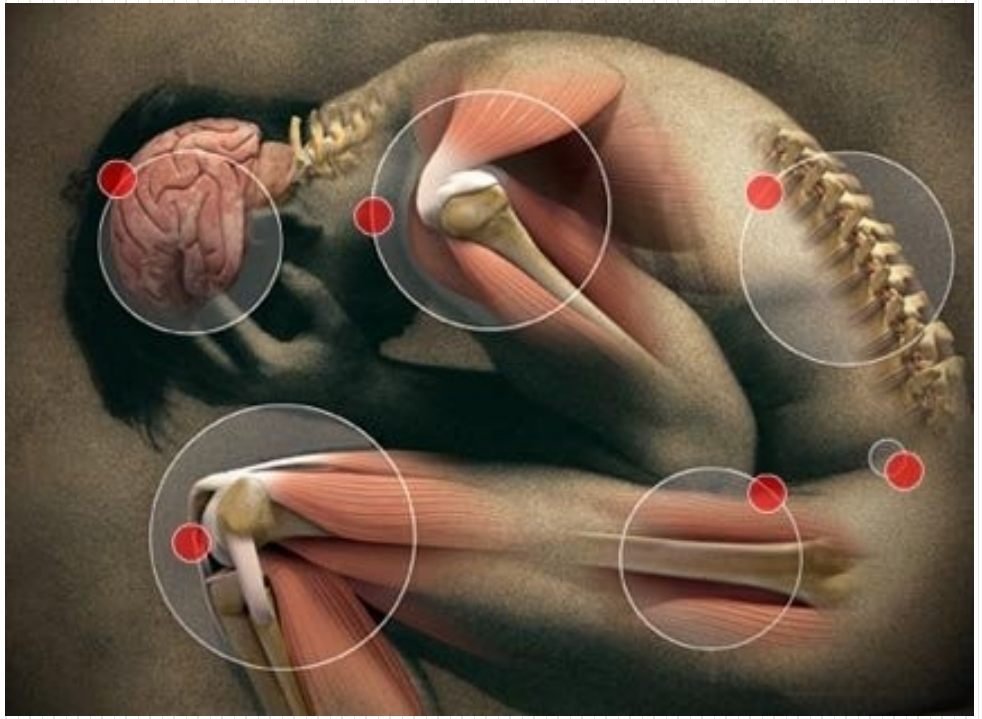
Pharmacotherapy of Pain



The Pain Pathway

1.) Peripheral nociceptors

- bradykinin, substance P, histamine, acetylcholine, serotonin, ↓ pH (H^+), prostaglandins (inflammatory mediators)

2.) Primary afferent fibres → dorsal horn of spinal cord

- substance P, neurokinin A, glutamate
- Inhibition of pain transmission on spinal level = **descending pathways** from midbrain and medulla to dorsal horn (serotonine, noradrenaline, **GABA**, enkefalins…)

3.) Spinothalamic and spinorecticular tract (spine → thalamus/brainstem reticular formation)

- Localisation a emotional aspects of pain

4.) Thalamocortical pathway (thalamus → cortex)

- Localisation, cause of pain + coordination of a response

NSAIDs

- *Non-steroidal antiinflammatory drugs*
- **Inhibition of cyclooxygenase** = ↓ prostaglandins
- Treatment of „common“ pain, inflammatory diseases (gout, rheumatoid arthritis etc.), reduction of fever, combination of analgesics in stronger pain
- Administration – p.o., rectal, topical, parenteral
- Binding to **plasma proteins** – possible interactions
- Good GIT absorption, passage into the **synovial fluid**, through BBB, placenta…

Classification: **1.) NON-SELECTIVE** (COX1 ~ COX2)

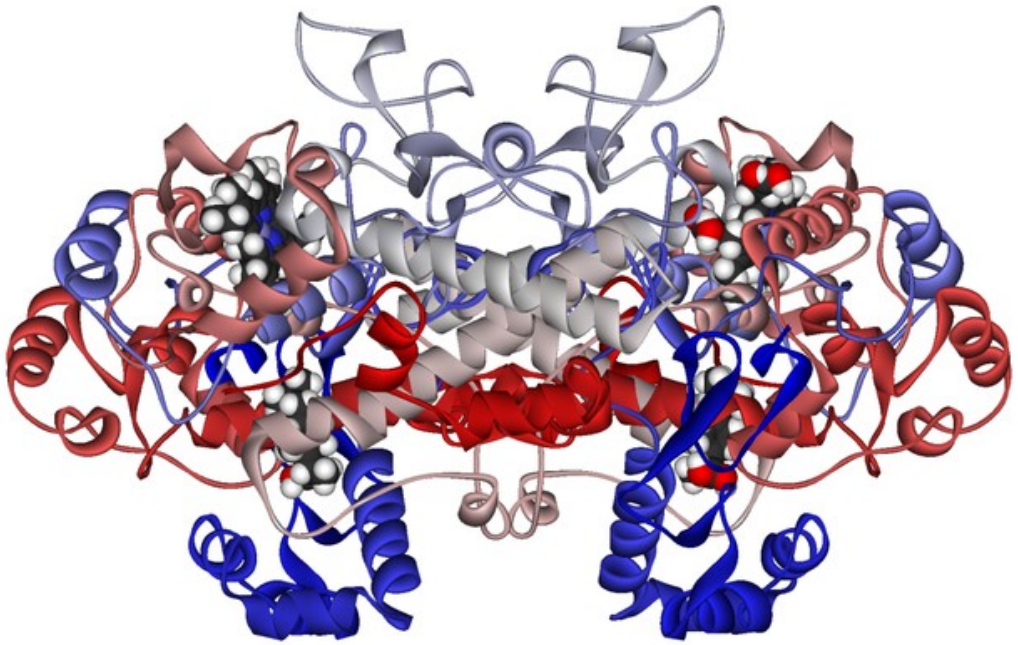
2.) PREFERENTIAL (COX1 < COX2)

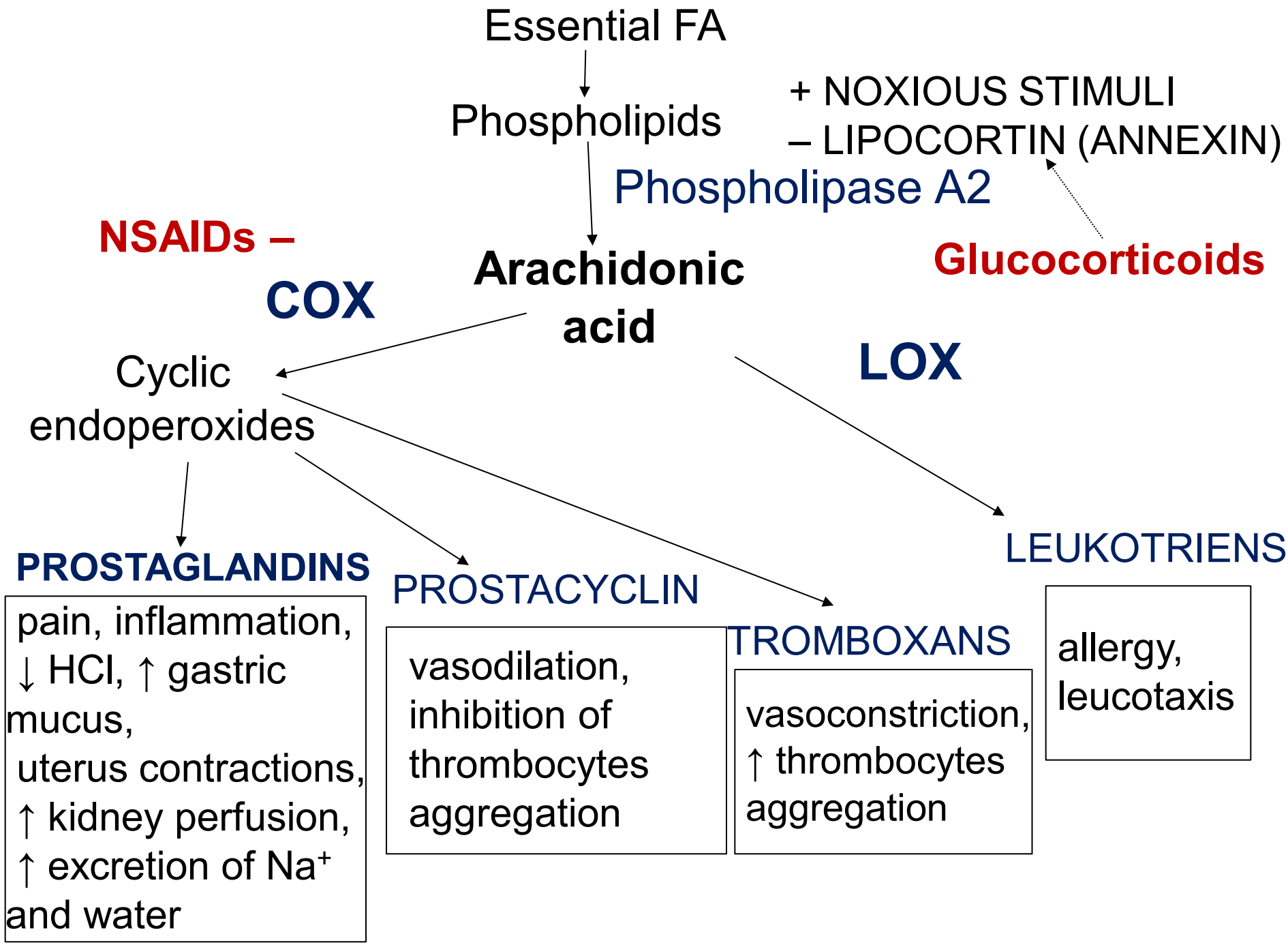
3.) SELECTIVE (COX1 <<< COX2)

Cyclooxygenase

- Isoenzymes: physiological, inducible, (CNS?)

- **COX1** – protection of gastric mucosa, kidney vasodilation, aggregation of thrombocytes
- **COX2** – site of inflammation, expressed due to ILs and TNF-α
- **COX3** – CNS?




Essential FA
Phospholipids
+ NOXIOUS STIMULI
– LIPOCORTIN (ANNEXIN)
Phospholipase A2
NSAIDs –
COX
Arachidonic acid
Glucocorticoids
LOX
Cyclic endoperoxides
PROSTAGLANDINS
pain, inflammation, ↓ HCl, ↑ gastric mucus, uterus contractions, ↑ kidney perfusion, ↑ excretion of Na+ and water
PROSTACYCLIN
vasodilation, inhibition of thrombocytes aggregation
TROMBOXANS
vasoconstriction, ↑ thrombocytes aggregation
LEUKOTRIENS
allergy, leucotaxis

Acetylsalicylic acid

- non-selective, **irreversible COX inhibitor**
- plasmatic esterases: ASA → SA + AA
- 30-100 mg **antiaggregant**, 500 mg **analgesic-antipyretic**, over 1000 mg **antiphlogistic**
- gastric absorption, possible irritation and ulceration of GIT (MoA + acidity), renal excretion
- **contraindications:**
  children up to 12 years old – Reye‘s syndrome
  gastric ulcers, asthma
  before surgery
- **elderly** – more susceptible to AE
- **„aspirin asthma“**
  = leucotriens predominance
- other salicylates: choline salicylate, sulfasalazine…

Paracetamol (Acetaminophen)

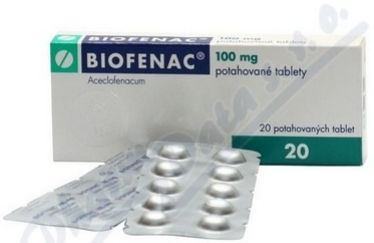
- **analgesic-antipyretic** = without antiphlogistic and antiaggregant activity, no gastrotoxicity
- mechanism of action unclear:
  - COX3? serotonin? TRPV ion channels?
- dose: 10-15 mg/kg – frequently underdosed!
- **max. dose 4000 mg (8 tablets à 500 mg)**
- **hepatotoxicity** = NAPQI, detoxification by glutathione
  - overdosing – **N-acetylcysteine** therapy
- **combinations** with tramadol, codein, propyphenazone, antispasmodics
- suitable for **children, elderly**

Acetic Acid Derivatives

Diclophenac

- joint diseases → **passage into synovial fluid**
- shorter half-life, capsules with prolonged release
- **cardiotoxicity** – higher doses, contraindication

Aceclofenac



- oral use only in the treatment of joint diseases
- relatively low gastrotoxicity
- also contraindicated for patients with CVD

Indomethacin

- strong effect, only for short-term treatment
- **uricosuric effect** = ↑ excretion of uric acid in the urine
  - used in acute gout attack
- ↑ **gastrotoxicity**, changes in blood count, headache and CNS disorders (all of them very frequent)
- **contraindicated for children**

Propionic Acid Derivatives

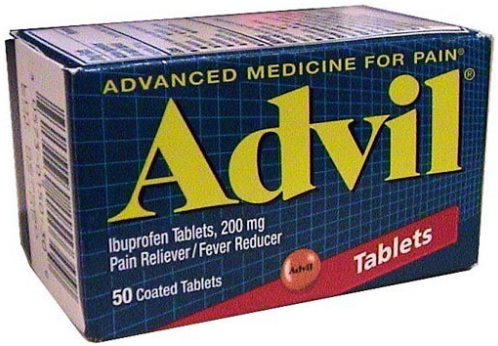
Ibuprofen – good tolerability, safe
- 200-400 mg **analgesic, antipyretic**
- 1400-1600 mg **antiphlogistic**
- **max. dose 2400 mg**
- suitable for children

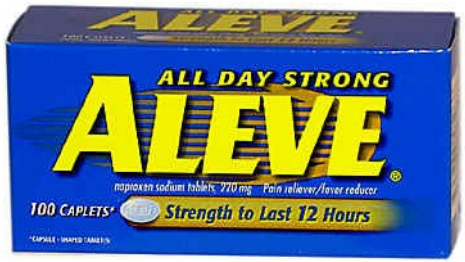
Ketoprofen – topical use (skin phototoxicity!)

Dexketoprofen – oral use

Flurbiprofen – topical oral use (lozenges/pastilles)

Naproxen – relatively low gastrotoxicity, longer half-life, good for headache and toothache





Other Important Analgesics

Propyphenazone – with paracetamol and caffeine

Metamizole

- analgesic-antipyretic with mild antispasmodic effect
- **no antiphlogistic effect**
- **myelotoxicity** (changes in BC) → only for short-term use
- combinations with antispasmodics (e.g. pitofenone, fenpiverinium)

Oxicams – long biological half-life:

- **Piroxicam** – topical use, very long half-life (high risk of accumulation if taken orally)
- **Meloxicam** – **preferential effect on COX2**
  - joint diseases – good passage into synovial fluid
  - reduction of GIT adverse effects
- **Lornoxicam** – non-selective effect on COX

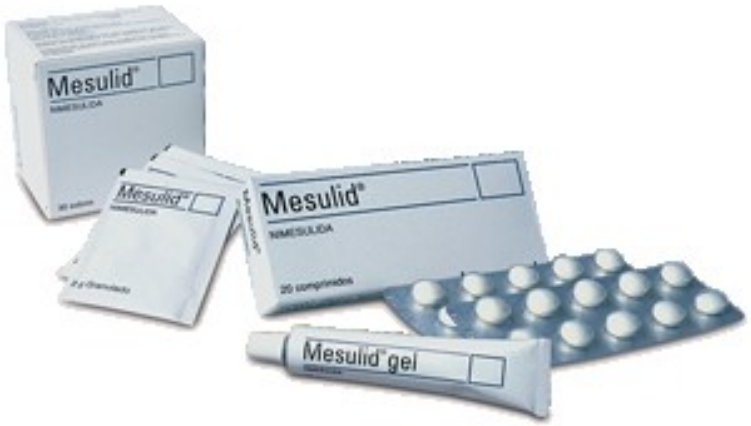
Preferential COX2 Inhibitors

- **COX1 < COX2**
- reduction of GIT adverse effects
- analgesic, antiphlogistic and antiaggregant effect

Nimesulide

- inhibits also collagenases and elastases degrading cartilages + ROS scavenger
- **hepatotoxicity** → only for short

Meloxicam



Selective COX2 Inhibitors = Coxibs

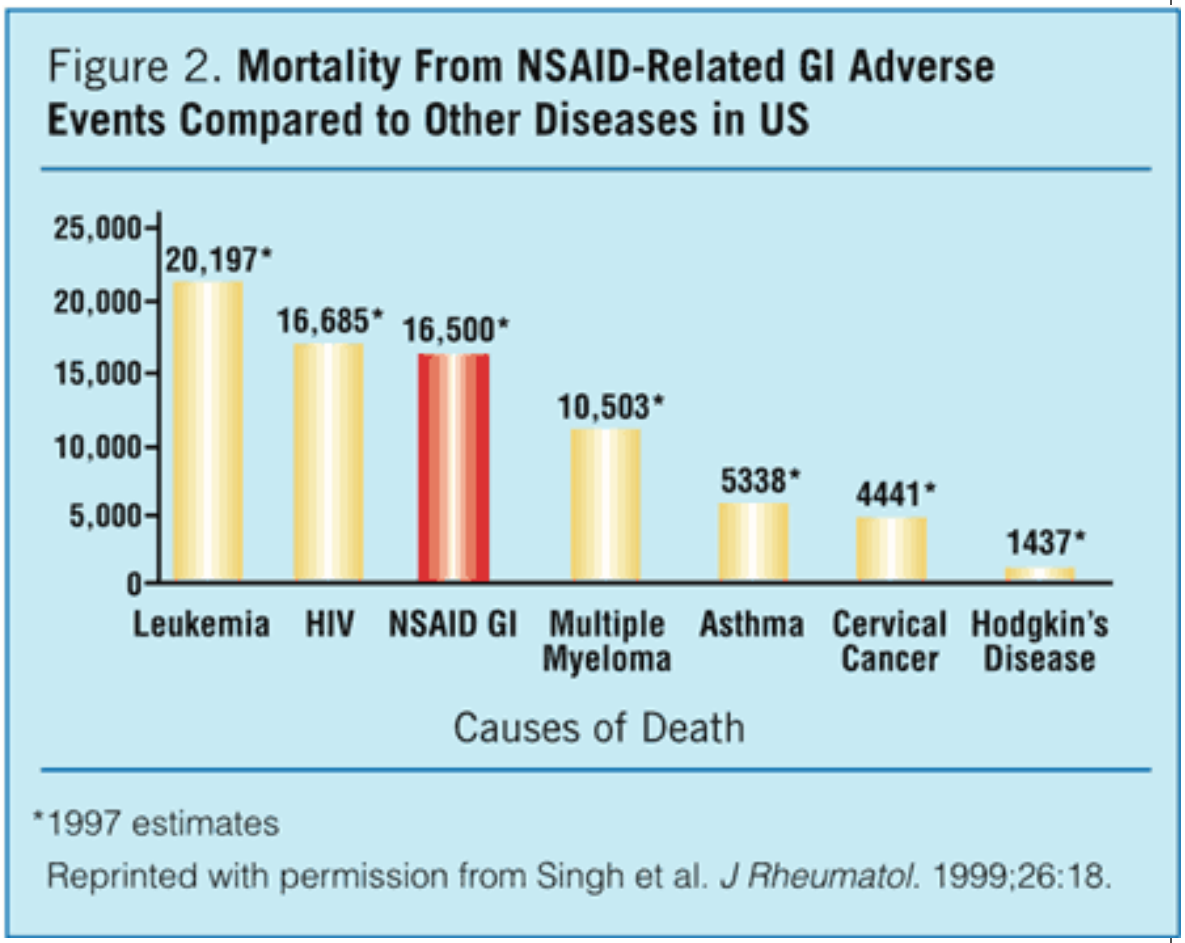
- **COX1 <<< COX2**
- minimal GIT adverse effects
- joint diseases

- **cardiovascular AE** – **thrombotic diseases** (due to inhibition of prostacyclin in endothelia)
  - **contraindicated** for patients with CVD
  - some of them **withdrawn** and lost market authorisation for severe CV and skin AE (rofecoxib)

- **celecoxib, parecoxib, etoricoxib**

Protection against NSAIDs toxicity

- use of **safe dosage**
- fight against **overuse, misuse**, „dependence“
- **protection** of gastric and intestinal mucosa (PPI – omeprazole)
- **education** of both patients and health professionals
- **avoidance of** drug-drug **interactions**



Opioid analgesics

Opiod analgesics = anodynes

- OPIUM – *Papaver somniferum*, Papaveraceae
- **Bind to opiod receptors** – changes in ion homeostasis of neurons → **hyperpolarization**, inability to conduct electrical impulses + **changes in GABA** signalling in specific parts of the brain

OPIOID RECEPTORS:

μ [mu] – supraspinal and spinal analgesia

κ [kappa] – spinal and peripheral analgesia

δ [delta] – spinal analgesia

σ [sigma] – dysphoria, hallucinations, changes in perception (not an opioid receptor, bud some opioids have affinity for it)

Classification of Opioids

According to their receptor effects:

1.) Agonists:

a) strong effect (morphine, pethidine, methadone, fentanyl)

b) medium and mild effect (codeine, dextropropoxyphene)

2.) Partial agonists (buprenorphine)
and agonists-antagonists (butorphanol)

3.) Atypical opioids (tramadol, tilidine, tapentadol)

4.) Antagonists (naloxone, naltrexone)

According to their origin:

a) endogenous (enkephalins, endorphins, dynorphins)

b) natural (morphine, codeine…)

c) semisynthetic (oxycodon, dihydrocodeine…)

d) synthetic (pethidine, butorphanol, methadone, fentanyl...)

Opioid Agonists: Effects

- mostly originate from activation of **μ receptors**

Central effects:

- depression of CNS: **sedation** → somnolence → coma
- **depression of breathing** – ↓ sensitivity of respiratory center
- **antitussive effect** – ↓ sensitivity of cough center
- **emesis, nausea** – first doses, irritation of *area postrema*
- **miosis** – via *n. oculomotorius*
- changes in hormonal levels: cortisol, ADH, GnRH → FSH, LH, testosteron…)

Peripheral effects:

- ↑ **smooth muscle tone** – constipation, urine retention, spasm of sphincters in GIT and GUT **(contraindicated for colics!)**
- CVS – histamine liberation, vazodilation, postural hypotension
- RESP – possible bronchoconstriction (histamine)

Opioid Agonists

Pharmacokinetics:

- good absorption from GIT, but frequently **high first pass effect** (= not suitable for oral use)
- pharmacologically active metabolites (e.g. codeine)

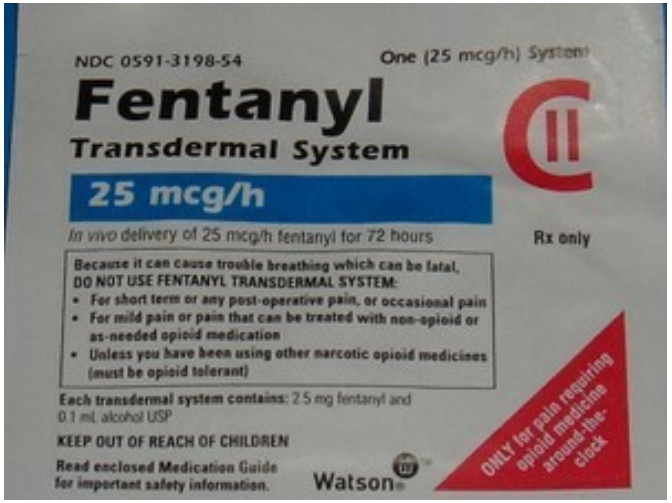
Addictive potential

- dependency producing substances
- **tolerance** – need for higher doses
- **craving** for another dose
- abstinence syndrome
- Act No. 167/1998 Coll. on Dependency Producing Substances
- instructions for prescription and use
- **methadone** – substitution therapy for the addicted

Opioid Agonists with Strong Effect

- **MORPHINE** – 10 mg i.m., s.c., p.o., lasts 4-5 h
- **METHADONE** – longer half-life, substitution therapy
- OXYCODON, HYDROCODON
  - with paracetamol (acetaminophen)
- PETHIDINE

Fentanils



- the most effective opioids
- **lipophilic** → good absorption
- shorter effect → infusions, TTS
- anesthesiology, algesiology
- **FENTANYL** or FENTANIL
- SUFENTANIL – 500 times more effective than morphine

Opioid Agonists with Medium and Mild Effect

CODEINE

- metabolised to morphine
- **analgesic** – combined therapy (paracetamol)
- **antitussive**: 10-30 mg
  - decreases secretion in bronchi and bronchioles
  - **contraindicated for children**

DIHYDROCODEINE

- cancer pain
- tablets with prolonged release

Partial agonists and Agonists-Antagonists

BUPRENORPHINE

- **partial agonist of μ opioid receptors**
- strong **FP effect** – parenteral administration (buccal tablets)
- **RMP Suboxone** – combination therapy with naloxone (opioid addiction)

- ↓ AE, ↓ dependency
- mild analgesic effect

BUTORPHANOL

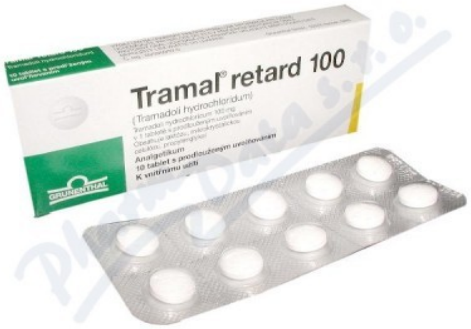
PENTAZOCINE

- κ a δ agonist
- μ antagonist
- mild analgesic effect
- σ and κ activation = hallucinations, euforia, dysforia, abnormal dreams

Atypical Opioids

TRAMADOL

- **low affinity for μ receptors** + **blockade of 5-HT and NA re-uptake** (neurotransmitters of pain pathway)
- max. dose 600 mg
- frequently causes **nausea and emesis**
- oral drops, tablets, modified release
- advantages: no attenuation of respiratory center
  no constipation



TILIDIN, TAPENTADOL

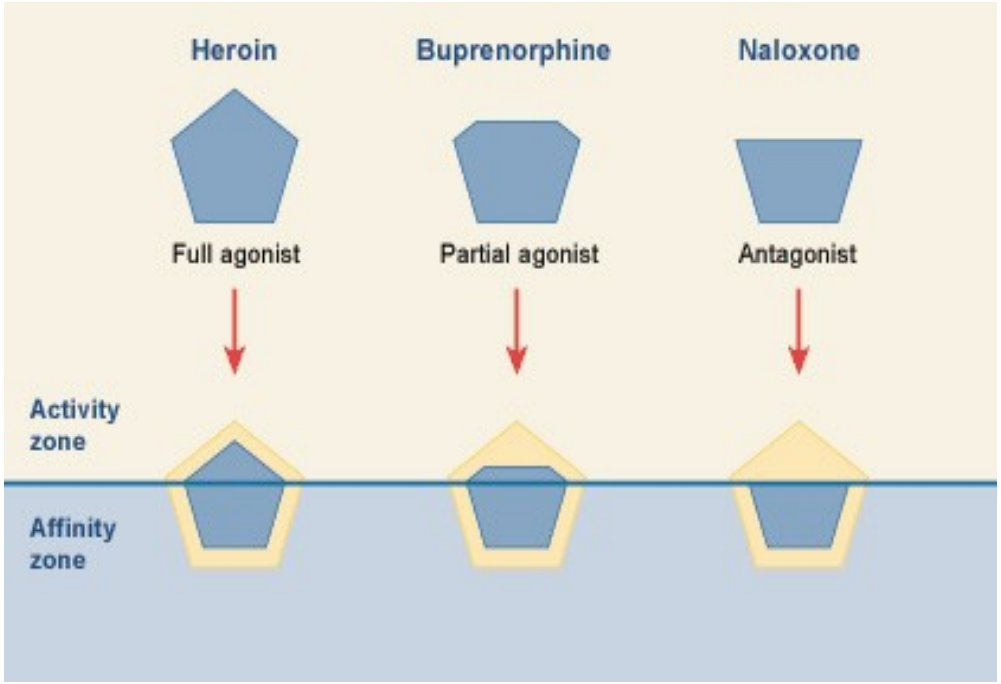
Opioid Antagonists

- treatment of acute opioid **intoxication** and **overdosing**
- treatment of **addiction to opioids**, heroin
- treatment of **alcohol addiction** (nalmefene)
- quick effect (in minutes), lasts 2-3 h
- parenteral use, oral use (nalmefene)

NALOXONE

NALTREXONE

NALMEFENE



Strategy in the Treatment of Pain

1. CAUSAL TREATMENT

- cause of pain

2. SYMPTOMATIC TREATMENT

- pain itself

WHO PAIN LADDER

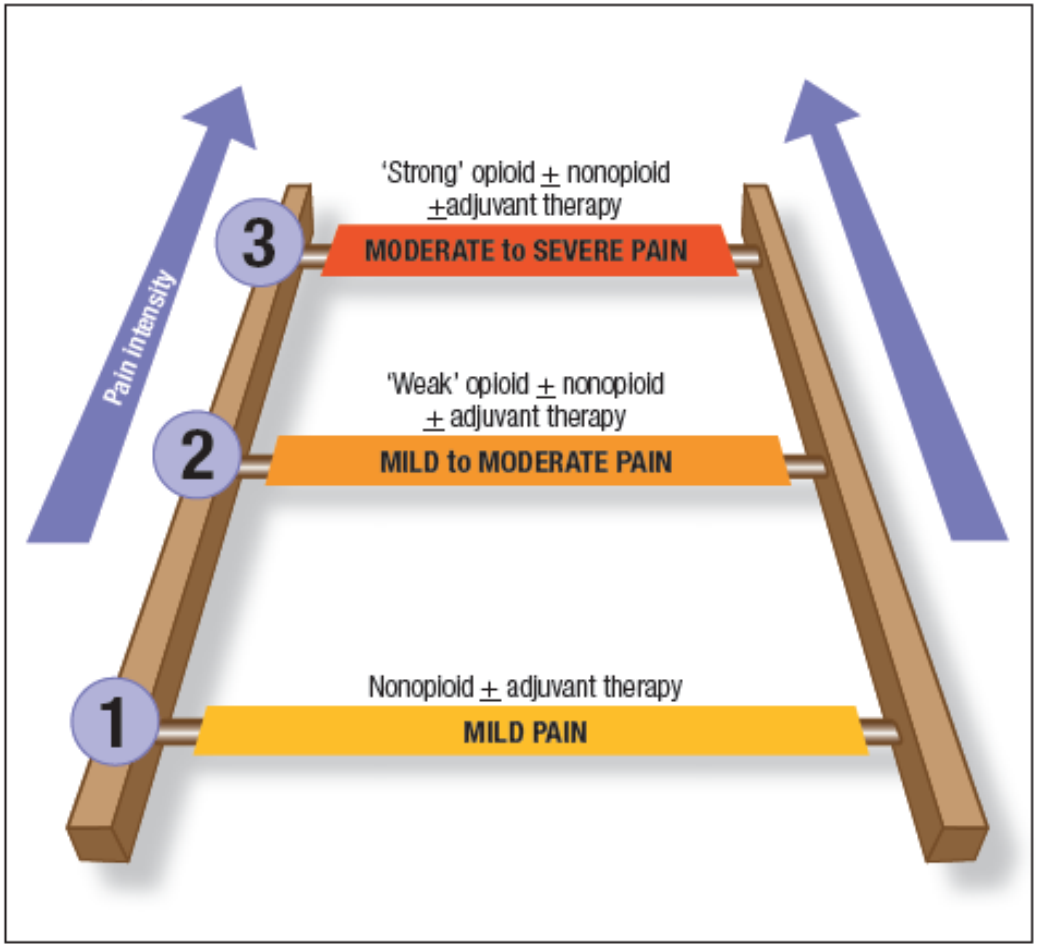


Figure 1. WHO Three-step Pain Ladder. This analgesic step ladder has been the treatment standard most used during the past 3 decades.

Anti-rheumatics – Therapy of RA

DMARDs – *disease-modifying antirheumatic drugs*

- **SULFASALAZINE**
  - bowel microflora decomposition → 5-aminosalicylic acid and sulfapyridine
- GOLD COMPOUNDS
  - e.g. sodium aurothiomalate
  - inhibition of phagocytosis
- CHOLOROQUIN
  - originally for treatment and prevention of malaria
  - inhibition of chemotaxis of leukocytes
- **METHOTREXATE**
  - immunosupressive therapy
  - folic acid antimetabolite
  - used in high dosis as cytostatic drug (cancer therapy)
  - highly effective
  - effect starts after 3-4 weeks

Anti-rheumatics

Targeted therapy:

- Targeted interference with immune cells and mediators
- Monoclonal antibodies, genetically engineered proteins…
- Expensive, prescribed only when conventional treatment fails
- **Mechanisms of action:**
  - anti-TNF-α drugs: **ADALIMUMAB**, infliximab, etanercept, certolizumab, golimumab
  - blockade of IL-6 receptor: tocilizumab
  - blockade of IL-1 receptor: anakinra
  - interference with T and B lymphocytes: abatacept, rituximab

NSAIDs:

- Alleviation of morning joint stiffness
- Analgesic and antiinflammatory effect
- **DICLOFENAC, IBUPROFEN; MELOXICAM, CELECOXIB and the others…**