Pharmaceutical Care

Pain

Learning outcomes of today

- ✓ **What** is pain
- ✓ **How** is it treated
- ✓ Use of non-opiod analgetics
- ✓ Use of NSAIDs
- ✓ Use of opiod analgetics

Analgesics in pharmacy

1. self-treatment (OTC drugs) - headache, teeth, musculosceletal system

- Right analgesic doses
- Risks - Many different brand names, combinations

2. Rx analgesics - chronic pain – dispensing minimum

- Sustained-release tablets, TTS, sprays, sublingual tablets – instructions for patients
- duplicate medications from various doctors
- overuse of analgesics, eg. NSA - **GI risks**
- **opioids** - **documentation**, risk of addiction, abuse

Important:

- **To communicate with the patient,** ask questions

- Knowledge of OTC medicines, **brand names**, including their risks
- Check combinations (Rx, OTC, different names)
- Know the limits of **self-medicaiton**
- **The correct use of various analgesic medication forms**, their dosing schedules, adverse effects

When send the patient to the physician?

- if the patient **serious pain for the first time** and the **cause of pain is not clear**
- The pain lasts **much longer and he suffers from a variety of illnesses** and uses a combination of medication
- the pain is **associated with some other disorder** (back pain with wounding and **stool leakage**, headaches with **difficulty in hand movement)**
- similar pain but this time it is **significantly stronger, it has a different character, localization** (it was blunt, this time it is sharp, it is cut (it has back pain, but this time it is significantly stronger)

Pharmaceutical specifics

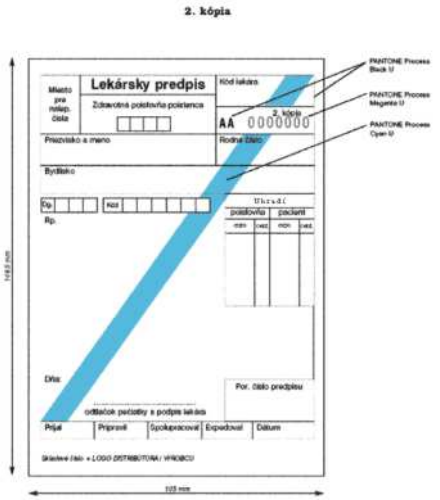
- Why sustained-release tablets, especially opioids?
- transdermal therapeutic system
- sublingual, bucal, nasal application

- **Technologies**, advantages and disadvantages?

- **The technology principles**

- Rules for proper dosage, application

- Dispensation minimum
- Prescription restrictions



Therapy of pain:

- **Analgesics**
- Antidepressants (AD)
- Alpha 2-adrenergic agonist - clonidine
- Corticosteroids
- GABA agonists, and Anticonvulsants
- Local anesthetics
- Calcitonin
- Bisphosphonates
- Antispasmodics

What is pain? - definition

- ✓ Pain is an **unpleasant sensory, emotional and mental feeling (experience)** associated with accompanying **psychic and eventually vegetative reactions** and **behavioral change**
- ✓ It is caused by tissue damage by disease, injury, surgery, heat..
- ✓ **How much is the emotional part involved** – depends on the individual..
- ✓ pain is not just a nociceptic, but a complex biological and psychological experience that also has a social connection
- ✓ a mechanism to preserve the individual → warns against the consequences of the action that would lead to **irreversible damage of tissue**

✓ How would you clasify pain?

- ✓ **Nociceptive pain** from pain receptors (twisted ankle)
- ✓ **Neuropatic pain:** from nervous system (trigeminal neuralgia, postherpetic neuralgia)
- ✓ Pain with **no apparent cause**

Types of pain:

- ✓ Acute
- ✓ Chronic non-malignant
- ✓ Chronic - malignant

Acute pain

- Lasts for a short period of time (hours, days, weeks)
- Warning function
- Usually localized, **more acceptable**
- Generally **fast improvement**
- Its **cause can be determined**
- First is to **treat the cause**
- The most important factor is the **intensity** and **location** of pain
- Is accompanied by adrenergic (**stress**) response

Acute pain

- Initially stronger and faster-acting analgesic is chosen
- Note: **Weak opioids do not have a stronger analgetic effect than non-opioid analgesics!** It was proven by meta-analysis of clinical trials that it is true in acute pain
- **“Step down„ model:** we begin with a strong analgesic, gradually reducing the dose and passing on weaker analgesics.

Chronic pain

- Lasts for longer than **3 months**
- Has **no** biologically useful **function**
- The goal of treatment is **not necessarily a full recovery**, but modification condition of the patient
- Is accompanied by **psychiatric** disorders (eg. depression, sleep disturbance)

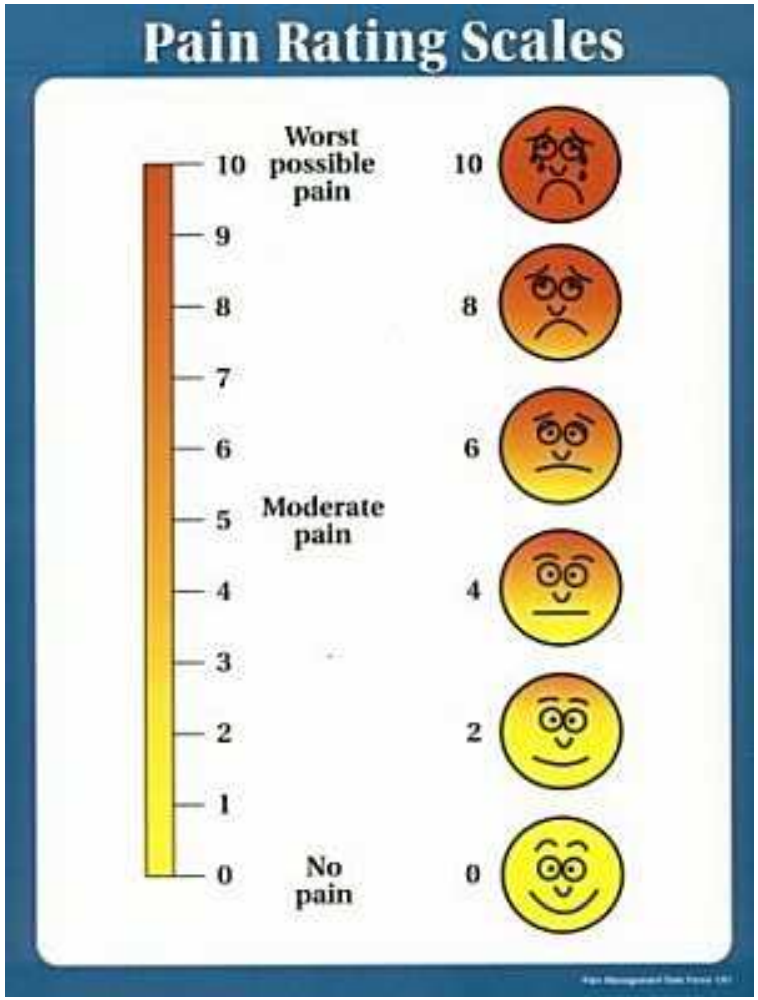
Chronic pain

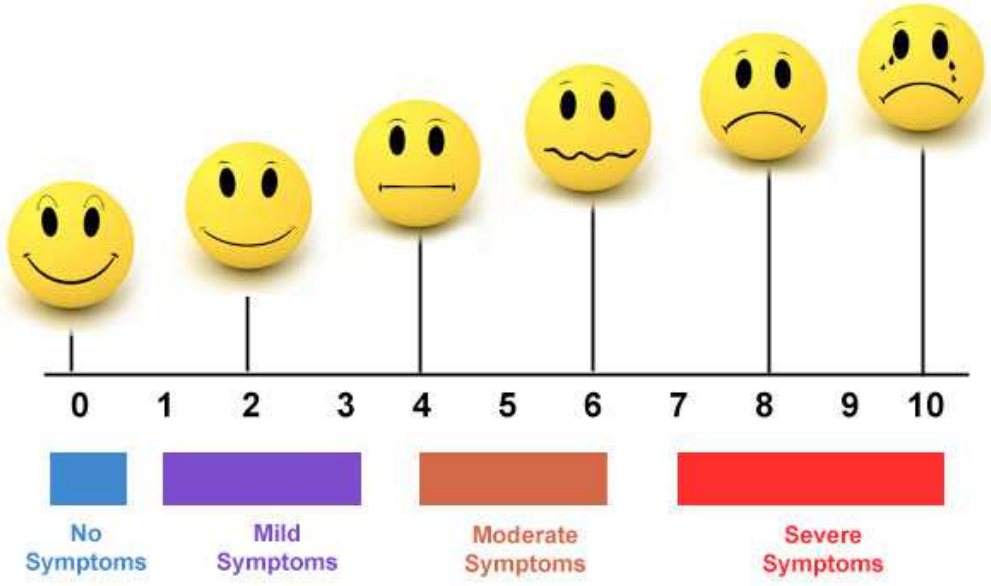
- The **aim of treatment for chronic pain** is not necessarily a full recovery of the individual, but the modification and possible restoration of physical, mental and social health
- **The "step up„ model:** The procedure according to analgesic ladder from the bottom up, gradual dose increases + possible combination with other adjuvant drugs.

Pain evaluation – visual analogy scale

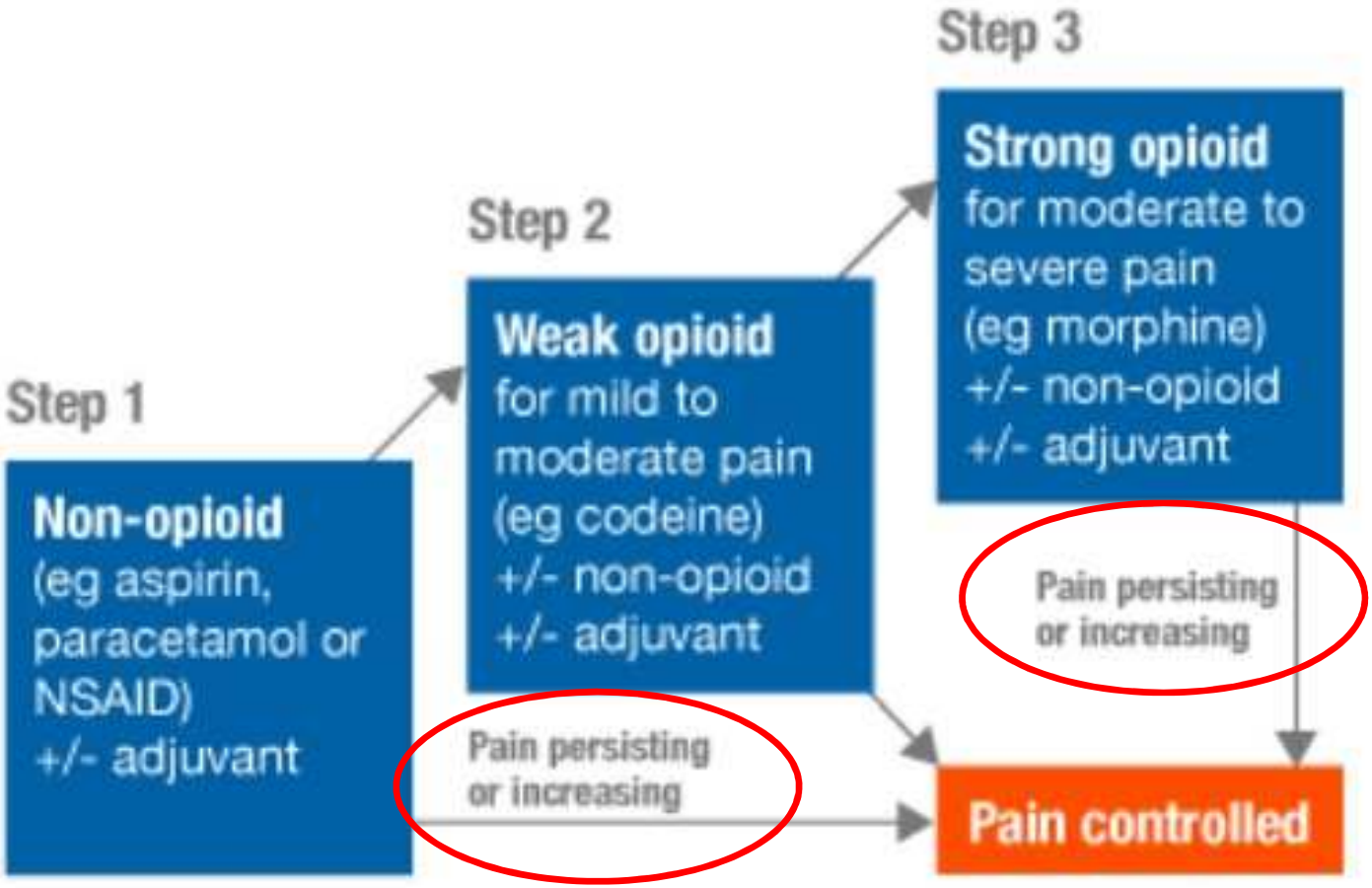
3 times/a day (once daily)

„diary od pain“





WHO Analgesic Ladder



Pharmacotherapy Algorithm of routine short term pain

1) First step in mild to moderate pain

ibuprofen 200 mg

diclofenac (50) 25 mg

metamizol 500mg

(650-1000 mg **ASA**)

paracetamol 650-1000 mg or **tramadol** 75-100 mg

Pharmacotherapy Algorithm of routine short term pain

2) Second degree in moderate to severe pain

ibuprofen 400 mg (up to 800 mg)

diclofenac 50 mg (up to 100 mg)

nimesulide 100 mg

analgesic combinations

tramadol do 400 - 600 mg/d

dihydrokodein (DHC) do 240mg/d

paracetamol 650 mg -1,000 mg + **codeine** 60 mg

paracetamol 650 mg + 75 mg **tramadol**

500 -1000 mg **metamizole**

Pharmacotherapy Algorithm of routine short term pain

3) Third step - severe pain

Strong opioid (+ paracetamol)

oxycodone 10 - 20 mg

hydromorphone slow release 4-6mg

morphine 30 mg or more

fentanyl TTS 25-100 µg/h

buprenorphin TTS 35-140 µg/h

injection: **morphine, pethidine**

Anelgesics - Antipyretics

- **Paracetamol / acetaminophen** - at therapeutic doses (ie up to 1000 mg after 4 h, up to 4 g daily) are among the relatively safest painkillers. Importantly, however, give it a sufficient dose, ie 650 - 1000 mg for an adult **(fever – 500mg)**
- **Acetylsalicylic acid** - as an analgesic has been mostly superseded by other more effective and safer NSAIDs. MDD 4g
- **Pyrazolone derivatives** - for example, **metamizole** (500 - 1000 mg for an adult dose, 4000-6000 mg per day) or propyfenazon. They have a **very good analgesic efficacy without serious** gastrointestinal risks. Rarely can cause **dangerous blood disorder (agranulocytosis)** or anaphylactic shock reaction. Their use is not recommended as first medication the election.

  They are not suitable for chronic pain.

Acetaminophen (paracetamol)

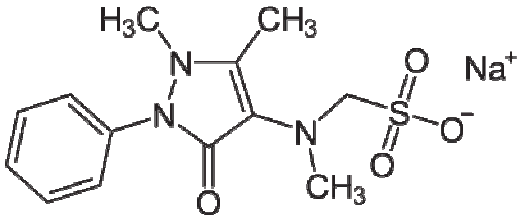
- no anti-inflammatory effects
- Fewer adverse effects than other nonopioid analgesics
- Adverse effects
  - Renal toxicity
  - Risk for hepatotoxicity at high doses
    - Increased risk with **liver disease or chronic alcoholism**
    - risk for hepatic toxicity is minimized at doses below 4 grams per day
- No effect on platelet function

Paracetamol – analgetic dose 1000mg !!!

- **Single analgesic dose** of paracetamol per os **10-15 mg/kg**, daily maximum of **60 mg/kg**
- Note: Micromedex admits 10-15 mg / kg **5 times a day**, in adults 1 g at the earliest after 4 hours, **but not more than 4 g daily (8 tablets)**

- Dosage of paracetamol - based on patient's body weight
- > 50kg the dose of one 500mg tablet is inadequate
- 51-70 kg, 1.5 tablets (750mg)
- **weight 71-100 kg needs 2 tablets (1000mg)**

Metamizol (dipyrone)



- **1000mg - highly potent analgetic dose**
- ADR: rarely hematopoietic disorders leukopenia, agranulocytosis, thrombocytopenia or haemolytic anemia.
- probably on an immunological basis

- **The drug was not authorised** in the United States or the United Kingdom. withdrawn from the market in most developed countries, registered in Germany, France, Spain and eastern European countries
- No case of agranulocytosis has been reported to SUKL during its registration, which does not exclude its occurrence

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NSAIDs

1. NSAIDs inhibit **acute pain** according to a meta-analysis with the **same probability as morphine!**
2. The current findings suggest that the analgesic efficacy, on average, not very different (for individual patients may vary considerably).
3. The **analgesic effect is dose dependent** and is not typical for them "ceiling effect" in effect.
4. A preferred feature is the minimum tolerance even after prolonged use and the absence of physical dependence.
5. The combination of NSAIDs is not rational, and only increases the ADRs

NSAIDs

- **Ibuprofen** - GIT's gentlest traditional NSAIDs (at doses up to 1200 mg / day). It inhibits pain already in-the-counter dose of 200 mg. Dos. up to per day - 2400 mg (1200 mg).
- **Diclofenac** - differentiate products with normal and retarded release. Dos. max per die - 150 mg.
- **Piroxicam** - is unlike other NSAIDs very long half-life (approximately 50 h). Piroxicam has a high gastrointestinal risk. Dos. up per day - 20 mg.
- **Naproxen** - **has a longer half-life** (about 13 h). Dos. up to per day - 1000 mg.
- **Ketoprofen** - a high risk of gastrointestinal bleeding. Dos. max for die - 300 mg.
- **Indomethacin** - a strong analgesic effect, a high risk of gastrointestinal bleeding, not suitable for chronic use. Dos. max for die - 200 mg short term.

Aceclofenac (Biofenac)

- used for over 20 years
- NSA with **high selectivity to COX-2** - with **low gastrotoxic potential**
- 100% bioavailability and up to 60% concentration in synovial fluid
- **rapid onset of action** and minimal risk of bleeding from GIT (except coxibs)
- symptomatic treatment of pain and inflammation in osteoarthritis and rheumatoid arthritis at doses of 200 mg (1 tbl) max 2 times daily
- and also in the form of a soluble suspension
- the effect of acute pain is lower (compared to other analgesics)

- 20x100mg **por plv sol**

Dexketoprofen

- S - (+) - stereoisomer of ketoprofen
- is about a 30-fold more potent COX-1 inhibitor and about 100 times more potent COX-2 inhibitor then ketoprofen

- **Faster onset of action**, half-time 6 hours
- **25 mg each 8 hours**. Total daily dose of max 75 mg

- short-term administration, **low risk of ADRs**
- **musculoskeletal, postoperative, colic and tumor pain, headache and dysmenorrhea**

Doležal T.: dexketoprofenum, Remedia 2003

Preferential COX-2 inhibitors

- **Nimesulide** - a good analgesic effect, tbl. and effervescent drug form
  - ! It is not without gastrointestinal side effects.
  - ! It was confirmed **hepatotoxicity with prolonged use**
  - Dos. max for die - 200 mg (2 tablets)

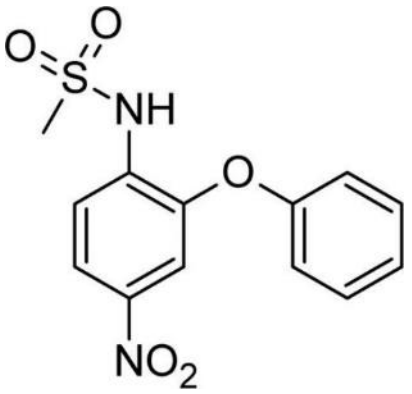
- **Meloxicam** - designed primarily for **rheumatic diseases**, but can be used for other pain. Dos. up per day - 15 mg, one tablet a day

- **Celecoxib** - registered only for treatment of rheumatic pain.
  - ! Cerebrovascular and cardiovascular ADRs.
  - Dos. max for die - 400 mg.

meloxicam (Movalis and generic drugs)

- is indicated for **short-term symptomatic treatment of exacerbations of osteoarthritis and long-term symptomatic treatment of rheumatoid arthritis**
- significantly improves GIT tolerance over other NSAs
- KV risk comparable to that of non-selective NSAs
- Selectivity for COX2 at low doses (15mg)
- no significant drug interactions
- anti-inflammatory "specialist"
- there is no evidence of increased warfarin efficacy when taking meloxicam

nimesulid (Aulin, Nimesil)



- analgesic-antipyretic effect, anti-inflammatory
- preference for COX-2, little ADRs
- rapid onset of action
- CV risk comparable to that of non-selective NSAs
- **Hepatotoxicity !!!! Contraindications:**
  - liver damage, abuse of alcohol and hepatotoxic substances
- 2007 - not to use **more than 15 days**
- 2009 - Confirmed + **only as second-line medicine**
- 2012 - treatment of acute pain and dysmenorrhoea

Hepatotoxicity of NSAID

- Hepatotoxicity is a rare but potentially serious side effect of NSAIDs? **group effect ("class effect")**
- It is an idiosyncratic type of hepatotoxicity

less hepatotoxicity

- Ibuprofen
- coxibs

higher hepatotoxicity

- nimesulide
- sulindac
- fluorobiprofen
- diclofenac

Coxibs contraindications

- **Active peptic ulcer** or active bleeding into the GI tract.
- **Pregnancy and breast-feeding**
- Hepatic dysfunction of the liver (serum albumin <25 g / l or Child-Pugh score ≥ 10).
- Decreased renal clearance <30 ml / min.
- Children and adolescents up to 16 years of age.
- Inflammatory bowel disease.
- Patients with **congestive heart failure** (NYHA II-IV).
- Patients with **hypertension** whose blood pressure is permanently elevated above 140/90
- Patients with **ischemic heart disease**
- **peripheral arterial disease**

Cardiotoxicity of NSAID

- an increased risk of coronary events is a **group effect of NSAIDs**

Cardiotoxic:

- Coxibs (celecoxib - Celebrex, etoricoxib - Arcoxia)
- Diclofenac

Less cardiotoxic:

- Naproxen
- Ibuprofen

Opioid Therapy: Side Effects

- Common
  - Constipation
  - Somnolence, mental clouding
- Less common
  - Nausea
  - Myoclonus
  - Itch
  - Urinary retention
  - Sweating
  - Amenorrhea
  - Sexual dysfunction
  - Headache
- Physical dependence
- Tolerance
- Addiction

miosis (eye pupil constriction)

Weak opioids

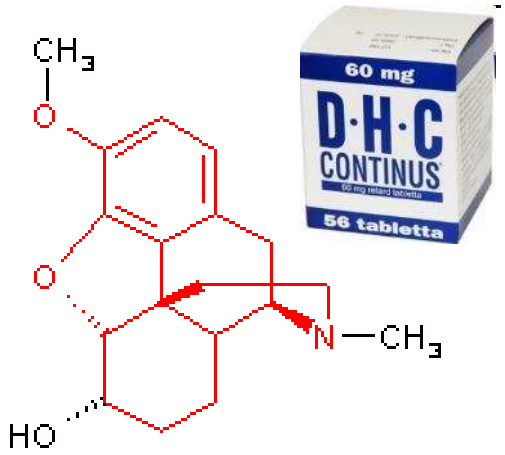
- **Tramadol** - the advantage is a **low risk of constipation**, of dependence
  - ! ADRs - dizziness and nausea, psychological effect.
  - Very good is the combination of paracetamol with tramadol.
  - Dos. max per day - 600 mg.
- **Codeine** - is a weak analgesic, used almost only in combination, preferably with paracetamol. **antitussic**
  - Dos. max for die - 240 mg.
- **Dihydrocodeine** - its analgesic efficacy after oral administration is similar to codeine. Maximum rational dos. for die - 360 mg.
- **Pentazocine, nalbuphine** - are intended for **acute or of short pain**, are not suitable for chronic pain.
  - These belong to so-called mixed agonist-antagonist.
  - For this group of **ceiling effect is applied** (for further increasing the dose does not increase the analgesic effect only side effects).

! Increased risk of psychological dependence.

N02A - opioid analgesics

- N02AA opium alkaloids
- **morphine, hydromorphone, oxycodone, dihydrocodeine**
- N02AB Phenylpiperidine derivatives
- **fentanyl**
- N02AC Diphenylpropylamine derivatives
- N02AD Benzomorphan derivatives
- N02AE Derivatives of oripavine
- **buprenorphine**
- N02AF Morphine derivatives
- N02AX Other opioid analgesics
- tramadol (+ combination)

N02AA Opium alkaloids



- N02AA01 Morphine
- N02AA02 Opium
- N02AA03 Hydromorphone
- N02AA05 Oxycodone
- N02AA08 Dihydrocodeine
- N02AA09 Diamorphine
- N02AA10 Papaveretum
- N02AA51 Morphine, combination
- N02AA58 Dihydrocodeine, combination
- N02AA59 Codeine, combinations except psycholeptics
- N02AA79 Codeine, combinations with psycholeptics

Strong opioids

- **Morphine - injectable form** is suitable for the treatment of severe acute pain.

  p.o. forms with gradual release working 12 hours or up to 24 h are used for chronic pain.

- **Fentanyl** – TTS *(transdermal therapeutic system)* is suitable for the treatment of severe chronic pain. The advantage of treatment in the fentanyl TTS is a very stable plasma concentrations.

- **Buprenorphine** - a partial agonist at μ receptors and an antagonist at kappa receptors -TTS

- **Pethidine** - in comparison with morphine has **lower spazmogennic effect,** it is preferable for acute colic pain. It has a shorter duration of action (2 h) and is not suitable for chronic treatment!

  - Unsuitable for the treatment of chronic pain results from psychomimetic effect and increased risk of psychological dependence.

- **Hydromorphone, oxycodone**

N02AA01 Morphine

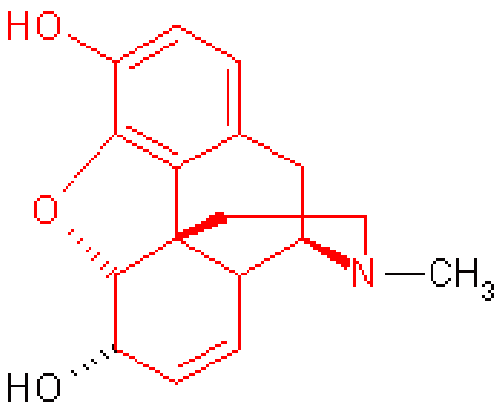
- Low (30%) availability after oral application
- Active metabolites
  - M-6-G - analgesia, convulsions
  - M-3-G - agitation, anxiety
- after. 30-60min, max 60-120min, 4-5hours

- Possible histamine release
- Constipation
- Individual pharmacokinetics
- - genetic polymorphism

~~MST continus~~

Vendal retard

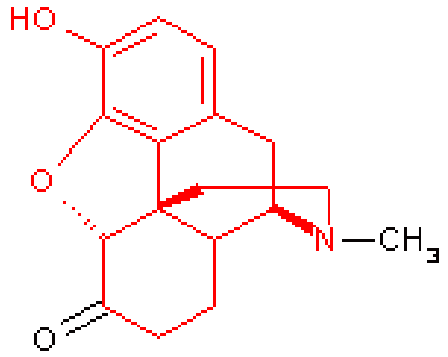
(Sevredol tbl)



N02AA03 Hydromorphone

- Semisynthetic derivative of morphine
- pure μ - agonist
- 4-6 times higher affinity for opioid receptors
- 2x better availability than morphine (over 60%)
- **Half-time-2-3 hours**
- Direct glucuronidation in the liver, an almost pharmacologically inactive metabolite (hydromorphone-3-glucuronide)
- Only 8% binding to plasma proteins
- Independence from CYP-450
- it could be the first choice opioid for cancer pain
- Similar to ideal opioid

- Palladone (12)



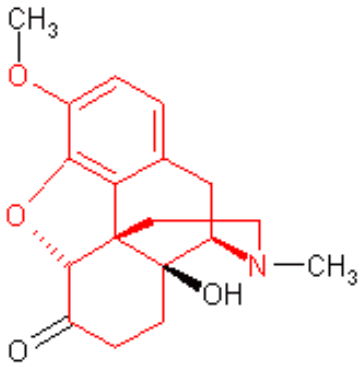
Hydromorphone (Palladone cps)

- **oral modified-release medicine** containing hydromorphone HCl
- gelatin capsule with pellets - biphasic drug release - fast initial blood concentrations followed by sustained release over 24 hours

- Twice a day after 12 hours
- The possibility of **asymmetric dosing** according to the circadian rhythm of pain intensity
  - Another dose for daily activity, other for night

N02AA05 Oxycodone

- A strong μ1 and μ2 agonist
- Availability after p.o. administration of 60-80%
- Sweating, euphoria, confusion
- Slightly analgesically acting metabolites
- best of opioids for neuropathic pain



N02AA05 Oxycodone

- Oxycontin (Mundipharma)
- Oxycodon Sandoz
- Oxycodon Ratiopharm

- AcroContin® biphasic absorption profile - immediate release of the drug over an hour and prolonged effect for 12 hours.
- The GI fluid dissolves the coating of the tablet and the **initial dose of oxycodone (37%)** is released immediately after contact. GI fluid penetrates into the matrix pores, dissolves the **remaining drug (62%),** which slowly diffuses from the matrix pores (t1 / 2 is 6.2 hours).

- pH independent release, constant throughout the GIT

Method of use - Sustained-release tablets

- **Do not chew**, do not divide, do not crush
- Palladone - can be opened – use pellets
- Use regularly at the **same time of day**, according to the dosing schedule, by the hour
- If low efficacy, **do not reduce the interval, increase the dose**
- Rebound effect (discontinue slowly)
- Interactions: IMAO, alcohol, hypnotics
- Affecting **the ability to drive car**

- **Adverse effects** - respiratory depression, bradycardia, myosis, somnolence, constipation
- Fluid intake, fiber, **softening laxatives**
- Prevention of orthostatic hypotension

N02AB03 Fentanyl (TTS)

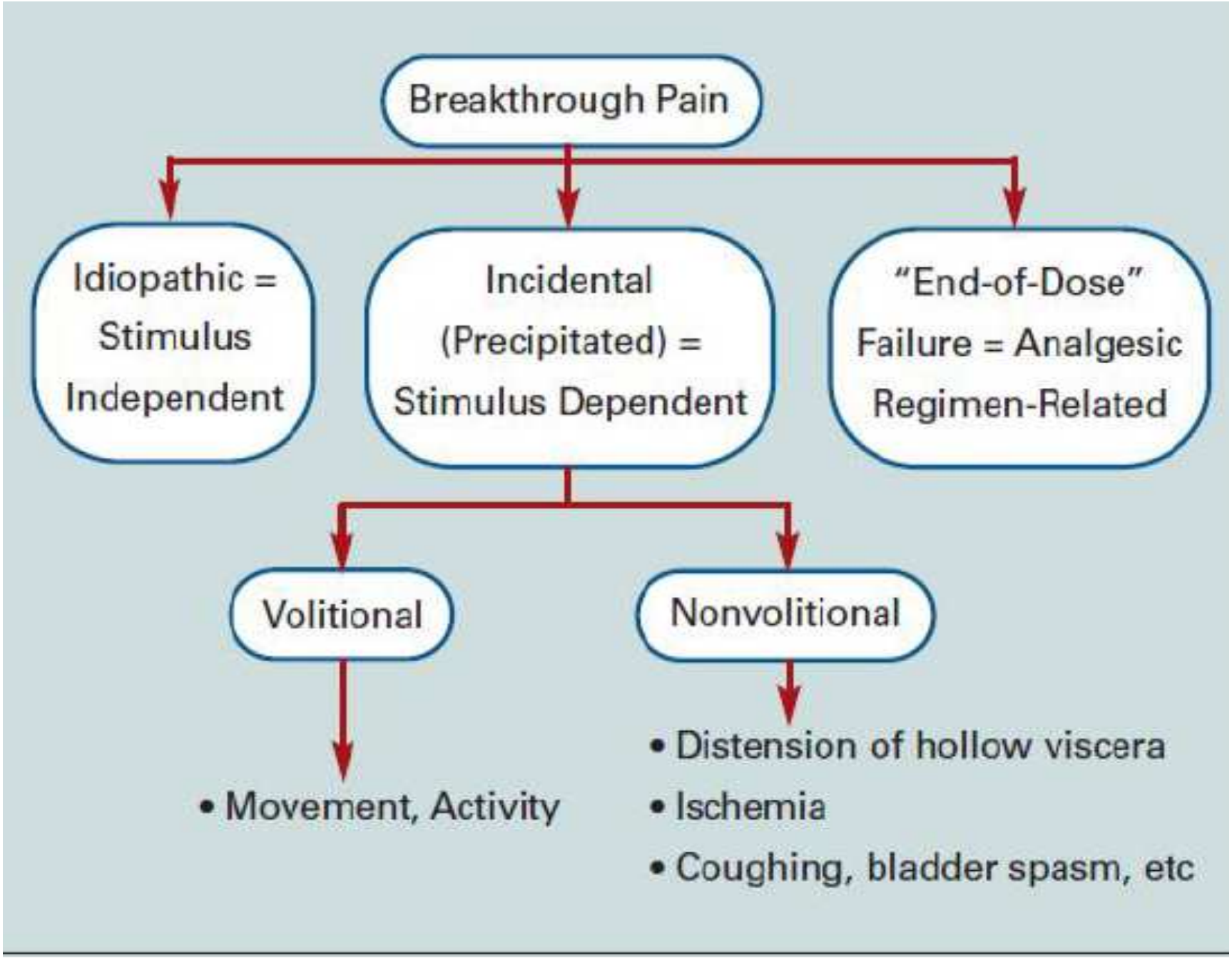
- is a synthetic opioid analgesic that exhibits **high selectivity to μ-subtype opioid receptors** with about **100 times more affinity than morphine**
- Highly lipophilic, **100 times faster penetrates skin than morphine**
- Biotransformation occurs mainly in the liver via CYP3A4, an ineffective metabolite
- High efficacy, selectivity and **low incidence of side effects**
- in patients with severe chronic pain
- The TTS form is an effective alternative to morphine, but is only suitable for patients with a stable opiate dose

Method of using TTS:

- Aply to skin without injury, not irritated, scarring, flat surface of the trunk, or arms
- Skin without hair do not shave (microtrauma)
- Children - upper half of the back
- Clean, dry, intact skin
- Press for 30 seconds
- Do not cover with other patches
- **Record the date and time of the application on the box**
- Change the place of application - at the same place after 7 days

- After applying return to the pharmacy
- It is possible to bath, take a shower, swim, not long in warm water and exposure to the sun
- Exposure to high temperatures (sauna, solarium, electric blankets) fever

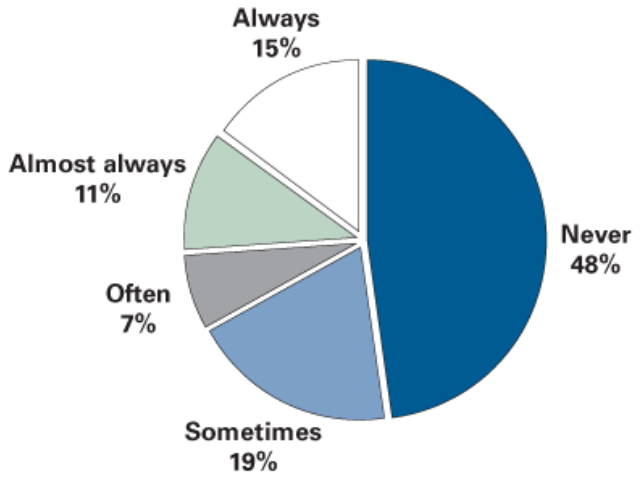
- The last dose of the tablet 12 hours after sticking the patch, the effect persists for 12-17 hours after peeling ...
- Cut / not cut ?????


Breakthrough Pain
Idiopathic = Stimulus Independent
Incidental (Precipitated) = Stimulus Dependent
"End-of-Dose" Failure = Analgesic Regimen-Related
Volitional
Nonvolitional
• Movement, Activity
• Distension of hollow viscera
• Ischemia
• Coughing, bladder spasm, etc

Rescue medication

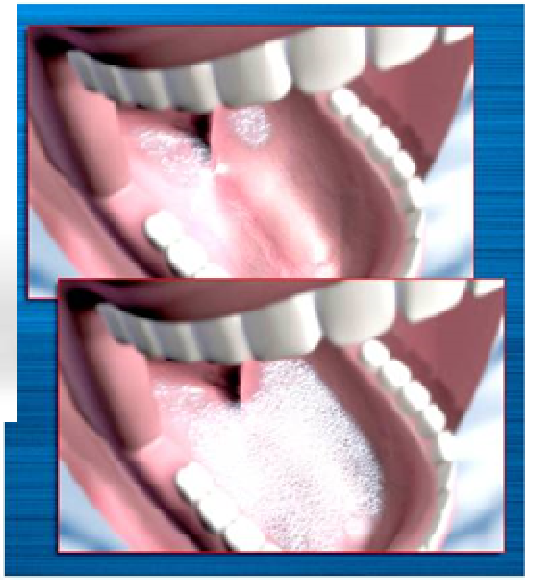
- Good efficacy
- Rapid onset of action
- Short duration of effect
- Good tolerability
- Easy to use
- Acceptable to the patient
- Available / affordable

Figure 3. Predictability of Breakthrough Pain



Source: Portenoy RK, et al. *Pain*. 1999;81:129-134.

Instanyl, Lunaldin, Breakyl, Effentora,



ADHERES → DISSOLVES → DELIVERS

- Bi-layered film technology
- Active drug in the muco-adhesive layer
- Backing layer facilitates unidirectional flow of drug

- Adheres to oral mucosa in < 5 seconds
- Completely dissolves within 15-30 minutes
- Minimal taste issues

- Rapid drug absorption
- Designed to optimize delivery across the mucosa

Adjuvant analgetics (AA)

Multi-effective AA - has adjuvant for most types of chronic pain.

Antidepressants (AD)

- I. generation - amitriptyline, clomipramine, dosulepin
- II. and III. generation - maprotiline, fluoxetine, paroxetine, citalopram - are indicated in case of increased risk of AD first generation.
- *(AD III. Generation (SSRIs) have lower self-analgesic effect than the AD first generation.)*

Alpha2-adrenergic agonist - clonidine, tizanidine can be effective in chronic refractory pain with sympathetic dysfunction

Corticosteroids - tend to have a supportive effect on some types of chronic refractory pain

Adjuvant analgetics (AA)

AA for neuropathic pain

GABA agonists, and Anticonvulsants - carbamazepine, valproic acid, gabapentin (*favorable safety profile, low incidence of drug interactions and efficiency are factors for which gabapentin is now listed as first choice anticonvulsant for neuropathic pain*), clonazepam

Local anesthetics - mexiletine, mesokain in slow infusion

Calcitonin, bisphosphonates - are effective for pain and sympathetic maintained pain in osteoporosis

Antispasmodics - butylskopolamin

Adjuvant analgetics (AA)

AA for musculoskeletal pain

Central muscle relaxants - can have an analgesic effect especially for some types of acute back pain