A Review of Non-Opioid Medications for Pain Management
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Objectives for Pharmacists
• Describe different types of pain
• Describe non-pharmacological therapies for pain management
• Identify the classes of non-opioid medications used in pain management
• Explain the recommended dosing and monitoring parameters for non-opioid medications

Objectives for Pharmacy Technicians
• Identify the different types of pain
• Recognize non-pharmacological therapies for pain management
• List non-opioid medications routinely prescribed for pain management
• List common side effects and adverse events associated with non-opioid pain medications

Disclosure
• I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

What is Pain?
• Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage

Biopsychosocial Model of Pain
Biological factors
Psychological factors
Social factors
Chronic Pain

Pain Management Training Work Group
**Types of Pain**

- **Acute**
  - Short-lasting, resolves with healing of injured tissues
  - Primary treatment goal is to diagnose and remove the source
- **Chronic**
  - Lasts beyond healing time of injury, continues or occurs frequently for greater than 3 to 6 months
  - Primary treatment goal is to minimize pain and improve function

**Non-Opioid Medications for Pain Management**

- Classes of non-opioid pain medications
  - Acetaminophen
  - NSAIDs
  - Anticonvulsants
  - Antidepressants
  - Fish oil
  - Topical agents

**Types of Pain**

- Nociceptive - typically due to stimulation of pain receptors in surface or deep tissues
  - Somatic – pain in skin, muscles, bone, joint, connective tissue
  - Visceral – pain in internal organs
- Neuropathic - due to nerve damage in either the peripheral or central nervous system

**Non-Opioid Medications for Pain Management**

- What medication to choose?
  - Accurate evaluation of the cause of pain and type of pain is essential
  - Guided by individual patient factors
    - Co-morbidities
    - Medication interactions
    - Potential side effects
  - May need to consider an approach using combination medications that target different pathways

**Non-Pharmacological Therapies**

- Heat/Cold therapy
- Massage
- Acupuncture
- TENS (transcutaneous electrical stimulation)
- Behavioral
- Exercise
- Weight loss
- Smoking/Alcohol cessation

**Non-Opioid Medications for Pain Management**

- Classes of non-opioid pain medications
  - Acetaminophen
  - NSAIDs
  - Anticonvulsants
  - Antidepressants
  - Fish oil
  - Topical Agents
Acetaminophen (Tylenol ®)

- Mechanism of Action:
  - Acts within the central nervous system by inhibiting synthesis of prostaglandins
- Indication:
  - Mild to moderate pain
- First-line pharmacologic therapy for osteoarthritic pain
- Dosing:
  - 325 to 650mg q4-6hrs
  - Max total daily dose: 3000mg
  - Dose limited to 325mg in combination products

Non-Opioid Medications for Pain Management

- Classes of non-opioid pain medications
  - Acetaminophen
  - NSAIDs
  - Anticonvulsants
  - Antidepressants
  - Fish oil
  - Topical Agents

Acetaminophen (Tylenol ®)

- Potential ADEs:
  - Hepatotoxicity
  - Skin reactions
    - Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis
- Monitoring:
  - LFTs
  - Skin reactions
  - Drug interactions (isoniazid, warfarin)

NSAIDs

- Mechanism of Action:

NSAIDs

- Indications:
  - Mild-moderate pain, typically of somatic origin
  - Osteoarthritis
  - Rheumatoid arthritis
  - Gout
### NSAIDs

#### Dosing:

<table>
<thead>
<tr>
<th>Type of NSAID</th>
<th>Typical Dosing Schedule</th>
<th>Max Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>600 - 800mg TID</td>
<td>3200mg</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>7.5 - 15mg daily</td>
<td>15mg</td>
</tr>
<tr>
<td>Etodolac</td>
<td>800 - 1200mg/day in divided doses</td>
<td>1200mg</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>100 - 150mg/day in divided doses</td>
<td>200mg</td>
</tr>
<tr>
<td>Salsalate</td>
<td>500 - 1000mg BID-TID</td>
<td>3000mg</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>25mg BID-TID</td>
<td>200mg</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>10 - 20mg daily</td>
<td>20mg</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250 - 500mg BID</td>
<td>1000mg</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Single IM dose – 30 - 60mg</td>
<td>30 - 60 mg</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>100mg BID</td>
<td>400mg</td>
</tr>
</tbody>
</table>

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### NSAIDs

#### Choice of NSAID based on risk factors:

<table>
<thead>
<tr>
<th>Low CV Risk</th>
<th>Moderate GI Risk</th>
<th>High GI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen or other low GI risk NSAID</td>
<td>1. Celecoxib alone 2. NSAID + PPI or misoprostol 3. NSAID + double dose H2-blocker</td>
<td>1. Avoid NSAIDs if possible 2. Celecoxib + PPI or misoprostol</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1. Naproxen + PPI or misoprostol 2. Naproxen plus double dose H2-blocker</td>
<td>Avoid NSAIDs</td>
</tr>
</tbody>
</table>

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### NSAIDs

#### Potential ADEs:
- **GI:** dyspepsia, gastric ulceration, perforation
- **Renal:** reversible renal insufficiency, acute interstitial nephritis
- **CV:** increased BP, CHF exacerbation, increased risk of MI and stroke

#### Monitoring:
- CBC, fecal occult blood test
- SCr, BUN
- Weight gain, edema

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### NSAIDs

#### Classifying GI Risks:

<table>
<thead>
<tr>
<th>GI Risk</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High GI Risk</strong></td>
<td>- History of complicated ulcer</td>
</tr>
<tr>
<td></td>
<td>- Use of anticoagulants</td>
</tr>
<tr>
<td></td>
<td>- Use of corticosteroids</td>
</tr>
<tr>
<td></td>
<td>- More than 2 moderate risk factors</td>
</tr>
<tr>
<td><strong>Moderate GI Risk</strong></td>
<td>- Age &gt; 65 years old</td>
</tr>
<tr>
<td></td>
<td>- History of uncomplicated ulcer</td>
</tr>
<tr>
<td></td>
<td>- Use of aspirin or other antiplatelet agent</td>
</tr>
<tr>
<td><strong>Low GI Risk</strong></td>
<td>- No risk factors listed above</td>
</tr>
</tbody>
</table>

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### NSAIDs

#### Clinical Pearls:
- No evidence to support one NSAID is more effective than others (including celecoxib!)
- Evaluate patient risk factors when choosing NSAIDs
- If at first you don’t succeed, try again
- If possible, use the lowest effective dose for the shortest duration of time
- Monitor CBC, SCr, BUN periodically

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### Non-Opioid Medications for Pain Management

#### Classes of non-opioid pain medications
- Acetaminophen
- NSAIDs
- Anticonvulsants
- Antidepressants
- Fish oil
- Topical Agents
Anticonvulsants

- Examples:
  - Pregabalin (Lyrica®)
  - Gabapentin (Neurontin®)

- Mechanism of Action:
  - Binds to the voltage-gated calcium channels and inhibits neurotransmitter release

Gabapentin (Neurontin®)

- Indications:
  - Postherpetic neuralgia
  - DM neuropathy (unlabeled use)
  - Neuropathic pain (unlabeled use)

- Dosing:
  - Initial dose:
    - 100-300mg once daily qhs OR 100-300mg TID
  - Max dose: 1200mg TID
  - CrCl < 60ml/min: dose adjustment required

Pregabalin (Lyrica®)

- Indications:
  - Fibromyalgia
  - DM neuropathy
  - Postherpetic neuralgia

- Dosing:
  - Initial dose: 50mg TID or 75mg BID
  - Max dose: 600mg/day in 2-3 divided doses
  - CrCl < 60ml/min: dose adjustment required

Gabapentin (Neurontin®)

- Potential ADEs:
  - Somnolence
  - Dizziness
  - Peripheral edema
  - Weight gain
  - Blurred vision

- Monitoring:
  - Weight gain, edema
  - Sedation
  - Visual disturbances

Converting from Gabapentin to Pregabalin

- Multiple techniques used:
  - Weekly interval taper
    - Example for patient taking 1200mg TID of gabapentin
      - Week 1: decrease gabapentin to 900mg TID
      - Week 2: 600mg TID
      - Week 3: 300mg TID
      - Week 4: d/c gabapentin and initiate pregabalin
  - Direct conversion
    - 6mg gabapentin = 1mg pregabalin
    - Example: 1200mg TID gabapentin = 200mg TID pregabalin
Anticonvulsants

- Clinical Pearls
  - Gabapentin and pregabalin have most data to support use in neuropathic pain
  - No evidence to support pregabalin is more effective than gabapentin for DM neuropathy
  - Dose adjustment needed for renal function
  - Side effect profile is essentially the same for both medications

Non-Opioid Medications for Pain Management

- Classes of non-opioid pain medications
  - Acetaminophen
  - NSAIDs
  - Anticonvulsants
  - Antidepressants
    - Selective Norepinephrine Reuptake Inhibitors (SNRIs)
    - Tri-cyclic Antidepressants (TCAs)
  - Fish oil
  - Topical Agents

SNRIs

- Examples:
  - Venlafaxine (Effexor®)
  - Duloxetine (Cymbalta®)
  - Milnacipran (Savella®)

  - Mechanism of Action:
    - Inhibits the reuptake of neuronal norepinephrine and serotonin

Venlafaxine (Effexor®)

- Indications:
  - Depression, anxiety, PTSD
  - Neuropathic pain (unlabeled use)

- Dosing (Extended release):
  - Initial dose: 37.5mg once daily
  - Typical dosage range: 75-225mg/day
  - CrCl < 60 ml/min: decrease dose by 25-50%

Venlafaxine (Effexor®)

- ADEs:
  - Headache
  - Insomnia
  - Anxiety
  - Hypertension

- Monitoring:
  - Blood pressure
  - Renal function
  - Mental status
  - Signs and symptoms of serotonin syndrome

Product information for Effexor

Duloxetine (Cymbalta®)

- Indications:
  - Diabetic neuropathy
  - Fibromyalgia
  - Chronic musculoskeletal pain
  - Depression, anxiety

- Dosing
  - Initial dose: 30-60mg once daily
  - Max dose: 120mg/day
  - Contraindicated with CrCl < 30ml/min

Product information for Cymbalta
**Duloxetine (Cymbalta®)**

- **ADEs:**
  - Nausea
  - Headache
  - Hypertension
- **Monitoring:**
  - Renal function
  - Blood Pressure
  - Mental status
  - Signs and symptoms of serotonin syndrome

**SNRIs**

- **Clinical Pearls**
  - Indications vary by medication, however typically used for nerve pain
  - Good option for patients with depression
  - If patient does not achieve pain relief with one SNRI, may consider trial of alternative SNRI
  - Monitor blood pressure and renal function with all SNRIs
  - Increased risk of serotonin syndrome when used with other agents that increase serotonin concentrations

**Milnacipran (Savella®)**

- **Indications:**
  - Fibromyalgia
- **Dosing:**
  - Titration schedule:
    - Day 1: 12.5mg once
    - Days 2-3: 12.5mg BID
    - Days 4-7: 25mg BID
    - Day 8 and thereafter: 50mg BID
  - May increase to 100mg BID if needed
  - Dose reduction required for CrCl < 30ml/min

**TCAs**

- **Examples:**
  - Amitriptyline (Elavil®)
  - Nortriptyline (Pamelor®)
  - Desipramine (Norpramin®)

  **Mechanism of Action:**
  - Increases the synaptic concentration of serotonin and/or norepinephrine in the CNS

**Milnacipran (Savella®)**

- **ADEs:**
  - Headache
  - Nausea
  - Hypertension
  - Hot flashes
- **Monitoring:**
  - Blood pressure
  - Renal function
  - Mental status
  - Signs and symptoms of serotonin syndrome

**TCAs**

- **Indications:**
  - Depression
  - Chronic pain management (unlabeled use)
  - Diabetic neuropathy (unlabeled use)
  - Post-traumatic stress disorder (unlabeled use)
  - Migraine prophylaxis (unlabeled use)
TCAs

- **Dosing:**
  - Amitriptyline:
    - Initial: 25mg qhs
    - May increase as tolerated to 100mg daily
  - Nortriptyline:
    - Initial: 10-25mg qhs
    - May increase as tolerated to 150mg daily
  - Desipramine:
    - Initial: 25mg qhs
    - May increase as tolerated to 150mg daily

TCAs

- **ADEs:**
  - Sedation
  - Urinary retention
  - Constipation
  - QTc prolongation
- **Monitoring:**
  - ECG
  - Blood levels
    - Nortriptyline: 50-150 ng/ml
    - Amitriptyline: 100-250 ng/ml
  - Signs and symptoms of serotonin syndrome

Non-Opioid Medications for Pain Management

- **Classes of non-opioid pain medications**
  - Acetaminophen
  - NSAIDs
  - Anticonvulsants
  - Antidepressants
  - Fish oil
  - Topical Agents

Fish Oil

- **Mechanism of Action:**
  - Omega-3 fatty acids decrease prostaglandin production
  - Decreases inflammation
- **Indications:**
  - Osteoarthritic/skeletal pain
  - Possible alternative to NSAIDs or adjunct to NSAIDs to decrease inflammation

TCAs

- **Clinical Pearls**
  - Mainstay treatment for nerve pain
  - Good option for patients with depression
  - Not recommended in the elderly
  - Be proactive to prevent side effects

Fish Oil

- **Dosing:**
  - Initial: 1 gram BID-TID
  - Increase as tolerated every 2-3 weeks, max daily dose 8 grams/day
- **ADEs:**
  - Fishy taste
  - Heart burn
  - Increased risk of bleeding
  - Increased LDL
  - Prostate cancer?
Fish Oil

- Monitoring:
  - Cholesterol
  - Signs and symptoms of bleeding
- Clinical Pearls:
  - May be a good alternative to NSAIDs or adjunct medication for pain caused by inflammation
  - Doses up to 6 to 8 grams/day may be needed for analgesic effects
  - Little evidence exists regarding increased risk of prostate cancer

Topical Medications

Lidocaine (patch, ointment)
- Mechanism of action:
  - Stabilizes neuronal membranes required for the initiation and conduction of impulses

Non-Opioid Medications for Pain Management

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Topical Medications

- Lidocaine
- Capsaicin
- Diclofenac
- Biofreeze

Topical Medications

Lidocaine ointment
- Indication:
  - Topical anesthetic
- Dosing/Application:
  - Apply thin film 2-3 times daily

Topical Medications

Lidocaine (patch, ointment)
- Monitoring:
  - Side effects:
    - Burning and irritation at site of application
  - Drug Interactions:
    - Class I anti-arrhythmics (mexilitine, tocainide)
    - Hepatic Function
      - Not recommended in patients with severe hepatic impairment

Lexi-Comp Drug Information Handbook
Topical Medications

Lidocaine patch (Lidoderm®)
• Indication:
  • Post-herpetic neuralgia
  • Allodynia
• Dosing/Application:
  • Apply on most-painful area, up to 12 hours in a 24 hour period
  • Max: 3 patches/24 hour period

Capsaicin 8% Patch (Qutenza®)
• Indication:
  • Post-herpetic neuralgia
• Dosing/Administration:
  • Administration by health care professional only
  • Apply patch for 60 minutes, may repeat every 3 months
  • Max: 4 patches
  • Treat acute pain during and following the procedure with local cooling and/or analgesics

Capsaicin (cream, patch)
• Mechanism of Action:
  • Derived from chili peppers
  • Depletes substance P from primary afferent neurons
  • Agonist for the transient receptor potential vanilloid 1 receptor (TRPV1)

Capsaicin 8% Patch (Qutenza®)
• Monitoring:
  • Application associated pain
  • Treat acute pain with local cooling and/or analgesic medication
  • Increase in blood pressure
  • Related to treatment-related increases in pain
  • Monitor blood pressure periodically during treatment

Capsaicin Cream
• Indication:
  • Chronic musculoskeletal or neuropathic pain
• Dosing/Administration:
  • Available in 0.025% and 0.075% strength
  • Apply 3-4 times daily
• Monitoring:
  • Side effects:
    • Burning, stinging, erythema

Diclofenac (gel, patch, solution)
• Mechanism of Action:
  • NSAID; inhibits prostaglandin synthesis, which leads to anti-inflammatory and analgesic effects
**Topical Medications**

**Diclofenac (gel, patch, solution)**

- **Monitoring:**
  - Black Box Warnings
  - Increased risk of cardiovascular thrombotic events
  - Increased risk of serious GI adverse events
  - Contraindicated in the peri-operative setting of CABG

- **Drug Interactions:**
  - ASA, anti-coagulants, lithium, methotrexate, cyclosporine, oral NSAIDs

- **Labs:**
  - CBC, BMP, LFTs

**Topical Medications**

**Diclofenac 1.3% patch (Flector®)**

- **Indications:**
  - Acute pain due to minor strains, sprains, and contusions

- **Dosing/Administration:**
  - One patch to most painful area twice daily

**Topical Medications**

**Diclofenac 1% gel (Voltaren®)**

- **Indication:**
  - Osteoarthritis of the knee(s) and hand(s)

- **Dosing/Administration:**
  - Lower extremities: Apply the gel (4 g) to the affected area 4 times daily
  - Upper extremities: Apply the gel (2 g) to the affected area 4 times daily

**Topical Medications**

**Diclofenac 1.5% Topical Solution (Pennsaid®)**

- **Indication:**
  - Osteoarthritis of the knee(s)

- **Dosing/Administration:**
  - 40 drops per knee
  - Apply 4 times daily

**Topical Medications**

**Biofreeze (Menthol 3.5%, Camphor 0.2%)**

- **Mechanism of action:**
  - Cooling therapy blocks pain transmission

- **Indication:**
  - Minor aches and pains (muscle, joint)

- **Dosing/Administration:**
  - Rub thin film over affected area not more than 4 times/day

**Topical Medications**

**Clinical Pearls**

- Most effective for well-localized pain
- Advantages of topical agents include delivery to site of insult, less systemic absorption, less systemic side effects
- Lidocaine effective for nerve pain
- Capsaicin effective for musculoskeletal and nerve pain
- Diclofenac effective for osteoarthritic pain
- Biofreeze effective for minor muscle and joint pain
Questions?

References