Acute Pain Management in the Hospital Setting

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What is Pain?

- “An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”
- “Whatever the patient says it is”
Epidemiology

• ~25 million experience acute pain from injury or surgery/year
• ~80% of patients experience post-operative pain
  ▫ <50% report adequate pain relief
  ▫ 10-50% will develop chronic pain
  ▫ 2-10% have severe chronic pain
• Pain is the most common symptom experienced by patients in the hospital
Significance

Inadequate acute pain treatment

- Chronic pain
- Prolonged rehabilitation
- Reduction in quality of life
- Negative social/psychological effects

Appropriate pain management

- Reduction in hospital length of stay and costs
- Increase patient satisfaction
Patient Case: Maria, 65 yo F

- **CC:**
  - Increasing abdominal pain
- **PMH:**
  - Stage 3 colon cancer, CKD Stage 3, seizure hx
- **Drug allergies:**
  - Morphine
- **Home pain regimen:**
  - Oxycodone/acetaminophen 10-325 mg q6h
- **Inpatient pain regimen:** Pain score 7/10
  - Oxycodone/acetaminophen 10-325 mg q6h
  - Acetaminophen 650 mg PO q4h prn mild pain (x0 doses)
  - Morphine 2 mg IV q4h prn mod-severe pain (x6 doses)
Types of Pain

- Acute vs. chronic
- Musculoskeletal
- Nociceptive
  - Somatic
  - Visceral
- Neuropathic
- Inflamatory
Pathophysiology

- Stimulation
- Transmission
- Modulation
- Perception
## Tolerance, Physical Dependence, Addiction, Pseudoaddiction

<table>
<thead>
<tr>
<th>Tolerance</th>
<th>Diminishing of drug effect over time as a consequence of exposure to the drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical dependence</td>
<td>The occurrence of an abstinence syndrome following administration of an antagonist drug or abrupt dose reduction or discontinuation</td>
</tr>
<tr>
<td>Addiction</td>
<td>A behavioral pattern characterized by loss of control over drug use, compulsive drug use, and continued use of a drug despite harm</td>
</tr>
<tr>
<td>Pseudoaddiction</td>
<td>Behavior that may suggest addiction, but is actually a reflection of unrelieved pain</td>
</tr>
</tbody>
</table>
Multimodal Approach

Patient Education (realistic goals)

Psychological (behavioral, counseling)

Pharmacological Treatment (NSAIDs, opioids, adjuvants)

Interventional Therapy (surgical)

Physical Therapy
WHO 3-Step Pain Ladder

- **Moderate-Severe**
  - Strong
  - Opioid/Nonopioid ± Adjuvants

- **Mild-Moderate**
  - Weak Opioid/Nonopioid ± Adjuvants

- **Mild**
  - Nonopioid ± Adjuvants

- **Nonopioid analgesics:**
  - Acetaminophen
  - NSAIDs
  - Aspirin
  - Salicylates

- **Weak opioids:**
  - Codeine
  - Hydrocodone
  - Tramadol

- **Strong opioids:**
  - Morphine*
  - Hydromorphone*
  - Fentanyl
  - Methadone
  - Oxycodone*

*(can be used for mild-moderate pain at low doses)*
Patient Assessment

- Description of pain
- What relieves the pain?
- What causes or increases pain?
- Effects of pain on physical, emotional, and psychological function
- Patient’s pain and functional goals
## True Allergy vs. Pseudoallergy

### Classifications of Opioids

<table>
<thead>
<tr>
<th>Phenanthrenes</th>
<th>Phenylpiperidine</th>
<th>Phenylheptane</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Morphine</td>
<td>- Meperidine</td>
<td>- Methadone</td>
</tr>
<tr>
<td>- Codeine</td>
<td>- Fentanyl</td>
<td></td>
</tr>
<tr>
<td>- Hydromorphone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oxycodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hydrocodone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Switch to another opioid class (low cross sensitivity)
- Switch to a higher potency opioid
Opioid-Naïve vs. Opioid-Tolerant

- Opioid-tolerant patient: Use of the following for at least 7 days or longer -
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hr
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - An equianalgesic dose of another opioid
Opioid Naïve: Dose Initiation

• Acute, severe pain:
  ▫ **Morphine**
    • 2-5 mg IV q4h PRN
    • Elderly – start low, go slow
  ▫ **Hydromorphone**
    • 0.5-1 mg IV q4h PRN
  ▫ **Oxycodone**
    • 2.5-7.5 mg q4h PRN
Scheduled Regimens

• Chronic pain:
  ▫ Long-acting opioid + short-acting opioid

• Breakthrough pain
  ▫ 10% of total daily dose (24-hr) -> every hr PRN
Incomplete Cross-Tolerance

Mu opioids bind to mu receptors

Many mu receptor subtypes:
- Mu opioids produce subtle differences in pharmacological response based on activation profiles of mu receptor subtypes

Explain:
- Inter-patient variability in response to mu opioids
- Incomplete cross-tolerance among mu opioids
- Importance of calculating % dose reductions when switching opioids
Opioid Rotation

Calculate equianalgesic dose of new opioid

Reduce equianalgesic dose by 25-50%*

*75-90% reduction for methadone

| Current opioid regimen | Current pain control | Elderly/medically frail | Same drug, different route |
# Equianalgesic Opioid Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parenteral (mg)</th>
<th>Oral (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>N/A</td>
<td>20</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>N/A</td>
<td>30</td>
</tr>
<tr>
<td>Codeine</td>
<td>130</td>
<td>200</td>
</tr>
<tr>
<td>Meperidene</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Hepatic Impairment: Opioid Metabolism

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Extraction Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>0.52</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.80-1.0</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.51</td>
</tr>
<tr>
<td>Methadone</td>
<td>&lt;0.30</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.52</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.76</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>0.80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Opioid Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 (Phase 1)</td>
<td>Fentanyl, oxycodone, tramadol</td>
</tr>
<tr>
<td>CYP2D6 (Phase 1)</td>
<td>Codeine, hydrocodone</td>
</tr>
<tr>
<td>Glucuronidation (Phase II)</td>
<td>Hydromorphone, oxymorphone, morphine</td>
</tr>
</tbody>
</table>
## Hepatic Impairment: Recommendations

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Codeine</strong></td>
<td>Not recommended; prodrug, reduced conversion to active metabolite -&gt; poor analgesic effect</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>99% metabolized in liver; careful monitoring</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Use with caution; monitor for overdose due to reduced metabolism of parent compound</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Use with caution; undergoes phase II reaction and intermediate extraction ratio</td>
</tr>
<tr>
<td>Methadone</td>
<td>Use with caution; risk of accumulation due to increased free drug</td>
</tr>
<tr>
<td><strong>Meperidine</strong></td>
<td>Not recommended; toxic metabolite, normeperidine, may accumulate</td>
</tr>
<tr>
<td>Morphine</td>
<td>Use with caution; monitor for overdose due to high extraction ratio</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Use with caution; reduce dose by 25-50%</td>
</tr>
<tr>
<td><strong>Oxymorphone</strong></td>
<td>Contraindicated in moderate-severe hepatic impairment</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
# Renal Impairment: Dosing

## % Dose Reduction

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>Morphine</th>
<th>Hydromorphone</th>
<th>Oxycodone</th>
<th>Methadone</th>
<th>Fentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>N/A</td>
<td>0-50%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>10-50</td>
<td>50-75%</td>
<td>50%</td>
<td>50%</td>
<td>N/A</td>
<td>0-25%</td>
</tr>
<tr>
<td>&lt;10</td>
<td>Not recommended</td>
<td>25%</td>
<td>Not recommended</td>
<td>0-25%</td>
<td>50%</td>
</tr>
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</table>
# Renal Impairment: Recommendations

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<th>Opioid</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Codeine</td>
<td>Not recommended due to accumulation</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Appears safe; adjust dose if needed</td>
</tr>
<tr>
<td>Hydrocodone/oxycodone</td>
<td>Use with caution; adjust dose if needed</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Use with caution; adjust dose if needed</td>
</tr>
<tr>
<td>Methadone</td>
<td>Appears safe; adjust dose if needed</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Not recommended due to metabolites</td>
</tr>
<tr>
<td>Morphine</td>
<td>Not recommended due to metabolites</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
## Management of Adverse Effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritis</td>
<td>• Non-IgE mediated mast cell binding and histamine release</td>
</tr>
<tr>
<td></td>
<td>• Antihistamines, anticholinergics</td>
</tr>
<tr>
<td>N/V</td>
<td>• Stimulation of chemoreceptor trigger zone (CTZ)</td>
</tr>
<tr>
<td></td>
<td>• Antipsychotics, metoclopramide, serotonin antagonists</td>
</tr>
<tr>
<td>Constipation</td>
<td>• Stimulates mu receptors in GI tract causing slowed GI motility</td>
</tr>
<tr>
<td></td>
<td>• Scheduled prophylaxis bowel regimen (doc/senna, PEG, fluids, fiber)</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>• Caution in patients with chronic lung disease (COPD, asthma)</td>
</tr>
<tr>
<td></td>
<td>• Incidence is very low and associated with overdose</td>
</tr>
<tr>
<td>Sedation</td>
<td>• CNS depressants (benzodiazepines, alcohol use)</td>
</tr>
<tr>
<td></td>
<td>• Stimulants (methylphenidate)</td>
</tr>
</tbody>
</table>
Medication Pearls
Acetaminophen

- Analgesic effects only (not anti-inflammatory)
- Maximum dose <4g/day
- Alcohol use increases risk for hepatic toxicity
- Oral – onset <1 hr
- Rectal – slow, unpredictable absorption
- IV – $$$
NSAIDs

- **Use:**
  - Mild-moderate-severe pain, cancer-related bone pain
- **Avoid combining NSAIDs (additive toxicities)**
- **Increase to maximum dose → change if ineffective**
- **Ketorolac:**
  - IV/IM; short term use only (max = 5 days)
- **Add GI prophylaxis:**
  - Assess CVD risk vs. GI bleed risk
- **A/E: renal toxicity**
  - D/c NSAID if BUN or Cr doubles
Adjuvant Analgesics

- **Use**
  - Chronic pain (inflammatory, neuropathic)
- **Anticonvulsants**
  - Decrease neuronal excitability
- **TCAs and SNRIs**
  - Enhance pain inhibition
- **Topical anesthetics**
  - Decrease nerve stimulation
Codeine

- Commonly used combined
  - Mild-mod pain
- FDA BW:
  - Risk of death in CYP450-2D6 rapid metabolizers
- Poor analgesic potency
- A/E:
  - Increased nausea and constipation
- Active metabolite:
  - Morphine
Hydrocodone

- Commonly used in combination
- A/E
  - Nausea, constipation (less than codeine)
- Reduce dose in severe hepatic impairment
- Metabolites accumulate in renal insufficiency
Tramadol

- **MOA**
  - Binds to mu-opioid receptors
  - Inhibits serotonin and norepinephrine reuptake
- **Use**
  - Mod-severe pain
  - Chronic pain, neuropathic pain
- **A/E**
  - N/V
- **Serotonin syndrome and seizure risk - (max 400 mg/day)**
  - Use with other drugs that reduce seizure threshold
  - Hx of seizures
  - Reduce dose in renal impairment and elderly
Morphine

- Gold standard for conversions
- Drug of choice
  - Severe pain, ACS pain (decrease in myocardial oxygen demand)
- Multiple dosage forms
  - PO, IV/IM/SC, Spinal IT, epidural, SL, rectal
- A/E
  - Orthostatic hypotension, pruritis
- Renal impairment
  - M3G metabolite accumulates in renal impairment → neurotoxicity, seizures
- Hepatic impairment
  - Lengthen frequency in administration
Oxycodone

- Useful
  - Moderate-severe pain
  - IR or ER for acute or persistent pain
  - Available in combination
- >potent than morphine
- PO only
Hydromorphone

- Compared to morphine
  - More potent than morphine
  - Better oral absorption
  - Similar pharmacological profile

- Renal impairment
  - Toxic metabolite hydromorphone-3-glucuronide (H₃G)
Oxymorphone

- > potent than morphine, oxycodone
- Available in
  - PO, rectal, IV
- Poor oral bioavailability (~10%)
- Administration
  - Take on empty stomach
- Good option for patients complaining of pruritis reaction from morphine
  - Higher potency and reduced histamine release
Fentanyl

• High potency, short acting
  ▫ 10 mg morphine IV q4h ~ 100 mcg fentanyl IV q1h
• Avoid
  ▫ Opioid naïve patients
• Useful
  ▫ Around the clock pain, bowel obstruction, severe opioid-induced constipation or pruritis
• Available
  ▫ Patch - 72h duration, chronic pain use only
    • 12-24 hrs for full onset, up to 6 days to reach steady state
    • Good alternative for pts on stable regimens
  ▫ IV, IT, SL
Methadone

• Pearls
  ▫ Oral efficacy, extended duration of action, low cost
  ▫ Prolongs QT – risk of torsades de pointes
  ▫ Unpredictable half life, possible excessive sedation, difficulty in titration

• MOA:
  ▫ Mu and Kappa opioid agonist effects
  ▫ NMDA antagonist
  ▫ SNRI

• Useful
  ▫ Neuropathic and chronic pain
  ▫ Poor pain control with opioids
  ▫ Renal dysfunction (no active metabolites)
  ▫ Less constipating

• Available
  ▫ PO, IV, IM, SL
Meperidine

- Neurotoxicity, seizures = Max (300 mg/day IV)
  - Higher risk in elderly or renal impairment – accumulation of toxic metabolite, normeperidine
- Weak analgesic effect ~ 10-fold < potent than morphine
  - Short duration of action - more frequent and higher doses for pain relief
- Not recommended for long term use
Buprenorphine

- Indication: treatment for opioid dependency
Naloxone

- **MOA**
  - Pure opioid antagonist
  - Binds competitively to opioid receptors w/o analgesic effects

- **Use**
  - Opioid reversal agent

- **Dose**
  - 0.04 – 0.4 mg
Patient Case: Maria, 65 yo F

- **CC:**
  - Increasing abdominal pain
- **PMH:**
  - Stage 3 colon cancer, CKD Stage 3, seizure hx
- **Drug allergies:**
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- **Home pain regimen:**
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  - Morphine 2.5 mg PO q4h prn mod-severe pain (x6 doses)
- **Pain score 7/10**
Patient Case: Maria, 65 yo F

- What are some patient-specific considerations?
- What are her preferred treatment options?
- What is your recommendation?
- When to consider a long-acting agent?
Patient Case: Maria, 65 yo F

- **Patient specific factors**
  - Age, hepatic and renal impairment, hx of seizures, morphine allergy, opioid-tolerant
- **Preferred treatment options?**
  - Switching morphine -> hydromorphone
  - Switching to fentanyl
  - Increasing oxycodone-apap dose
- **Not recommended**
  - Meperidine and tramadol (hx of seizures, renal impairment)
- **When to consider a long-acting agent?**
  - If patient has a chronic pain condition
  - Had ~3 or more prn doses for severe pain
Questions?
References


