Opioid Stewardship and the Pharmacology of Medication Assisted Treatment

MHA Medication Safety Learning and Networking Day
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Disclosures

• I have no financial interests to disclose.

• Some of these slides have been adapted from materials created by:
  • Gavin Bart, MD, PhD (Hennepin Healthcare)
  • Provider’s Clinical Services Support (pcssnow.org)
    buprenorphine waiver training
Learner Objectives

1. Explain rationale supporting each medication for opioid use disorder (MOUD)

2. Discuss safety considerations for each medication

3. Describe analgesic implications of each MOUD
Pharmacology Foundations
Pharmacology 101: Receptor interaction

- **Affinity** - strength of drug’s physical coupling
  - Not activity at receptor

- **Dissociation** – speed (slow or fast) that drug uncouples from the receptor

- **Efficacy** - response to binding (e.g., agonism)

- **Potency**
  - Amount of drug to produce a given effect
  - A combination of affinity and efficacy
Pharmacology 101: Receptor effect (or not)

- Agonist
  - Binds and activates receptor
  - Morphine, methadone, fentanyl

- Partial agonist
  - Binds and activates receptor with partial efficacy
  - Buprenorphine, tramadol

- Antagonist
  - Binds receptor and blocks effect of agonist
  - Naloxone, naltrexone
Opioids

- Endogenous
  - Beta-endorphin
  - Enkephalins
  - Dynorphins

- Natural
  - Codeine, morphine

- Semi-synthetic
  - Oxycodone, hydrocodone
  - Buprenorphine

- Synthetic
  - Fentanyl, tramadol
  - Methadone

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Gavril W. Pasternak, and Ying-Xian Pan Pharmacol Rev 2013;65:1257-1317

Fentanyl
Opioid receptors

• G-protein coupled 7-transmembrane receptors
  • Secondary messenger system produces effect
  • Differences in secondary messengers may produce differences in effects

• **Mu**: primary effect of analgesia, euphoria/reward, stress, respiratory, immune

• **Delta**: mood and some pain modulation

• **Kappa**: mood (dysphoria)

• **Nociceptin**: mood
Distinguishing factors of addiction

- Impaired control
- Social impairment
- Risky use
  - (Doesn’t count when chronically prescribed)
Treatment Mechanisms

- Block reinforcing effects of opioids
  - Gradual extinction of learned behaviors (conditioned responses)
- Suppress cravings for opioids
- Manage withdrawal and associated negative affect
Medications for Opioid Use Disorder

- Methadone (agonist)
- Buprenorphine (partial agonist)
  - Transmucosal (i.e., generic, Suboxone, Subutex, Zubsolv, Bunavil)
  - Implantable (Probuphine)
  - Subcutaneous depot injectable (Sublocade)
- Naltrexone (antagonist)
  - Oral (ReVia)
  - Intramuscular depot injectable (Vivitrol)
Impact of chronic opioid use and opioid maintenance therapy

Normal variation. Your body’s opioid level increases with exercise, friendship, sex, food. Also rises in response to acute trauma to compensate for pain. Level decreases with depression, etc.

Persistent use resets homeostasis. Other behaviors may become secondary, and drug use may become compulsive. Withdrawal develops, and goal of use gradually shifts from “get high” to “feel less bad.”

At the new baseline level, a person’s own opioid system is suppressed. They’re less able to cope with new painful stimuli, including withdrawal.

In the predisposed person, exposure to an opioid results in an outsized response that dwarfs other stimuli.

Treatment goals:
1. No opioid cravings
2. No illicit opioid use
3. Feel normal
4. Safe dose, no diversion

Buprenorphine/Methadone

Some patients expect to taper eventually. Recovery of function is uncertain.

Planned tapers should include close support, and recommendation to continue buprenorphine if destabilizing symptoms arise.

Studies suggest >85% of people with opioid addiction relapse without agonist medication. A few people do well; unfortunately, we poorly predict who, how, or when to taper successfully.

Created by Brian Grahan, MD, PhD on 4/1/18
Hennepin Healthcare Opioid & Addictions Care ECHO
Clinical pharmacology of MOUD

- Full Agonist: Methadone, Heroin, etc.
- Partial Agonist: Buprenorphine
- Antagonist: Naltrexone
- Respiratory suppression, death

Log dose vs. Opioid Effects

= Withdrawal

Hennepin Healthcare
**Full Agonist at mu receptor**

**Long acting**
- Half-life ~ 15-60 Hours

**Monitoring**
- Significant respiratory suppression and potential respiratory arrest in overdose
- Does not impair driving at stable doses
Pharmacotherapy for Opioid Use Disorder: Methadone

• Effective dose:
  • Dose 20-40 mg for acute withdrawal (suppression by 60 mg)
  • 80-120 mg for craving and “blockade” (although weak mu receptor affinity)
• Analgesia mean duration 5-8 hours
  • NMDA antagonist
• Many drug-drug interactions given complicated hepatic metabolism
• May prolong QTc

Monitoring
• To evaluate stability, ask about take-home doses
• Only R-methadone enantiomer has opioid activity, so total levels uninterpretable
• Multiple medication interactions due to multi-faceted CYP450 metabolism
Clinical use: Methadone

- Most effective
  - survival, treatment retention, employment
  - illicit opioid use, hepatitis and HIV infections, criminal activity
- Highly regulated, dispensed at Opioid Treatment Programs (OTP)
  - Supervised daily liquid administration with take-home doses if stable in treatment
  - Counseling, urine testing
  - Psychiatric, medical services often not provided
  - Illegal to prescribe methadone for addiction in general practice
- Excellent outcomes for pregnant women with OUD
- May prescribe for 3 days of directly observed therapy while arranging entry into OTP
- May prescribe indefinitely to hospitalized patient
  - Already on methadone, or
  - With an untreated OUD hospitalized for any reason other than OUD as primary dx
Buprenorphine
Pharmacotherapy for Opioid Use Disorder: Buprenorphine

**Partial agonist** at mu receptor
- Minimal respiratory suppression and no respiratory arrest when used as prescribed

**Long acting**
- Half-life ~ 24-36 Hours

**High affinity** for mu receptor
- Blocks other opioids
- Displaces other opioids (can precipitate withdrawal)

**Slow dissociation** from mu receptor
- Stays on receptor for a long time

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SAMHSA, 2018
Orman & Keating, 2009
Pharmacotherapy for Opioid Use Disorder: Buprenorphine

- Primary metabolism by CYP3A4
  - Extensive 1st pass metabolism (poor oral bioavailability)
  - Few drug-drug interactions
- Biliary tract >> urinary excretion
  - Buprenorphine and norbuprenorphine detectable in urine
- Target dose ~ 16mg daily, max dose 24mg for OUD
  - Higher dose may have greater analgesic effect

Mendelson et al., 1997
SAMHSA, 2016.; SAMHSA, 2018
Clinical use: Buprenorphine

  • Legalized office-based addiction treatment by physicians  
  • Required 8-hr training and federal waiver for physicians, 24-hr for APPs

• 2002: Suboxone (buprenorphine/naloxone) FDA approved  
  • Schedule III  
  • Outcomes much superior to psychosocial treatment alone  
  • Longer treatment duration more effective

• Compared to methadone:  
  • Similar abstinence from illicit opioids and decreased craving  
  • Slightly lower retention in treatment  
  • Can be prescribed in general practice
Sublingual Buprenorphine: Maintenance vs. Taper

Fiellin et al., 2014
Subcutaneous injectable depot buprenorphine

- FDA approved formulation = Sublocade (Indivior)
  - 4 week depot SC injection
  - Recommended dose 300 mg injection x2, then 100 mg injections
  - Comparable adverse effects + injection site pruritis (6%)
  - Administered after ≥7 day stabilization on SL buprenorphine 8-24 mg
  - No comparison trials with sublingual or buccal buprenorphine
Common adverse effects of buprenorphine

- Headaches
  - Management: aspirin, ibuprofen, acetaminophen (if there are no contra-indications)

- Nausea
  - Management: Consider spitting the saliva out after adequate absorption instead of swallowing

- Constipation
  - Management: Stay well-hydrated, high-fiber diet, stool softeners, laxatives, naloxegol

- Xerostomia (Dry mouth) – side effect of ALL opioids
  - Complications: Gingivitis, Periodontitis
  - Management: Stay well-hydrated, Maintain good oral hygiene
Buprenorphine and benzodiazepines

- Benzodiazepines present in most fatal poisonings involving buprenorphine

<table>
<thead>
<tr>
<th>Human studies</th>
<th>Minimal effects on respiration when both are taken at therapeutic doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal studies</td>
<td>May remove the protective “ceiling effect” and allow buprenorphine to produce fatal respiratory suppression in overdose</td>
</tr>
</tbody>
</table>

- **Used-as-prescribed benzodiazepines** in combination with buprenorphine have only been associated with more accidental injuries, not with mortality and other safety or treatment outcomes

Bardy et al., 2015; Jones et al., 2012
Nielsen & Taylor, 2005; Schuman-Olivier et al., 2013
## Changes in FDA Recommendations

<table>
<thead>
<tr>
<th>08/2016</th>
<th>09/2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Boxed Warning for combined use of opioid medicines with benzodiazepines or other CNS Depressants (e.g. Alcohol)</td>
<td>▪ Buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS).</td>
</tr>
<tr>
<td>▪ Risks of slowed or difficult breathing; Sedation; Death</td>
<td>▪ The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks.</td>
</tr>
<tr>
<td></td>
<td>▪ Careful medication management by health care professionals can reduce these risks.</td>
</tr>
</tbody>
</table>
Rationale for combining buprenorphine with naloxone

- When used as prescribed (sublingual or buccal administration), there is minimal bioavailability of naloxone.

- Compared to bup alone, the bup/nlx combination:
  - is more likely to precipitate withdrawal if injected by a current opioid user.
  - produces a slowed onset effect when injected or insufflated in those who are physically dependent on buprenorphine.
  - per prescription, is less likely to be diverted.

Mendelsohn, 1997; Comer et al., 2010; Jones et al., 2015; Stoller et al., 2001
Buprenorphine diversion

▪ Has intravenous misuse potential but <1% report bup use for intoxication
▪ Variable market preference for tablets vs films
▪ Mono-product (Subutex) tablets probably preferred on street to bup/nlx
▪ In a survey of more than 4,000 patients in treatment programs in the United States, relative rates of diversion per prescribed dose were:
  • buprenorphine/naloxone film: 1 (reference)
  • buprenorphine/naloxone tablet: 2.2
  • buprenorphine tablet: 6.5
▪ Therefore, buprenorphine/naloxone is standard of care

Comer et al., 2010; Jones et al., 2015
Larancea et al., 2014; Lavonas et al., 2014
Benefits of agonist MOUD: Decreased Mortality

Death rates:

- General population
- Medication-assisted treatment

Standardized Mortality Ratio

Dupouy et al., 2017
Evans et al., 2015
Sordo et al., 2017
Naltrexone
Pharmacotherapy for Opioid Addiction: Naltrexone

**Full Agonist** at mu receptor
- Competitive binding

**Long acting**
- Active 1st metabolite (6-beta-naltrexol)
- IM $t_{1/2} \sim 5-10$ days

**High affinity** for mu receptor
- Blocks & displaces other opioids

**Formulations**
- Tablets not used due to poor adherence
- Extended-Release IM injection: Vivitrol®

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**Pharmacotherapy for Opioid Addiction:**

- Full agonist (e.g. morphine, methadone)
- Partial agonist (buprenorphine)
- Antagonist (naloxone, naltrexone)

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**Hennepin Healthcare**

SAMHSA, 2018
Intramuscular depot naltrexone for opioid use disorder

- Requires 3-7 days of opioid abstinence prior to initiation with pre-injection naloxone challenge or negative urine drug test

- In comparative RCT of bup/nlx vs IM depot naltrexone (XR-NTX) in patients at detox (Lee JD et al, 2017):
  - XR-NTX 28% drop out before induction versus only 6% for Suboxone
  - Cravings only suppressed in ~60% of patients
  - Nearly all induction failures had early relapse
  - Once inducted, XR-NTX and BUP-NX similar effect for 6 months
  - Overdose and other serious adverse event rates did not differ
Sublingual buprenorphine (BUP-NX) vs IM depot naltrexone (XR-NTX)

No mortality data for naltrexone

Intention-to-treat

Per protocol

<table>
<thead>
<tr>
<th>Number at risk (censored)</th>
<th>Time to relapse (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUP-NX</td>
<td>287 229 100 155 140 130 0 (124) 270 222 184 149 134 126 0 (120)</td>
</tr>
<tr>
<td>XR-NTX</td>
<td>283 165 142 125 109 103 0 (98) 204 164 141 124 109 103 0 (98)</td>
</tr>
</tbody>
</table>

Lee JD et al. Lancet. 2017
MOUD in Pregnancy

• Agonist therapy is standard of care in pregnancy
  • No risk of birth defects
  • Opioid risks or miscarriage and premature labor associated with withdrawal in early 1st trimester and late 3rd trimesters

• Risk of neonatal opioid withdrawal syndrome
  • Not associated with long-term cognitive, developmental, or other sequelae

• Stable mother and family best predictor of infant success

• No reasonable evidence related to naltrexone on pregnancy and fetal outcomes
Overdose Prevention

- Naloxone ("Narcan") reverses opioid overdose
- Overdose education and naloxone is an effective harm reduction strategy
- For those at high risk of overdose and their friends or family
  - Steve’s Law in MN allows third party prescribing
  - Easy to protocol for pharmacy distribution
- Populations: syringe exchange, release from incarceration, in drug treatment, high risk prescribed opioids
- Prescribe to Prevent educational modules: http://wwwopioidprescribing.com/naloxone_module_1-landing
Notes on overdose

• Fentanyl and analogues are very potent
  • Increased chance of adverse effects esp. if low tolerance

• Very high potency ≠ affinities are too high for:
  • Naloxone to reverse overdose
  • MOUD to be effective

• Related but not equal to MME
Notes on opioid analgesia

• Methadone and buprenorphine provide opioid-responsive analgesia for 4-6 hours/dose

• Other opioid analgesics may still work in setting of agonist therapy
  • Higher doses (1.5-2x) of usual full opioid agonist often required
    • Usual duration and frequency of therapy
  • Higher affinity opioids often needed with buprenorphine
    • May need to reduce buprenorphine dose <16 mg daily

• Opioid analgesia very difficult while on naltrexone
  • Possible with high dose IV fentanyl drip in ICU
Caveat emptor: Morphine Milligram Equivalents (MME)

- Not based on pharmacology per se
- Based on pain relief response
- Doesn’t apply to MOUD
- Acute versus chronic therapy
- Not meant for dose conversions
- Helpful for pharmacoepidemiology
Morphine Milligram Equivalents (MME)

<table>
<thead>
<tr>
<th>Type of Opioid (strength units)</th>
<th>MME Conversion Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine film/tablet³ (mg)</td>
<td>30</td>
</tr>
<tr>
<td>Buprenorphine patch⁴ (mcg/hr)</td>
<td>12.6</td>
</tr>
<tr>
<td>Buprenorphine film (mcg)</td>
<td>0.03</td>
</tr>
<tr>
<td>Butorphanol (mg)</td>
<td>7</td>
</tr>
<tr>
<td>Codeine (mg)</td>
<td>0.15</td>
</tr>
<tr>
<td>Dihydromorphine (mg)</td>
<td>0.25</td>
</tr>
<tr>
<td>Fentanyl buccal or SL tablets, or lozenge/troche³ (mcg)</td>
<td>0.13</td>
</tr>
<tr>
<td>Fentanyl film or oral spray⁴ (mcg)</td>
<td>0.18</td>
</tr>
<tr>
<td>Fentanyl nasal spray (mg)</td>
<td>0.16</td>
</tr>
<tr>
<td>Fentanyl patch³ (mg)</td>
<td>7.2</td>
</tr>
<tr>
<td>Hydrocodone (mg)</td>
<td>1</td>
</tr>
<tr>
<td>Hydromorphone (mg)</td>
<td>4</td>
</tr>
<tr>
<td>Levorphanol tartrate (mg)</td>
<td>11</td>
</tr>
<tr>
<td>Meperidine hydrochloride (mg)</td>
<td>0.1</td>
</tr>
<tr>
<td>Methadone³ (mg)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;0, &lt;= 20</td>
<td>4</td>
</tr>
<tr>
<td>&gt;20, &lt;= 40</td>
<td>8</td>
</tr>
<tr>
<td>&gt;40, &lt;= 60</td>
<td>10</td>
</tr>
<tr>
<td>&gt;60</td>
<td>12</td>
</tr>
<tr>
<td>Morphine (mg)</td>
<td>1</td>
</tr>
<tr>
<td>Opium (mg)</td>
<td>1</td>
</tr>
<tr>
<td>Oxycodeone (mg)</td>
<td>1.5</td>
</tr>
<tr>
<td>Oxydorphone (mg)</td>
<td>3</td>
</tr>
<tr>
<td>Pentazocine (mg)</td>
<td>1.0</td>
</tr>
<tr>
<td>Tapentadol (mg)</td>
<td>0.4</td>
</tr>
<tr>
<td>Tramadol (mg)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Hennepin Healthcare
Integrated Opioid & Addiction Care

• Fun, case-based, interactive tele-mentoring via videoconference
• Network of mentors & colleagues
• Thursdays 12:15 – 1:15
• Free AMA PRA Category 1 Credit™ per session
How does Project ECHO work?

- Complex conditions
- Guided practice over time
- Brief “didactics”
- Case review

“Moving knowledge, multiplying patients”
Is Project ECHO telemedicine?

Source: Michelle Iandiorio, MD, Project ECHO New Mexico
# Medications for Opioid Use Disorder Summary

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Buprenorphine (Oral)</th>
<th>Naltrexone (IM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Full Agonist on Opioid Receptor</td>
<td>Partial Agonist on Opioid Receptor</td>
<td>Antagonist on Opioid Receptor</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>80mg-100mg (Usual Dose)</td>
<td>4-32mg</td>
<td>380mg Depot Injection</td>
</tr>
</tbody>
</table>
| **Advantages**       | Provided in a highly structured supervised setting where additional services can be provided on-site and diversion is unlikely
  - Maybe effective for individuals who have not benefited sufficiently from partial agonists or antagonists
  - Improved safety due to partial agonism
  - Availability in office-based settings
|                      | No addictive potential or diversion risk
  - Available in office-based settings
  - Option for individuals seeking to avoid any opioids

Schuckit, 2016
Questions?

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