Basics of Pain Management and Special Considerations for HIV-infected Individuals

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Learning Goals

• Differentiate between types of pain.
• Describe the mechanisms of action of various classes of medications used to treat pain.
• Develop a pain management strategy for an HIV-infected individual.
Pain

• It is estimated that >100 million persons in the United States live with chronic pain.
  – 56%-83% of individuals with AIDS have unrelieved or inadequately relieved pain

• Chronic pain results in
  – >550 million missed work days
  – >$50 billion in health care cost

Nagda J and Bajwa ZH. In: Principles and Practice of Pain Medicine
Classification of Pain

• Classification of pain
  – Neurophysiologic mechanisms
  – Temporal aspects
  – Etiology
  – Region of the body affected
Neurophysiologic Classification

• Nociceptive
  – Pain caused by tissue injury.
  – Subdivided into somatic and visceral pain.

• Non-nociceptive
  – Results from injury to neural structures within the peripheral or central nervous system.
Nociceptive Pain

- Results from the activation or sensitization of nociceptors in the periphery.
- Impulses are transmitted to the spinal cord by peripheral neurons.
- Processed in the CNS.
Physiology of Nociceptive Pain

Transduction
• Stimulation of nociceptors causes release/activation of cytokines and chemokines.

Conduction
• Generation of action potentials that are conducted along nerve fibers.
Physiology of Nociceptive Pain

**Transduction**
- Stimulation of nociceptors causes release/activation of cytokines and chemokines.

**Conduction**
- Generation of action potentials that are conducted along nerve fibers.

**Transmission**
- Pain fibers stimulate the release of excitatory transmitters like glutamate and substance P in dorsal horn.

**Perception**
- Pain is a conscious experience.
Physiology of Nociceptive Pain

• Modulation
  – The signal can also be attenuated/inhibited by descending pathways that consist of endogenous opioids (e.g., enkephalins, and β-endorphins) γ-aminobutyric acid (GABA), norepinephrine, or serotonin.
  – Blockade of N-methyl-D-aspartate (NMDA) receptors may increase the μ-receptors’ responsiveness to opiates.
## Nociceptive Pain

### Somatic pain
- Stimulation of nociceptors in the periphery.
- Characterized as being well localized topographically, intermittent or constant, and is described as “aching, stabbing, gnawing, or throbbing.”

### Visceral Pain
- Diffuse and poorly localized.
- Referred pain
- Accompanied by motor and autonomic reflexes, such as the nausea, vomiting, and lower back muscle tension.
Non-nociceptive Pain

- **Neuropathic pain**
  - Three subsets: peripherally generated, centrally generated, and sympathetically maintained.
  - Sustained by aberrant somatosensory processing in the periphery or central nervous system.
  - Described as sharp or burning.

- **Idiopathic pain**
## Temporal Classification

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic (Pathophysiologic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Maybe directly related to tissue damage or trauma.</td>
<td>• Considered a disease state.</td>
</tr>
<tr>
<td>• Self-liming.</td>
<td>• Outlasts the normal time of healing.</td>
</tr>
<tr>
<td>• Serves a useful biologic purpose.</td>
<td>• May arise from psychological states.</td>
</tr>
<tr>
<td>• Less than 3-6 months in duration.</td>
<td>• Lasts at least 6 months and has no recognizable end-point.</td>
</tr>
<tr>
<td></td>
<td>• Serves no biologic purpose.</td>
</tr>
</tbody>
</table>
Assessment of Pain

• When did the pain begin?
• Did something trigger the pain?
• Describe the pain.
• What makes the pain better or worse?
• How does this pain compare with other pain you have experienced?
• Does the intensity of the pain change with time?
Assessment of Pain

PAIN ASSESSMENT TOOL

0 1 2 3 4 5 6 7 8 9 10

- No Pain
- Mild
- Moderate
- Severe
- Very Severe
- Worst Pain Possible

0 1-3 4-6 7-9 10
Pain in HIV-Infected Individuals

• Multifactorial
• May result from:
  – Direct action of the virus on the nervous system
  – Immune suppression
  – Opportunistic infections
  – Side effects of anti-retrovirals
    • NRTIs: stavidine > didanosine or zalcitabine
  – Causes not related to HIV

Management of Pain

• Nonpharmacologic therapies should always be considered first-line for acute or chronic pain.
  – Physical manipulation, heat or cold, massage, biofeedback, cognitive behavioral therapy, relaxation, acupuncture, or relaxation.
WHO Pain Management Ladder

**Step 1 (Pain score 1-4)**
- Non-opioid + Adjuvant

**Step 2 (Pain score 5-7)**
- Opioid for moderate pain + Non-opioid ± Adjuvant
- Opioids: Codeine, hydrocodone, or oxycodone in combination with NSAID or acetaminophen or tramadol

**Step 3 (Pain score 8-10)**
- Opioid for moderate to severe pain + Non-opioid ± Adjuvant
- Opioids: Morphine, hydromorphone, oxycodone, levorphanol, methadone, or fentanyl

**Non-opioid:** NSAID or acetaminophen

**Adjuvants:** Antidepressants, antiepileptics, topicals, muscle relaxants
Non-Opioid Agents

• Acetaminophen
  
  Mechanism: Believed to inhibit prostaglandin by inhibiting cyclooxygenase (COX) synthesis in the CNS and block peripheral nerve impulse.
  
  – Does not have anti-inflammatory properties.
  – Does not inhibit platelet aggregation.
  
  Dose: 650mg every 4-6 hours (maximum daily dose 3,250 mg)
  
  Drug interactions: Minimal
  
  ADR: Primary concern is hepatotoxicity
Non-Opioid Agents

• Nonsteroidal Anti-inflammatory Drugs
  Mechanism: Act by decreasing central and peripheral production of prostaglandins by inhibiting cyclooxygenase (COX).
  – Reduces pain, swelling, and edema.
  More than 20 available agents
  – Use ketorolac with caution (Risk of bleeding and renal injury)
  – Trial of at least 1 month. May try a different agent.
  Drug interactions: Interaction with metabolic pathways varied among agents.
  – Typically because of anti-platelet effects and fluid retention
## Metabolism of NSAIDs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Substrate</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celocoxib</td>
<td>CYP2C9, CYP3A4</td>
<td>CYP2D6, CYP2C8</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>CYP3A4</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>CYP2C9, CYP2C19</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>CYP2C9, CYP2C19</td>
<td>CYP2C9, CYP2C19</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>CYP2C9, CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>CYP1A2, CYP2C9</td>
<td></td>
</tr>
</tbody>
</table>

Overall the risk if metabolic interaction is relatively low.

Non-Opioid Agents

• Nonsteroidal Anti-inflammatory Drugs
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  – Trial of at least 1 month. May try a different agent.

Drug interactions: Interaction with metabolic pathways varied among agents.
  – Typically because of anti-platelet effects and fluid retention

ADR: GI bleed (lower with ibuprofen), renal failure, fluid retention, GI
Risk of GI Bleed with NSAIDs


400mg every 6 hours = 1,600mg daily
Nephrotoxicity with NSAIDs

• Normally the afferent arteriole is dilated because of prostaglandins.
• Inhibition of prostaglandin synthesis by NSAIDs reduces blood flow to the glomerulus leading to decreased pressure and GFR.
Non-Opioid Agents

Nonsteroidal Anti-inflammatory Drugs

• Pain relief is slightly improved (10%) by doubling dose.
  – Have a ceiling effect for pain (ibuprofen 400 mg)
  – Higher doses may improve anti-inflammatory effect.

• Start with a low dose and escalate to effect.

• Higher doses may increase the rate of side effects.

In 2014, 245 million prescriptions for opioids were filled in the United States.

- 3%-4% of the adult population in on long-term opioid therapy.
- 37% of drug-overdose deaths were attributable to prescription opioids.

Prescription Opioids in Michigan

Source: MDHHS 2016
Prescription Opioids in Michigan

Rate per 10,000 population

Source: MDHHS 2016
Prescription Opioids in Michigan

- Counties with the highest prescribing rates:

<table>
<thead>
<tr>
<th>County</th>
<th>Rate per 10,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bay</td>
<td>19,365</td>
</tr>
<tr>
<td>Iosco</td>
<td>17,975</td>
</tr>
<tr>
<td>Roscommon</td>
<td>17,617</td>
</tr>
<tr>
<td>Montmorency</td>
<td>17,495</td>
</tr>
<tr>
<td>Oscoda</td>
<td>16,917</td>
</tr>
<tr>
<td>Lake</td>
<td>16,778</td>
</tr>
<tr>
<td>Ogemaw</td>
<td>16,705</td>
</tr>
<tr>
<td>Arenac</td>
<td>16,498</td>
</tr>
<tr>
<td>Crawford</td>
<td>16,352</td>
</tr>
<tr>
<td>Gladwin</td>
<td>16,122</td>
</tr>
</tbody>
</table>
Prescription Opioids in Michigan

- Counties with the highest prescribing volumes

<table>
<thead>
<tr>
<th>County</th>
<th>Number of Prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wayne</td>
<td>2,283,994</td>
</tr>
<tr>
<td>Oakland</td>
<td>1,126,356</td>
</tr>
<tr>
<td>Macomb</td>
<td>1,026,084</td>
</tr>
<tr>
<td>Genesee</td>
<td>608,868</td>
</tr>
<tr>
<td>Kent</td>
<td>563,320</td>
</tr>
<tr>
<td>Ingham</td>
<td>273,653</td>
</tr>
<tr>
<td>Muskegon</td>
<td>260,949</td>
</tr>
<tr>
<td>Kalamazoo</td>
<td>248,810</td>
</tr>
<tr>
<td>Saginaw</td>
<td>248,314</td>
</tr>
<tr>
<td>Washtenaw</td>
<td>243,936</td>
</tr>
</tbody>
</table>
Opioids

• Act by stimulating μ-opioid receptors in the brain.
  – Modulates calcium and potassium ion channels to inhibit neuronal activity.
  – Accounts for analgesia, euphoria, and respiratory depression.
Opioids

• Repeated administration will result in tolerance and physical dependence.
  – Tolerance to analgesic effect and euphoric effects develops quickly.
  – Tolerance to respiratory depression occurs slowly.
  – No tolerance develops to constipation.
  – Physical dependence is not addiction.
    • Physiological adaptation.
    • Abrupt discontinuation results in withdrawal symptoms.
Opioids

• Addiction
  – Occurs slowly.
  – Risk factors
    • Higher doses (>100 morphine milligram equivalents)
    • Long-term use (>3 months)
    • Depression
    • Substance-use disorder (including alcohol)
    • Adolescence

Morphine Milligram Equivalents

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Conversion Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Fentanyl transdermal</td>
<td>2.4</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>4</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>4</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>0.4</td>
</tr>
</tbody>
</table>

WHO Pain Management Ladder

Step 1 (Pain score 1-4)
- Non-opioid + Adjuvant

Step 2 (Pain score 5-7)
- Opioid for moderate pain
  - + Non-opioid
  - + Adjuvant

Opioids: Codeine, hydrocodone, or oxycodone in combination with NSAID or acetaminophen or tramadol

Step 3 (Pain score 8-10)
- Opioid for moderate to severe pain
  - + Non-opioid
  - + Adjuvant

Opioids: Morphine, hydromorphone, oxycodone, levorphanol, methadone, or fentanyl

Non-opioid: NSAID or acetaminophen

Adjuvants: Antidepressants, antiepileptics, topicals, muscle relaxants
Opioid Use Guidelines

• Nonpharmacologic and nonopioid therapies are recommended for chronic pain.
• Before starting opioids, establish goals for pain and function with patients.
• Discuss risks and realistic benefits of opioids.
• Start with immediate-release opioids.

# Opioid Onset of Action

<table>
<thead>
<tr>
<th>Opioid (Generic)</th>
<th>Other Names</th>
<th>Onset of Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>With acetaminophen: Tylenol with codeine</td>
<td>45-60 min</td>
</tr>
<tr>
<td>Fentanyl transdermal</td>
<td>Duragesic</td>
<td>6 hours</td>
</tr>
</tbody>
</table>
| Hydrocodone      | With acetaminophen: Norco, Vicodin  
                  | With ibuprofen: Vicoprofen | 45-60 min |
| Hydromorphone    | Dilaudid    | 30 min |
| Morphine IR      |             | 30-45 min |
| Oxycodone        | With acetaminophen: Percocet | 45-60 min |
| Oxymorphone      | Opana       | 20-40 min |
| Tapentadol       | Nucynta     | 30-45 min |
### Opioid Drug Interactions

<table>
<thead>
<tr>
<th>Opioid (Generic)</th>
<th>Phase I Metabolism</th>
<th>Clinical Relevance</th>
<th>Interacting Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>CYP2D6, CYP3A4</td>
<td>Decreased analgesic effect when administered with CYP2D6 inhibitors</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>CYP3A4</td>
<td>Increased opioid effects when administered with CYP3A4 inhibitors (Black Box Warning)</td>
<td>Protease Inhibitors Azole Antifungals</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>CYP2D6, CYP3A4</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>CYP3A4, CYP2B6, CYP2D6</td>
<td>High (complex)</td>
<td>Protease Inhibitors Azole Antifungals</td>
</tr>
<tr>
<td>Morphine</td>
<td>CYP3A4</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>CYP2D6, CYP3A4</td>
<td>Increased opioid effects when administered with CYP3A4 inhibitors (Black Box Warning)</td>
<td>Protease Inhibitors Azole Antifungals</td>
</tr>
<tr>
<td>Tramadol</td>
<td>CYP2D6, CYP3A4</td>
<td>Moderate</td>
<td>Protease Inhibitors Azole Antifungals</td>
</tr>
</tbody>
</table>
Opioid Use Guidelines

• Start with low doses and escalate.
  – Reassess doses of >50 MME per day.
  – Dose around the clock as long as responsive stimulus is present.

• For acute pain, prescribe no greater quantity than needed for the expected duration of pain.
  – Three days or less is usually enough.

• Consider prescribing naloxone.
  – History of overdose, substance abuse, >50 MME/day, or concurrent benzodiazepine use.

Opioid Use Guidelines

- Review patient’s use of controlled substances when starting opioids and during use.
- Use urine drug testing to verify use.
- Avoid benzodiazepines.

Opioid Use in HIV-Infected Individuals

• High potential for addiction.
  – Alcohol and intravenous drug use
• Treat underlying psychosocial conditions
• Watch our for drug-drug interactions.
  – Many opioids are metabolized by CYP2D6 and CYP3A4
  – Several interact with various protease inhibitors
Summary

• Not all pain is the same.
• Opioids are typically not first line for pain.
• HIV-infected individuals maybe at risk of overdose and drug-drug interactions with opioids.