A Review of Unique Opioids and Their Conversions

Jacqueline Cleary, PharmD, BCACP
Assistant Professor
Albany College of Pharmacy and Health Sciences
Adjunct Professor SAGE College of Nursing
DISCLOSURES

- Kaleo
- Remitigate, LLC
OBJECTIVES

• Compare and contrast unique pharmacotherapy options for the treatment of chronic pain including: methadone, buprenorphine, tapentadol, and tramadol

• Select methadone, buprenorphine, tapentadol, or tramadol based on patient specific factors

• Apply appropriate opioid conversion strategies to unique opioids

• Understand opioid overdose risk surrounding opioid conversions and the use of unique opioids
UNIQUE OPIOIDS

METHADONE, BUPRENNORPHINE, TRAMADOL, TAPENTADOL
IS METHADONE AN OPIATE OR AN OPIOID?

While opiates are still classified as natural opioid drugs, opioids include all opioid drugs. Opioids, like methadone, are narcotic drugs.
METHADONE- INDICATIONS

- FDA labeled indications – (1) chronic pain (2) detoxification
  - Oral soluble tablets for suspension NOT indicated for chronic pain treatment
- Initial inpatient detoxification of opioids by a licensed trained provider with methadone and supportive care is appropriate
- Methadone maintenance provider must have special credentialing and training as required by state
  - Outpatient prescription must be for pain ONLY and say “for pain” on RX
- Continuation of methadone maintenance from outside provider while patient is inpatient for another condition is appropriate

MECHANISM OF ACTION

• Potent µ-opioid agonist
• NMDA receptor antagonist
• Norepinephrine reuptake inhibitor
• Serotonin reuptake inhibitor
ADVERSE EVENTS

- Constipation, N/V, sedation, itching, edema, sweating, dizziness, confusion, endocrine dysfunction, urinary retention, fall risk in elderly

- QTC prolongation
  - Dose dependent
  - QTC correction strategies, population variations
  - Other QTC prolonging drugs?
    (ex: TCAs, fluoroquinolones, antipsychotics)

- Serotonin syndrome

PHARMACOKINETIC PROFILE

- Extensively protein bound (85-90%)
- High and variable volume of distribution
- Long half-life
- Prolonged time to reach steady state
- Elimination half-life significantly longer than analgesic effect
  - Frequent dosing escalations → toxic drug accumulation

START LOW, GO SLOW!

## OPIOID ANALGESIC P-KINETICS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Time to Peak (hr)</th>
<th>Half-life (hr)</th>
<th>Analgesic Onset (min)</th>
<th>Analgesic Duration (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (IM)</td>
<td>0.5-1</td>
<td>2</td>
<td>10-20</td>
<td>3-5</td>
</tr>
<tr>
<td>Hydromorphone (IM)</td>
<td>0.5-1</td>
<td>2-3</td>
<td>10-20</td>
<td>3-5</td>
</tr>
<tr>
<td>Levorphanol (IM)</td>
<td>0.5-1</td>
<td>12-17</td>
<td>10-20</td>
<td>5-8</td>
</tr>
<tr>
<td>Hydrocodone (PO)</td>
<td>1</td>
<td>4</td>
<td>30-60</td>
<td>4-6</td>
</tr>
<tr>
<td>Codeine (IM)</td>
<td>0.5-1</td>
<td>3</td>
<td>10-20</td>
<td>4-6</td>
</tr>
<tr>
<td>Oxycodone (PO)</td>
<td>0.5-1</td>
<td>2-3</td>
<td>30-60</td>
<td>4-6</td>
</tr>
<tr>
<td>Meperidine (IM)</td>
<td>0.5-1</td>
<td>3-4</td>
<td>10-20</td>
<td>2-5</td>
</tr>
<tr>
<td>Fentanyl (IM)</td>
<td>10-20</td>
<td>3-4</td>
<td>7-15</td>
<td>1-2</td>
</tr>
<tr>
<td>Methadone (IM)</td>
<td>0.5-1</td>
<td>15-300</td>
<td>10-20</td>
<td>&gt;8 (chronic)</td>
</tr>
</tbody>
</table>

SUB-POP, PHARMACOGENETIC

CYP3A4

R-methadone
Parent Drug

EDDP
inactive metabolite

CYP2B6

S-methadone
Parent Drug

EDDP
inactive metabolite

S: Cardiotoxic effects, QT prolongation with potential of Torsade de pointes

R: Responsible for analgesia

CYP2B6 demonstrates selectively metabolizes S-enantiomer
Potential risk?

Gerber JG et al. Stereoselective Metabolism of Methadone N-Demethylation by Cytochrome P4502B6 and 2C19. CHIRALITY 2004;16:36-44.
DOSE EQUIVALENCE CONVERSIONS

- Conversion to and from methadone is NOT bidirectional
- Genetic polymorphisms = inter-patient variability
- 3 proposed conversions
  - Ripamonti et al 1998: cancer related pain and heroin maintenance, 38 patients
    - 3 breakpoints: 3.7:1, 7.75:1, 12.25:1
  - Ayonrinde and Bridge 2000: 6-month conversion period, 14 neuropathic pain patients
    - 6 breakpoints: 3:1, 5:1, 10:1, 12:1, 15:1, 20:1
  - Mercadante et al 2001: 52 palliative care patients in Italy
    - 3 breakpoints: 4:1, 8:1, 12:1

DOSE EQUIVALENCE CONVERSIONS

- Fudin et al 2012 developed a mathematical model to eliminate breaks and peaks
- Useful if >300mg of morphine equivalents per day
- Based on previous publications
- Available for use in Practical Pain Management’s opioid calculator

MY FAVORITE DRUG BECAUSE...

BENEFITS OF USE

• Inexpensive
• Good oral bioavailability
• No maximum recommended dose
• Utilization in dialysis patients
• No known active metabolites
• Unique receptor activity profile

Is Buprenorphine An OPIATE?

While buprenorphine is considered an opioid, its effects are present in a decreased capacity in comparison to drugs that are full antagonists, such as methadone or heroin.

BUPRENORPHINE
Pharmacologically scintillating...
BUPRENORPHINE

• FDA approved for treating opioid abuse disorder AND for the treatment of moderate to severe pain

• Dehydroxylayed phenanthrene

• **Partial agonist** at the mu-opioid receptor (analgesia) and antagonist at kappa receptor (ceiling effect for respiratory depression)
WHAT IS BUPRENORPHINE

FDA Labeled Indication

- For induction and maintenance treatment of opioid dependence
  - Prescribing requires DATA 2000 waiver to obtain DEA X license number

Therapeutic Role

- Lower the potential for misuse of heroin and other opioids
- Diminish the effects of physical dependency to opioids, such as withdrawal symptoms and cravings
- Increase safety in cases of overdose
UNIQUE MECHANISM OF ACTION

![Diagram showing the unique mechanism of action for Heroin, Buprenorphine, and Naloxone.](source Image)

Source: Mike Sillings, Reckitt Benckiser, Inc.
Buprenorphine reduces sensitivity of the brainstem to increases in carbon dioxide tension, achieving a ceiling effect on respiratory depression.
BUPRENORPHINE

"Perceived Feeling" Graph

- Normal High
- Normal Low
- Heroin
- Methadone
- Buprenorphine

10 = Best
0 = Worst possible feeling

Normal Range

© Copyright NAABT, Inc. 2007
PHARMACOKINETIC PROFILE

- Substrate: CYP2C9 (major), CYP3A4 (minor)
- Inhibition: CYP2C8 (moderate), CYP2D6 (moderate)

- Patient case example
  - 56 YO M on Butrans 20mcg/hour transdermal patch and carbamazepine 200mg PO BID
  - Patient suffers from chronic low back pain and OA, and also has a history of COPD, DM, CHD, fluctuating kidney function
  - Patient continues to complain of increased pain
FORMULATIONS

- Five formulations
  1. Buprenex (IV or IM)
  2. Suboxone (transmucosal film)
  3. Subutex (sublingual tablet)
  4. Butrans (transdermal patch)
  5. Belbuca (buccal film)
SUBOXONE (BUPRENORPHINE)

- Indicated for the treatment of opioid dependence
- Formulated with naloxone
- 3 products available: Bunavil, Zubsolv, Suboxone (NOT bioequivalent)
- Requires specific DEA number for prescribing (X)
- 2mg SL ~39-50% receptor saturation
- 16mg SL ~ 79-95% receptor saturation
SUBUTEX (BUPRENORPHINE)

- Indicated for treatment of opioid dependence
- Off-label use in the treatment of chronic pain when long-term full opioid agonists are not an option
- Dosage forms: 2mg and 8mg tablets SL
- Swallowing reduces bioavailability
- Documented deaths in opioid naive patients
BUTRANS (BUPRENNORPHINE)

- Indicated for the treatment of moderate to severe pain
- Dosage forms: 5, 7.5, 10, 15, 20mcg/hour transdermal patch
- Two patches can be worn at once in two separate adjacent sites
- Rotate sites every 7 days
- IR opioids indicated in the first 72 hours of titration (time to steady state)
- Patient using >80mg of morphine equivalents NOT a candidate for Butrans
- HOLD patch for at least 72 hours when switching therapies
BELBUCA (BUPRENORPHINE)

- Indicated for management of “pain requiring around-the-clock, long-term opioid treatment not adequately controlled by alternatives”
- Dosage forms: 75, 150, 300, 450, 600, 750, 900mcg
- Butrans 20mcg/hour can be replaced by 150mcg q12 Belbuca (not 100% equivalent)
- Patient using >160mg of morphine equivalents NOT a candidate for Belbuca
- 30 minute dissolve time
ACUTE PAIN MANAGEMENT

Planned Procedure

• Hold high dose buprenorphine for 1 week (min 72 hours)

• Monitor closely - concern for relapse

• Buprenorphine’s half-life for dissociation from the mu receptor is 166 min as opposed to 7 min for fentanyl

Unplanned Procedure

• Augment therapy with NON opioid medications:
  • NSAIDs
  • IV acetaminophen
  • Anticonvulsants
  • NMDA antagonists

• High dose opioids - hydromorphone, fentanyl

TRAMADOL VS. TAPENTADOL

What's the difference?
TRAMADOL

• Mu-opioid agonist (ascending pathway)
  • Binding affinity 6000X less than that of morphine
  • Considered a partial agonist

• Norepinephrine reuptake inhibitor (descending pathway)

• Serotonin reuptake inhibitor (descending pathway)

ADVERSE EVENTS

- Constipation, N/V, sedation, itching, edema, sweating, dizziness, confusion, endocrine dysfunction, urinary retention, xerostomia, fall risk in elderly
- Headache
- Central nervous system stimulation
- Insomnia
- Serotonin syndrome
- Seizures- most commonly, tramadol-induced seizures appear to be generalized tonic-clonic seizures that occur within 24 hours of medication ingestion

TRAMADOL METABOLISM

M1: more potent analgesic than tramadol, however LESS pain relief observed

Difficulty penetrating into CNS

## CYP2D6 PHENOTYPE BY ETHNICITY

<table>
<thead>
<tr>
<th>CYP2D6 Phenotype</th>
<th>African (%)</th>
<th>African American (%)</th>
<th>Americas (%)</th>
<th>Caucasian (Europe &amp; North America) (%)</th>
<th>East Asian (%)</th>
<th>Middle Eastern (%)</th>
<th>Oceanian (%)</th>
<th>South/Central Asian (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM</td>
<td>4.5</td>
<td>3.4</td>
<td>4.8</td>
<td>3.2</td>
<td>1.2</td>
<td>11.5</td>
<td>20.5</td>
<td>2.8</td>
</tr>
<tr>
<td>EM</td>
<td>71.9</td>
<td>77.7</td>
<td>81.2</td>
<td>76.8</td>
<td>85.5</td>
<td>74.4</td>
<td>76.7</td>
<td>88.5</td>
</tr>
<tr>
<td>IM</td>
<td>12.6</td>
<td>13.2</td>
<td>4.5</td>
<td>6.9</td>
<td>8.8</td>
<td>5.6</td>
<td>0.5</td>
<td>6.9</td>
</tr>
<tr>
<td>PM</td>
<td>1.9</td>
<td>3.1</td>
<td>3.7</td>
<td>6.1</td>
<td>0.9</td>
<td>1.2</td>
<td>0.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

% rounded to nearest tenth

Supplemental Table S1. Frequencies of CYP2D6 alleles in major race/ethnic group. Accessed at: https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/
TRAMADOL VS. TAPENTADOL

Tramadol

- Norepinephrine, serotonin, and u-opioid activity
- IR and ER formulations
- Max dose 300mg/day
- Dosage adjustment in renal impairment
- Common AEs: dizziness, headache, drowsiness, constipation, vomiting
- 3A4, 2B6 activity and 2D6 required for active metabolite formation

Tapentadol

- FDA indication for chronic diabetic neuropathic pain
- Norepinephrine and u-opioid activity
- IR and ER formulations
- Max dose 500mg/day
- No data in renal patients (CrCl <30ml/min
- Common AEs: dizziness, drowsiness, N/V, constipation
- 2C9 and 2D6 substrate

Ultram ER (tramadol) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals Inc; July 2014.
Nucynta ER (tapentadol) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals; April 2014.
IS TAPENTADOL (NUCYNTA®) A GLORIFIED TRAMADOL?

<table>
<thead>
<tr>
<th>Properties</th>
<th>Tramadol</th>
<th>Tapentadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu Binding Affinity</td>
<td>6000x less than morphine</td>
<td>18x less than morphine</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Significant CYP 450</td>
<td>Conjugation, O-Glucuronide</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>See previous</td>
<td>See previous</td>
</tr>
<tr>
<td>Neuroamine Activity</td>
<td>5-HT / NE</td>
<td>NE</td>
</tr>
</tbody>
</table>
UNIQUE OPIOID CONCLUSIONS

• Methadone is an EXCEPTIONAL opioid when used appropriately
• Buprenorphine has a ceiling effect that can be VERY useful
• Tramadol does have ABUSE potential and is not foolproof
• Tapentadol has NE activity and no 5-HT activity but is expensive

• DO YOU HAVE A PATIENT THAT WOULD BENEFIT FROM ONE OF THE ABOVE?
How do you do opioid conversions?

DON’T BE SHY!
AVAILABLE ONLINE OPIOID CONVERSION CALCULATORS

WA State Agency
Med Calc
Pain Research
Pain Physicians
Hopkins
Palliative Care
Global RPh

- **Practical Pain Management (PPM)**

OTHERS...?
ISSUES WITH MEDD & OPIOID CONVERSIONS

- Pharmacogenetic variability
- Drug interactions
- Lack of universal morphine equivalence
- Specific opioids that should never have an MEDD
  - Methadone, Buprenorphine, Tapentadol, Tramadol
OPIOID CONVERSION POINTERS...

• Use more than one calculator
• What is the patient’s current pain level?
• What is the patient’s current PRN use?
• How does the drug come?
• Cross-sensitivity -> similarities of opioid structures
# Comparative Opioid Chemistry

<table>
<thead>
<tr>
<th>PHENANTHRENES</th>
<th>BENZOMORPHANS</th>
<th>PHENYLPIPERIDINES</th>
<th>DIPHENYLHEPTANES</th>
<th>PHENYLPROPYL AMINES</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Morphine" /></td>
<td><img src="image2" alt="Pentazocine" /></td>
<td><img src="image3" alt="Fentanyl" /></td>
<td><img src="image4" alt="Methadone" /></td>
<td><img src="image5" alt="Tapentadol" /></td>
</tr>
<tr>
<td><strong>MORPHINE</strong></td>
<td><strong>PENTAZOCINE</strong></td>
<td><strong>FENTANYL</strong></td>
<td><strong>METHADONE</strong></td>
<td><strong>TRAMADOL</strong></td>
</tr>
<tr>
<td>Buprenorphine*</td>
<td>Diphenoxylate</td>
<td>Allentanil</td>
<td>Methadone</td>
<td>Tapentadol</td>
</tr>
<tr>
<td>Butorphanol*</td>
<td>Loperamide</td>
<td>Fentanyl</td>
<td>Propoxyphene</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>Pentazocine</td>
<td>Meperidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan*</td>
<td></td>
<td>Remifentanil</td>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td></td>
<td>Sufentanil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin (diacetyl-morphine)</td>
<td></td>
<td></td>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levorphanol*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylnaltrexone**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine (Opium, conc)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nalbuphine*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naloxone*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naloxegol*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxymorphone*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Illicit Fentanyl**

- Furanyl fentanyl
- Acetyl fentanyl
- Fluoro-fentanyl
- Carfentanil

**CROSS-SENSITIVITY RISK**

<table>
<thead>
<tr>
<th>PROBABLE</th>
<th>POSSIBLE</th>
<th>LOW RISK</th>
<th>LOW RISK</th>
<th>LOW RISK</th>
</tr>
</thead>
</table>

*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group

**6-position is substituted with a ketone group and tolerability is similar to hydroxylation

Jeffrey Fudin, BSPharm, PharmD, DAIPM, FCCP, FASHP, FFSEM

OPIOID CONVERSION EXAMPLE

• Patient O.A. is a 58 y.o. AA male who is currently taking oxycontin 20mg PO TID with oxycodone 5mg PO q6 prn

• His provider would like to switch him to a fentanyl patch. Which of the following is an appropriate starting dose?
  A. Fentanyl 12.5mcg/hr with NO PRN oxycodone
  B. Fentanyl 12.5mcg/hr with PRN oxycodone 5mg PO q6 prn
  C. Fentanyl 25mcg/hr with NO PRN oxycodone
  D. Fentanyl 25mcg/hr with PRN oxycodone 5mg PO q6 prn
  E. Fentanyl 37.5mg/hr with NO PRN oxycodone
OPIOID CONVERSION EXAMPLE

- Fentanyl and oxycodone in two different opioid classes (consider cross-tolerance)
- Patient could be taking 80mg of oxycodone total (20mg X3 + 5mg X4 = 80mg)
- PPM w/o cross tolerance = 33.3mcg patch (HOURLY DOSE)
  - 50% cross tolerance = 16.7 mcg patch
  - 25% cross tolerance = 25mcg patch
- How does fentanyl come?
  - 12.5, 25, 50, 75, 100 mcg/hour patches
- 12.5mg w/o PRN too little
- 37.5 (25 + 12.5) w/o PRN too little
CONVERSION CONCLUSIONS

• Assess patients pain level prior to conversion
• Assess PRN use prior to conversion
• Determine long term goal (ex: no PRN use, etc.)
• Consider cross-tolerance
• How does the opioid come?
• USE MORE THAN ONE CALCULATOR -> phone a friend!
• Follow up with you patient
• Do they have naloxone?
QUESTIONS?
Jacqueline Cleary, PharmD, BCACP
Assistant Professor
Albany College of Pharmacy and Health Sciences
Adjunct Professor SAGE College of Nursing