Individualised therapy with the use of analgesic drugs

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Conflict of interest:
nothing to disclose
Question 1

Does chronic pain be the shorter version of acute pain?

Question 2

Should a therapeutic team always use the same pain assessment scale with the same individual?
Question 3

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

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
Pain

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

What are the basic types of pain?
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

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)
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

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
Acute pain - treatment goals

- Early intervention, with prompt adjustments in the regimen for inadequately controlled pain
- Reduction of pain to acceptable levels
- Facilitation of recovery 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

CHRONIC PAIN MAKES
FUNCTIONAL AND MORPHOLOGICAL
CHANGES DESTROYING
THE NERVOUS SYSTEM
Acute pain vs Chronic pain

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute pain</th>
<th>Chronic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Generally known</td>
<td>Often unknown</td>
</tr>
<tr>
<td>Duration of pain</td>
<td>Short, well-characterized</td>
<td>Persists after healing, ≥ 3 months</td>
</tr>
<tr>
<td>Treatment approach</td>
<td>Resolution of underlying cause, usually self-limited</td>
<td>Underlying cause and pain disorder; <strong>outcome is often pain control not cure</strong></td>
</tr>
</tbody>
</table>
Pharmacological management of pain

- Comprehensive evaluation of pain factors: intensity, quality, pattern, duration

Pain assessment scales

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

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

Verbal Rating Scale (VRS)

0 – no pain  
1 – very mild pain
2 – mild pain
3 – severe pain
4 – very severe pain
5 – worst possible pain

patient’s activity

no pain  
easily ignored
cannot be ignored
focuses your attention
disturbs in activity except eating, hygienic activities
forced to take medicine and/or lying down
Numeric Rating Scale (NRS)

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

0 or 0%          5 or 50%          10 or 100%
No pain          Moderate pain    Worst possible pain

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
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)

What are the main principles of chronic pain management
Taking into account individual needs of a patient?
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)

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Mild to moderate pain</th>
<th>1-4 NRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>Moderate to severe pain</td>
<td>4-6 NRS</td>
</tr>
<tr>
<td></td>
<td>Weak opioids</td>
<td>+ Non-opioids</td>
</tr>
<tr>
<td></td>
<td>+ Adjuvant analgesics</td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td>Severe pain</td>
<td>&gt; 6 NRS</td>
</tr>
<tr>
<td></td>
<td>Strong opioids</td>
<td>+ Non-opioids</td>
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<td></td>
<td>+ Adjuvant analgesics</td>
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</table>
Non-steroidal anti-inflammatory drugs (NSAIDs) – mechanism and effects

Physiological stimulus

Constitutive COX-1

- TXA2
- PGI2
- PGE2

Physiological functions

Adverse effects of NSAIDs

Inflammatory stimulus

Inducible COX-2

- Proteases
- PG
- other inflammatory mediators

INFLAMMATION

Therapeutic effects of NSAIDs

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
Severe pain requires strong medication

but

in respectively lower doses

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
**Weak opioids**

- Codeine
- Hydrocodeine
- Tramadol

**Strong opioids**

- Morphine
- Fentanyl
- Alfentany
- Methadone
- Oxycodone
- Buprenorphine
- Oxymorphone etc

**Mechanisms of action:**
- Agonists/partial agonists of opioid receptors: mu, 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
Opioids’ side effects

- constipation
- vomiting
- nausea
- urinary retention
- respiratory depression
- pruritus (itchy skin)
- sedation

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

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

Combination pharmacotherapy

additive effect  synergistic effect
Paracetamol 325 mg + Tramadol 37,5 mg

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

**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
**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

**Combination pharmacotherapy – not recommended**

- NSAID + NSAID = increase in side effects
- paracetamol + codeine = decrease in paracetamol absorption in small intestine
- weak opioid + strong opioid = “ceiling effect” of weak opioids
- nefopam + tramadol = increase in risk of serotonin syndrome
Strategies recommended

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

Pharmaceutical formulations

- nasal spray, sublingual tablets, buccal tablets, effervescent forms

  - faster onset of analgesic action
  - faster $C_{\text{max}}$ 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
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°C
- short half-life time $T_{1/2} < 10$ h

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
Patient-controlled analgesia (PCA)

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

Strategies recommended

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

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

Strategies recommended

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

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
Multidisciplinary team needed !!!

physician-pain specialist  pharmacist

specialist in rehabilitation

nurse

physical therapist

mental healthcare provider  specialist in addiction

.... 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
Thank you for your attention

Question 1

Does chronic pain be the shorter version of acute pain?

NO
Question 2

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

YES

Question 3

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

NO
For that you did not use WHO ladder properly!