
Pyrrolo derivates
Pyrazolon derivates
Benzoxazocin derivates
Salicylates:
Oxicam derivates
Fenamic acid derivates
Indol derivates
Aryl acetic acid & Anthranilic acids derivates

NSAIDs: contraindications

Nursing and pregnancy

Serious bleeding

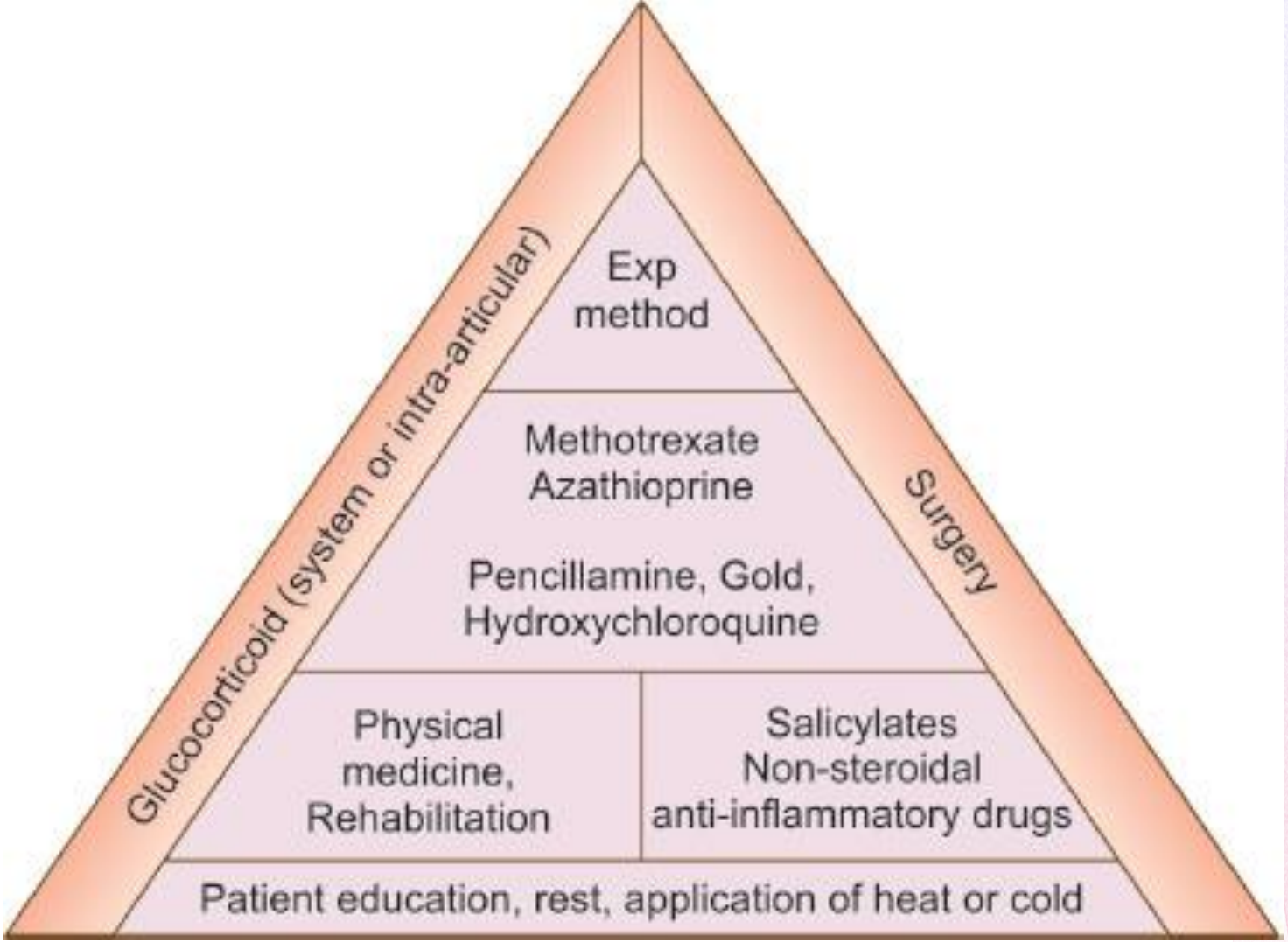
Allergy/ Asthma/ Angioedema

Impaired renal function

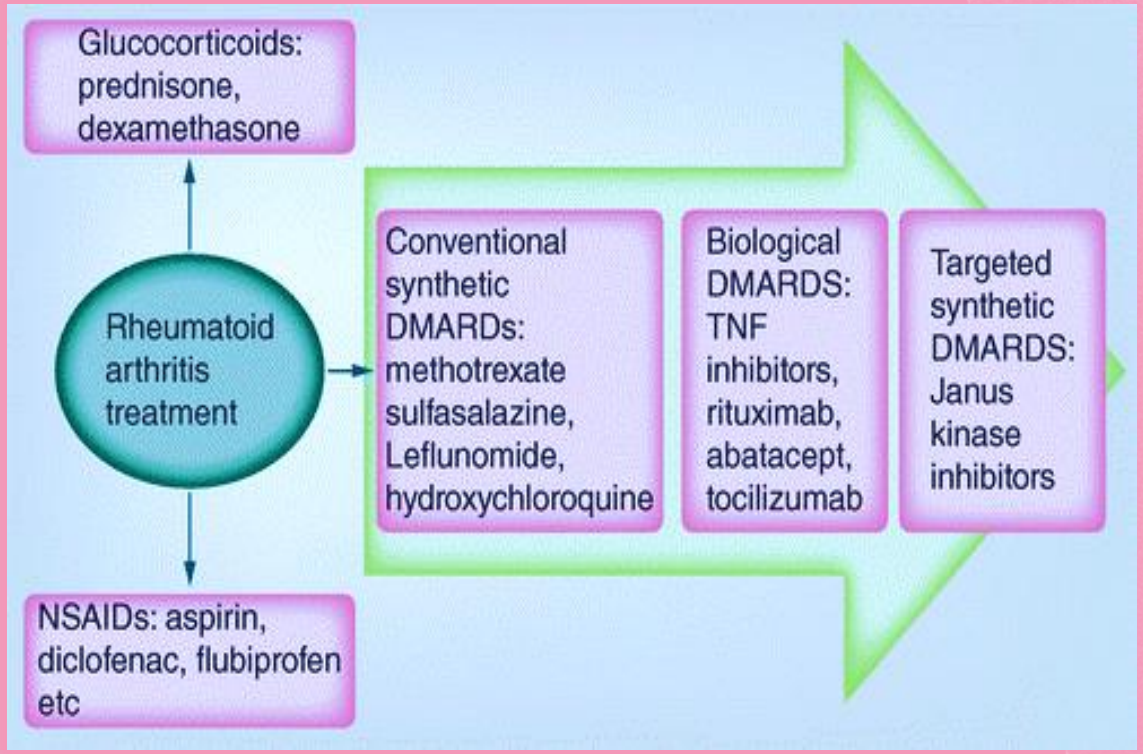
Drug (anticoagulant)

RHEUMATOID ARTHRITIS

Therapeutic approach:



Rheumatoid arthritis



90% of the joints involved in RA are affected within the first year

SO TREAT IT EARLY

Antiinflammatory drugs with specific rheumatic activity:

Gold compounds:

- Sodium aurotiomalate
- Sodium aurotiosulfate
- Auranofin
- Aurotioprol

4 – aminoquinoline derivatives:

- Chloroquine
- Hydroxychloroquine

Azo - compounds:

- Sulfasalazine
- Salazopiridazine

Cytotoxic drugs:

- Metothrexate
- Azathioprine

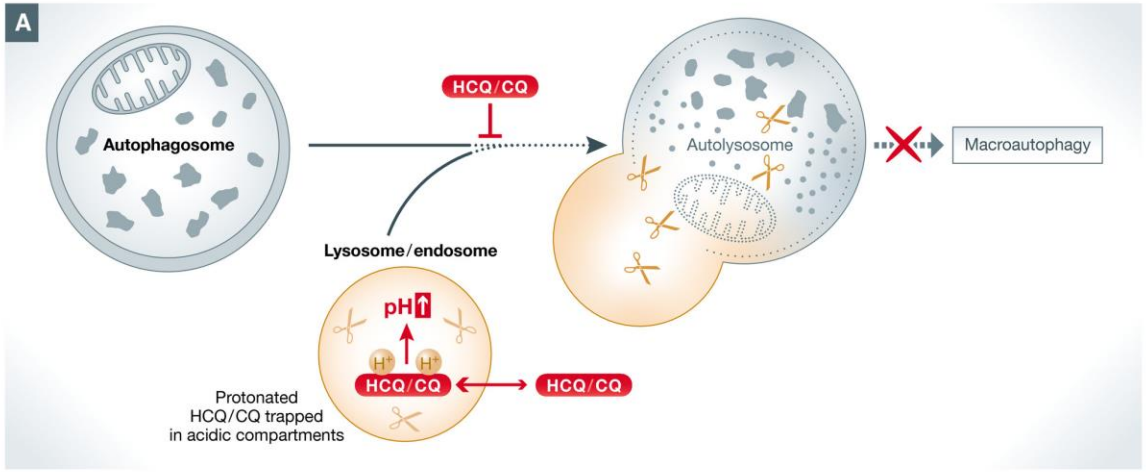
Anti – TNFα drugs:

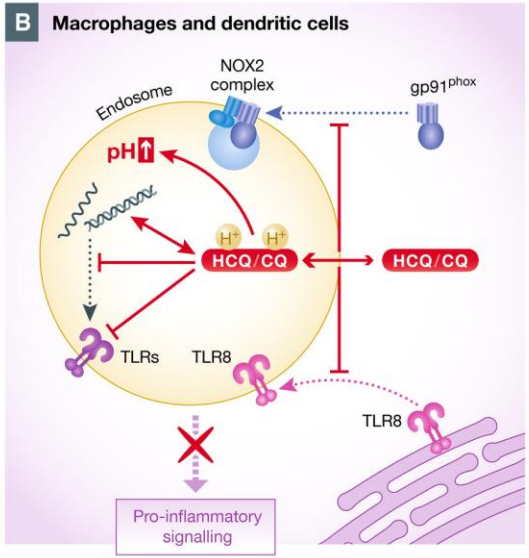
- Infliximab
- Etanercept

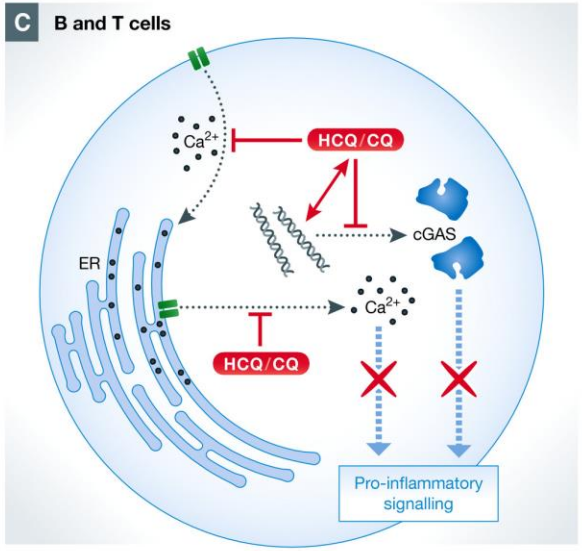
Thiol derivatives:

- Penicilamine

Pharmacodynamics of 4 – aminoquinoline derivatives:







RHEUMATOID ARTHRITIS:

Indications of 4 – aminoquinoline derivatives:

- **discoid lupus erythematosus;**
- **disseminated lupus erythematosus;**
- **rheumatoid arthritis;**
- **palindronic rheumatism;**
- **seronegative spondyloarthropathies;**
- **juvenile dermatomyositis;**
- **eosinophilic fasciitis**

Not just Joints or Bones

But So Much More

DMARDs

- Disease Modifying Anti-Rheumatic Drugs
- Reduce swelling & inflammation
- Improve pain
- Improve function
- Have been shown to reduce radiographic progression (erosions)

- Methotrexate (2,5; 5; 10 mg)
- Sulfasalazine (Salazopyrin®)
- Hydroxychloroquine (Plaquenil®)
- Leflunomide (Arava®)
- Gold (Myochrisine® Auranofin-tab 3 mg)
- Others
  - Cyclosporine (caps 10, 25, 50 mg)
  - Azathioprine
  - Cyclophosphamide (tab 50mg)

Synthetic DMARDs

- Methotrexate
- Sulphasalazine
- Chloroquine
- Hydroxychloroquine
- Leflunomide

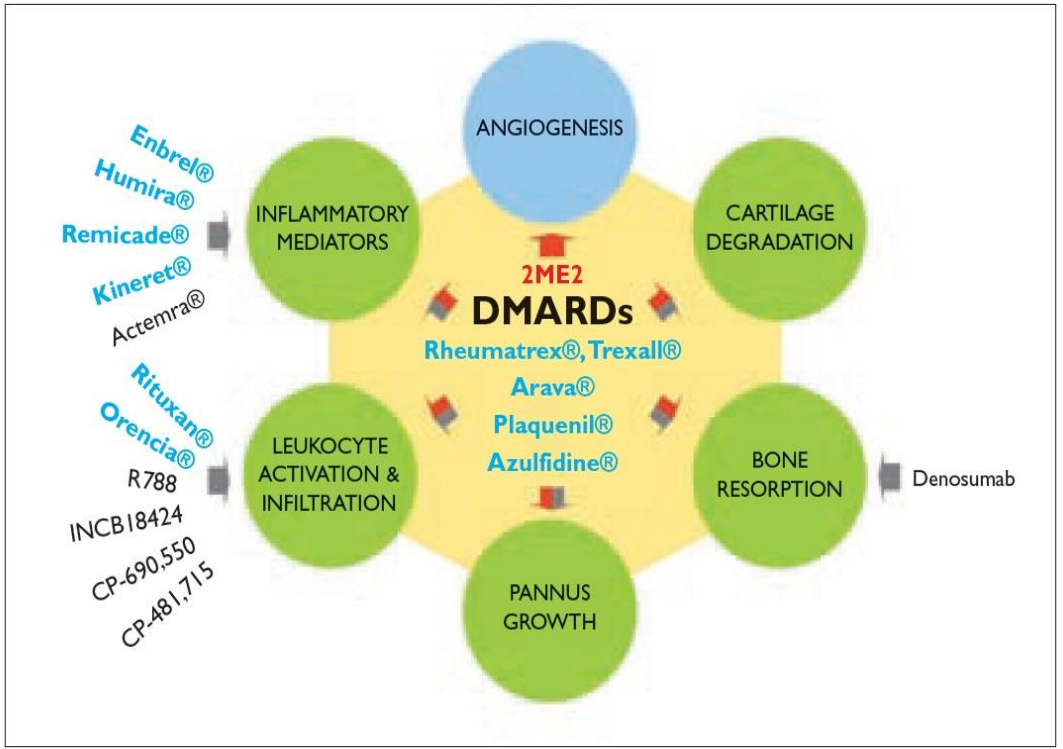


Figure 1

Therapeutical aproaches:

Triple Therapy

- Methotrexate, Sulfasalazine, Hydroxychloroquine

Double Therapy

- Methotrexate & Leflunomide
- Methotrexate & Sulfasalazine
- Methotrexate & Hydroxychloroquine

Biologic therapy

- Complex protein molecules
- Created using molecular biology methods
- Produced in prokaryotic or eukaryotic cell cultures

Current available biologics:

- **TNF Inhibitors**
  - Adalimumab
  - Etanercept
  - Infliximab (Remicade)
- **IL-1 Inhibitors**
  - Anakinra (Kineret)
- **T-Cell Co-Stimulatory Blockade**
  - Abatacept (Orencia)
- **B-Cell Depletion**
  - Rituximab (Rituxan)
- **Monoclonal Antibodies to TNF**
  - Infliximab
  - Adalimumab
- **Soluble Receptor Decoy for TNF**
  - Etanercept
- **Receptor Antagonist to IL-1**
  - Anakinra
- **Monoclonal Antibody to CD-20**
  - Rituximab

COMMONLY PRESCRIBED BIOLOGICS		
Brand Names	**Product**	**Common Dose**
Enbrel	Etanercept	50 mg injection once weekly or 25 mg injection twice weekly
Humira	Adalimumab	40 mg injection every other week
Kineret	Anakinra	100 mg injection every other week
Orencia	Abatacept	500 to 1000 mg intravenous infusion every 4 weeks
Remicade	Infliximab	200 – 1000 mg intravenous infusion every 6 to 8 weeks
Rituxan	Rituximab	1000 mg intravenous infusion given twice two weeks apart

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Thank you for your attention!