The Obscurity of Opioids

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Disclosures

- Nothing to disclose
Learning Objectives

- Describe the unique pharmacologic profile of methadone, levorphanol, buprenorphine, and nalbuphine in the treatment of pain and related symptoms

- Recognize unique risks and adverse effects of methadone, levorphanol, buprenorphine, nalbuphine and develop monitoring strategies for minimizing negative outcomes

- Identify appropriate simulated patients for consideration of treatment with methadone, levorphanol, buprenorphine, nalbuphine for the treatment of a given pain syndrome or related symptom
2015 DEA Production Quotas

In Kilograms, Schedule II Opioid Analgesics

- Oxycodone: 145850
- Hydrocodone: 106625
- Codeine: 99500
- Morphine: 66250
- Methadone: 66000
- Oxymorphone: 36750
- Tapentadol: 12500
- Hydromorphone: 7000
- Fentanyl: 2150
- Dihydrocodeine: 226.375
- Alfentanil: 17.75
- Levoephonol: 7.125

Methadone
Methadone

- **Availability (US)**
  - Oral solution 10 mg/mL & 1 mg/mL
  - Oral tablet 5mg, 10 mg, 40 mg (restricted)
  - Parenteral solution 10 mg/mL
- **DEA Schedule II**
- **Oral bioavailability**
  - 36% to 100%
- **Distribution**
  - $V_{dss}$ 1 to 8 L/kg; extremely lipophilic
- **Metabolism via CYP 3A4, 2B6, & 2C19**
- **Terminal half life 8 to 59 hours**


Methadone Onset of Action, Analgesia

▪ Oral
  - 0.5 to 1 hour
  - Peak effect 3 to 5 days

▪ Parenteral
  - 10 to 20 minutes
  - Peak effect 1 to 2 hour

Methadone Mechanism of Action

- **R-methadone**
  - Mu-opioid receptor (MOR) 1 and MOR 2 agonist (50x that of R-isomer)
  - Kappa opioid receptor (KOR) agonist
  - Norepinephrine and serotonin reuptake inhibition

- **S-methadone**
  - Na\textsubscript{V} 1.5 inhibition
  - K\textsubscript{IR} 3 inhibition

- **Racemic**
  - \(\alpha4\beta2\) and \(\alpha3^*\) nicotinic antagonist
  - \(\alpha7\) nicotinic agonist
  - Noncompetitive N-methyl D-aspartate (NMDA) antagonist
  - Delta opioid receptor (DOR) densensitization/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

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

Electrocardiogram Monitoring & Response

- **Baseline**
  - Prior to initiation in those at risk for QTc prolongation

- **Follow-up**
  - Within 2 to 4 weeks of initiation in those at risk
  - When total oral daily dose exceeds 30 mg
  - When total oral daily dose exceeds 100 mg
  - If signs/symptoms of ventricular arrhythmia become apparent

- **Management**
  - Avoid or discontinue methadone if QTc $\geq$ 500 ms
  - Correct reversible causes of prolongation prior to methadone initiation if QTc 451–500 ms
  - Consider switching from methadone or reducing dose if QTc 451–500 ms on follow up ECG

Methadone Initiation & Dosing

- Initiation & titration in opioid naïve (REMS defined)
  - 2.5 mg PO Q8 hours
  - 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 30 mg to 40 mg 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 Techniques

- Dolophine prescribing insert

## Conversion Conversation

<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>≤ 100mg</td>
<td>3 to 1</td>
<td>33.3</td>
</tr>
<tr>
<td>101 to 300mg</td>
<td>5 to 1</td>
<td>20.0</td>
</tr>
<tr>
<td>301 to 600mg</td>
<td>10 to 1</td>
<td>10.0</td>
</tr>
<tr>
<td>601 to 800mg</td>
<td>12 to 1</td>
<td>8.3</td>
</tr>
<tr>
<td>801 to 1,000mg</td>
<td>15 to 1</td>
<td>6.7</td>
</tr>
<tr>
<td>≥ 1001mg</td>
<td>20 to 1</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Methadone Drug Interactions

- Methadone is metabolized through multiple cytochrome (CYP) P450 enzymes
  - Major: CYP3A4 and CYP2B6
  - Minor: CYP2D6 and CYP2C19
- Recall methadone is a racemic mixture

<table>
<thead>
<tr>
<th>Enantiomer</th>
<th>Characteristic</th>
<th>CYP Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-methadone</td>
<td>Analgesic activity</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>S-methadone</td>
<td>Adverse effects including QTc prolongation</td>
<td>CYP2B6</td>
</tr>
</tbody>
</table>

- Genetic polymorphisms to CYP2B6 exist

Case Quandary 1

JD is a 39-year-old male previously employed as a roofer who injured his back following a fall from a 2 story building. He has undergone a discectomy (2005), laminectomy (2007), and most recently an ALIF (2012).

PMHx: Failed back surgery syndrome, GAD

Meds:
- Gabapentin 1200 mg PO Q8 hour
- Sertraline 150 mg PO QHS
- IR oxycodone 15 mg PO Q6 hour as needed (uses all 4 doses)
- CR oxycodone 80 mg PO Q12

OTC: none

Allergies: NKDA

SHx: Denies tobacco, EtOH, recreational drugs

FHx: Unremarkable
Case Quandary 1

What should JD’s initial methadone dose be?

a. 2.5 mg PO Q8 hours
b. 5 mg PO Q8 hours
c. 10 mg PO Q 8 hours
d. 15 mg PO Q 8 hours
Should we still use methadone for chronic pain?

Buprenorphine
Buprenorphine

- **Availability (US)**
  - Sublingual tablet 2mg, 8mg
  - Transdermal patch 5mcg, 7.5mcg, 10mcg, 15mcg, 20mcg
  - Parenteral solution 0.3 mg/mL

- **DEA Schedule III**

- **Bioavailability**
  - Sublingual 29%
  - Transdermal 15%

- **Distribution**
  - $V_{dss}$ 97 to 187 L/kg

- **Metabolism via CYP 3A4 to norbuprenorphine (active)**

- **Terminal half life**
  - Sublingual 37 hrs
  - Transdermal 26 hrs

- **Onset**
  - Sublingual 0.5 to 1 hr
  - Transdermal $\leq$ 72 hrs

Buprenorphine

- MOR partial agonist, KOR & DOR antagonist, ORL-1 agonist
  - Norbuprenorphine weak MOR full agonist
- Comparatively high binding affinity for MOR-1
- Antihyperalgesic 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 ex-US
  - 1:100 for TD buprenorphine : PO morphine
  - 1.4:1 for TD buprenorphine : TD fentanyl
  - 1:80 for SL buprenorphine : PO morphine

**Buprenorphine Patch Dosing**

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

Buprenorphine Reversal

Box A. Reversal of Buprenorphine-induced Respiratory Depression

1. Discontinue buprenorphine (stop CSCI/CIVI, remove TD patch).
2. Give oxygen by mask.
3. Give IV naloxone 2mg stat over 90sec.
4. Commence naloxone 4mg/h by CIVI.
5. Continue CIVI until the patient’s condition is satisfactory (probably <90min).
6. Monitor the patient frequently for the next 24h, and restart CIVI if respiratory depression recurs.
7. If the patient’s condition remains satisfactory, restart buprenorphine at a reduced dose, e.g., half the previous dose.
Case Quandary 2

PC is a 64-year-old female with OA hip and knees. She was previously very active in her garden, but recently has become more sedentary and has asked for a walker. She states her pain is worse in her knees than in her hips. She has failed intra-articular corticosteroids (hip & knee) and hyaluronidase (knee). She rates her pain an 8/10 now, 7/10 average, 5/10 least, and 9/10 worst. Her PDMP, UDS, and refill records support her adherence to medications.

PMHx: OA, CKD Stage IIIb, HTN

Meds:

- Diclofenac gel 1% 4gms to each knee Q8H
- Acetaminophen 500mg 2 tabs Q6H
- Fentanyl TTS patch 25mcg/hr 1 patch Q72 hrs

OTC: none

Allergies: PCN

SHx: Denies tobacco, EtOH, recreational drugs

FHx: + OA, CAD (Fa)
Case Quandary 2

Which of the following doses of buprenorphine TDS would be appropriate for PC?

a. 5 mcg/hour
b. 7.5 mcg/hour
c. 10 mcg/hour
d. 15 mcg/hour
e. 20 mcg/hour
Levorphanol
Levorphanol

- Availability (US)
  - Oral tablet 2 mg
- DEA schedule II
- Bioavailability
  - Sublingual 18 to 29%
- Distribution
  - $V_{dss}$ 97 to 187 L/kg
- Glucuronidation only
- Terminal half life
  - 11 to 16 hours
- Onset
  - 10 to 60 minutes
- Duration of analgesia
  - 6 to 15 hours

Levorphanol

- 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>600-799mg</td>
<td>25 to 1</td>
</tr>
<tr>
<td>801-999mg</td>
<td>No data</td>
</tr>
<tr>
<td>&gt; 1000mg</td>
<td>No data</td>
</tr>
</tbody>
</table>

NMDA Activity of Levorphanol

Levorphanol & Chronic Pain

<table>
<thead>
<tr>
<th>Central nervous system</th>
<th>12</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Central pain after stroke or focal brain lesion</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peripheral nervous system</th>
<th>31</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postherpetic neuralgia</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Peripheral neuropathy or focal peripheral-nerve injury</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

Levorphanol and the QTc Interval

- Levorphanol does NOT affect the QTc interval
- No EKG monitoring needed
Nalbuphine
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**
  - $V_{dss}$ 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

Nalbuphine

- MOR partial antagonist
- KOR 1 & KOR 3 agonist
- NOP agonist
- Equipotent to 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 in nausea and pruritus

Nalbuphine ± Morphine IVPCA

Does gender matter?

Nalbuphine for ED / EMS

<table>
<thead>
<tr>
<th></th>
<th>Rapid regimen (2×10 mg)</th>
<th>Cautious regimen (4×5 mg)</th>
<th>Difference</th>
<th>p Value for difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean total dose of nalbuphine</td>
<td>14.8 mg</td>
<td>10.7 mg</td>
<td>4.1 mg</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean change in pain score</td>
<td>4.29</td>
<td>3.49</td>
<td>0.79</td>
<td>0.028 (0.09 to 1.5)</td>
</tr>
<tr>
<td>Patients with a pain score &gt;3 immediately before A&amp;E admission (%)</td>
<td>44 (53)</td>
<td>48 (55)</td>
<td>2%</td>
<td>0.761 (−17.0 to 12.8%)</td>
</tr>
<tr>
<td>Patients receiving hospital analgesia within 30 minutes of arrival (%)</td>
<td>8 (15)</td>
<td>6 (11)</td>
<td>4%</td>
<td>0.583 (−10.0 to 17.1%)</td>
</tr>
<tr>
<td>Change in pulse rate</td>
<td>−5.20</td>
<td>−3.00</td>
<td>2.20</td>
<td>0.284 (−6.26 to 1.85)</td>
</tr>
<tr>
<td>Change in respiratory rate</td>
<td>−2.29</td>
<td>−1.63</td>
<td>0.66</td>
<td>0.579</td>
</tr>
<tr>
<td>Change in systolic BP</td>
<td>−1.75</td>
<td>−6.28</td>
<td>4.53</td>
<td>0.108</td>
</tr>
<tr>
<td>Change in GCS</td>
<td>−0.14</td>
<td>−0.23</td>
<td>0.09</td>
<td>0.348</td>
</tr>
<tr>
<td>Any side effect (%)</td>
<td>51 (62)</td>
<td>36 (41)</td>
<td>21%</td>
<td>0.004 (6.0 to 35.0%)</td>
</tr>
<tr>
<td>Drowsiness (%)</td>
<td>35 (42)</td>
<td>19 (21)</td>
<td>21%</td>
<td>0.003 (7.0 to 34.1%)</td>
</tr>
<tr>
<td>Dizziness (%)</td>
<td>21 (25)</td>
<td>15 (17)</td>
<td>8%</td>
<td>0.143 (−3.8 to 20.8%)</td>
</tr>
<tr>
<td>Nausea or vomiting (%)</td>
<td>17 (21)</td>
<td>14 (16)</td>
<td>5%</td>
<td>0.338 (−6.9 to 16.6%)</td>
</tr>
</tbody>
</table>

Table 2 Change in pain score after nalbuphine administration

<table>
<thead>
<tr>
<th></th>
<th>Pre-drug (SD)</th>
<th>Post-drug (SD)</th>
<th>Change (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score (all patients)</td>
<td>8.38 (1.34)</td>
<td>4.41 (2.29)</td>
<td>−3.97 (−4.38 to −3.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain score (chest pain)</td>
<td>8.11 (1.40)</td>
<td>4.12 (2.46)</td>
<td>−3.98 (−4.64 to −3.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain score (trauma)</td>
<td>8.66 (1.22)</td>
<td>4.69 (2.08)</td>
<td>−3.97 (−4.46 to −3.47)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Oral Nalbuphine

ORAL NALBUPHINE AFTER DENTAL EXTRACTIONS

Pain intensity Nalbuphine > Dihydrocodeine
ADE Nalbuphine = Dihydrocodeine

TABLE II. Mean pain intensity (LAS). *P < 0.05 analysis of variance (Fisher-Tukey approach)

<table>
<thead>
<tr>
<th>Assessment time</th>
<th>Nalbuphine 60 mg</th>
<th>Dihydrocodeine 30 mg</th>
<th>Differences between treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>52.4</td>
<td>53.7</td>
<td>1.3</td>
</tr>
<tr>
<td>30 min</td>
<td>40.8</td>
<td>44.7</td>
<td>3.9</td>
</tr>
<tr>
<td>1 h</td>
<td>31.2</td>
<td>36.8</td>
<td>5.6</td>
</tr>
<tr>
<td>2 h</td>
<td>27.5</td>
<td>40.6</td>
<td>13.1*</td>
</tr>
<tr>
<td>3 h</td>
<td>25.8</td>
<td>41.8</td>
<td>16.0*</td>
</tr>
<tr>
<td>4 h</td>
<td>34.3</td>
<td>43.7</td>
<td>9.4*</td>
</tr>
<tr>
<td>Mean total pain intensity difference (P = 0.028)</td>
<td>103.2</td>
<td>56.7</td>
<td>46.5</td>
</tr>
</tbody>
</table>

Conclusions

- Opioids are effective analgesics in the treatment of pain
- Many opioids have unique pharmacologic profiles which leads to drug specific variability
- Misuse, abuse, and diversion liability of MOR agonists may lead to renewed interest in older opioid analgesics