Buprenorphine, Benzos, and Beyond

Chris Herndon, PharmD, BCPS, CPE
Associate Professor
Southern Illinois University Edwardsville

Disclosures
• None

Learning Objectives
- Describe the unique pharmacology of clinically relevant opioids
- Explain adverse effects of opioids and benzodiazepines when used concurrently
- Discuss the role of personalized medicine in the treatment of chronic pain

Methadone
- Availability (US)
  - Oral Solution 10 mg/mL & 1 mg/mL
  - Oral Tablet 5mg, 10mg, 40mg (restricted)
  - Parenteral Solution 10mg/mL
- DEA Schedule II
- Oral Bioavailability
  36% to 100%
- Distribution
  - Vd 1 to 8 L/kg; extremely lipophilic
- Metabolism via CYP 3A4, 2B6, & 2C19
- Terminal half-life 8 to 59 hrs

Source: Am Fam Physician 2005.
Methadone Onset of Action, Analgesia
- Oral
  - 0.5 hr to 1 hr
  - peak effect 3 to 5 days
- Parenteral
  - 10 to 20 minutes
  - peak effect 1 to 2 hr

Methadone Mechanism of Action
- R-methadone
  - MOR 1 and MOR 2 agonist (50x that of R-isomer)
  - KOR agonist
  - Norepinephrine and serotonin reuptake inhibition
- S-methadone
  - Na+, K+ inhibition
  - K+, Na inhibition
- Racemic
  - α4β2 and α3* nicotinic antagonist
  - α7 nicotinic agonist
  - Noncompetitive NMDA antagonist
  - DOR desensitization / agonism

New Methadone Guidelines
- Patient selection, education, & counseling
- ECG monitoring
- Initiation dose and dosing strategy
- Non cardiac adverse event monitoring
- Urine drug screening
- Medication interactions
- Use in pregnancy

Electrocardiogram Monitoring
- Prior to initiation in those at risk for QTc prolongation
- Within 2 to 4 weeks of initiation in those at risk
- When total oral daily dose exceeds 30mg
- When total oral daily dose exceeds 100mg
- If signs / symptoms of ventricular arrhythmia become apparent
- Avoid or discontinue methadone if QTc ≥ 500ms
- Correct reversible causes of prolongation prior to methadone initiation if QTc ≥ 500ms
- Consider switching from methadone or reducing dose if QTc ≥ 500ms on followup ECG

Patient Selection & Education
- Appropriate patient selection
- Likelihood of adherence
- Risk for misuse or abuse
- Patient education
- Risk of cardiac arrhythmias
- Expectations for onset of analgesia
- Risk of drug interactions and notification of prescribers

Methadone Initiation & Dosing
- Initiation & titration in opioid naïve (REMS defined)
  - 2.5mg PO Q8 hrs
  - Dose increases ≤ 5mg / day every 5 to 7 days
- Initiation & titration in opioid tolerant
  - 75% to 90% reduction in calculated equianalgesic dose
  - No higher than 30mg to 40mg PO daily
  - Dose increases ≤ 10mg / day every 5 to 7 days
- Face to face or phone assessments within 3 to 5 days following initiation or titration
Methadone Conversion

(Modified Morley-Makin)
- Dolophine prescribing insert

Conversion Conversion

<table>
<thead>
<tr>
<th>Current daily oral morphine equivalent dose</th>
<th>Conversion Ratio morphine to methadone</th>
<th>Conversion Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg</td>
<td>3 to 1</td>
<td>3.33</td>
</tr>
<tr>
<td>101 to 300 mg</td>
<td>5 to 1</td>
<td>2.00</td>
</tr>
<tr>
<td>301 to 600 mg</td>
<td>10 to 1</td>
<td>1.00</td>
</tr>
<tr>
<td>601 to 800 mg</td>
<td>12 to 1</td>
<td>0.83</td>
</tr>
<tr>
<td>801 to 1,000 mg</td>
<td>15 to 1</td>
<td>0.67</td>
</tr>
<tr>
<td>&gt;1001 mg</td>
<td>20 to 1</td>
<td>0.50</td>
</tr>
</tbody>
</table>


Should we still use methadone for chronic pain?

Personalized Medicine?

CYP 1A2
- Inhibitors
  - Ciprofloxacin
  - Fluvoxamine
- Inducers
  - Modafinil
  - Omeprazole
  - Tobacco

CYP 2B6
- Inhibitors
  - Clopidogrel
  - Ticlopidine
- Inducers
  - Carbamazepine

(r)-methadone
- EDDP
- Inactive, numerous

CYP 1A2
- Inhibitors
  - Carbamazepine
  - CYP 3A4

CYP 2B6
- Inactive, numerous

Buprenorphine

- Availability (US)
  - Sublingual tablet 2mg, 8mg
  - Transdermal patch 5mcg, 7.5mcg, 15mcg, 20mcg
  - Parenteral Solution 0.3 mg/mL
- DEA Schedule III
- Bioavailability
  - Sublingual 29%
  - Transdermal 1%
- Distribution
  \[V_d = 0.7 \times 10^7 \ \text{L/kg}\]
- Metabolism via CYP 3A4 to norbuprenorphine (active)
- Terminal half life
  - Sublingual 87hrs
  - Transdermal 24 hrs
- Onset
  - Sublingual 0.5 to 1 hr
  - Transdermal <72 hrs

Buprenorphine
- MOR partial agonist, KOR & DOR antagonist, ORL-1 agonist
- Norbuprenorphine weak MOR full agonist
- Comparatively high binding affinity for MOR-1
- Antinociceptive versus analgesic
- Ceiling effect for analgesia and respiratory depression dose-response
- Theoretically lower risk for opioid induced respiratory depression
- Lower risk of opioid induced hypogonadism
- Little to no effect on biliary pressures
- Unclear equianalgesic properties for SL and TD
- Much higher TD dose availability
- 1:100 for TD buprenorphine : PO morphine
- 1.4:1 for TD buprenorphine : TD fentanyl
- 1:80 for SL buprenorphine : PO morphine

Box A. Reversal of Buprenorphine-induced Respiratory Depression
1. Discontinue buprenorphine (i.e., CSA/CIVL, remove TD patch).
2. Give oxygen by mask.
3. Give IV naloxone 0.4 mg over 30 sec.
4. Give IV naloxone 0.4 mg every 3 minutes.
5. Continue IV naloxone 0.4 mg every 3 minutes until the patient’s condition is satisfactory (probably 10-20 mg).
6. Monitor the patient frequently for the next 24 hours and readjust CIVL if respiratory depression recurs.
7. If the patient condition remains satisfactory, restart buprenorphine at a reduced dose, e.g., half the previous dose.

Buprenorphine patch dosing

<table>
<thead>
<tr>
<th>Daily morphine equivalents</th>
<th>Starting dose of buprenorphine patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30mg / 24 hours</td>
<td>5 mcg/hr buprenorphine patch</td>
</tr>
<tr>
<td>30-80mg / 24 hours</td>
<td>10 mcg/hr buprenorphine patch</td>
</tr>
</tbody>
</table>

Morphine equivalents > 80mg / 24 hours may not be suitable candidates
Patients should be weaned to <30mg morphine equiv / 24 hours for 7 days
Dose titration may occur every 72 hours

Buprenorphine and Pain
- Chronic low back pain
- Osteoarthritis
- Cancer pain
- HIV neuropathy
- Post-op gynecologic surgery pain
- Acute fracture pain
- Central neuropathic pain

Buprenorphine and QTc

Levorphanol
Levorphanol

- Availability (US)
  - Oral Tablet 2mg
- DEA Schedule II
- Bioavailability
  - Sublingual 18 to 29%
- Distribution
  - $V_d = 97$ to $187$ L/kg
- Glucuronidation only
- Terminal half life
  - 11 to 16 hours
- Onset
  - 10 to 60 minutes
- Duration of analgesia
  - 6 to 13 hours

Levorphanol is a

- MOR 1 agonist
- KOR 1 & KOR 3 agonist
- Norepinephrine reuptake inhibition
  - $K_i = 1.2$ (imipramine $K_i = 0.01$)
- Serotonin reuptake inhibition
  - $K_i = 0.09$ (imipramine $K_i = 0.02$)

Levorphanol Dosing

<table>
<thead>
<tr>
<th>Oral morphine equivalent</th>
<th>Morphine: Levorphanol ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100mg</td>
<td>12 to 1</td>
</tr>
<tr>
<td>100-299mg</td>
<td>15 to 1</td>
</tr>
<tr>
<td>300-599mg</td>
<td>20 to 1</td>
</tr>
<tr>
<td>600-999mg</td>
<td>25 to 1</td>
</tr>
<tr>
<td>&gt; 1000mg</td>
<td>No data</td>
</tr>
</tbody>
</table>

Levorphanol & chronic pain

- Central nervous system: 12, 13
- Spinal cord: 4, 4
- Peripheral nerve: 5, 5
- Peripheral pain: 15, 15

Levorphanol and QTc prolongation

Nalbuphine

- MOR partial antagonist
- KOR 1 & KOR 3 agonist
- NOP agonist
- Equi- or more potent than IV morphine
- Few studies on oral administration
- Less hemodynamic effects with similar analgesia to morphine post-op
- Increased sphincter of Oddi manometry
- May be more attractive for intrathecal administration

Nalbuphine as post-op PCA in Gyn

- Morphine > nalbuphine in VAS reduction
- Morphine > nalbuphine in rescue analgesia requirement
- Morphine > nalbuphine on Ramsay sedation
- Morphine > nalbuphine on nausea and pruritus

Nalbuphine ± morphine IVPCA

Does gender matter?

- Male
  - nalbuphine 3 mg alone
  - morphine 3 mg alone
  - nalbuphine 4 mg + morphine 3 mg
  - morphine 4 mg + morphine 3 mg

- Female
  - nalbuphine 3 mg alone
  - morphine 3 mg alone
  - nalbuphine 4 mg + morphine 3 mg
  - morphine 4 mg + morphine 3 mg

Nalbuphine for ED / EMS

- Morphine > nalbuphine in VAS reduction
- Morphine > nalbuphine in rescue analgesia requirement
- Morphine > nalbuphine on Ramsay sedation
- Morphine > nalbuphine on nausea and pruritus

Nalbuphine

- Availability (US)
  - Parenteral 10mg/mL, 20mg/mL
  - Oral ER tablet currently in development for pruritus
- DEA Schedule: not controlled
- Bioavailability
  - 11.8%, highly variable
- Distribution
  - Vdss 315.5 L/kg
  - Glucuronidation only
- Terminal half-life
  - 3.7 hours
- Onset
  - 2 to 3 minutes (parenteral)
- Duration of analgesia
  - 6 to 15 hours
Oral Nalbuphine?

<table>
<thead>
<tr>
<th>Assay</th>
<th>Normalization</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>2.5</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>5</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>


- Consider onset of action and duration vs. half-life
- Significantly increase risk of sleep disordered breathing
- Avoid concomitant use with opioids
- Consider abuse potential and diverted value

Benzodiazepines

- Consider onset of action and duration vs. half-life
- Significantly increase risk of sleep disordered breathing
- Avoid concomitant use with opioids
- Consider abuse potential and diverted value

Opioids & Benzodiazepines

Effects on sleep

- Ataxic (Briot) Breathing
- Inhibition of central chemoreceptors
- Typically associated with neurologic disease
- Irregular and variable respiratory rate and effort
- Obstructive Sleep Apnea
- Increased accessory muscle rigidity
- Decreased airway patency via neural inhibition
- Central Sleep Apnea
- Blunted response to hypoxic respiratory drive via peripheral chemoreceptors
- Blunted compensatory response to airway resistance or loading


Dose dependent sleep apnea

Unanswered questions

- Are we using the wrong agents?
- Are we using too high of doses?
- Should opioids and benzodiazepines be contraindicated for concurrent use
Conclusions

- Clinical use of various opioids aside from hydrocodone and oxycodone may be warranted.
- Personalized medicine in pain management is an emerging method for improving patient safety.
- Tolerance to respiratory depressant effects of opioids may be an outdated concept.
- Concurrent use of benzodiazepines and opioids should be avoided if possible.