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OPIOID ANALGESICS (ANALGESICS – ANODYNES)

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Pain

- Definition:

  „subjective unpleasant sensory or emotional experience accompanied by real or potential damage of tissues, with motoric and vegetative responses “

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Pain – types and classification

A) by duration

B) according to pathophysiology

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Pain – types and classification

A) According to length of experience

1) acute: sign of and disease, danger or damage to organism...

2) chronic: more than 3 months / **unusually long for a given disease or disorder**

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Pain – types and classification

A) According to length of experience

1) acute: physiological sensory perception,
   - tissue damage,
   - mobilizes defensive forces of the organism in order to remove the inducing cause of the pain

2) chronic: pathological,

   pain may persists even after the removal of the causes → difficult to determine whether the pain arose as a result of persistent pathological activity in the nerve endings in the periphery, or is the source of the CNS

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Pain – types and classification

B) According to pathophysiology

1) nociceptive – irritation of nociceptors

   Therapy: „analgesic ladder“ according WHO

   (see below; not used for aggressive procedure in the treatment for cancer or breakthrough pain)

2) neurological and neuropathic pain

   Therapy: antidepressants and **anticonvulsants**

   (in combination with opioids or some muscule relaxants; neuroprotective vitamins – thiamine; antimigraine drugs from the group of the so-called triptans; antipsychotics = neuroleptics)

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Pain – types and classification

B) According to pathophysiology

3) psychogenic pain

somatization, hypochondric and somatoform disorder

Therapy: psychopharmac drugs (antidepressants – TCA, SSRI, anxiolytics, antipsychotics)

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Special types of pain

- **neuralgia**

  sharp, paroxysmal pain, affects peripheral or cranial nerves (often the trigeminus, facialis) → after traumatological damage, compression, viral infects (herpetic), metabolic (DM)

- **pain in the chronic compression of peripheral nerves and nerve roots**

  hernia of the intervertebral discs, compression of the nerve in the spinal cord → pain + paresthesia, pain acquires a hot character

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Special types of pain

- **ischemic pain**

  due to disorders of blood circulation in the myocardium, smooth or skeletal muscle

- **migraine**

  migraine is characterized by attacks of pulsating, mostly unilateral headache lasting typically 4-72 hours with nausea, possible vomiting, photofobia and phonofobia, suffering from 12% of the adult population

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Special types of pain

■ phantom pain

surgically or traumatically removed parts of the human body, most commonly the lower limb or other parts of the body (ablation of the breast, as well as after the removal of the visceral organs - the colon);

apply pathophysiological influences peripheral, central and psychogenic;

■ breakthrough pain

sudden, transient, mostly short-term worsening of pain in patients who have well-controlled baseline pain;

usually in patients treated with opioids for cancer diagnosis; typically in progression of cancer

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Special types of pain

- **delivery pain**

- belongs to the strongest pain reliever, nevertheless, that before the birth are rising thresholds for somatic and visceral pain

- the tissue is developed by excessive pressure, they are strongly being pushed and lacerations occur

- tissues are under influence of bradykinin, H^+, K^+, histamine and serotonin

- induction of stress → ↑ cortisol, epinephrine, norepinephrine, dopamine → somatic and psychological reactions

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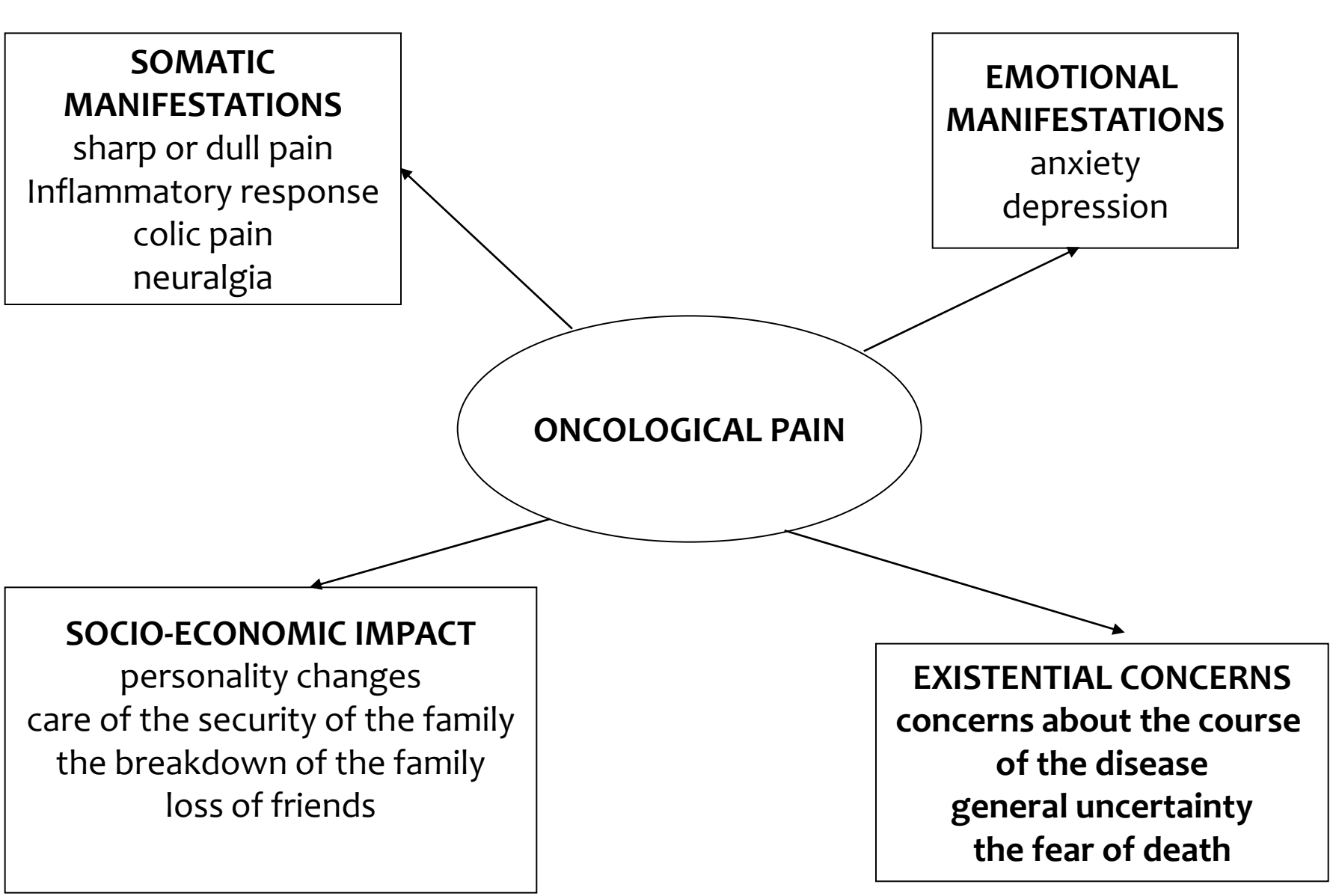
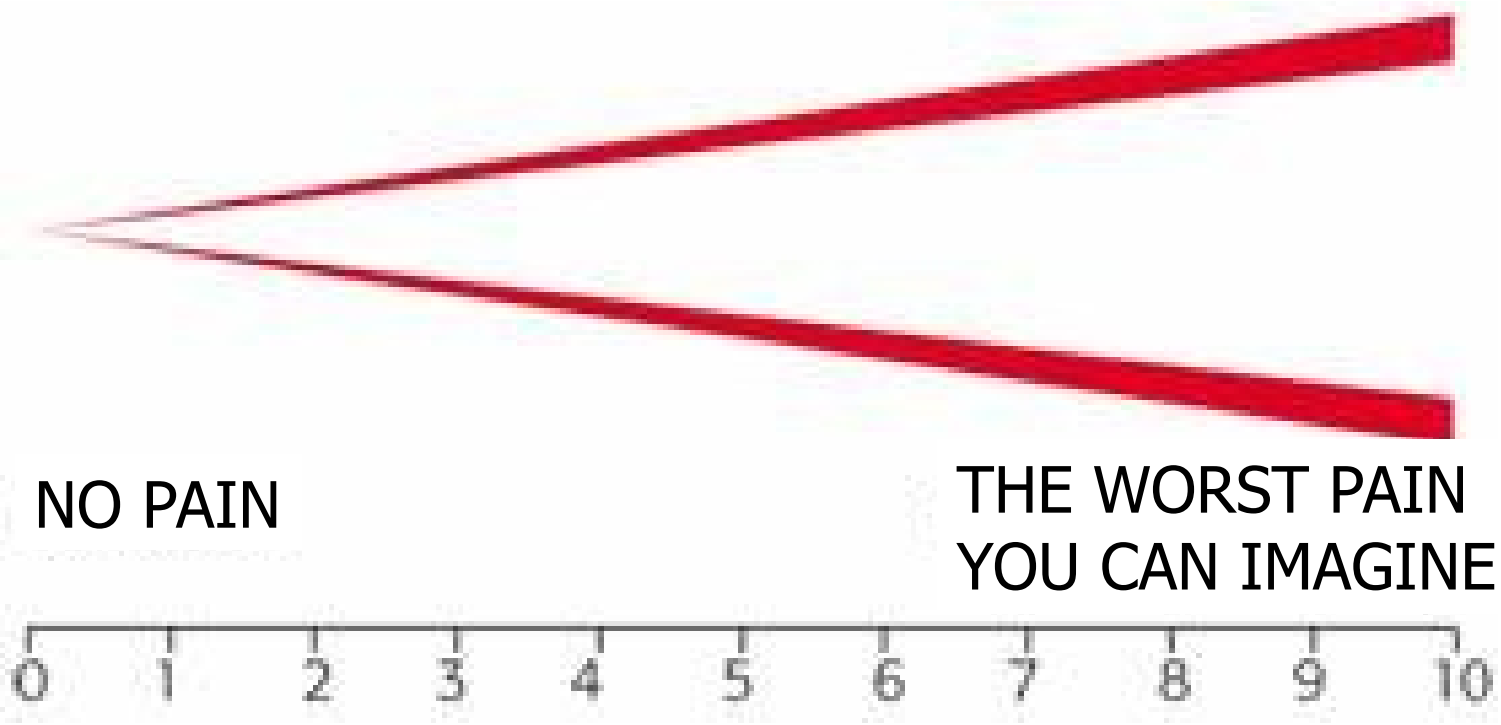

SOMATIC MANIFESTATIONS
sharp or dull pain
Inflammatory response
colic pain
neuralgia
EMOTIONAL MANIFESTATIONS
anxiety
depression
ONCOLOGICAL PAIN
SOCIO-ECONOMIC IMPACT
personality changes
care of the security of the family
the breakdown of the family
loss of friends
EXISTENTIAL CONCERNS
concerns about the course of the disease
general uncertainty
the fear of death

Diagnostics of Pain

VAS: Visual analogue scale



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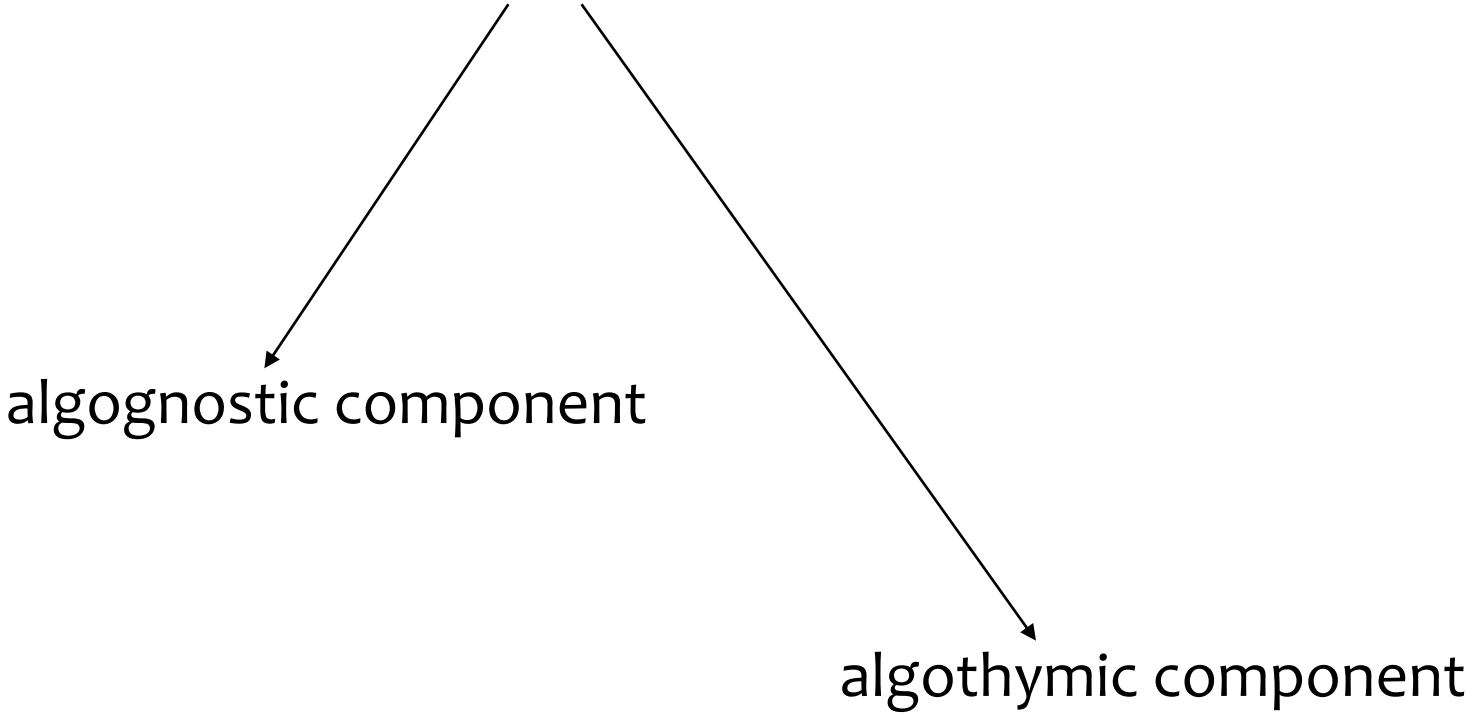
Process of pain perception



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Pain – causes and mechanism

tissue damage production of prostaglandines and other substances effects on the free nerve endings transduction of signal up to the brain neurons **PAIN**

Mediators of pain

(act on the nociceptors = pain receptors)

„algogenic substances“

bradykinin ——— + ——— ↑PGE (mediators of inflammation), increase sensitivity of nociceptors

histamine

acetylcholine

substance P (pain)

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Pain – causes and mechanism

Endogenous pain suppressing (analgesic) substances:

endorphins

enkephalins

dynorphins

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Pain transduction – 3 neuron`s tract

MAIN PAIN PATHWAYS

tractus spinothalamicus (spinothalamic tract) vs. *tractus spinoreticulothalamicus* (spinoreticulothalamic tract)

the tracks leading from the spinal cord (spinal ganglia) to specific areas of the brain (finally to the cerebral cortex)
information about pain is received and processed

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Pain transduction – 3 neuron`s tract

→ **spinothalamic tract** – 3 neuron`s phylogenetically younger pathway

– sharp, well localized pain

→ **spinoretikulothalamic tract** – phylogenetically older polysynaptic system, impulses are transmitted to the higher centres through short axonal pathways

– dull, poorly localized pain

- vegetative response: blood pressure change, tachypnea, mydriasis, diaphoresis, increased muscle tone,...

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Pharmacological modulation of pain

Analgesics – anodynes (opioids)

Non-opioid analgesics (analgesics – antipyretics NSAIDs)

Local anaesthetics

General anaesthetics

Adjuvant therapy (antidepressants, neuroleptics - antipsychotics, antiepileptics - anticonvulsants, antimigrenics, central/peripheral myorelaxants, corticoids, bisphosphonates, caffeine…)

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Pharmacological modulation of pain

Analgesics – suppress perception of pain (increase the pain threshold) selectively without influencing perception of other stimuli

analgesics – anodynes (opioids)

act on spinal and supraspinal level, cause effects on somatic and visceral pain, strong effects on consciousness, act substantially more strongly than non-opioid analgesics

non-opioid analgesics

mostly peripheral effects (some have central effects!), effects on inflammation, weaker effects in general, no effects on visceral pain, no addiction

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Analgesics - anodynes

blocking transmission of pain signals between cells of the CNS (in the spinal cord, brain), as well as endogenous opioids:

endorphins, enkephalins, dynorphins

→ binding to opioid receptors (agonists)

Opiates

substances similar structurally to morphine with analgesic effect (natural origin, currently produced synthetically)

Opioids

+ synthetic, semisynthetic and endogenous opioid peptides + exogenous opioid analgesics

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Opioid receptors - μ κ δ (σ)

- G-protein coupled
- the interaction of the opioid with receptor → G- protein inhibition → reduction of neurotransmitter release + inhibition of neuronal activity
- adenylylcyclase inhibition, facilitation of K^+ channels opening postsynaptically, inhibition of Ca^{2+} channels opening presynaptically

- **μ**
- κ
- δ
- (σ)

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Opioid receptors - μ κ δ (σ)

- **μ** – supraspinal analgesia, euphoria, sedation, miosis, breath depression, addiction, GIT effects
- **κ** – spinal + peripheral analgesia, sedation, dysphoria, miosis, GIT effects, (somatic addiction)
- **δ** – spinal analgesia, breath depression, inhibition of GIT motility
- [**σ**] – dysphoric effect, psychotomimetic effect [(hallucinations, perception disturbances), anxiety]

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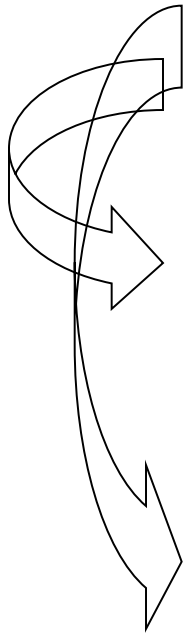
Opioid receptors - μ κ δ (σ)



FOR ANALGESIC EFFECT IS CRUCIAL ESPECIALLY ACTIVATION OF RECEPTORS:

μ – supraspinal analgesia

κ – spinal + peripheral analgesia

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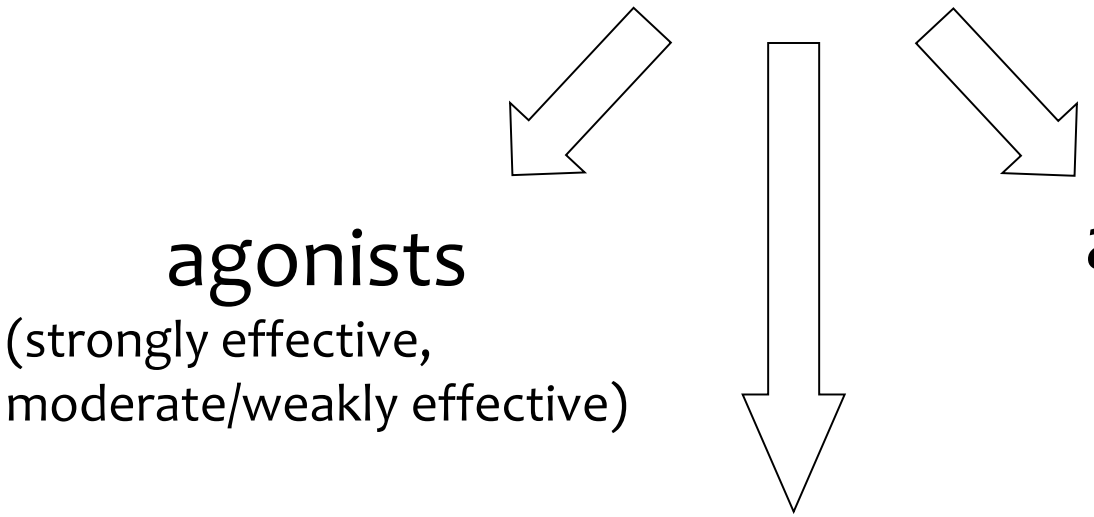
Pharmacological influence on opioid receptors



agonists
(strongly effective,
moderate/weakly effective)

antagonists

partial agonists – dualists
mixed agonists - antagonists

Atypical opioids

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Pharmacological effects of analgesics - anodynes

CENTRAL:

analgesic

suppression of respiratory center

sedation (+-)

suppression of anxiety

euphoria/dysphoria

antitussive effect

nausea and vomiting

↑ tendency to convulsions/cramps

miosis

↑secretion of ADH,

↓ GnRH, corticotropine, FSH, LH, ACTH, cortisol, testosterone)

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Pharmacological effects of analgesics - anodynes

TOLERANCE !!!

(to all effects of opioids except constipation and miosis!)

ADDICTION !!!

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Pharmacological effects of analgesics - anodynes

PERIPHERAL:

- decrease intestinal motility, slowdown propulsion of GIT content
- increase muscle tone of GIT and urinary bladder
- increase sphincter tone of gall bladder and urinary bladder
- constriction of pyloric sphincter, delayed gastric emptying
- vasodilation, orthostatic hypotension
- histaminoliberation
- inhibition of ciliated epithelium

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Pharmacological effects of analgesics - anodynes

PERIPHERAL:

- urological tract – increase tone of renal pelvis, ureter, *m. detrusor* and sphincter of bladder…urine retention, especially in post-operative conditions
- uterus - ↓ tone and motility, may prolong labor

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Pharmacokinetics of analgesics - anodynes

ABSORPTION	parenteral oral (<u>„first pass effect“ !!!</u>) perrectal transdermal sublingual transmucous (nasal)
DISTRIBUTION	parenchymatous organs muscles adipose tissue (lipophilic drugs ➔ e.g. fentanyl) pass well across BBB ➔ brain (fentanyl, heroin,..)

Can cross placental barrier !!!

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Pharmacokinetics of analgesics - anodynes

BIOTRANSFORMATION primarily in liver

↓

polar metabolites

- inactive metabolites
- active metabolites (codeine, tramadol, morphine…)

EXCRETION
- kidneys - urine
- liver - bile

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Opioid agonists

morphine

- 10 % of opium content, together with codeine, thebaine

  + other phenanthrene alkaloids

- isolated in 1803 (Sertürner)

- high affinity to μ receptors – selective μ agonism

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Opioid agonists

morphine

- see above effects
- application routes:
- orally (also p.o. with sustained release)
- parenterally (i.v., i.m., s.c., epidural,…)
- perrectally

Indications: chronic cancer pain, pain after surgery, injuries, (pain during acute myocardial infarction → today, given preference to other opioids)

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Other strong opioid analgesics

methadone

- less sedation and euphoria than in morphine
- ↑ bioavailibility after oral administration, ↑$t_{½}$
- acts on opioid + NMDA receptors
- **Use:** addiction treatment (heroin) ➔ 2 benefits

  ➔ change from injection application to oral administration

  ➔ ↑$t_{½}$ decreases plasmatic fluctuation of methadone ➔ less withdrawal symptoms

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Other strong opioid analgesics

heroin (= diacetylmorphine)

- not used in clinical medicine (in Czech Republic)
  (but in Great Britain can be therapeutically used!)
- causes severe addiction; abused!
- heroin belongs to the most health and personality
  devastating substance!!!

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Other strong opioid analgesics

fentanyl, sufentanil, remifentanil,…

- pass well across HEB (↑ concentrations in CNS)
- strong, short analgesia (fentanyl 100 x more potent than morphine, sufentanil 1000 x more potent than morphine)
- strong respiratory depression!, ↓ emetogenic potency, CAVE ➔ can cause muscle rigidity
- risk of serotonin syndrome in combination with 5-HTergic drugs

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Other strong opioid analgesics

fentanyl, sufentanil, remifentanil,…

- **<u>Indications, use:</u>**
- **in anaesthesiology** ➞ neuroleptanalgesia

  (= neuroleptic (AP) + opioid)

  ➞ analgosedation (e.g. opioid + BZD)
- therapy of strong pain – acute myocardial infarction, cancer pain,…
- fentanyl in TTS (↑ duration of action – can be used in chronic cancer pain), transmucous (can be used in breakthrough pain)

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Other strong opioid analgesics

piritramid

- less respiratory depression than morphine
- less emetogenic potency
- usually well tolerated parenteral administration
- **Use:** therapy of acute strong pain, e.g. after surgery (PCA), acute myocardial infarction, pain after injuries,…

Others: oxycodone, hydromorfone (not registered in Czech Rep.), **oxymorphone** (not registered in Czech Rep.)

CAVE: all strong opioids are prescribed to forms with blue band („opiate forms“), very strict accounted and subjected to the rules for handling with narcotics and psychotropic drugs and their precursors!!!

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Other strong opioid analgesics

pethidine (=meperidine)

- ↓suppression of respiratory center than morphine
- ↓analgesic potency than morphine (5-10 x weaker)
- metabolite norpethidine is proconvulsive and causes hallucinations
- administration orally and parenterally

Indications: cancer pain, pain after injuries, pain during acute myocardial infarction, pain after surgery, premedication before general anaesthesia…today not often used (high risk of abuse, hallucinations!)

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Opioid agonists (moderate and weak potent)

codeine

- 10 % mtb. to morphine
- antitussive effect in subanalg. doses
- analgesic effect in combinations (paracetamol, ASA)

  analgesic potency: codeine 50mg ~ ASA 1g

- ↓ risk of addiction than strong opioids
- CAVE ↑ risk of addiction of combined (compositive) analgesics
- causes obstipation
- not used in children!!!

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Opioid agonists (moderate and weak potent)

dihydrocodeine

- suitable in pains combined with cough (this co-incidency is not necessary for dihydrocodeine indication)
- in Czech Rep. dihydrocodeine in sustained release drug form (effect 12 h) ➞ indication for chronic moderate and strong pain

Side effects: obstipation, ↑liver tests, histaminoliberation

CAVE: codeine and dihydrocodeine are prescribed to normal forms - without blue band!

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Partial agonists + mixed agonists - antagonists

- lower affinity to **μ** receptors, high affinity to **κ** rec.,
- respectively **κ-agonists - μ-antagonists** or partial **μ** receptor agonists (buprenorphine)
- less potential for addiction, but exists!
- lower analgesic effect than full agonists
- less side effects than full agonists

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Partial agonists + mixed agonists - antagonists

buprenorphine

- partial μ rcp. agonist
- ↓tolerance in comparism with other opioids
- ↓abuse potential, obstipation and other GIT effects
- ↑ „first pass effect“ ! Do not administer orally!!!
- **Use:**

1) strong chronic pain (TTS!)

2) substitution therapy of opioid (heroin) addiction ➞ combined with opioid antagonist naloxone in one drug form (sublingual) ➞ in injection application naloxone antagonizes effects of buprenorphine (in sublingual administration naloxone does not act!)

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Partial agonists + mixed agonists – antagonists – other representatives

- mixed agonists – antagonists
- usually μ-antagonists and κ-agonists (event. also δ-agonists)
- possibility of σ-receptor activation → psychotomimetic and hallucinogenic effects)
- analgesic effects are weaker than full agonists
- today minimal use
- **pentazocin, butorfanol** – in Czech Rep. not registered

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Partial agonists + mixed agonists – antagonists – other representatives

nalbuphine

- for short-term therapy of moderate and strong pain
- unsuitable for long-term therapy
- parenteral administration (i.v., i.m., s.c.)
- causes respiratory depression comparable to morphine, but suppression of respiratory center has drug ceiling effect
- **Use: perioperative pain, suppression of pain in obstetrics** (BE AWARE: in newborns risk of breathing depression, bradycardia, cyanosis and hypotension → newborn`s monitoring necessary!)

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Atypical opioids

tramadol

low affinity to μ receptors + norepinephrine and serotonin reuptake inhibition (= atypical mechanism of action, similar to some antidepressants from SSRI group; effect of tramadol can not be fully antagonized by opioid antagonists)

- approximately 1/6 – 1/10 of morphine analgesic potency
- very suitable combination with paracetamol
- less side effects (minimal respiratory depression)
- risk of serotonin syndrome
- in Czech Rep. very often prescribed analgesic, prescription to normal forms without blue band; more drug forms
- RISK OF ADDICTION!!!

Use: therapy of moderate and strong pain (acute and chronic)

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Atypical opioids

tapentadol

- **dual mechanism of action**
  - **μ agonist + NRI (+ σ agonist)**
    NEW GROUP – MOR-NRI (μ receptor agonism – noradrenaline reuptake inhibitor)
- more effective than tramadol, analgesia comparable with oxycodone, but less adverse effects
- suitable for the treatment of acute (but also chronic pain – e.g. vertebrogenic; also effective in diabetic neuropathy - neuropathic pain!!!)
- relatively few adverse effects (compared to classical strong opioids, e.g. oxycodone)
- p.o. administration (also tbl. with sustained release)

CAVE: tapentadol is prescribed to forms with blue band („opiate forms“), very strict accounted and subjected to the rules for handling with narcotics and psychotropic drugs and their precursors!!!

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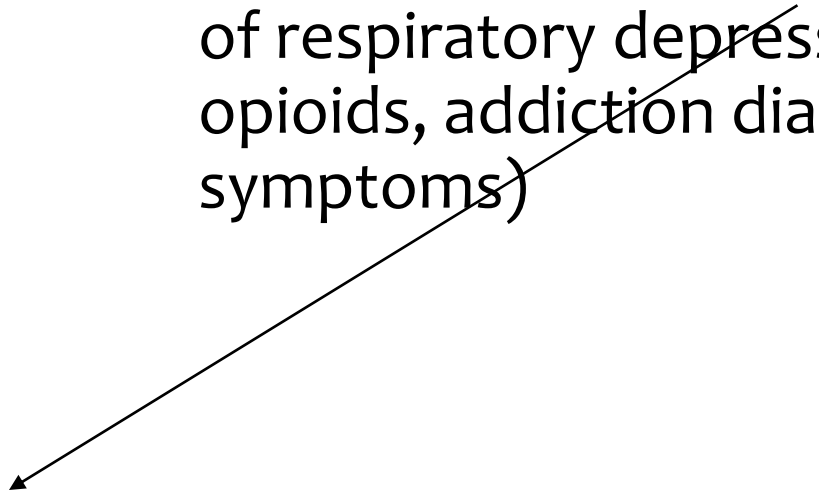
Antagonists of opioid receptors

naloxone, naltrexone

Indications: treatment of opioid intoxication, treatment of respiratory depression induced by opioids, addiction diagnostics (withdrawal symptoms)



TRIAD: coma, respiratory depression, miosis

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Opioid-induced side effects

- **respiratory depression (suppression of breathing)**
- **nausea and vomiting**
- **sedation, inhibition of cognitive functions**
- **constipation** (solution = oxycodone + naloxone)
- **ADDICTION**
- **be carefull in pro-convulsive states! (e.g. epilepsy – proconvulsive action – decrease of the threshold for seizures)**
- **↑ intracranial pressure**

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Intoxication by opioid agonists

nausea, „flush“, tinnitus

apathy, sedation, sleep, miosis

superficial breathing

cyanotic, cold skin, tachycardia

asphyxia

TRIAD: coma, respiratory depression, miosis

Treatment:

naloxone i.v.

ventilation, vital functions,

parenteral liquids in unconsciousness

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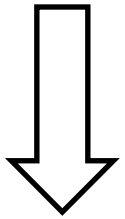
Withdrawal symptoms



occur approximately after 3-4 weeks of opioid administration

„craving“ („drogenhunger“), „craving“ for the another dose

(psychic addiction arises easiest to heroin, oncology patients treated with opioids ➔ < 1% of patients)

unrest, depression

anxiety, weakness, nervousness, mydriasis

lacrimation, ↑ nose secretion, frisson (goosebumps),

↑ perspiration, pain, stenocardia

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Rotation of opioids

- Switch in case of AE
- Sometimes even in equianalgesic dose increase of effect

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Other indications of opioids

- **antitussive effect**
  - can be induced by **codeine** and **dextromethorphan** in dry non-productive cough

- **constipative effect**
  - can be induced by **loperamide** and **diphenoxylate** in functional diarrhea

- **p r e m e d i c a t i o n before anaesthesia and surgery under general anaesthesia**
  - leads to calm the patient and based on the synergism of drugs reduces the total dose of narcotics (thereby increasing the safety of anaesthesia)
  - particularly fentanyl and its derivatives are used
  - combination of opioid analgesic with neuroleptic (fentanyl + droperidol) within neuroleptanalgesia

- **r e p l a c e m e n t (substitution) therapy of addiction to heroin or other opioids – methadone, buprenorphine**

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General rules of pain pharmacotherapy management

- **WHO's pain relief ladder**
- Step 1 (VAS 0-4)
  - non-opioid analgesics ± adjuvant treatment
- Step 2 (VAS 4-7)
  - pain persists, intensifies, no change in the objective finding
  - weak/moderate opioid analgesics ± non-opioid analgesics ± adjuvant treatment
- Step 3 (VAS 7-10)
  - pain persists, intensifies, there is no indication for another treatment
  - strong opioid analgesics ± non-opioid analgesics ± adjuvant treatment ± weak/moderate opioid analgesics

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NSAIDs, Antipyretics

Antigout drugs

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- **Analgesics-antipyretics (A-A)** drugs against fever and pain

- **Nonsteroidal antiinflammatory drugs (NSAIDs)** - against inflammation, fever and pain

A-A and NSAIDs overlap partially

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Mechanism of action

- all of them have similar mechanism of action– inhibition of eicosanoids synthesis (with higher or lower selectivity and strength)

- NSAIDs differ in the strength of COX1/COX2 inhibition and the incidence of typical AE (ulcer disease, bleeding)

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Cyclooxygenases

- **COX-1 – constitutive** – prostanoids involved in physiological processes (gastroprotective effects, platelet activities)
- **COX-2 – inducible** – activity enhanced by proinflammatory factors (IL-1, IL-2, TNF-α, oncogenes,..)
  - prostanoids → inflammation, fever, pain
- **COX-3** ? – central mechanism of analgesic and antipyretic effect (localization: heart + CNS)

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Classification by COX1/COX2 inhibition

1. Nonspecific inhibitors
   - ASA, ibuprofen, diclofenac, …
2. Preferential inhibitors of COX-2
   - meloxicam, nimesulid
3. Specific inhibitors of COX-2
   - coxibs

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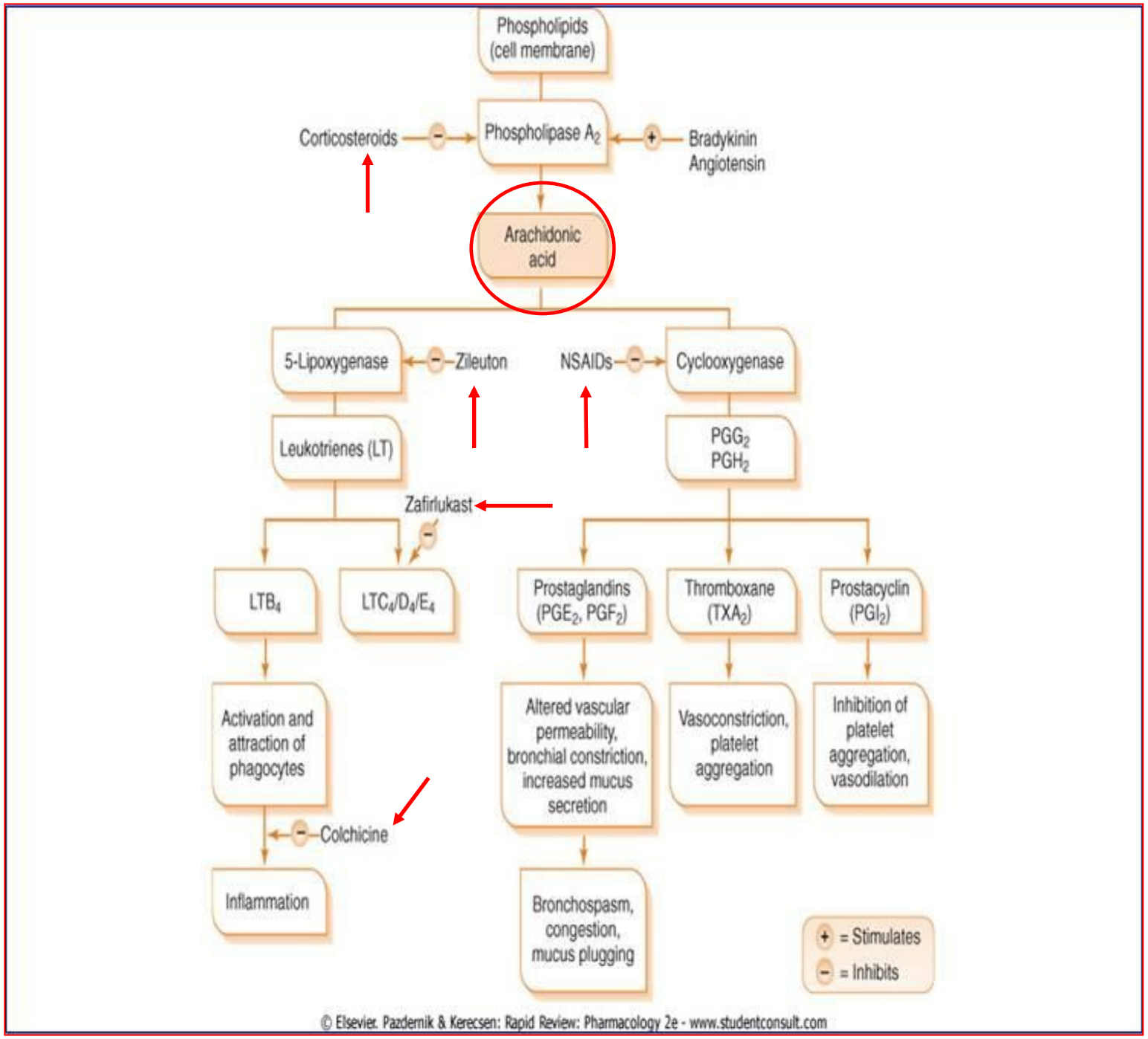
Phospholipids (cell membrane)
Corticosteroids
Phospholipase A_2
Bradykinin
Angiotensin
Arachidonic acid
5-Lipoxygenase
Zileuton
NSAIDs
Cyclooxygenase
Leukotrienes (LT)
PGG_2
PGH_2
Zafirlukast
LTB_4
$LTC_4/D_4/E_4$
Prostaglandins (PGE_2, PGF_2)
Thromboxane (TXA_2)
Prostacyclin (PGI_2)
Activation and attraction of phagocytes
Altered vascular permeability, bronchial constriction, increased mucus secretion
Vasoconstriction, platelet aggregation
Inhibition of platelet aggregation, vasodilation
Colchicine
Inflammation
Bronchospasm, congestion, mucus plugging
+ = Stimulates
− = Inhibits
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Classification

1. Salicylic acid derivatives
2. Aniline derivatives
3. Propionic acid derivatives
4. Pyrazolones
5. Acetic acid derivatives
6. Oxicams
7. Coxibs
8. Other

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1. Salicylates

Effects:

- analgesic
- antiinflammatory
- antipyretic
- antirheumatic
- antiaggregation → inhibition of platelet function

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Salicylic acid derivatives – drugs

<u>NSAIDs:</u>

- ASA (acetylsalicylic acid)
- sodium salicylate
- cholinsalicylate

<u>Therapy of inflammatory bowel desease:</u>

- sulfasalazine
  - → sulfapyridine + 5-aminosalicylic acid
- mesalazine

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Acetylsalicylic acid

- efficiency standard of AA and NSAIDs
- selective inhibitor of COX1 (100-200 : 1)
- irreversible acetylation of COX-1 active centre
- pharmacokinetics:
  - weak acid, complete and rapid absorption in stomach and proximal part of intestine
  - **salicylic acid (SA)** is product of metabolisation
  - $T_{1/2}$ ASA 15-20 min, $T_{1/2}$ SA 30 hrs depending to dose
  - 80-95% binding to plasma proteins, elimination and exkretion via kidneys
  - higher doses – risk of cumulation in a body

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Usual dosages

antipyretic	**500 mg**
analgesic	**500 mg (4 - 6 hrs)**
anti-phlogistic, -rheumatic, -uratic	**3,6 – 4 g/day**
antiaggregative	**30 –100 mg**
total daily dose	**4 g/day**

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ASA – adverse effects

- **salicylism (↑d.)** – hearing impairment, tinnitus, deafness, vertigo
- **allergy** - itching, rash, anaphylaxis,…
- **aspirin-induced asthma** - ↑LT
- **GIT** - nausea, dyspepsia, bleeding, ulcer disease
- **„analgetic“ nephropathy** – reversible decrease of glomerular filtration
- **increased bleeding**

CAVE

- pregnancy- differs in trimesters
- children- Rey‘s syndrome
- elders- more sensitive to AE

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ASA interactions

- **anticoagulants**
- **NSAIDs** and other analgesics (except of opioids)
- **other**
  - valproate, sulfonylureas – competition on plasma proteins – increase of efficacy
  - SSRI – potentiate ASA antiaggregative effect (citalopram, fluoxetine)
  - glucocorticoids decrease ASA plasma levels, but increase the risk of GIT bleeding and ulceration

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ASA - contraindications

- hemophilia and other diseases influencing blood coagulation
- administration prior to surgery
- gastroduodenal ulcers, gastritis
- **children to 12 years**
  - **Rey‘s syndrome** (hyperpyrexia, acidosis, seizures, vomiting, psichiatric disorders, hepatopathy)
- pregnancy (only temporary)
- asthma, allergy, nasal polyps

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2. Aniline derivatives

Paracetamol (=acetaminophen)

- analgesic, antipyretic, **is not antiinflammatory active**
- does not influence blood coagulation or uric acid levels
- mechanism of action is unclear:
  - central mechanism due to COX-3 inhibition
  - indirect effect on 5-HT_3 spinal receptors
  - elevates PGG_2 to PGH_2conversion in peripheral tissues
  - influencing the endocannabinoid and vanillin system and Ca^{2+} channels

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Usual doses

- comparable effect to ASA, but better tolerance
- **drug of choice to ↓ fever and pain in children younger than 12 years**
- pain in adults
  - 300 to 500 mg every 3-4 hrs
  - 650 mg every 4 to 6 hrs
  - 1000 mg every 6 hrs
- total daily dose up to **4 g**

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Pharmacokinetics:

- p.o. good absorbtion, maximum in 30-60 min, low plasma protein binding, hepatic metabolism
- production of hepatotoxic mtb. – binding to gluthathione
- overdose (10 – 15 g) → antidote **N-acetylcysteine**

AE, CI:

- allergy
- hepatotoxicity after ↑ doses
- comorbidities:
  - alcohol addiction
  - nephropathy
  - hepatopathy

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3. Pyrazolones

Propyphenazone

- in combinations (with paracetamole and caffein)
- **AE:** GIT intolerations, rash, bronchospasm, hematopoetic disorders

Metamizole

- analgetic, antipyretic + spasmolytics effect
- combined with spasmolytics (pitofenone, fenpiverine)
- **AE:** rare but serious - the most serious are agranulocytosis and pancytopenia

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4. Propionic acid derivatives

Ibuprofen

- good analgesic and antiinflammatory effect
- used often for acute pain therapy
- low AE incidence, well tolerated NSAID, indicated for children

Ketoprofen

- phototoxicity

Dexketoprofen

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4. Propionic acid derivatives

Naproxen

- longer $T_{1/2}$ (12-15 hrs)
- low gastro- and cardiovascular toxicity compared to other NSAIDs

Tiaprofenic acid

- good penetration to synovial fluid → joints diseases

Flurbiprofen

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5. Acetic acid derivatives

Diclophenac

- antiinflammatory, analgesic, weak antipyretic ef.
- bioavailability 30-70%
- short biological halftime → retarded DDF
- more AE than ASA, less than indomethacin
  - mild: cephalgia, insomnia, GIT disorders, photosensitivity
  - significant risk of cardiovascular AE

Aceclofenac

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5. Acetic acid derivatives

Indomethacin

- very strong nonselective COX inhibitor
- toxic → short-time treatment of acute states
- urikosuric effects→ used in gout attacks
- AE in 30 % of pacients
  - GIT, cephalgia, depression, confusion, hallucinations, hematoxicity, cartilages destruction

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6. Oxicams

- high plasma protein binding (interactions!)
- long biological halftime (once daily dosing)
- different COX affinity

Meloxicam

- COX-2 more selective
- lower AE incidence

Lornoxicam

- nonselective COX inhibitor
- low occurence of GIT adverse effect

Piroxicam

- nonselective COX inhibitor, high toxicity

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7. Coxibs

- 100 x more selective to COX-2 (**specific** COX-2 inhibitors)
  - lower AE in GIT
  - do not influence thrombocyte aggregation or renal perfusion
- good analgesic effect, not suitable for treatment of acute or transient pain → effect is progressing slowly
- prescription and indication restrictions
- **I:** osteoarthritis, rheumatoid arthritis, ankylosing spondylitis
- **AE:** increase of thrombembolisms (myocardial infarction, strokes) after chronic use

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7. Coxibs

Celecoxib

Parecoxib – only inj.

Etoricoxib

Pharmacokinetics:

- after p.o. administration good absorption from GIT, but not too fast, max levels reach in 2-4 hours
- fat diet slows down absorption

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8. Other

Nimesulide

- preferential inhibitor of COX-2
- inhibits enzymes destroys cartilage (elastases, collagenases), due to occurrence of AE, indication of treatment of painful osteoarthritis has been taken
- is not the first choice medicine in any of indications
- **PK:** lipophilic, short elimination half-life (1,5-5 hrs), analgesia up to 12 hrs
- **AE:** hepatotoxicity (max duration of therapy 15 days)

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Adverse effects

- because of COX-1 inhibition:
  - GIT - ↓ cytoprotective PGE_2, PGI_2
    ⇒ ***erosions, ulcerations***
  - thrombocytes - ↓ TXA_2: inhibition of thrombocytes aggregation
    ⇒ ***increased bleeding***
  - PGE_2, PGI_2 regulation of renal functions
    ⇒ ***renal failure***
  - ↑ LT production induces in predisposed people bronchoconstriction
    ⇒ ***asthma attack***
  - uterus - ↓ PGE/F: inhibition of constriction
    ⇒ ***prolongation and complications during delivery***

- coxibs:
  - thromboembolic cardiovascular and cerebrovascular complications

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Prevention of AE

- dose reduction or DDF change
- combination with protective drugs
  - **proton pump inhibitors** (lansoprazole, omeprazole)
  - **prostaglandine analogues** (misoprostol)
  - **H_2 antihistamines** (ranitidine, famotidine)

- think about preferential or specific COX-2 inhibitors

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NSAIDs for local aplication

- ketoprofen, ibuprofen, naproxen, indomethacin, diclophenac, nimesulide, piroxicam
- flurbiprofen (lozenges), choline salicylate (oral gel)
- **DDF:** creams, gels, solutions (sprays), patches, lozenges
- **AE:** hypersensitivity reaction, phototoxic reaction

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Treatment of gout

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Drugs

1. **Acute gout attack**
   - strong anti-inflammatory action
   - pain-killers
   - inhibition of leucocyte migration to the joint
2. **Hyperuricemia therapy / prevention of gout attack**
   - increase of uric acid excretion
   - block of synthesis

+ diet

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Treatment of acute gout attack

NSAIDs
higher doses (i.m., p.o., p.r.)
some have preferably uricosuric effect
indometacine, diclofenac, piroxicam

colchicine
alcaloid obtained from *Colchicum autumnale*
p.o. every 2-4 hrs
mitotic poison, inhibits phagocytosis and leukocyte migration
AE: severe diarrhea – rehydratation!

glucocorticoids
local adm. (i.a.) – **triamcinolone**
systemic (p.o., i.m., i.v.) – **prednison**, **methylprednisolon**

canakinumab
IL-1 inhibitor, human monoclonal antibody
patients who do not tolerate NSAIDs and GC
s.c. aplication

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Chronic treatment of gout

1. Uricosurics

- inhibit reabsorption of uric acid in primary tubulus

Lesinurad

- only in combination with xantin oxidase inhibitors

Probenecide

- sometimes used with antibiotics or antivirotics to make them stay longer in the body
- Not registered in Czech Rep.

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2. Antiuratics

- inhibit syntesis of urine acid by inhibition **xantin oxidase (XO)**

Allopurinol

- isomer of hypoxanthin, competitive inhibition of xanthin oxidase
- inhibits *de novo* syntesis of purines
- not combine with cytostatics of purine structure (azathioprin, 6-mercaptopurin) – allopurinol ↑ their toxicity!
- **AE:** usually well tolerated, most common:
- rash, GIT intoleration, hypersensitive reaction

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Febuxostat

- **MA:** non-purine inhibitor of xantinoxidase
- clinical trials proved higher efficacy than allopurinol
- **AE:** gout attacts, liver function abnormalities, diarrhoea, nausea, headache

Pegloticase (recombinant uricase)

- **MA:** transforms uric acid to alantoin with better solubility
- **AE:** anaphylactic shock, reaction to infusion, gout attacts at the beginning of therapy
- i.v. aplication (only to inpatient)

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