Management of Chronic, Non-Terminal Pain

Michael A. Smith, PharmD, BCPS
Clinical Assistant Professor, University of Michigan College of Pharmacy
Pain and Palliative Care Clinical Pharmacy Specialist, Michigan Medicine

Disclosures

• No financial disclosures or conflicts of interest to report

Outline

• Objectives
• Review
  – Applicable state laws
  – Osteoarthritis
  – Low back pain
  – Neuropathies
• Cases

Learning Objectives

• Describe the role of opioid, non-opioid, and adjuvant analgesics in the management of chronic, non-terminal pain syndromes
• Recommend specific treatment modalities given a patient case

Applicable State Laws

• Effective December 2016: Registered nurses who hold a specialty certification (nurse practitioner/nurse midwife) MAY:
  – Prescribe controlled substances in schedules II-V under the supervision of a physician
  – Prescribe controlled substances in schedule II regardless of location of practice
    • Limited to no more than a 30 day supply

Drug Schedules

• Schedule II
  – Opioids*, marijuana**
• Schedules III – IV
  – Benzodiazepines, ketamine, tramadol, pregabalin

**Board of Medicine, Rule 338.2411. (Page 7)
Pain

- Unpleasant sensory and emotional response associated with actual or potential tissue damage
- Acute – occurs suddenly, short-lived, resolves as acute illness resolves
- Chronic – lasts longer than expected healing process (or > 3 months), affects ADLs

Pain Processing

- Inflammation and transduction
- Conduction
- Transmission
- Modulation
- Perception

Pathogenesis

- Nociceptive
  - Visceral
  - Somatic
- Neuropathic
  - Central
  - Peripheral

Goals of Chronic Pain Management

- Keep patient functional
- Improve mental health
- Decrease pain perception and dependence on drug therapy
- Decrease rate of physical deterioration
- Reduce pain as much as possible without undue adverse effects

Assessment of Pain

- Thorough patient history
  - CC, HPI, ROS, PMH
- Validated pain scales (visual analog scales)
- Physical exam
- Imaging and diagnostic studies

Assessment of Pain

- P – what Provokes the pain?
- Q – Quality of the pain?
- R – does the pain Radiate?
- S – Severity of the pain?
- T – Time of the pain?
Non-Pharmacologic Therapy

- Physical/Occupational therapy
- Transcutaneous electrical nerve stimulation
- Psychotherapy
- Cold/heat
- Massage
- Prayer/meditation/spiritual
- Distraction
- Exercise
- Music

Pharmacologic Therapy

Pharmacologic Options

- Acetaminophen
- NSAIDs
- Muscle relaxants
- TCAs
- SSRIs, SNRIs
- Gabapentinoids
- Anticonvulsants
- Anti-arrhythmics

- Lidocaine
- Capsaicin
- Cannabinoids
- Opioids
- Ketamine
- Corticosteroids
- Bisphosphonates

Mechanistic Approach

<table>
<thead>
<tr>
<th></th>
<th>Peripheral Nociceptive</th>
<th>Neuropathic</th>
<th>Centralized</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Surgery/Injections</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>TCAs</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>SNRIs</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Gabapentinoids</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Osteoarthritis

- JS is a 68 year old female who endorses bilateral knee pain
- PMH:
  - Liver cirrhosis (secondary to NASH)
  - T2DM
  - Asthma

- How do you want to treat?

Osteoarthritis

- Acetaminophen
- NSAIDs
- Topical therapies
- Intra-articular injections
**Acetaminophen**

- Centrally acting analgesic and anti-pyretic
  - Inhibits COX-2 enzymes in CNS
  - Other possible mechanisms: cannabinoid receptor activation, nitric oxide production inhibition, substance P inhibition, serotonergic/opioid pathway modulation

- Generally very well tolerated
  - Hepatotoxicity seen with acute and/or chronic use

**NSAIDs**

- Analgesic, anti-inflammatory, anti-pyretic
  - Inhibits COX enzymes
  - COX-1 (normal tissue) vs. COX-2 (inflammation)

**NSAID Adverse Effects**

- Gastrointestinal
  - GI upset, GI bleeding
- Cardiovascular
  - HF, MI, HTN
- Hepatic
- Renal

**Acetaminophen vs NSAIDs**

- Osteoarthritis
  - Hands – topical or oral NSAIDs
  - Hips – acetaminophen, NSAIDs
  - Knees – the above plus intraarticular injections

**Acetaminophen vs NSAIDs**

**Osteoarthritis**

- JS is a 68 year old female who endorses bilateral knee pain
- PMH:
  - Liver cirrhosis (secondary to NASH)
  - T2DM
  - Asthma
- Patient received: topical diclofenac, transdermal fentanyl, and tramadol

**Low Back Pain**

- OB is a 60 year old female presenting for routine follow-up
- PMH:
  - HIV
  - Vision loss (secondary to cortical stroke)
  - Chronic low back pain
  - T2DM
  - Depression
- How do you want to treat?

**Low Back Pain**

- Acetaminophen
- NSAIDs
- Muscle relaxants

**Acetaminophen vs NSAIDs**

- Low back pain
  - Acute – likely prefer NSAIDs
  - Chronic – patient preference
  - New guidelines recommend NSAIDs (1st), then either tramadol (2nd) or duloxetine (2nd)

**Muscle Relaxants**

- Can reduce acute low back pain up to ~30%
  - Use with caution in patients with fall risks
  - Should not be used for chronic back pain or those with injury unrelated to muscles
- No data exists regarding chronic back pain

**Muscle Relaxants**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Avoid</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobenzaprine</td>
<td>5-10 TID</td>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>Methocarbamol</td>
<td>750 QID</td>
<td>MG</td>
<td></td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>350 QID</td>
<td>AIP</td>
<td>CIV</td>
</tr>
<tr>
<td>Chlorzoxazone</td>
<td>250-750 TID-QID</td>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>Metaxalone</td>
<td>800 TID-QID</td>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>100 BID</td>
<td>MG, Elderly</td>
<td></td>
</tr>
<tr>
<td>Tizanidine</td>
<td>4 TID-QID</td>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>Baclofen</td>
<td>5-20 TID</td>
<td>Heart</td>
<td>Renal dose</td>
</tr>
</tbody>
</table>
OB is a 60 year old female presenting for routine follow-up

PMH:
- HIV, vision loss, chronic low back pain, T2DM, depression

Patient was receiving: Oxycodone ER 80 mg TID + oxycodone IR 5 mg Q6H PRN

No studies > 1 year of opioid vs. placebo, etc.
- Most studies ≤ 6 weeks in duration

Long-term opioid use is associated with an increased risk of opioid abuse or dependence
- Risk of opioid abuse or dependence increases with:
  - History of substance abuse, younger age, major depression, psychotropic medication use
  - Risk of overdose increases above 50 oral morphine equivalents (OME)

Non-pharmacologic therapy and non-opioid therapy are first line
- Only use opioids if benefits outweigh risks and continue to use non-pharmacologic and non-opioid based therapies

Establish treatment goals before opioid use

Frequently re-evaluate and re-educate

Use immediate release formulations

Use the lowest dose necessary
- Re-assess benefits if exceeding 50 OME for total daily dose (TDD)
- Avoid increases above 90 OME TDD

Long-term use often starts with treating an acute pain episode
- Prescribe no more than is reasonably necessary for that condition

Evaluate patients 1 to 4 weeks after starting opioids and at least every 3 months thereafter

Consider mitigating strategies like narcotic contracts, naloxone co-prescriptions, prescription drug monitoring program checks, urine drug screens, avoid benzodiazepine co-prescriptions, and consider referral for opioid use disorders as needed

Acute – non-drug therapy first, then NSAIDs

Chronic – non-drug therapy first, NSAIDs (1st), tramadol (2nd), duloxetine (2nd)
- “Only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients”
JS is a 47 year old female complaining of worsening pain

PMH:
- Hypothyroidism
- Hypertension
- T1DM
- ESRD on HD (MWF)
- Peripheral arterial disease
- OSA on CPAP

How do you want to treat?

Neuropathic Pain

Drug | CV | Renal | Liver | Notes
--- | --- | --- | --- | ---
Amitriptyline | X | √ | √ | Sedating, ACh
Nortriptyline | X | √ | √ | Orthostasis
Imipramine | X | √ | √ | Sedating, ACh
Duloxetine | √ | X | X |
Venlafaxine | Caution | Caution | Caution | Headaches, low = SSRI
Gabapentin | Caution | Caution | √ | Renal dosing
Pregabalin | V | Caution | V | Renal dosing
Carbamazepine | Caution | Caution | Caution | Drug interactions
Lamotrigine | √ | Caution | Caution | Renal/Hepatic dosing
Opioids | V | No morphine | Extend tramadol frequency |
Lidocaine | X | √ | V | Consider smaller areas of treatment

Neurotransmitter Inhibition

Neuropathic Pain

BRAIN
- Descending Inhibition
  - NE/Serotonin
  - Opioid receptors
- TCAs
- SSRIs
- SNRIs
- Tramadol
- Opoids
- Peripheral sensitization
- SPINAL CORD
  - Na¹
  - NCX
  - OX2
  - PTX
  - TMA
  - LTG
  - Lidocaine
  - Mexiletine
  - TCAa
- Central Sensitization
  - Ca²⁺
  - NMDA
  - Ketamine
  - Dexmedetomidine
  - Memantine
  - Memantine
  - Methadone
  - Others
  - Dexamethasone
  - Levothyroxine
  - NSAIDS
  - COX inhibitors

Neuropathic Pain

Treatment Options

Drug | Initial Dose (mg) | Target Dose (mg) | Maximum Daily Dose (mg)
--- | --- | --- | ---
Amitriptyline | 25 QHS | 100 QHS | 150
Nortriptyline | 25 QDay | 100 QDay | 150
Imipramine | 25 QHS | 100 QHS | 150
Duloxetine | 30 QDay | 60 QDay | 60
Venlafaxine | 75 QDay | 150-225 QDay | 225
Gabapentin | 300 QDay | 1800 TDD | 3600
Pregabalin | 50 TID | 100 TID | 600
Carbamazepine | 200 QDay | 400-800 QDay | 1200
Lamotrigine | 25 QDay | 200-400 QDay | 600
Opioids | LOWEST | LOWEST | LOWEST
Lidocaine | One patch | - | Three patches

Monitoring

- Onset of analgesic effect
- Duration of analgesic effect
- PRN medication use
- Adverse drug effects of medications
- Concomitant medication use

Patient was receiving: Amitriptyline, gabapentin, oxycodone/acetaminophen
Management of Chronic, Non-Terminal Pain

Michael A. Smith, PharmD, BCPS
Clinical Assistant Professor, University of Michigan College of Pharmacy
Pain and Palliative Care Clinical Pharmacy Specialist, Michigan Medicine