Pharmacologic Management of Pain

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The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.
Disclosures

- The speaker has nothing to disclose.
- Exhibits coordinated through the Henry Jackson Foundation.
- Refreshments provided through the Henry Jackson Foundation.
Objectives

- Review the different types of pain
- Apply pain assessment tools and discuss how to correctly assess a patient’s pain
- Discuss types of pharmacologic agents used in pain management
  - NSAIDs and acetaminophen
  - Opioids
  - Gabapentin and pregabalin
- Review the role we can play in managing a patient’s pain
Pain as the 5th Vital Sign

- Joint Commission on Accreditation of Healthcare Organizations (JCAHO) recognizes pain as a 5th vital sign
  - Require that health care staff record pain assessment each time vital signs are recorded
    - Temperature, blood pressure, respirations, pulse

Joint Commission on Accreditation of Healthcare Organizations (2000), Implementing the new pain management standards. Oakbrook Terrace, Ill.: JCAHO.
Types of Pain

- Nociceptive
- Neuropathic

Nociceptive Pain

- Somatic pain
  - Arises from skin, bone, joint, muscle, or connective tissue
  - Throbbing, dull, aching
  - Well localized

- Visceral pain
  - Arises from internal organs
  - Diffuse, deep, aching
  - Poorly localized and feeling as if it is coming from other structures

Neuropathic Pain

- Pain sustained by abnormal processing of sensory input
- May be caused by nerve damage or persistent stimulation
- Burning, shooting, pricking, numbness, tingling sensation
Objectives

- Review the different types of pain
- **Apply pain assessment tools and discuss how to correctly assess a patient’s pain**
- Discuss types of pharmacologic agents used in pain management
  - NSAIDs and acetaminophen
  - Opioids
  - Gabapentin and pregabalin
- Review the role we can play in managing a patient’s pain
Pain Assessment Tools

- Numerical rating scale (NRS)

Pain Assessment Tools

• Visual Analogue Scale

Place a vertical mark on the line below to indicate how bad you feel your pain is today

No pain ———————————————————— Worst pain imaginable

Visual Analog Scale (VAS) (10 cm line).
[Score = 0 - 100 mm] - measuring in millimeters from the left hand end of the line to the point that the patient marks.

Objectives

- Review the different types of pain
- Apply pain assessment tools and discuss how to correctly assess a patient’s pain
- Discuss types of pharmacologic agents used in pain management
  - NSAIDs and acetaminophen
  - Opioids
  - Gabapentin and pregabalin
- Review the role we can play in managing a patient’s pain
Nonopioid agents

- Acetaminophen
- Aspirin
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
Acetaminophen (Tylenol®)

- **Properties**
  - Analgesic and antipyretic
  - Lacks anti-inflammatory activity or effects on platelet function

- **Preferred for**
  - Patients whom aspirin is contraindicated
  - Patients with underlying renal disease

Acetaminophen (Tylenol®)

- **Dosage**
  - PO/rectal: 325 – 650 mg q4-6 hrs prn
  - IV: 1000 mg q6 hrs prn

- **Available dosage forms**
  - Oral tablets, capsules, solution
  - Rectal suppository
  - IV solution (Ofirmev®) – 1000mg/100ml

Acetaminophen (Tylenol®)

- Maximum dose
  - Current recommendations are 4000 mg/day
  - Suggestions to decrease maximum dose to 3,000 mg/day
    - FDA asked drug manufacturers to limit strength of APAP in prescription drug products to 325 mg/tablet

# Acetaminophen (Tylenol®)

## Side effects

### Oral/Rectal Administration

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash/pruritus</td>
<td>5%</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Increased LFTs</td>
<td>(&gt;7.5g) and chronic doses &gt; 4 g</td>
</tr>
</tbody>
</table>

### Intravenous Administration

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>(&gt;10%)</td>
</tr>
<tr>
<td>Edema</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Increased LFTs</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

Aspirin

- **Properties**
  - Analgesic, antipyretic and anti-inflammatory
  - Affects platelets so useful in preventing or reducing risk of myocardial infarction
  - Not too useful for pain because requires high doses

- **Also useful for**
  - Juvenile arthritis
  - Rheumatoid arthritis
  - Osteoarthritis

Aspirin

- **Dosage**
  - PO/rectal: 325-650 mg q4 hrs prn
  - Max dose: 4000 mg/day

- **Available dosage forms**
  - Oral tablets – 81 mg, 325 mg, 650 mg
  - Rectal suppository – 300 mg, 600 mg

## Aspirin

### Side effects

<table>
<thead>
<tr>
<th>Oral/Rectal Administration</th>
<th>Bleeding</th>
<th>Rash</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Nausea</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Heartburn</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Increased transaminases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased serum creatinine</td>
<td></td>
<td></td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Reye’s syndrome</td>
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<td></td>
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</tr>
</tbody>
</table>

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- **Properties**
  - Analgesic, antipyretic and anti-inflammatory

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Cyclooxygenase (COX)

- **Physiological stimulus**
  - Arachidonic Acid
  - TXA₂ (platelet aggregation, vasoconstriction)
  - PGI₁ (vasodilation, GI-mucosal protection)
  - PGE₁ / PGE₂ (kidney, GI-tract, CNS)

- **Inflammatory Stimulus**
  - Inflammatory site (PGE₂) (pain sensitization, vasodilation)
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Indications
  - Mild to moderate pain

- Available dosage forms
  - Many types of NSAIDs and forms available
    - Capsules, tablets, oral suspension, intravenous solutions

### Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

<table>
<thead>
<tr>
<th>Acetic Acid Derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac (Voltaren®)</td>
</tr>
<tr>
<td>Etodolac (Lodine®)</td>
</tr>
<tr>
<td>Indomethacin (Indocin®)</td>
</tr>
<tr>
<td>Ketorolac (Toradol®)</td>
</tr>
<tr>
<td>Sulindac (Clinoril®)</td>
</tr>
<tr>
<td>Tolmetin (Tolectin®)</td>
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<table>
<thead>
<tr>
<th>Carboxylic acid derivatives</th>
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</thead>
<tbody>
<tr>
<td>Diflunisal (Dolobid®)</td>
</tr>
<tr>
<td>Salsalate (Disalcid®)</td>
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<table>
<thead>
<tr>
<th>Enolic acid derivatives</th>
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</thead>
<tbody>
<tr>
<td>Meloxicam (Mobic®)</td>
</tr>
<tr>
<td>Piroxicam (Feldene®)</td>
</tr>
<tr>
<td>Nabumetone (Relafen®)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Naphtylkanone derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabumetone (Relafen®)</td>
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<table>
<thead>
<tr>
<th>Propionic acid derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurbiprofen (Ansaid®)</td>
</tr>
<tr>
<td>Ibuprofen (Motrin®)</td>
</tr>
<tr>
<td>Ketoprofen (Orudis®)</td>
</tr>
<tr>
<td>Naproxen (Naprosyn®)</td>
</tr>
<tr>
<td>Oxaprozin (Daypro®)</td>
</tr>
</tbody>
</table>
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Adverse Effects

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Fluid retention</th>
<th>Renal complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartburn</td>
<td></td>
<td>• Decreased renal blood flow</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet dysfunction</td>
<td>Bronchospasms</td>
<td>Hypersensitivity</td>
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</tbody>
</table>

Gastrointestinal Side Effect

- Patients at high risk for GI SE
  - Advanced age
  - Alcoholic liver disease
  - History of gastric ulcers
  - Alcohol ingestion
  - Higher dose
  - Longer duration

Opioids

- Indications
  - Severe forms of acute pain
  - Cancer pain

- Binds to opiate receptors to block perception of pain

Opioids

- Onset of analgesic effects
  - PO:
    - Immediate release: 15-30 minutes
    - Controlled release: 30 min-2 hours
  - IM/SC: 15-30 minutes
  - IV: about 5 minutes

- No ceiling effect
  - No maximum dose
  - Titrate based on pain scale

Opioid Mechanism of Action

http://www.medicalnewstoday.com/info/oic/
# Opioid Receptors

<table>
<thead>
<tr>
<th>3 Main Receptor Subtypes</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ1</td>
<td>Analgesia</td>
</tr>
<tr>
<td></td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
</tr>
<tr>
<td>µ2</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Euphoria</td>
</tr>
<tr>
<td></td>
<td>Physical dependence</td>
</tr>
<tr>
<td>δ</td>
<td>Analgesia</td>
</tr>
<tr>
<td></td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>κ</td>
<td>Analgesia</td>
</tr>
<tr>
<td></td>
<td>Respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
</tr>
</tbody>
</table>

# Opioid Classes

<table>
<thead>
<tr>
<th>Phenanthrenes (morphine-like agonists)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (MS Contin, Kadian, Oramorph®)</td>
<td>Hydromorphone (Dilaudid®)</td>
<td>Oxymorphone (Numorphan, Opana®)</td>
</tr>
<tr>
<td>Codeine</td>
<td>Hydrocodone (Vicodin, Norco, Lortab®)</td>
<td>Oxycodone (Oxycontin®)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phenylpiperidines (meperidine-like agonists)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine (Demerol®)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diphenylheptanes (methadone-like agonists)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone (Methadose, Dolophine®)</td>
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</table>

<table>
<thead>
<tr>
<th>Central Analgesic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol (Ultram®)</td>
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</tbody>
</table>

# Opioids

## Side Effects

<table>
<thead>
<tr>
<th>Short term</th>
<th>Long term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>Cognitive Disturbances</td>
</tr>
<tr>
<td>Constipation (do not develop tolerance)</td>
<td>Dependence</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Addiction</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Tolerance</td>
</tr>
</tbody>
</table>

Opioids

- Side effects
  - Overdose: respiratory depression
    - Administer opioid antagonist (ie: naloxone)
      - Important to assess patient if low respiratory rate

Opioids

• Side effects
  ◦ Tolerance develops to most side effects EXCEPT constipation
    • Almost all patients will require a stool softener (ie: docusate) and a mild stimulant laxative (ie: senna, bisacodyl)

Opioid Allergies

- True allergy to opioids are rare
- Use agent from a different class of opioids
  - Morphine-like
  - Meperidine-like
  - Methadone-like
  - Central analgesic

Cupp, M. Analgesic Options for Patients with Allergic-Type Opioid Reactions. Pharmacist’s Letter/Prescriber’s Letter 2006; 22(2):22021
Specific Opioid Agents

- **Morphine** (MS Contin, Kadian, Oramorph®)
  - **Metabolites**
    - Morphine-6-glucuronide → more potent than parent compound
    - Morphine-3-glucuronide → side effects
  - **Excreted renally**
    - Requires dosage adjustment in renal impairment
  - **Caution in renal dysfunction and elderly**

Specific Opioid Agents

- **Codeine**
  - Mild to moderate pain
  - Pro-drug $\rightarrow$ metabolized to morphine
    - Avoid use in hepatic impairment
  - Used in combination with NSAIDs, aspirin, acetaminophen
  - Has antitussive properties

Specific Opioid Agents

- Hydromorphone (Dilaudid®)
  - 7x more potent than morphine
  - May cause less constipation
  - Metabolized in liver via glucuronidation
  - No active metabolite
    - May be better for renal and hepatic insufficiency

Specific Opioid Agents

- Hydrocodone (Vicodin, Norco, Lortab®)
  - Only available in combination products
  - NOTE: combinations contain acetaminophen so careful with overdose
    - Dose limiting factor acetaminophen dose

**Specific Opioid Agents**

- **Oxycodone (Oxycontin®)**
  - Most effective when used with NSAIDs, aspirin, acetaminophen
  - Severe chronic pain

- **Oxymorphone (Opana®)**
  - Metabolite of oxycodone
  - Not used much
  - No pharmacologic advantage over morphine
Specific Opioid Agents

- Meperidine (Demerol®)
  - Not used for chronic pain
  - Used for rigors
  - Toxic metabolite – normeperidine
    - Can cause seizures
    - Not reversible by naloxone (Narcan®)
    - Renally excreted
  - Max use of 3 days

Specific Opioid Agents

- Fentanyl (Actiq, Fentora, Duragesic®)
  - No active metabolites
  - Preferred in renal insufficiency
  - Many available formulations
    - IV, PO, transdermal
  - No histamine release → decreased pruritis

Specific Opioid Agents

• Fentanyl
  ◦ Patch (Duragesic®)
    • Patient must be opioid tolerant
      • Equivalent of oral morphine 60 mg for 7 days or longer
    • Applied every 72 hours
    • Takes up to 12-24 hours to work
    • Heat increases absorption
    • Risk of burns during MRI
  ◦ Oral lozenge (Actiq®)
  ◦ Buccal tablet (Fentora®)

Opioid Naïve vs. Tolerant

- **Naïve**
  - Patients who are not chronically receiving opioids on a daily basis

- **Tolerant**
  - Patients chronically receiving opioids
  - Equivalent daily opioid dosing
    - 60 mg oral morphine
    - 30 mg oral oxycodone
    - 8 mg oral hydromorphone
    - 25 mcg/hr fentanyl patch

Specific Opioid Agents

- Methadone (Methadose, Dolophine®)
  - Used for chronic pain
  - Also used to treat opioid abuse
    - Lacks profound euphoria
    - Withdrawal symptoms milder than morphine
  - Duration of action a lot shorter than elimination half-life
  - Careful in hepatic impairment

Specific Opioid Agents

- **Tramadol (Ultram®)**
  - Synthetic codeine analogue
  - Weak affinity for opioid receptor
  - Active metabolite renally excreted
    - Careful in renal impairment

Principles of Opioid Rotation

- Practice of switching to a different opioids when dose-limiting toxicities lead to poor responsiveness
- Should NOT be initiated in patients stable on their medication
- Genetic polymorphisms in genes for mu-receptor subtypes lead to different responses in each individual


### General Opioid Conversions

#### Equianalgesic Dosing

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>10 mcg IV Fentanyl</td>
<td>1 mg IV Morphine</td>
<td>0.2 mg IV hydromorphone (Dilaudid®)</td>
</tr>
<tr>
<td>0.2 mg IV hydromorphone (Dilaudid®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2 mg IV hydromorphone (Dilaudid®)</td>
<td>1 mg PO hydromorphone (Dilaudid®)</td>
<td></td>
</tr>
<tr>
<td>1 mg IV Morphine</td>
<td>3 mg PO morphine</td>
<td></td>
</tr>
<tr>
<td>10 mg PO oxycodone</td>
<td>15 mg PO morphine</td>
<td>15 mg PO hydrocodone</td>
</tr>
</tbody>
</table>

For methadone or assistance, contact the pharmacist at 619-532-8596
Opioid Conversion Example

- Patient receives 0.5 mg/hr of hydromorphone (Dilaudid®) from PCA

- How many mg of morphine is 12 mg of IV hydromorphone equivalent to?

\[
12 \text{ mg IV hydromorphone} \times \frac{1 \text{ mg IV morphine}}{0.2 \text{ mg IV hydromorphone}} = 60 \text{ mg IV morphine}
\]

\[
60 \text{ mg IV morphine} \times \frac{3 \text{ mg PO morphine}}{1 \text{ mg IV morphine}} = 180 \text{ mg PO morphine}
\]
Opioid Overdose

- When to administer naloxone (Narcan®)
  - Patient nonresponsive
  - Severe respiratory depression
- Goal is to restore adequate spontaneous respirations
  - Monitor for respiratory changes and opiate withdrawal symptoms
    - Anxiety, hypertension, tachycardia, diarrhea, seizures

Naloxone (Narcan®)

- Use lowest possible dose that maintains adequate ventilation
- Dose
  - 0.4-2 mg IV/IM/SQ titrated to effect; doses can be repeated every 2-3 minutes
    - IV route preferred because more rapid
    - IM and SQ routes have erratic absorption

Agents used for Neuropathic Pain

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

- **Dosing**
  - Requires dose titration and multiple daily doses
  - Typically use 300-600 mg three times daily
  - Dosages 1,800-3,600 mg per day were effective

- **Adverse Effects**
  - Fatigue, weight gain, back pain, somnolence, dizziness

- **Use with caution in renal impairment**

- **Well-tolerated**

Pregabalin (Lyrica ®)

- Maximum FDA approved dose is 300 mg daily
  - Initiate at 50 mg TID and increase within 1 week
- Adverse effects
  - Dizziness, somnolence, peripheral edema, blurry vision, weight gain
- Requires dosage adjustments in renal impairment

Objectives

- Review the different types of pain
- Apply pain assessment tools and discuss how to correctly assess a patient’s pain
- Discuss types of pharmacologic agents used in pain management
  - NSAIDs and acetaminophen
  - Opioids
  - Gabapentin and pregabalin
- Review the role we can play in managing a patient’s pain
Our Role

- Type of pain
- Frequent assessment of patient’s pain
- Choice of agent
  - Mild to moderate – NSAIDs, aspirin, acetaminophen
  - Severe – opioids
- Opioid naïve vs. tolerant
- Administration
- Monitoring for side effects
References


- Cupp, M. Analgesic Options for Patients with Allergic-Type Opioid Reactions. Pharmacist's Letter/Prescriber's Letter 2006; 22(2):22021


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