UNM Pain Update Course
Opioid Analgesics: Safe Prescribing
Conflict of Interest

- No conflicts of interest to disclose
Objectives

• At the end of this presentation, the participant will:
  ➢ Compare onset of and duration of action of short acting and long acting opioid medications
  ➢ Calculate equianalgesic dosing of common short acting opioid
  ➢ Devise an opioid pain plan in patient who is opioid naïve and appropriate for chronic opioid therapy
  ➢ Calculate the conversion from short acting opioids to a long acting opioid dose
  ➢ List 6 common side effects of opioids and their treatment
Opioids—moderate to severe pain

• Opioids (morphine is prototype)
  • All produce pain relief via interaction with opioid receptors in the brain/spinal cord and peripheral opioid receptors
    • The $\mu$ receptor is the dominant analgesic receptor, but other receptors play a role in analgesia for certain opioids
Higher Dose, Higher Risk

• “Among patients receiving opioid prescriptions for pain, higher opioid doses were associated with increased risk of opioid overdose death”.

*JAMA.* 2011;305(13):1315-1321.
Higher Dose, Higher Risk

- Use opioids for pain:
  - 750 unintentional OD vs. 154,684 controls
- Total frequency of unintentional OD: 0.04%
  - Unintentional OD for >100mg/day vs. <20mg/day
    - Substance use disorder: HR 4.54, CI 2.46-8.37
    - Chronic pain: HR 7.18, CI 4.85-10.65
    - Acute pain: HR 6.64, CI 3.31-13.31
    - Cancer HR 11.99, CI 4.42-32.56
    - No difference for short vs. long acting pain medications

*JAMA. 2011;305(13):1315-1321.*
# Opioid Equivalency Table

<table>
<thead>
<tr>
<th>Short acting</th>
<th>Dose (mg) IV/SQ</th>
<th>Dose (mg) Oral</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td>2-4</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
<td>2-4</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>2</td>
<td>2-4</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
<td>30</td>
<td>2-4</td>
</tr>
</tbody>
</table>
Opioids

• Metabolized by the liver, excreted by the kidneys
  • Therefore, caution in hepatic or renal impairment
Short acting (SA) opioids

• Duration of action: 2-4 hours (IV and PO)
  • Oral onset is 20-30 minutes; peaks in 60-90 minutes
    • In contrast, IV peaks in 10-15 minutes
Oral Long Acting (LA) opioids (except methadone)

• Morphine SR (s.a. MSContin) and Oxycodone SR (s.a. Oxycontin)
  • Provide 8-12 hours of analgesia
    • Minimum dosing interval is q 8 hours
    • Provide onset of analgesia within 2-3 hours of taking first dose
• Oral long acting opioids other than methadone can be dose escalated every 24 hours
  • Transdermal fentanyl only every 72 hours!
# Time course of SA and LA agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset</th>
<th>Peak Effect</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fentanyl IV</strong></td>
<td>&lt; 1 min</td>
<td>&lt; 5 min</td>
<td>0.5 – 2 hr</td>
</tr>
<tr>
<td><strong>IV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>1–2 min</td>
<td>10 – 15min</td>
<td>2 – 4 hr</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PO – SA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>20 – 30 min</td>
<td>60 – 90 min</td>
<td>3–6 hr</td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PO – LA</strong></td>
<td></td>
<td>PLATEAU</td>
<td>8 – 12 hr</td>
</tr>
<tr>
<td>MS Contin</td>
<td>Within 2 hr</td>
<td>3 – 8 hr</td>
<td></td>
</tr>
<tr>
<td>Oxycontin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fentanyl Patch</strong></td>
<td>13 – 24 hr</td>
<td>BROAD PLATEAU</td>
<td>48 – 72 hr</td>
</tr>
</tbody>
</table>
Fentanyl Patches

- Fentanyl patches are good for *chronic stable pain*.
  - They should never be prescribed to an opioid naïve patient
  - They are *not good* for rapidly escalating pain since they are very difficult to titrate!
    - Take 13-24 hours after application to become effective and 3 days to change dose....
      - Similarly, when a patch is removed, it takes 13-24 hours to be eliminated from the system

- ALWAYS educate patients and families about the 13-24 hour onset and appropriate usage
  - Ex. You can’t cut a patch, you can’t take it off and put it back on, etc.
Fentanyl patch dosing

- Fentanyl patch dose (mcg) x 2 = oral morphine equivalent in a 24 hour period
  - 25 mcg/hr patch = 50mg oral morphine in a 24 hour period
  - 100mcg/hour fentanyl patch = 200mg oral morphine in a 24 hour period
Case

- Mr. Peters, 56 yo man, has a history of chronic back pain
  - Dx: Failed back surgery syndrome, or post laminectomy syndrome
  - Tried: NSAIDs, Gabapentin, Cyclobenzaprine, TENS unit, PT
    - Pain still 9/10 (severe)
    - Risk Assessment for opioid abuse: Low risk
  - After thorough evaluation and assessment, you decide to use opioids for his pain
Common starting doses:

<table>
<thead>
<tr>
<th></th>
<th>Adult &gt;50kg; normal renal and liver function</th>
<th>Elderly or <em>moderate</em> renal or liver disease</th>
<th>HALF DOSE (if you use at all)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine PO</td>
<td>5 mg q4h prn</td>
<td>2.5 mg q4–6hr</td>
<td></td>
</tr>
<tr>
<td>Oxycodone PO</td>
<td>5 mg q4h prn</td>
<td>2.5 mg q4–6</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone PO</td>
<td>5 mg q4h prn</td>
<td>2.5 mg q4–6h</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone PO</td>
<td>1 mg q4h prn</td>
<td>0.5 mg q4–6h</td>
<td></td>
</tr>
</tbody>
</table>
Case

• You choose oxycodone 5mg po q4 hours prn moderate to severe pain
  • Advise about risks, benefits, side effects
  • Opioid Agreement signed
• You see him back in clinic in 10 days
Case

• He reports his pain better at 7/10 (goal is <4-5/10). He is able to go back to work, but still with some difficulty secondary to pain
• He is taking 5 mg oxycodone every 4 hours for the pain
  • Finds it distracting from his work and life to stop every 4 hours to take a medication
  • Would like his pain somewhat better controlled to reach his goal (<4-5/10)
  • He wonders about a long acting pain medication
Case

• How would you calculate the dose of a long acting medication?
  • You decide on using long acting morphine (s.a. MS Contin) since this is the only long acting medication covered on his insurance plan
• How would you convert from short acting oxycodone to long acting morphine?
1. Find total 24h dose (of old regimen)
   - 6 tabs x 5mg oxycodone = 30mg oxycodone/ 24hr

2. Use ratio from opioid equivalence chart

   \[
   \frac{30\text{mg oxy}}{X \text{mg morphine}} = \frac{20\text{mg oxycodone}}{30 \text{mg morphine}}
   \]

   • \(30\text{mg} \times \frac{30}{20} = 45\text{mg morphine/24hr}\)
Adjustments

- Would this give him better pain control than Oxycodone 5mg po q4 hours?
  - **NO!** It is the same dose
  - Pain is still moderate (7/10).
Adjust for the ADEQUACY of pain control on the prior regimen

- If the patient has **mild** pain (1-3/10) while taking the prior regimen, we increase the dose by **0-25%**.

- If pain is at a **moderate** level (4-7/10) on the prior regimen, we increase the dose by **25-50%**.

- If pain is **SEVERE** (8-10/10) on the prior regimen, we increase the dose by **50-100%**.
Conversion to Long-Acting

- Find 24h dose:
  - 45mg morphine/ 24h

- Adjust for better pain control? Yes- increase by 25%
  - 45mg x .25 = 11.25 mg MS Contin
  - 45 mg + 11.25mg = 56.25 mg MS Contin/24 hours
Adjustments

• Incomplete cross-tolerance
  • What is that?
Incomplete Cross-Tolerance

- Each opioid stimulates a different subset of mu receptors.

*Oxycodone*  
*Morphine*
Incomplete Cross-Tolerance

With chronic use (>5-7d), tolerance to stimulation develops at this subset of receptors.

**Oxycodone**
Incomplete Cross-Tolerance

- The new opioid will stimulate some of these old (tolerant) receptors and a subset of different Mu receptors.

Oxycodone

Morphine
Incomplete Cross-Tolerance

- There may be a more profound response due to stimulation of the new (non-tolerant) receptors.

- To account for this “incomplete cross-tolerance” the equianalgesic dose of the new opioid is often decreased by 25-50% for initial dosing.
Conversion to Long Acting

- Adjust for incomplete cross-tolerance? Yes
  - 56.25 mg x 25% *decrease* = 42 mg / 24h

- Divide by number of doses / 24hr
  - Final result: 42mg / 2 =
    - 21 mg MS Contin q12h or
    - 14mg MS Contin po q8 hours

- Note: Use closest available dosing strength with breakthrough coverage if number does not come out as an available pill strength. Lowest dose of MS Contin is 15mg.
  - Possibilities:
    - MS Contin 15mg po q 12 hours (rounding down)
    - MS Contin 15mg po q 8 hours (roughly equal)
Breakthrough Medication

- Decide if you are going to use a breakthrough, short acting pain medication as well as a long acting medication.
- For chronic, non-malignant pain, often a long acting medication is sufficient.
The 10% Rule

- If you plan to use a breakthrough, short acting pain medication in addition to the long acting pain medication:
  - Use 10% of the total daily long acting pain medication, prescribed in the “short acting” form
- Example: For this patient, total daily dose is 45mg MSContin
  - 10% of 45mg MS Contin is 4.5 mg morphine immediate release po q4 hours prn mod-severe pain
    - OR roughly 2.5 or 5mg oxycodone po q4 hours prn mod-severe pain
      - I would probably use 5mg since this is what he was taking before, IF I was going to use a break through short acting medication in addition to the long acting medication
Pearls

• General Guidelines: Start low and go slow; observe; adjust over time

• If you are treating pain, and it is not getting better- are you using the right drug (i.e. would adjuvant work better?) Right amount? Is there a non-physical component to the pain?
  • “Total Pain”-physical, psychological, social, spiritual, existential sources of pain
Pearls

• Always start with a *short acting* opioid in an opioid naïve patient

• Long acting opioids should never be “prn”
  • Or dosed any more often than q8-12 hours...
Pearls

• Never prescribe more than one short or long acting opioid drug at any one time (except in very rare circumstances)
  • Avoid polypharmacy of different opioids
Pearls

- Avoid opioids available as combination products (with acetaminophen or aspirin) in people with escalating pain because of concern of toxicity of non-opioid component
  - Ex. Codeine, hydrocodone, and oxycodone *with* acetaminophen
  - Max acetaminophen in 24 hours in patients with normal hepatic function is 3 grams
    - Elderly <2 grams
Pearls

• Specific opioids
  • Avoid
    • **Codeine** (most emetogenic and constipating of opioids)
    • **Demerol** (meperidine) except for one time dosing (s.a. procedure); lowers seizure threshold
    • **Darvon or Darvocet (propoxyphene)** - *Now off the market*
  • Avoid morphine in renal insufficiency (increased risk for neurotoxicity, eg. myoclonus); use other opioids if you need an opioid
Pearls

• You cannot crush long acting opioids (s.a. MS Contin) or cut a fentanyl patch!
  • Therefore, can’t use Oxycontin or MS Contin in a G-tube
• Generics are cheaper than name brands
Pearls

• If a patient develops mental status changes (sedation, confusion) on a stable dosing of opioid (without new renal or hepatic insufficiency)
  • It *may* be the opioid but *may not* be the opioid
    • Beware of prescribing opioids with other sedating medications (such as benzodiazepines)
    • Treat appropriately and also search for other causes
Pearls

• Methadone is different:
  • Do not initiate methadone *for pain* without guidance from a pain specialist
    • Very tricky to use correctly! Needs close monitoring
    • Extremely long half life
      • Dose can be adjusted safely only every 5 days (and for some, weeks)
    • QT interval prolongation (arrhythmia); requires EKG monitoring
  • Many drug/drug interactions
Data: Methadone

- NYT July 2012: Methadone accounted for 1/3 deaths from opioids in 2009
  - But only 2% of opioid prescriptions written
    - 1/3 patients prescribed methadone were opioid naive
- New Mexico
  - 1998-2002: 143/1120 (12.8%) drug related deaths caused by methadone
    - 75% from illicit drug use
    - 300% increase in prescribing of methadone in this time period

*Addiction* 2005, 100, 176–188
## Opioid Side Effects and Treatments

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Duration</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONSTIPATION!!!</strong>*</td>
<td>Chronic</td>
<td>Bowel stimulant, s.a. senna, +/- osmotic agent</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>3-7 days</td>
<td>Compazine, phenergan, reglan, odansetron</td>
</tr>
<tr>
<td>Sedation</td>
<td>2-3 days</td>
<td>Decrease opioid dose, look for other causes as well</td>
</tr>
<tr>
<td>Pruritis/Itching</td>
<td>&lt;5 days</td>
<td>Anti-histamine, steroids</td>
</tr>
<tr>
<td>Confusion/Hallucination</td>
<td>&lt;2 days</td>
<td>Different opioid, lower dose, haldol</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td></td>
<td><strong>Non-responsive and decr. respirations NALOXONE</strong></td>
</tr>
</tbody>
</table>

*Constipation is the only side effect to which people do not become tolerant while on opioids*
References

• Johnson SJ. Opioid Safety in Patients with Renal or Hepatic Dysfunction. www.Pain-Topics.org
• Kral LA. Opioid Tapering: Safely Discontinuing Opioid Analgesics. www.Pain-Topics.org