PAIN EDUCATION
Module 2:
Multimodal management of chronic pain
Learning objectives

Upon completion of this training module you should have gained an increased understanding of:

- The multifactorial nature of chronic pain
- The importance of effective and early treatment of chronic pain
- The importance of a comprehensive approach to chronic pain management
- Non-pharmacological treatment
- Risks and benefits of different pharmacological options for pain treatment
- Factors influencing the success of pharmacological treatment

For additional information and further educational content related to the multimodal management of chronic pain, please see Module 2 of the CME-accredited e-learning PAIN EDUCATION modules, available at www.pain-cme.net
Comprehensive pain assessment and effective communication

- Foundations of effective pain management are:
  - Good communication between physician and patient
  - Understanding of the patient’s situation, and individualizing treatment goals
  - Multidimensional assessment of chronic pain
  - Evaluation of the impact of chronic pain on patient function, well-being, and quality of life

- Create treatment plans based on:
  - An understanding of the patient’s pain characteristics
  - An appreciation of underlying pain pathology and mechanisms
  - Patient-physician treatment goals
Acute and chronic pain

Pain persistence

Acute pain
- Signals tissue damage
- Serves a protective function
- Signals increased nervous system activity
- Resolves upon healing

Chronic pain
- No longer serves a useful purpose
- Persists beyond the expected period of healing
- Secondary to physiological changes in pain signaling and detection
- Degrades health and function

Cancer pain
Non-cancer pain

References
Physical and psychological burden of severe pain

Patients with chronic pain have one of the lowest observed health-related quality of life ratings of any medical condition, and place a heavy burden on health services.

- Chronic pain affects the quality of working and social life
  - Reduced mobility
  - Sleep disturbances
  - Appetite disturbances
  - Anxiety and depression
  - Absenteeism from work

Cross-sectional European survey > 600 participants
Increased severity of pain significantly reduced quality of life

Mean EQ-5D health state value

- Mild: 0.67
- Moderate: 0.46
- Severe: 0.16

References
Nociceptive and neuropathic pain components

Accurate diagnosis of neuropathic pain is a milestone in choosing appropriate therapy.

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 1,131</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mainly nociceptive</td>
<td>58</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>Mainly neuropathic</td>
<td>16</td>
<td>34</td>
<td>52</td>
</tr>
<tr>
<td>Unknown</td>
<td>27</td>
<td>30</td>
<td>25</td>
</tr>
</tbody>
</table>

References
Goals of chronic pain treatment

- The goals of chronic pain management differ from those of acute pain management
- Goals of chronic pain treatment include achieving a reduction in pain and changing in the patient’s pain experience

Patient and physician partnership → Reduction of pain and a combination of coping strategies → Individualized therapeutic aims and goals of reverting/preventing pain chronification → Improved QoL and function

References
Importance of early and effective pain treatment

- Chronic pain may lead to intractable chronic pain states if not efficiently treated
- Chronic pain is associated with brain atrophy
  - 5–11% reduction in grey matter volume in chronic back pain patients vs control subjects
- A failure to treat chronic pain effectively at an early stage can result in the development of pain that is more difficult to treat

It is important in the clinical management of pain to identify, early on, factors that may lead to unsuccessful treatments and negative outcomes.

References
Multimodal treatment strategies for chronic pain patients

The aim of multimodal therapy is to help patients improve functionality and to promote patient responsibility for managing disease.

References
Pharmacological elements

Pharmacotherapy

Prostaglandin synthesis inhibitors
- NSAIDs
- Paracetamol

Opioid analgesics
- Morphine
- Oxycodone
- Codeine
- Tramadol

Ion channel blockers
- Lidocaine

Reuptake inhibitors
- SSRIs
- SNRIs

Pharmacological therapy should be seen as part of an integrated plan to:
- Improve physical and social functions
- Support a rehabilitative approach
- The choice should be based upon an analysis of the underlying pain mechanisms

References
Action sites of analgesics

- Pain is mediated through peripheral and central mechanisms
  - Stimulation of peripheral nociceptors leads to transmission of pain signals to the brain via dorsal horn synapses in the spinal cord

- Analgesic agents can affect transmission, processing and perception of pain by
  - Normalizing ascending amplification
  - Supporting descending inhibition
  - Changing cognitive processing of pain signals
Analgesia and the pain pathway

- Pain development can be influenced by prostaglandin synthesis inhibitors
- Pain signalling and perception may be influenced by
  - Drugs affecting the opioidergic system such as opioids, ion channel blockers, and neurotransmitter reuptake inhibitors

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Anti-depressants</th>
<th>Anti-convulsants</th>
<th>Non-opioid analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>Amitriptyline</td>
<td>Gabapentin</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Codeine</td>
<td></td>
<td>Pregabalin</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
<td>metamizole</td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The use of two or more agents with differing mechanisms or multiple modes of action increases the likelihood that pain signals will be interrupted and pain is relieved

References
Non-opioid analgesics

- Inhibition of the COX enzyme results in inhibition of prostaglandin synthesis
- COX inhibitors
  - Non-acidic: paracetamol, metamizole
  - Acidic (NSAIDs): ibuprofen, diclofenac
- Non-selective NSAIDs act on COX-1 and COX-2
- NSAIDs only act on nociceptive pain and are not effective in chronic neuropathic pain
- Side effects of NSAIDs can include
  - Gastrointestinal problems
  - Cardiovascular effects, including myocardial infarction and stroke
  - Allergic reactions
  - Cholestatic hepatitis
  - Leukocytopenia and aplastic anaemia

NSAIDs must be used with caution in older patients with impaired renal function and heart failure

References
Non-opioid analgesics in chronic pain

An analysis of pain medication-use in Europe revealed that

- 96% of chronic pain patients were treated with analgesics not acting on the opioidergic system
- NSAIDs were the class of agent most frequently used
  - 76% of chronic pain patients received NSAIDs as part of chronic pain treatment
- In 70% of the cases, therapy had to be changed because of inadequate pain control

NSAIDs are not suited for long-term therapy for chronic pain because of their mode of action and the potential for serious side effects. The EMEA recommends that the lowest effective dosage and short-term use of NSAIDs is to be preferred.

References
**Other non-opioid analgesics**

- **Paracetamol**
  - Aniline derivative
  - Widely used as an analgesic and antipyretic
  - No significant anti-inflammatory effects

  **Side effects**
  Paracetamol is associated with risk of toxic liver damage at high doses

- **Metamizole**
  - Inhibitor of central prostaglandin synthesis
  - Analgesic, antipyretic, anti-inflammatory, and antispasmodic effects

  **Side effects**
  Metamizole is associated with risks such as allergic agranulocytosis

**References**
### Opioid analgesics

<table>
<thead>
<tr>
<th>Weak opioids</th>
<th>Opioids</th>
<th>Strong opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not have a narcotic, or controlled-drug status</td>
<td>Mainly effective in managing nociceptive pain</td>
<td>Have a controlled-drug status</td>
</tr>
<tr>
<td>Are often used in the management of musculo-skeletal and visceral pain</td>
<td>Partially effective in relieving neuropathic pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mainstay analgesic for control of post-operative pain and pain associated with cancer</td>
<td></td>
</tr>
</tbody>
</table>

The use of opioid-based analgesia should only be part of an overall plan for management of chronic non-cancer pain

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**References**

Opioids – natural ligands

Natural ligands for the opioid receptors are found in
- CNS
  - Limbic system
  - Thalamus
  - Hypothalamus
  - Striatum
- The spinal cord
  - Formatio reticularis
  - Substantia gelatinosa
- Peripherally

Natural ligands include neuropeptides such as enkephalins, endorphins, and dynorphins.

- Opioid receptors can be of μ, κ or δ subtype
- Opioid drugs act mainly via μ receptors
Opioids – mechanism of action

- At presynaptic level, opioid binding leads to
  - Reduced intracellular cAMP concentrations
  - Decreased calcium ion influx
  - Consequent inhibition of the release of excitatory neurotransmitters

- At post-synaptic level, opioid binding leads to
  - Hyperpolarization of the neuronal membrane
  - Decreased probability of action potential generation

Opioids reduce pain signal transmission, activate descending inhibitory pathways and affect central pain processing

References
Ananthan S. AAPS J, 2006;8:E118-25.
Opioid-induced side effects

Common side effects of opioids:
- Nausea, vomiting
- Constipation
- Increased risk of respiratory depression
- Sedative/hypnotic effects
- Hypotension (orthostatic dysregulation)
- Decreased heart rate
- Cholestasis and micturition disorders
- Urticaria
- Pruritus
- Bronchospasms in asthmatic patients
- Abnormal sensitivity to pain (hyperalgesia, allodynia)

References
Reuptake inhibitors – tricyclic antidepressants (TCA)

Tricyclic antidepressants:
- Inhibit neuronal uptake of noradrenaline and serotonin (5-HT)
- Are effective in managing chronic pain conditions including
  - Neuropathic pain
  - Complex regional pain syndrome
  - Tension headache
- Are not related to antidepressants in terms of their analgesic effects
- Take 3–7 days for their analgesic effect to be seen

References
Main TCA side effects

- Anticholinergic effects
  - Dry mouth and nose
  - Disturbed vision
  - Constipation
  - Urinary retention
- Cardiovascular effects
  - Orthostatic hypotension
  - Palpitations
  - Tachycardia
  - Disturbed conduction
- Weight gain

- CNS effects
  - Dizziness
  - Sedation
  - Insomnia
  - Tremor
  - Convulsions
  - Change in appetite
- Impaired liver function
- Sexual dysfunction
- Anaphylactic reactions
- Drug-drug interactions

References
Selective serotonin and noradrenaline reuptake inhibitors

SNRIs

- Are not associated with side effects linked with inhibition of adrenergic, cholinergic, or histaminergic systems
- May be better tolerated than TCAs
- Have moderate efficacy in pain management
- Have an analgesic effect mainly due to noradrenaline reuptake inhibition
- Are more effective in management of pain than SSRIs, because 5-HT has both inhibitory and facilitatory effects, and may thereby enhance pain

Side effects

- Nausea
- Vomiting
- Constipation
- Somnolence
- Dry mouth
- Increased sweating
- Loss of appetite
- Weakness

References
Anticonvulsants

- Effective in neuropathic pain and recommended as first-line analgesic in neuropathic pain conditions
- Binds to a subunit of presynaptic voltage-dependent calcium channels
- Needs slow individual titration

Gabapentin

- Used and recommended for first-line treatment in neuropathic pain conditions
- Provides its analgesic effect by interacting with N-type calcium channels
- Does not undergo hepatic metabolism
- Has a low risk of drug-drug interaction

Pregabalin

- Blocks calcium and sodium channels
- Is indicated for neuropathic pain conditions
- Is a liver enzyme inducer
- May be associated with drug-drug interactions

Carbamazepine

Side effects
- Sedation
- Dizziness
- Ataxia
- Peripheral oedema
- Nausea
- Weight increase

Side effects
- Dizziness
- Fatigue
- Nausea
- Vomiting

Side effects
- Arrhythmia
- Double vision
- Pruritus
- Changes in blood parameters

References
## Topical analgesics

<table>
<thead>
<tr>
<th>Rubefacients</th>
<th>NSAIDs</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Traditional formulations based on salicylate and nicotinate esters, capsaicin and capsicum extracts and derivatives</td>
<td>• Diclofenac</td>
<td>• Benzydamine</td>
</tr>
<tr>
<td></td>
<td>• Felbinac</td>
<td>• Mucopolysaccharide polysulphate</td>
</tr>
<tr>
<td></td>
<td>• Ibuprofen</td>
<td>• Salicylamide</td>
</tr>
<tr>
<td></td>
<td>• Ketoprofen</td>
<td>• Cooling sprays</td>
</tr>
<tr>
<td></td>
<td>• Piroxicam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Naproxen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Flurbiprofen</td>
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</tr>
</tbody>
</table>
Lidocaine 5% medicated plaster

Mechanism of action

<table>
<thead>
<tr>
<th>Mechanical protective component</th>
<th>Pharmacological component</th>
</tr>
</thead>
</table>
| • Soft plaster: barrier against skin rubbing, which provokes pain and alldynia  
  • Immediate cooling and soothing effect | • Lidocaine diffuses into the skin and blocks over-excitable Na\(^+\)-channels on damaged nociceptors  
  • Stabilisation of neuronal membrane potential of A- and C-fibres, resulting in a reduction of ectopic activity  
  • At the long-term, reduction of peripheral input may counteract central sensitization |

- Analgesia without anaesthetic effect (numbness)
- Acts locally directly at the area of pain
- Is indicated for neuropathic pain following a herpes zoster infection (post-zoster neuralgia)

References
## Other treatment options

<table>
<thead>
<tr>
<th>Capsaicin plaster</th>
<th>Ralfinamide</th>
<th>Lacosamide</th>
<th>Tapentadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Overstimulates TRPV1 channels</td>
<td>• Is a novel sodium channel blocker</td>
<td>• Is an antiepileptic drug and an ion channel blocker</td>
<td>• Is a centrally acting analgesic, combining 2 mechanisms of action</td>
</tr>
<tr>
<td>• Inhibits initiation of pain transmission in the spinal cord</td>
<td>• Is under investigation as a potential treatment for neuropathic pain</td>
<td>• Is under investigation as a potential treatment for neuropathic pain</td>
<td>• μ-opioid receptor agonism (MOR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Noradrenaline reuptake inhibition (NRI)</td>
</tr>
<tr>
<td></td>
<td>• Is a centrally acting analgesic, combining 2 mechanisms of action</td>
<td></td>
<td>• Hence, belongs to a new class called “MOR-NRI”</td>
</tr>
</tbody>
</table>

### References
Limitations of pharmacological pain management

- Drug treatment of severe chronic pain is often ineffective
  - Balancing analgesic efficacy and drug tolerability
  - Especially difficult if neuropathic component is present
- Dose titration may improve efficacy and tolerability
  - Depending on patient-related factors such as underlying causes of pain, comorbidities, psychological state and drug responsiveness

A clear understanding of possible factors involved in poor treatments and treatment discontinuations is important to optimize pharmacological treatment and outcome for the individual patient

Reference
The Vicious Circle: poor analgesia

Pharmacological treatment

Poor analgesia

Reason:
• Wrong substance / wrong dose?
• Wrong diagnosis of pain type or components?
• Others?

Side effects

Adequate analgesia

Dose reduction

Poor efficacy + Good tolerability

Dose increase

Good efficacy + Poor tolerability

Patient struggles but stays / Patient drops out opioid rotation

• Low quality of life
• Inefficient pain management and higher costs in health care system

References
The Vicious Circle: side effects

Pharmacological treatment

- Poor analgesia
- Side effects
- Adequate analgesia

Reason:
- Low tolerability?
- Interaction?
- Polymedication?

Dose reduction
- Poor efficacy + Good tolerability
- Good efficacy + Poor tolerability
Dose increase

Patient struggles but stays / Patient drops out opioid rotation
- Low quality of life
- Inefficient pain management and higher costs in health care system

References
The Vicious Circle: adequate analgesia

Pharmacological treatment

- Poor analgesia
- Side effects
  - Dose reduction
  - Poor efficacy + Good tolerability
  - Dose increase
  - Good efficacy + Poor tolerability
- Adequate analgesia
  - Still good treatment
  - Analgesic tolerance
  - Poor analgesia

Patient struggles but stays / Patient drops out opioid rotation
- Low quality of life
- Inefficient pain management and higher costs in health care system

References
Treatment discontinuation

Two studies on clinical trials investigating WHO step II and III opioids
- One in 5 patients discontinued due to adverse events
- 6.5–10% discontinued due to lack of efficacy

References
Summary

- Early and effective pain treatment is important
- Treatment decisions should be based on underlying mechanisms and not only based on pain intensity
- A multimodal approach is needed for managing chronic pain which is a multifactorial condition
- Pharmacological therapy is a mainstay in the treatment of chronic pain
- Influencing factors for pharmacological treatment success need to be carefully considered
- Increasing awareness of the Vicious Circle among the medical community could reduce treatment discontinuation
- A referral to a multidisciplinary pain team should be considered