Individualised therapy with the use of analgesic drugs

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Conflict of interest:

nothing to disclose

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Question 1

Does chronic pain be the shorter version of acute pain?

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Question 2

Should a therapeutic team always use the same pain assessment scale with the same individual?

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Question 3

Should a physician always start treating severe pain with non-steroidal anti-inflammatory drugs, according to WHO analgesic ladder?

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Global data

- 1 in 5 adults suffers from pain
- 1 in 10 adults is diagnosed with chronic pain

- Causes of pain: cancer
  osteo- and rheumatoid arthritis
  operations and injuries
  spinal problems

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Pain

- IASP Taxonomy „An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”

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What are the basic types of pain?

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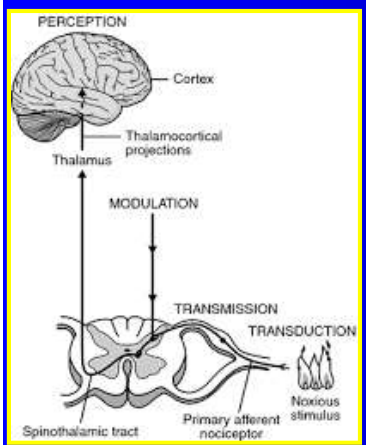
Types of pain

- **Physiological** – is formed as a warning signal when noxious stimulus affects the healthy tissue



Depended on:

- genetic background
- individual pain threshold
- variable sensitivity between individuals
- individual resistance to noxious stimuli
- prone to the development of chronic pain

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Types of pain

- **Physiological** – is formed as a warning signal when noxious stimulus affects the healthy tissue

- **Pathological** – tissue damage or inflammation

hyperalgesia (greater and prolonged pain)

allodynia (pain caused by sub-threshold stimulus)

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Types of pain on the mechanistic basis

- **Nociceptive pain** arises as a result of activation of nociceptive receptors
- **Neuropathic pain** caused by either peripheral or central nervous system lesions, the most common form of opioid-poorly-responsive pain

- **Psychogenic pain** caused by psychological factors, formed without tissue damage

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Types of pain on the basis of the duration

- **Acute pain** caused by surgery, broken bones, dental work, burns or cuts, labor and childbirth
- **Chronic pain** lasts over 3 months, caused by headache, low back trouble, cancer, arthritis, psychogenic factors

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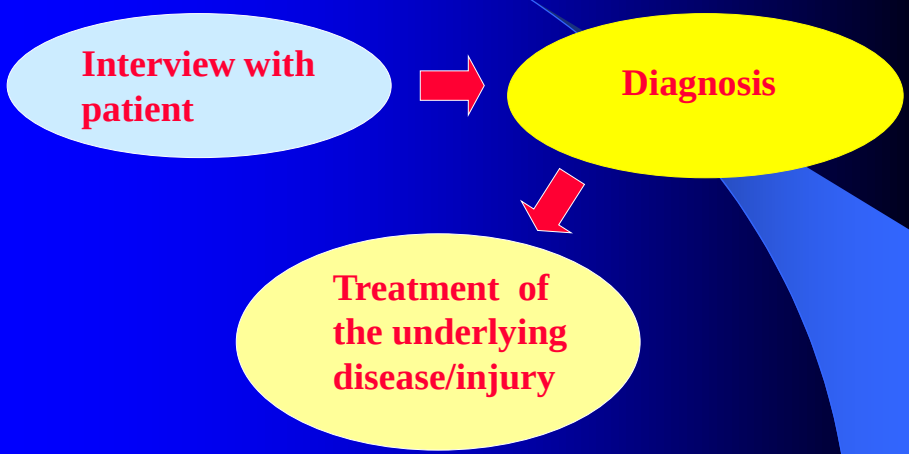
Acute pain



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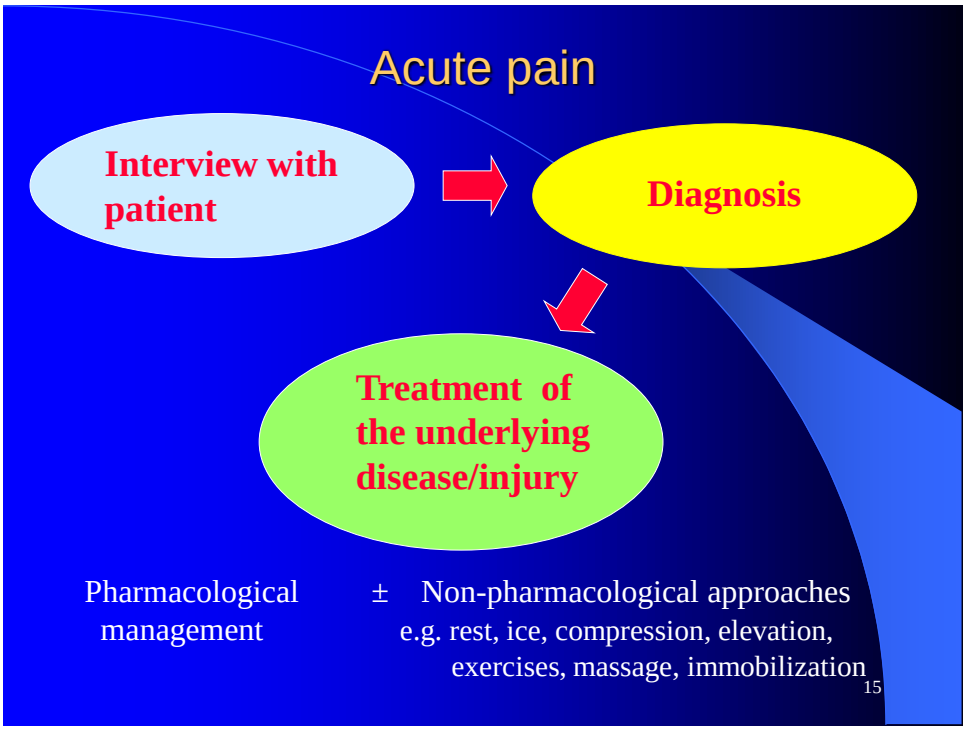
Acute pain - treatment goals

- Early intervention, with prompt adjustments in the regimen for inadequately controlled pain
- Reduction of pain to acceptable levels
- Facilitation of recover from underlying disease or injury


Acute pain
Interview with patient
Diagnosis
Treatment of the underlying disease/injury
Pharmacological management
± Non-pharmacological approaches
e.g. rest, ice, compression, elevation, exercises, massage, immobilization
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CHRONIC PAIN MAKES
FUNCTIONAL AND MORPHOLOGICAL
CHANGES DESTROYING
THE NERVOUS SYSTEM
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Acute pain vs Chronic pain

Characteristic	Acute pain	Chronic pain
Cause	Generally known	Often unknown
Duration of pain	Short, well-characterized	Persists after healing, ≥ 3 months
Treatment approach	Resolution of underlying cause, usually self-limited	Underlying cause and pain disorder; **outcome is often pain control not cure**

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Chronic pain - treatment goals

- Diminish suffering, including pain and associated emotional distress
- Increase/restore physical, social, vocational, and recreational function
- Optimize health, including psychological well-being
- Improve coping ability (e.g. develop self-help strategies, reduce dependence on health care system) and relationships with others (e.g. family, friends, health care professionals)

National Pharmaceutical Council 18

Pharmacological management of pain

- Comprehensive evaluation of pain factors: intensity
  quality
  pattern
  duration

Pain assessment scales

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Pain assesment scales

- Wong-Baker FACES Pain Rating Scale
- Verbal Rating Scale (VRS)
- Numeric Rating Scale (NRS)
- Visual Analogue Scale (VAS)

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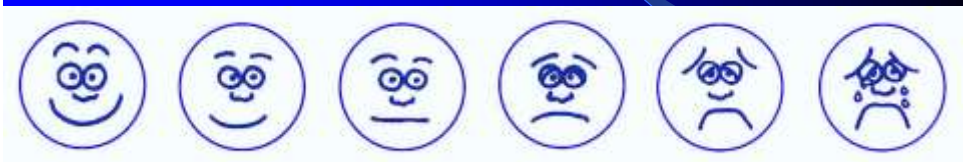
Wong-Baker FACES Pain Rating Scale



No hurts | Hurts Little Bit | Hurts Little More | Hurts Even More | Hurts Whole Lot | Hurts Worst

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Verbal Rating Scale (VRS)

	patient's activity
0 – no pain	no pain
1 – very mild pain	easily ignored
2 – mild pain	cann't be ignored
3 – severe pain	focuses your attention
4 – very severe pain	disturbs in activity except eating, hygienic avtivities
5 – worst possible pain	forced to take medicine and/or lying down

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Numeric Rating Scale (NRS)

- Patient determines pain intensity indicating the appropriate number on the scale

0 or 0%
No pain

5 or 50%
Moderate pain

10 or 100%
Worst possible pain

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Visual Analogue Scale (VAS)

- The scale of the graphical section 10 cm long, on which the patient selects the currently perceived pain intensity.
  „0” – no pain
  „10” – worst possible pain

No pain

Worst possible pain

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Pharmacological management of chronic pain

- Multiple factors of pain: intensity, quality, duration, pattern

effective and individualised treatment

a rational plan care

(patient's age and condition, time of onset, dosing frequency, side effect profile, patient's preferences like route of administration)

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What are the main principles of chronic pain management

taking into account individual needs of a patient?

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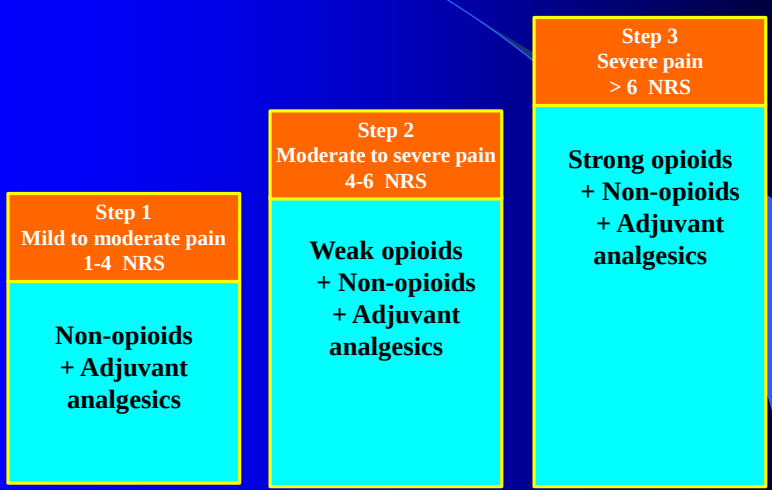
Principles of chronic pain management

- The intensity of pain and the treatment outcomes should be regularly assessed
- Patient should be informed about pain and pain management and be encouraged to take an active role
- Analgesics should be prescribed on a regular basis according to WHO „analgesic ladder" in regular intervals
- Tailor the dosage, the type and the route of drugs administered according to each patient's needs. **The oral route of administration should be advocated as the first choice** (short-acting drugs every 4 h, 50-100% of a dose for night-sleep)
- Rescue doses of medications other than the regular basal pain therapy must be use for breakthrough pain episodes

ESMO Clinical Practice Guidelines, Annals of Oncology, 2012, 23, 139-154 27

WHO Analgesic ladder (1986)



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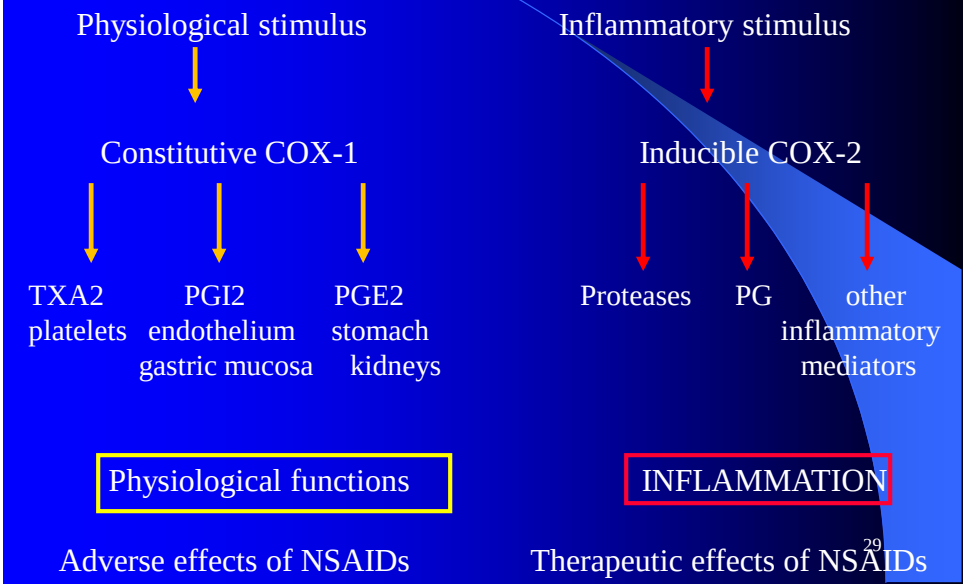
Non-steroidal anti-inflammatory drugs (NSAIDs) – mechanism and effects



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NSAIDs – classification

- Specific inhibition of COX-1 – **aspirin** at low doses
- Non-specific inhibition of COX-1 and COX-2 – **aspirin** at higher doses, **ibuprofen**, **naproxen**, **ketoprofen**, **nabumetone**
- Preferential inhibition of COX-2 (2-100-fold more potent) – **meloxicam**, **nimesulide**, **dex-ketoprofen**, **dex-ibuprofen**
- Specific inhibition of COX-2 (>100-fold more potent) – **celecoxib**
- Inhibition of COX-3 – **paracetamol**, **metamizole**

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Severe pain requires strong medication

but

in respectively lower doses

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Early start with opioids

- Contra-indications towards NSAIDs
- Rapid development of the disease
- Initial severe pain episode

Reaching minimal effective concentration of an analgesic in serum as soon as possible and maintaining it during the whole time of pain treatment

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Weak opioids

Codeine
Hydrocodeine
Tramadol

Strong opioids

Morphine
Fentanyl
Alfentanyl
Methadone
Oxycodone
Buprenorphine
Oxymorphone etc

Mechanisms of action:

- agonists/partial agonists of opioid receptors: mi, kappa, delta
- inhibitor re-uptake of serotonin and noradrenaline
- antagonist of NMDA receptors

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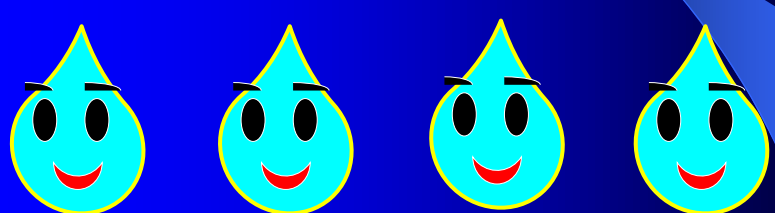
Titration of an opioid

In order to obtain the tailored dosage for adequate pain relief with an acceptable degree of side effects

Individual titration of dosages every 4 h + rescue doses for BTP



Regular dose of a slow-release opioid with an equi-analgesic dose

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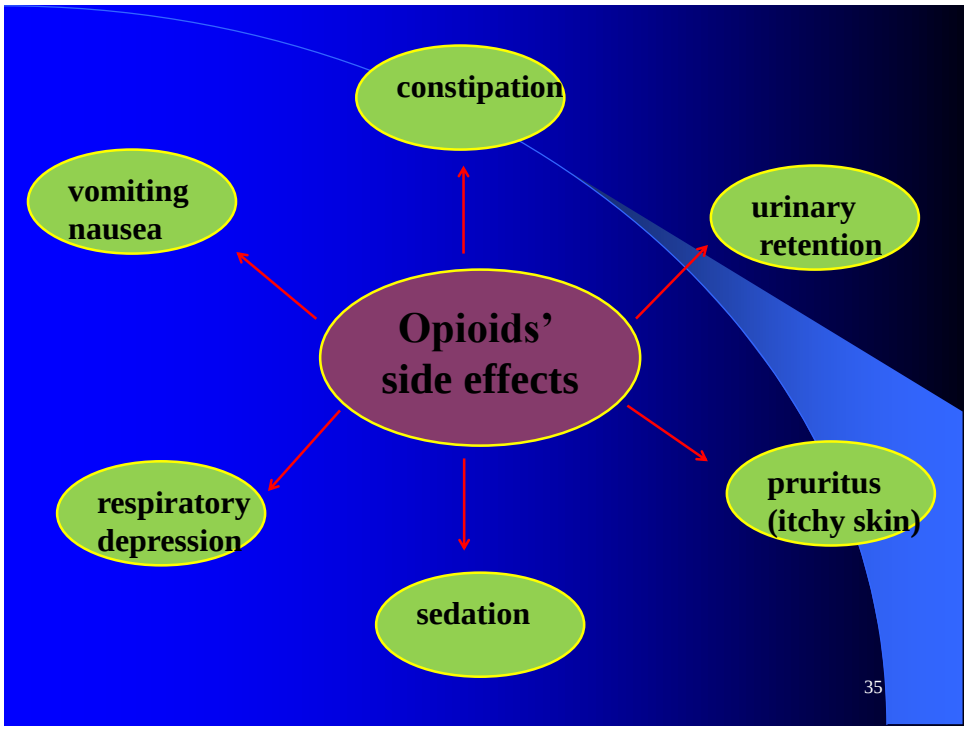
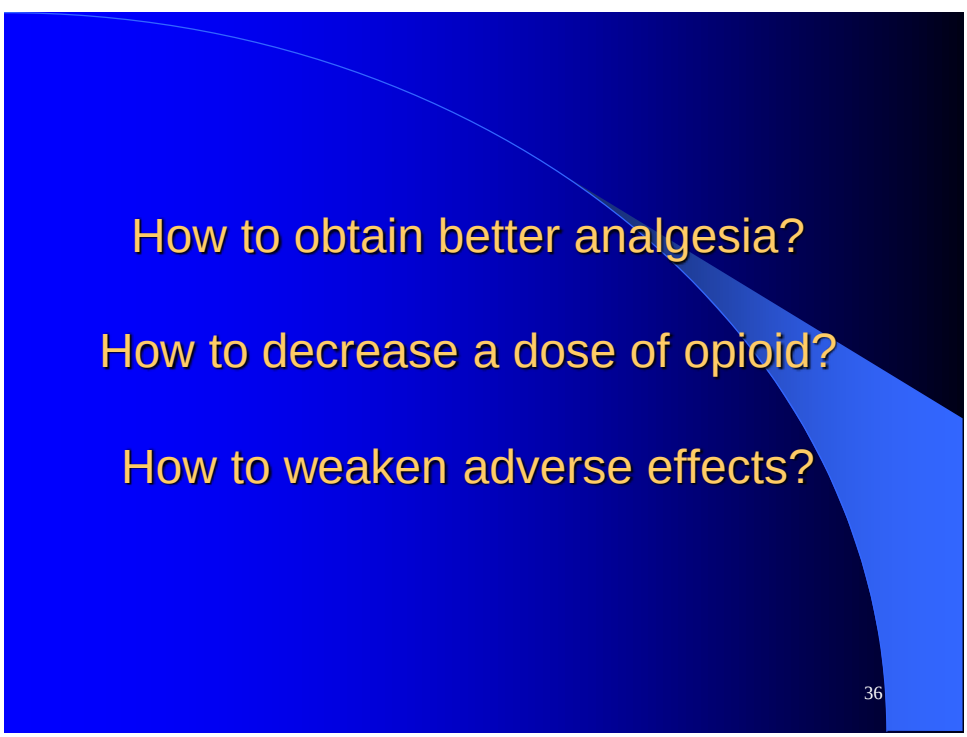

constipation
vomiting
nausea
urinary
retention
Opioids'
side effects
respiratory
depression
pruritus
(itchy skin)
sedation
35


How to obtain better analgesia?
How to decrease a dose of opioid?
How to weaken adverse effects?
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Strategies recommended

- Decrease the dose of opioid
- Change the route of administration
- Symptomatic treatment
- Switching to an alternative opioid

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Adjuvant analgesics

- Antidepressant drugs (amitriptiline, clomipramine, imipramine, mianserine)
- Anti-epileptic drugs (carbamazepine, lamotrigine, gabapentine)
- Local anesthetic drugs (lidocaine, mexyletine)
- Glucocorticoids (dexamethazone)
- Bisphosphonates and calcytoin
- NMDA receptor antagonists (ketamine, memantine)

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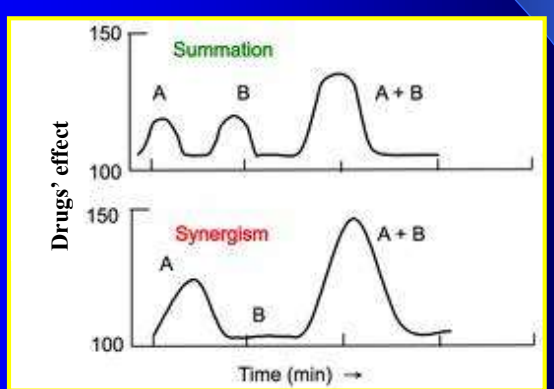
Combination pharmacotherapy

additive effect synergistic effect



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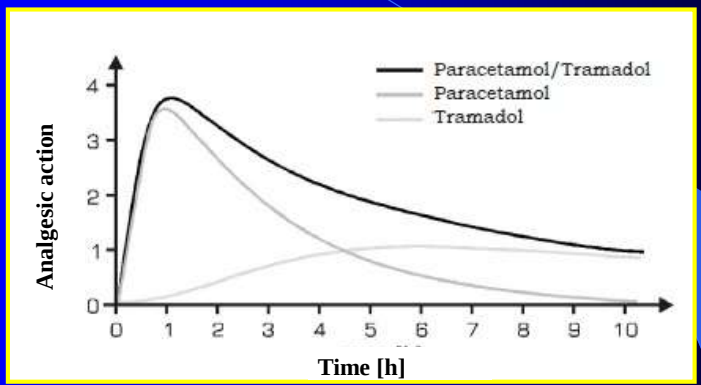
Paracetamol 325 mg + Tramadol 37,5 mg



Benefits:

- lower doses of both drugs
- combination acts faster and longer than a single drug

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Combination pharmacotherapy – recommended

- paracetamol + NSAIDs = reduction needs for opioids after surgery
- NSAIDs + triptane = additive effect in migraine
- NSAIDs + paracetamol + caffeine = synergistic effect in migraine
- NSAIDs + paracetamol + opioid = synergistic effect

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Combination pharmacotherapy – recommended

- morphine + memantine = synergistic effect in neuropathic pain
- oxycodone or morphine + ibuprofen = additive effect in dentist surgery, rheumatoid arthritis
- oxycodone + morphine = synergistic effect
- oxycodone + naloxone = constipation prevention

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Combination pharmacotherapy – not recommended

- NSAID + NSAID = increase in side effects
- paracetamol + codeine = decrease in paracetamol absorption in small intenstine
- weak opioid + strong opioid = „ceiling effect" of weak opioids
- nefopam + tramadol = increase in risk of serotonin syndrome

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Strategies recommended

- Decrease the dose of opioid
- Change the route of administration
- Symptomatic treatment
- Switching to an alternative opioid

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Pharmaceutical formulations
nasal spray, sublingual tablets, buccal tablets, effervescent forms

- faster onset of analgesic action
- faster C_{max} and good efficacy
- short time of action
- low risk of side effects
- used as a rescue drug in breakthrough pain

- effervescent forms preferred in patients:

- age over 65 years,
- with dysphagia (22% population over 50 years)
- difficulties in swallowing (62% population including children)
- over 58% open capsules and break tablets

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Pharmaceutical formulations
transdermal therapeutic system (patch)

- molecular weight < 1000 daltons
- high lipophilicity (Log P 1-4)
- analgesic efficacy 30-100-fold higher than morphine
- low daily dose < 4 mg/24 h
- low melting point < 200^{0}C
- short half-life time $T_{1/2}$ < 10 h

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Transdermal patches

- constant dose of an opioid
- untolerable morphine's side effects (constipation)
- difficulties in swallowing
- renal impairment
- irregular intake of analgesics

Benefits:

- lack of first-pass effect
- no effect on the gastrointestinal tract
- convenient way of administration
- acceptance of the patient and family

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Patient-controlled analgesia (PCA)

- Small doses of an opioid
- Delivery device
- Settings: loading dose, lockout interval, limit over time
- Possible continous background infusion

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Strategies recommended

- Decrease the dose of opioid
- Change the route of administration
- Symptomatic treatment
- Switching to an alternative opioid

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Symptomatic treatment

Drugs compatible with morphine or tramadol	Indications
Metoclopramide 30-60 mg daily	vomiting
Haloperidol 1.5-15 mg daily	vomiting, hallucinations
Levomepromazine 12.5-50 mg daily	vomiting, hallucinations
Buscolisyn 40-100 mg daily	visceral pain colic, ineffective coughing
Midazolame 5-20 mg daily	painful skeletal muscle spasms, anxiety
Somatostatine	persistent symptoms of intestinal obstruction
Lactulose Docusate sodium, senna leaves	constipation

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Strategies recommended

- Decrease the dose of opioid
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- Switching to an alternative opioid

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Switching to an alternative opioid

- Different affinity for opioid receptor subtypes
- Different inner activity
- Different lipophilicity
- Additional mechanisms of action e.g. NMDA antagonism
- Metabolites' properties
- Different interactions with other drugs

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Monitoring of patients on opioid therapy

- **Analgesia – every week**
- **Activities of daily living**
- **Adverse events**
- **Aberrant drug-taking behaviors**

- personal history of substance abuse
- family history of substance abuse
- younger age
- personality factors
- family dynamics
- social factors

- **Addiction**
- **Physical dependence**
- **Tolerance**

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Multidisciplinary team needed !!!

physician-pain specialist

pharmacist

specialist in rehabilitation

nurse

physical therapist

mental healthcare provider

specialist in addiction

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…. right to the relief of suffering is one of the fundamental human rights and each patient has the right to expect its completion ….

Declaration of Montréal of 2010: declaration that access to pain management is a fundamental human right

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Thank you

for your attention

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Does chronic pain be the shorter version of acute pain?

N O

58

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Should a therapeutic team always use the same pain assessment scale with the same individual?

Y E S

59

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Should a physician always start treating severe pain with non-steroidal anti-inflammatory drugs, according to WHO analgesic ladder?

N O

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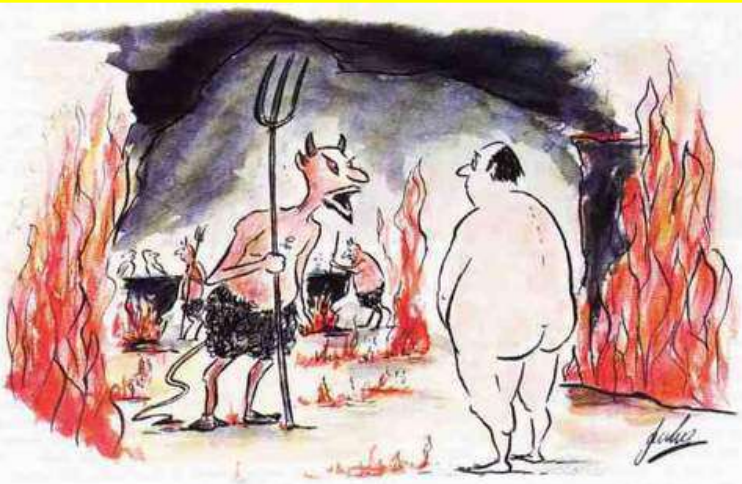

For that you did not use WHO ladder properly!

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