Pharmacological Actions Of Analgesics

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Conflict of Interest Disclosure

Disclosure

I do not have any financial relationships to disclose.
Objectives

- Explain the mechanisms of action for opiate and other agents in the treatment of pain.
- Discuss the major ADRs related to opiates.
- Explain PD and PK of most commonly used analgesic agents.
Analgesic classification

1. *Narcotics*
   - no ceiling effect except partial agonists and mixed agonist-antagonist

2. *Non-narcotics*
   - NSAIDs

3. *Adjuvant analgesic or coanalgesics*
   - tricyclic antidepressants
   - antiepileptics
   - steroids
   - bisphosphonates
Medical Management of Pain

- **WHO Ladder**

1. Mild pain
   - NSAID/APAP ± adjuvant

2. Moderate pain
   - weak narcotic ± NSAID ± adjuvant

3. Severe pain
   - strong narcotic ± NSAID ± adjuvant

4. Regional analgesia
<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Best Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic back pain</td>
<td>Acetaminophen, or an NSAID if that does not work</td>
</tr>
<tr>
<td>Headache</td>
<td>Acetaminophen, or an NSAID if that does not work</td>
</tr>
<tr>
<td>Menstrual cramps</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Migraines</td>
<td>Acetaminophen, or an NSAID</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>Acetaminophen, NSAIDs</td>
</tr>
<tr>
<td>Muscle pulls</td>
<td>NSAIDs, muscle relaxants</td>
</tr>
<tr>
<td>Nerve pain</td>
<td>Acetaminophen, NSAIDs, Anticonvulsants</td>
</tr>
<tr>
<td>Pain due to fibromyalgia4</td>
<td>Antidepressants, Anticonvulsants</td>
</tr>
<tr>
<td>Pain due to heartburn or GER</td>
<td>Antacids, H2 Blockers (e.g. Tagamet, Zantac), Proton Pump Inhibitors (e.g. Prilosec OTC)</td>
</tr>
<tr>
<td>Pain due to minor trauma (bruises, scrapes, minor sprains)</td>
<td>Acetaminophen, NSAIDs</td>
</tr>
<tr>
<td>Pain due to moderate or severe trauma (wounds, burns, fractures, severe sprains)</td>
<td>Opioids</td>
</tr>
<tr>
<td>Pain due to osteoarthritis</td>
<td>Acetaminophen, NSAIDs</td>
</tr>
<tr>
<td>Pain from a kidney stone</td>
<td>Acetaminophen, NSAIDs, Opioids</td>
</tr>
<tr>
<td>Post-surgical pain — minor</td>
<td>Acetaminophen, NSAIDs</td>
</tr>
<tr>
<td>Post-surgical pain — moderate to severe</td>
<td>Acetaminophen, NSAIDs and opioids</td>
</tr>
<tr>
<td>Sprains</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Toothaches and pain following dental procedures</td>
<td>NSAIDs and acetaminophen</td>
</tr>
</tbody>
</table>
Clinical Outcome in Pain Management

PAIN FREE

MINIMAL ADRs
Pain is Dynamic

- Assess each intervention
  - Chronic vs acute

- Titrate analgesia to comfort (<4-5/10)

- Simple comfort measures – ALWAYS

- Manage side effects
# Common Pain Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Opioids</th>
<th>NSAIDS</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Morphine</td>
<td>Ibuprofen</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>MOA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hippocrates
Greek: 460 BC-370 BC

• “First... Do No Harm”
Pharmacological Actions Of Opioid Agonists

• KEY CONCEPT: Generally, all opioid agonist drugs exert the same pharmacological effects in the CNS and periphery, but differ in pharmacokinetic properties

  – e.g., duration of action, potency, ability to cross blood-brain-barrier
Opioids

• Opioid
  – Compound with morphine-like activity

• Opiate
  – Substance extracted from opium
  – True opiate – morphine, codeine

• Modern definition of opioid
  – Molecule that interact with opioid receptor

• Opioid compound
  – Opioid receptor agonists, antagonists, agonists-antagonists
Opioid Receptors

• Most of available opioid analgesics
  – Act at μ-opioid receptor

• Activation of μ-opioid receptor
  → analgesia, euphoria, respiratory depress, nausea, vomiting, decreased gastrointestinal motility, tolerance, dependence

• δ-, κ-opioid receptor agonist
  – Produce analgesia
  – Not cause respiratory depression or to decease GI motility (??)
  → Analgesia without μ-opioid side effect
Cellular Action of opioid

- Opioid action on neuron
  - Presynaptic nerve terminal
    - Inhibit voltage-sensitive calcium channel
    → inhibit release neurotransmitter
      (substance P and glutamate)

  - Postsynaptic neuron
    - Opening potassium channel
      → hyperpolarize
Clinical Use of Opioid

• Opioid as analgesics
  – Systemically, epidurally, intrathecally apply
  – Moderate to severe acute pain, chronic cancer pain
  – Not recommended for chronic benign pain
• ➡ tolerance and dependence

• Adjunct to general anesthesia
  – Reduce hemodynamic response to intubation and surgical stimuli, amount of general anesthetic agent, coughing on emergence
  – Analgesia during early postoperative period
**Therapeutic Uses of Opiates**

- Analgesia: reduces perception of and emotional response to pain
- Intestinal disorders: reduces diarrhea; decreases dehydration
- Antitussive: cough suppressant *(codeine??)*
  dextromethorphan specific for “cough center”

**Pharmacology of Opiates**

- Tolerance and dependence develop
- Analgesic and euphoric effects are linked
- Analgesia and dependence liability are linked
Adverse Effects of Opiates

1. Respiratory depression: medulla in brainstem becomes less responsive to carbon dioxide in blood; additive with other depressants
2. Drowsiness and decreased mental alertness
3. Constipation [NO Tolerance]
4. Nausea and vomiting
5. Tolerance: cross tolerance with similar opiates
6. Acute Toxicity
   Narcotic Triad: coma, respiratory depression, pin point pupils

8. Psychological dependence: positive reinforcement from euphoria and negative reinforcement from rapid appearance of withdrawal symptoms
Opiate Effects

• **Small dose**
  – drowsiness, decreased sensitivity to internal and external stimuli, loss of anxiety and inhibition, muscle relaxation, **analgesia**, depressed respiration, constricted pupils, decreased ability to concentrate, "dreamy sleep".

• **Moderate dose**
  – elation/euphoria

• **High dose**
  – depression deepening into unconsciousness. inhibition of the respiratory center in the brain stem AND OD.
Morphine

THERE IS NO MAXIMUM DOSE OF NARCOTICS.

The dose must be titrated against effect.

- Dose requirements may vary from 2.5 mg to 2500 mg q 4 h.
- Constipation is the main persistent problem
- Decreased ganglionic transmission, causing vasodilatation and hypotension
- Histamine release, causing vasodilatation, urticaria, pruritus
Principles of Use

• Use when need is stronger than risks of use
  – Chronic malignant and non-malignant pain
  – Terminal illness

• Take medication around the clock for constant pain related to cancer

• Use a short acting agent for breakthrough pain
# Opioid Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (min)</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
<th>Half-life (h)</th>
<th>Dose Interval(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>Now</td>
<td>Now</td>
<td>?</td>
<td>1-2</td>
<td>PRN</td>
</tr>
<tr>
<td>Codeine</td>
<td>IM 10-30</td>
<td>0.5-1</td>
<td>4-6</td>
<td>3-4</td>
<td>3-6</td>
</tr>
<tr>
<td></td>
<td>PO 30-60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>IM 7-15 IV</td>
<td>Now</td>
<td>1-2</td>
<td>1.5-6</td>
<td>0.5-2</td>
</tr>
<tr>
<td></td>
<td>Now</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>PO 30-60</td>
<td>N/A</td>
<td>4-8</td>
<td>3.3-4.4</td>
<td>4-8</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>PO 15-30</td>
<td>0.5-1</td>
<td>4-6</td>
<td>2-4</td>
<td>3-6</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>PO 10-60</td>
<td>0.5-1</td>
<td>4.8</td>
<td>12-16</td>
<td>6-24</td>
</tr>
</tbody>
</table>

**single dose**
# Opioid Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (min)</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
<th>Half-life(h)</th>
<th>Dose Interval(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine</td>
<td>PO/IM/SC 10-15, IV &lt;5</td>
<td>0.5-1</td>
<td>2-4</td>
<td>3-4</td>
<td>2-4</td>
</tr>
<tr>
<td>Methadone**</td>
<td>PO 30-60, IV 10-20</td>
<td>0.5-1</td>
<td>Acute 4-6</td>
<td>15-30</td>
<td>6-12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronic &gt;8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>PO 15-60, IV &lt;5</td>
<td>PO 0.5-1</td>
<td>3-6</td>
<td>2-4</td>
<td>3-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV 0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>PO 10-15</td>
<td>0.5-1</td>
<td>4-6</td>
<td>3-4</td>
<td>3-6</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>5-15</td>
<td>0.5-1</td>
<td>3-6</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>PO 30-60</td>
<td>2-2.5</td>
<td>4-6</td>
<td>3.5-15</td>
<td>4-8</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>1-3</td>
<td>&lt;0.3</td>
<td>0.1-0.2</td>
<td>0.15-0.3</td>
<td>?</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>1.3-3</td>
<td>?</td>
<td>?</td>
<td>2.5-3</td>
<td>?</td>
</tr>
</tbody>
</table>

** single dose**
## Equianalgesic Doses of Opioid Analgesics (in mg)

<table>
<thead>
<tr>
<th>PO/PR</th>
<th>Analgesic</th>
<th>SC/IV/IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>Codeine</td>
<td>120</td>
</tr>
<tr>
<td>30</td>
<td>Hydrocodone</td>
<td>-</td>
</tr>
<tr>
<td>7.5</td>
<td>Hydromorphone</td>
<td>2-3</td>
</tr>
<tr>
<td>30</td>
<td>Morphine</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>Oxycodone</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>Fentanyl</td>
<td>0.1-0.25</td>
</tr>
</tbody>
</table>
Selecting a Starting Dose

- No prior opioid: Begin one of the opioids at a dose equivalent to 5 - 10 mg of MSO4 IV/SC every four hours
- Switching from another opioid: Calculate equianalgesic dose from standard table, then:
  - if pain control is good, reduce equianalgesic dose by 25-50% to account for incomplete cross-tolerance
  - if pain control is poor, and side effects not severe, reduce equianalgesic dose by 25% or less
HYDROCODODNE

- Effective antitussive (cough)
- Opioid used for mild to moderate pain
- 5 mg of hydrocodone = 30 mg of codeine = 10 mg morphine (orally)
- Over 200 hydrocodone containing compounds
HYDROCODONE

• Combinations:
  – Acetaminophen (Vicodin, Lortab)
  – Aspirin (Lortab ASA)
  – Ibuprofen (Vicoprofen)
  – Antihistamines (Hycomine)

• Hydrocodone:
  – Peak serum levels - 1.3 ± 0.3 hours
  – half-life - 3.8 ± 0.3 hours.
  – Complex pattern of liver metabolism
**OXYCODONE**

- Pure opioid agonist 1.5 times more potent than oral morphine
- 20 mg = 30 mg MS Oral
- Analgesic for moderate to severe pain
- Exists as a compounded drug (Percocet, Tylox)
- Controlled release drug (OxyContin)

MW 351.83
OXYCODONE

• **Actions:** Onset – 10 to 15 minutes
  Clinical Duration – 4 to 6 hours

• **Effects:** Analgesic, euphoric, anxiolytic, reduces GI motility (antidiarrheal)

• **Side Effects (dose-dependent):** Nausea, vomiting, somnolence, dizziness, constipation, pruritus, headache, dry mouth, asthenia, sweating, respiratory depression
METHADONE

- Long acting Mu agonist
- Long half-life and slow tissue accumulation
- N-methyl-D-aspartate (NMDA) antagonist (weak)
- Ability to prevent opioid abstinence symptoms longer than analgesic effect
- Side effects similar to morphine but significant risks of toxicity due to accumulation
Fentanyl (Sublimaze®)

• Rapid onset and termination of effect with bolus doses, minimal cardiovascular effects

• Available as transdermal patches (Duragesic®), and buccal lozenge (Actiq®)

• Alfentanil, sufentanil and remifentanil similar to fentanyl but more rapid onset
Transdermal Delivery

- Delayed Onset and termination of effect
- Intact skin required
- Cachexia and obesity may affect results
- Temperature sensitive absorption
- Erratic effects with cut or partial application
Tramadol (Ultram®)

• Weak Mu agonist

• Inhibits uptake of norepinephrine and serotonin

• Maximum daily recommended dose is 400 mg

• Decreased respiratory depression but still see N/V, dizziness, dry mouth, sedation, and headache
<table>
<thead>
<tr>
<th>IV Drug/Type</th>
<th>Used to Treat</th>
<th>Contraindicated In</th>
<th>Common Side Effects</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-Acting Opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>Uncontrolled or severe pain (7-10 VAS) due to malignant or non-malignant disease processes; dyspnea and other discomforts in end-of-life palliative care settings</td>
<td>Avoid repeated doses in patients with renal insufficiency</td>
<td>Constipation, nausea, sedation, pruritus, delirium, CNS toxicities</td>
<td>Base starting dose on patient’s prior history w/ opioids (naive versus tolerant); institute bowel regimen of stool softener and cathartic with therapy; increase fluids; make anti-emetic available</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Same as above</td>
<td>For patients with renal disease, start with lower dose</td>
<td>Same as above</td>
<td>More potent mg for mg than morphine.</td>
</tr>
<tr>
<td>Codeine</td>
<td>May be used in patients with morphine allergy</td>
<td></td>
<td></td>
<td>Unlike other short-acting opioids, codeine has a ceiling effect</td>
</tr>
<tr>
<td>Meperidine (Demerol)</td>
<td>Patients with unmanageable adverse reactions from other first-line opioids; treatment of drug- or transfusion-induced rigors</td>
<td>Patients with renal insufficiency</td>
<td>CNS toxicities, including seizures with accumulation of metabolite</td>
<td>Should not be used for &gt;48 hours or &gt;800 mg/day; currently not recommended for cancer pain</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>May be used in patients with morphine allergy</td>
<td></td>
<td>Same as other opioids</td>
<td>Potent; more commonly used in anesthesia settings</td>
</tr>
<tr>
<td><strong>Long-Acting Opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone*</td>
<td>Severe chronic pain from both malignant and non-malignant disease, neuropathic pain; especially useful for patients with high levels of opioid tolerance</td>
<td>All the same side effects as other opioids, including respiratory depression, cardiac conduction abnormalities (latter is rare but potentially life-threatening)</td>
<td>All the same side effects as other opioids, including respiratory depression, cardiac conduction abnormalities (latter is rare but potentially life-threatening)</td>
<td>More potent than morphine, with wide-ranging and unpredictable half-life (13-50 hours); safe in patients with renal disease and with morphine allergy</td>
</tr>
<tr>
<td><strong>Non-Opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Example: Toradol (ketorolac) [NSAID]</td>
<td>Moderate to severe pain</td>
<td>Patients with renal insufficiency or history of peptic ulcer disease</td>
<td>GI bleeding, hypertension</td>
<td></td>
</tr>
</tbody>
</table>
FDA Drug Safety: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy

2/13/2013
Codeine in Children

• Deaths have occurred in children with obstructive sleep apnea who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a cytochrome P450 2D6 polymorphism.

• These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine.

• Routine CYP2D6 genotype testing is not being recommended for use in this setting because patients with normal metabolism may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolizers.
### Prevalence of Ultra-rapid Metabolizers in Different Populations

UM = ultra-rapid metabolizer; CYP2D6 = cytochrome P450 2D6

<table>
<thead>
<tr>
<th>Population</th>
<th>UM Genotypes/Phenotypes</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(↑ Activity)</td>
<td>(UM/Total n)</td>
</tr>
<tr>
<td>African/Ethiopian⁴</td>
<td>UM (active duplicate genes)</td>
<td>29% (35/122)</td>
</tr>
<tr>
<td>African American⁵, ⁶</td>
<td>UM (three active duplicate genes)</td>
<td>3.4% (3/87) 6.5% (60/919)</td>
</tr>
<tr>
<td>Asian⁷, ⁸, ⁹</td>
<td>UM (active duplicate genes)</td>
<td>1.2% (5/400) 2%</td>
</tr>
<tr>
<td>Caucasian⁵, ⁶</td>
<td>UM (three active duplicate genes)</td>
<td>3.6% (33/919) 6.5% (18/275)</td>
</tr>
<tr>
<td>Greek¹⁰</td>
<td>CYP2D6*2xN/UM</td>
<td>6.0% (17/283)</td>
</tr>
<tr>
<td>Hungarian¹¹</td>
<td>UM (active duplicate genes)</td>
<td>1.9%</td>
</tr>
<tr>
<td>Northern European¹⁰, ¹²</td>
<td>UM (active duplicate genes)</td>
<td>1-2%</td>
</tr>
</tbody>
</table>
Health Canada’s review recommends codeine only be used in patients aged 12 and over.

Starting date: June 6, 2013
Posting date: June 6, 2013
Type of communication: Information Update
Subcategory: Drugs, Affects children, pregnant or breast feeding women
Source of recall: Health Canada
Issue: Important Safety Information
Audience: General Public
Identification number: RA-33915

Issue

Health Canada has reviewed the safety of prescription pain and cough medications containing codeine and is no longer recommending their use in children less than 12 years of age. This recommendation is based on very rare cases of serious side effects and deaths in children that have been attributed to codeine, when given directly to a child, or to babies from breast milk.

Once ingested, codeine is converted by the body into morphine. Some people ("ultra-rapid metabolizers") convert codeine into morphine more rapidly and completely than do others. The use of codeine by these ultra-rapid metabolizers can potentially lead to unexpected morphine overdose. However, not all of the serious side effects have been linked to overdose. Other risk factors, including surgery to remove tonsils, may increase the risk of known codeine side effects such as the slowing of breathing.
Patient Mrs. Jones is a 48 year-old woman with metastatic breast cancer to the spine. She is being admitted to service from a regional hospital. She is currently on morphine sulfate by IV at a continuous rate of 6 mg/hr. She has not used any breakthrough medication in the past 24 hours.

Place this patient on an appropriate dose of Oxycodone
The Steps to conversion

**Step One:** Add up the total daily amount of opioids IV or PO

**Step Two:** Convert IV to oral using CORRECT conversion

**Step three:** reduce dose by 33%

**Step Four:** Use CORRECT conversion factor to convert to another opioid
## Equianalgesic Potency Conversion

<table>
<thead>
<tr>
<th>Oral/Rectal Dose (mg)</th>
<th>Analgesic</th>
<th>Parenteral Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Codeine</td>
<td>60</td>
</tr>
<tr>
<td>-</td>
<td>Fentanyl</td>
<td>0.1</td>
</tr>
<tr>
<td>15</td>
<td>Hydrocodone</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Hydromorphone</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>Levorphanol</td>
<td>1</td>
</tr>
<tr>
<td>150</td>
<td>Meperidine</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>Methadone</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>Morphine</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>Oxycodone</td>
<td>-</td>
</tr>
</tbody>
</table>
# Equianalgesic Potency Conversion

Table 1: Equianalgesic potency conversion

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Equianalgesic Dose (mg)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM*</td>
<td>Oral</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30 (assuming repeated dosing)**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 (assuming single or intermittent dosing)</td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Pethidine</td>
<td>75</td>
<td>--</td>
</tr>
<tr>
<td>Codeine</td>
<td>130</td>
<td>200</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.4</td>
<td>0.8 (sublingual)</td>
</tr>
</tbody>
</table>

* Based on single-dose studies in which an IM dose of each agent listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an
CASE STUDY 1

Patient Mrs. Jones is a 48 year-old woman with metastatic breast cancer to the spine. She is being admitted to service from a regional hospital. She is currently on morphine sulfate by IV at a continuous rate of 6 mg/hr. She has not used any breakthrough medication in the past 24 hours.

Place this patient on an appropriate dose of methadone
The Steps

Step One: Add up the total daily amount of Morphine

For Mrs. Jones this would be:
6mg/hr IV x 24 hrs = 144 mg/day

Step Two: Convert IV to oral using conversion factor of 1:3

Using 144mg /day
144 x 3 = 432 mg po daily

Step three
reduce dose by 33%
=289 mg

Step Four:

Use conversion factor of 15:10
Divide 289 to 1.5 = 192 mg Oxycodone /day
or
Methadone 80 mg po q8hrs (Wrong, big TIME wrong)
Steady State [Methadone]
Morphine to Methadone Equianalgesia

- Less than 100 mg/day Morphine: 4:1
- 101 – 300 mg/day Morphine: 8:1
- 301 – 600 mg/day Morphine: 12:1
- 601 – 799 mg/day Morphine: 15:1
- 800 mg and greater/day Morphine: 20:1
METHADONE

- Synthetic opioid developed in Germany during WWII when morphine was in short supply
- Equipotent to oral morphine (wrong)
- 30 mg=30 mg (WRONG AGAIN)
- Used for severe pain and for detox/maint therapy for narcotic addicts
Methadone Dosing

• Since there is no scientific formula for calculating opioid tolerance, the prudent methadone-dosing advice is to initially *start low and go slow*

• Initial dose not to exceed 30 mg, or 40 mg total in first day USA (Federal Register 2001)

• Initial dose 10-20 mg if tolerance is low or uncertain; 25-40 mg if opioid tolerance established. UK (Strang 1999)

• 15-30 mg/d during the first 3 days (which represents time to 87.5% of steady state). Canada (Health Canada 2001)
• **Constipation**
  - Give laxative! Sorbitol, lactulose, bisacodyl, senna, MOM, enemas, Miralax
    - Docusate no real benefit – good for pregnant women and renal dysfunction
    - **Start with Senna (Senekot)**
  - Methylnaltrexone – blocks in GI wall, does not cross the BBB and does not affect the analgesia
    - Only approved for opioid induced constipation after other Tx failures
The Acute Opioid Withdrawal (Abstinence) Syndrome

- Strong Flu-like symptoms
- Gooseflesh (“going cold turkey”)
- Muscle tremor and twitches (“kicking the habit”)
- Abdominal cramps and diarrhea
- Increased heart rate, blood pressure
- Hyperventilation
Tolerance To Opioids

- Tolerance develops normally from repeated use
- Tolerance to sedating actions develops quickly
- Tolerance to respiratory depression can be marked
- Tolerance to analgesic effects is addressed by increasing the dose and/or adding other drugs
The Mixed Opioid Agonist-antagonists

• Thought to have decreased physical dependence and respiratory depression (??)

• Dysphoria, hallucinations common

• No therapeutic advantage over morphine
The Opioid Antagonists

• naloxone (Narcan ®)

• nalmefene (ReVex ®)

• naltrexone (ReVia ®)
The Bottom Line

• Opioids have the potential for abuse, but the actual incidence of abuse among pain patients is very low.

• “Addiction rarely occurs among those who use pain relievers as prescribed; the risk of addiction exists when these meds are used in ways other than prescribed.”

  – NIDA Position Statement 2001
ADDICTION

“Addiction is a brain disease shaped by behavioral and social context.”

Dr. Alan Leshner, Director
National Institute on Drug Abuse

“It’s like I’ve got a shotgun in my mouth, my finger’s on the trigger and I like the taste of gun metal.”

Robert Downey, Jr.
Actor
Attention Prescribers:
FDA seeks your help in curtailing the U.S. opioid epidemic

3/1/2013
Global Goal…..

- Prevention of the FIRST USE of Drugs and Alcohol

- We cannot avoid this issue
Physicians:

- The source of problems and solutions with prescription medication
- Physicians can fulfill important roles in the management and treatment of drug disorders in their patients, from identification, diagnosis, treatment referral, and monitoring
Physicians:

• 43% of patients with a drug disorder reported that their physicians never diagnosed the disorder;
  – an additional 10.7% reported their physicians knew about their disorder but did nothing about it.

• Critically important, almost 75% of patients reported their primary care physician was not involved in their decision to seek treatment
The Pain/Addiction-Dependence Conundrum

- DEA Drug Diversion control Program.
  - U.S. 4.6% of the world's population
  - Consume 80% of all opioids, Rx and illicit.
    - 46% of the illicit prescription opiates are diverted from legitimate prescriptions.
    - Prescription opioids are the gateway to heroin.
    - Independent Data from Multnomah County 72% of Heroin Addicts in drug court began with Rx Pain Medication.


- Users of regularly prescribed opioids had higher rates of opioid addiction 6-12%, Up to 40% misuse or abuse regularly

M Edlund et. al. Pain Medicine. 2007; 8(8) 647-56; Rabek et. al. Pain Physician 2006; 6(2)
Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010)

**Graph Description:**
- **Sales:** Green triangles, representing sales per kilograms per 10,000 people.
- **Deaths:** Purple squares, representing deaths per 100,000 people.
- **Treatment:** Orange circles, representing treatment admissions per 10,000 people.

**Sources:**
Where Are All These Drugs Coming From?
Opioid Prescriptions Dispensed by Retail Pharmacies—United States, 1991–2011

Public Health Impact of Opioid Use

For every 1 overdose death in 2012, there were

- Past Year Nonmedical Users: 733
- People with abuse/dependence: 108
- ED visits for misuse or abuse: 26
- Abuse treatment admissions: 10

Treatment admissions are for primary use of opioids from Treatment Exposure Data set.
Emergency department visits are from DAWN (Drug Abuse Warning Network), https://dawninfo.samhsa.gov/default.asp. Abuse/dependence and nonmedical use in the past month are from the National Survey on Drug Use and Health.
Hippocrates
Greek: 460 BC-370 BC

• “First... Do No Harm”
How Can I Help?

• Examine your own prescribing habits
• Reach for a non-opioid first
• Share Practice Plans & Pain Management Contracts (EDIE & with Primary Care)
• DON’T give false expectations to patients about their visit (know our guidelines)
• For Consultants, be available & expect “the call”
# Common Pain Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Opioids</th>
<th>NSAIDS</th>
<th>Others</th>
</tr>
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<tr>
<td>Example</td>
<td>Morphine</td>
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</tr>
<tr>
<td>Comments</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NSAIDS

Ali J. Olyaei, PharmD, BCPS
Professor of Medicine & Pharmacotherapy
Nephrology & Hypertension
Oregon State University and Oregon Health & Science University
Case 1-2

A 46-year old man presents with a sudden onset of pain, redness and swelling of the Rt knee. He cannot recollect any injury, and has never had it before.

A 21-year old man IVDU presents with a sudden onset of pain, redness and swelling of the Rt knee. He cannot recollect any injury, and has never had it before.
Aspirin History

(From the German acetylsalicysaure + chemical suffix – in)

First synthesized in pure form by Felix Hoffman of Friedr. Bayer & Co. in 1897.
Arthur Eichengrun, was very likely the inventor of ASA but his contribution was eliminated from the history of the drugs’ discovery by the Nazis because he was Jewish. *Aspirin: A Bitter Pill.* Dr Walter Sneader
Could Aspirin Save Your Life This Year?

- Today, 62 million Americans are at risk for cardiovascular disease
- Each year, 650,000 Americans will suffer a first heart attack
- Almost half of men and women under age 65 who have a heart attack (MI) die within 8 years

Unless you see the “Bayer Cross” on package or on tablets you are not getting the genuine Bayer Aspirin proved safe by millions and prescribed by physicians over twenty-seven years for:

- Colds
- Headache
- Neuritis
- Lumbago
- Toothache
- Rheumatism
- Neuralgia
- Pain, Pain

Each unbroken “Bayer” package contains proven directions. Handy boxes of twelve tablets cost few cents. Drugists also sell bottles of 24 and 100.

Aspirin is the trade mark of Bayer Manufacture of Monoaeteneicdenter of Salicylicacid
## List of NSAIDs Available by Prescription

<table>
<thead>
<tr>
<th>NON-SALICYLATES</th>
<th>SALICYLATES</th>
<th>COX-2 INHIBITORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac (Voltaren)</td>
<td><strong>Aspirin</strong>&lt;sup&gt;a&lt;/sup&gt; (Zorprin, Easprin)</td>
<td><strong>Celecoxib</strong> (Celebrex)</td>
</tr>
<tr>
<td>Diclofenac/Misoprostol (Arthrotec)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Diflunisal (Dolobid)</td>
<td>In Development</td>
</tr>
<tr>
<td>Fenoprofen (Nalfon)</td>
<td>Salsalate (Disalcid, Salflex)</td>
<td>Etoricoxib</td>
</tr>
<tr>
<td>Flurbiprofen (Ansaid)</td>
<td>Choline salicylate (Trilisate)</td>
<td>Parecoxib&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Ibuprofen</strong> (Motrin)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Magnesium salicylate (Magan)</td>
<td>Lumiracoxib</td>
</tr>
<tr>
<td>Indomethacin (Indocin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoprofen (Orudis)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meclofenamate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mefenamic acid (Ponstel)</td>
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<td></td>
</tr>
<tr>
<td>Nabumetone (Relafen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen (Naprosyn, Anaprox)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaprozin (Daypro)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piroxicam (Feldene)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulindac (Clinoril)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolmetin (Tolectin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meloxicam (Mobic)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Also available as over-the-counter preparations in the U.S.

<sup>b</sup> Combination tablet of NSAID/synthetic prostaglandin E<sub>1</sub>

<sup>c</sup> Parenterally administered

---

2014 Physician’s Desk Reference
COX-2

COX-1

COX-1

PGI₂

COX-1

COX-1

COX-2

Cardiac Fibrosis

BP

Systolic

Diastolic

TXA₂

COX-2

COX-2

COX-1

COX-1
Common Pharmacological Effects

- **Analgesic** (CNS and peripheral effect) may involve non-PG related effects
- **Antipyretic** (CNS effect)
- **Anti-inflammatory** (except acetaminophen) due mainly to PG inhibition.
  
  Some shown to inhibit activation, aggregation, adhesion of neutrophils & release of lysosomal enzymes
- **Some are** **Uricosuric** **[Indomethacin]**
Common Adverse Effects

• Platelet Dysfunction
• Gastritis and peptic ulceration with bleeding (inhibition of PG + other effects)
• Acute Renal Failure in susceptible
• Sodium+ water retention and edema
• Analgesic nephropathy
• Prolongation of gestation and inhibition of labor.
• Hypersenstivity (not immunologic but due to PG inhibition)
• GIT bleeding and perforation
Mortality: NSAID-Induced GI Complications vs. Other Diseases in US*

*Data from 1997

Detection of a Cardiovascular Signal

Intrinsic CV Risk

- HIGH
- INTER
- LOW

CABG

? RA

OA /

? Polyps

Drug Exposure and Selectivity in vivo

NNT &/or Trial Duration

HIGH

INTER

LOW
## The VIGOR Study

<table>
<thead>
<tr>
<th>Event</th>
<th>Rofecoxib</th>
<th>Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>9 (0.2%)</td>
<td>8 (0.2%)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>20 (0.5%)</td>
<td>4 (0.1%)</td>
</tr>
</tbody>
</table>
Boxed Warning for All Prescription NSAIDs

Cardiovascular Risk

- “xxxx” may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

- “xxxx” is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

- NSAIDs, including “xxxx”, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.
We Must Remember That the Absence of Evidence Is Not the Evidence of Absence
COX-1 and COX-2 in the Human Kidney

NSAIDs and Renal Effects

Arachidonic acid

NSAID

Cyclooxygenase

↓ Prostaglandins

↓ Renal blood flow

↑ Chloride absorption

↓ Renin

↑ ADH effect

↓ Aldosterone

↓ GFR

Sodium retention

↑ Renin

Potassium retention

Water retention

↑ BUN

↑ Creatinine

Edema

Hypertension

Hyperkalemia

Hyponatremia
Duration of Action and Renal Effects of NSAIDs

- Short acting NSAID, Modest dose
- Short acting NSAID, High dose
- Long acting NSAID

“Nephrotoxic or Cardiovascular Toxic” Concentration
### Observational Studies on the Association Between Current Use of NSAIDs and Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population characteristics, sample size</th>
<th>Outcome definition</th>
<th>RR/OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heerdink et al. n=10519</td>
<td>Cohort</td>
<td>Elderly recipients of diuretics and NSAIDs, identified in community pharmacies</td>
<td>First hospitalization with a primary or secondary diagnosis of heart failure</td>
<td>1.8 (1.4 – 2.4)</td>
</tr>
<tr>
<td>Page and Henry n=1023</td>
<td>Case-control</td>
<td>Patients admitted to the emergency department of a hospital</td>
<td>Hospitalization with a primary diagnosis of heart failure</td>
<td>2.1 (1.2 – 3.3)</td>
</tr>
<tr>
<td>Feenstra n=559</td>
<td>Cohort</td>
<td>Elderly recipients of NSAIDs, with one hospitalization for heart failure, identified in community pharmacies</td>
<td>Rehospitalization with a primary diagnosis of heart failure</td>
<td>2.2 (1.4 – 3.4)</td>
</tr>
<tr>
<td>Feenstra et al. n=5062 n=85</td>
<td>Cohort</td>
<td>Elderly recipients of NSAIDs in population: Without heart failure</td>
<td>First occurrence of heart failure</td>
<td>1.2 (0.8 – 1.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With incident heart failure</td>
<td>Hospitalization for relapse heart failure</td>
<td>9.9 (1.7 – 57.0)</td>
</tr>
<tr>
<td>DRUG</td>
<td>MECHANISM</td>
<td>EFFECT</td>
<td></td>
<td></td>
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<td>---------------</td>
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<td>------------------------------------------------------------------------</td>
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<tr>
<td>Anticoagulants</td>
<td>Displacement/additive effect</td>
<td>Increased anticoagulant activity via displacement. Also, some NSAIDS affect platelet function.</td>
<td></td>
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</tr>
<tr>
<td>Lithium</td>
<td>NSAIDS inhibit renal elimination of lithium</td>
<td>Elevated serum lithium levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>NSAIDS may cause fluid retention and edema</td>
<td>Decreased antihypertensive effects</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case 1-2

A 46-year old man presents with a sudden onset of pain, redness and swelling of the Rt knee. He cannot recollect any injury, and has never had it before.

A 21-year old man IVDU presents with a sudden onset of pain, redness and swelling of the Rt knee. He cannot recollect any injury, and has never had it before.
Acetaminophen [Tylenol]

• No significant anti-inflammatory effect, but used for its mild analgesic effect.
• Well-absorbed and without GIT irritation.
• Serious disadvantage: at high doses, severe hepatotoxicity results.
• 3-4 gms /day for chronic use
  – 1.5 gms in patients with liver disease and ETOH
Mechanisms of Action

• Analgesia – both centrally and peripherally.

- assoc with anti-inflammatory actions.

- results from inhibition of PG synthesis in inflamed tissues most likely through COX-3[??]
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<td>Use</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Pain</td>
<td>Best Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic back pain</td>
<td>Acetaminophen, or an NSAID if that does not work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Acetaminophen, or an NSAID if that does not work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual cramps</td>
<td>NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraines</td>
<td>Acetaminophen, or an NSAID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle aches</td>
<td>Acetaminophen, NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle pulls</td>
<td>NSAIDs, muscle relaxants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve pain</td>
<td>Acetaminophen, NSAIDs, Anticonvulsants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain due to fibromyalgia</td>
<td>Antidepressants, Anticonvulsants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain due to heartburn or GERD</td>
<td>Antacids, H2 Blockers (e.g. Tagamet, Zantac), Proton Pump Inhibitors (e.g. Prilosec OTC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain due to minor trauma (bruises, scrapes, minor sprains)</td>
<td>Acetaminophen, NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain due to moderate or severe trauma (wounds, burns, fractures, severe sprains)</td>
<td>Opioids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain due to osteoarthritis</td>
<td>Acetaminophen, NSAIDs</td>
<td></td>
<td></td>
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<tr>
<td>Pain from a kidney stone</td>
<td>Acetaminophen, NSAIDs, Opioids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-surgical pain — minor</td>
<td>Acetaminophen, NSAIDs</td>
<td></td>
<td></td>
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<tr>
<td>Post-surgical pain — moderate to severe</td>
<td>Acetaminophen, NSAIDs and opioids</td>
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<tr>
<td>Sprains</td>
<td>NSAIDs</td>
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<tr>
<td>Toothaches and pain following dental procedures</td>
<td>NSAIDs and acetaminophen</td>
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