PHARMACOLOGIC TREATMENT OF OPIOID USE DISORDER

Matt Iles-Shih, MD
Addiction Psychiatry Fellow
University Of Washington & VA Puget Sound Health Care System
OBJECTIVES

1. Quick overview of physiology & epidemiology of opioid use

2. Review Rx treatments for opioid use disorder:
   - Opioid receptor antagonists
     • Naloxone
     • Naltrexone
   - Opioid receptor agonists (full/partial)
     • Buprenorphine
     • Methadone
OPIOIDS: A (VERY) BRIEF REVIEW

MORPHINE
HEROIN
OXYCODONE
PENTAZOCINE
PETRIDINE
FENTANYL
SUFTENANIL
METHADONE
OPIOIDS: NATURAL & SYNTHETICS

Natural Alkaloids ("opiates"):  
- Morphine  
- Codeine  

Semisynthetics:  
- Heroin (diacetylmorphine)  
- Oxy/hydrocodone  
- Oxy/Hydromorphone  
- Desomorphine (krokodil)  
- Etc...  

Synthetics:  
- Methadone  
- Buprenorphine  
- Fentanyl  
- Merperidine  
- Etc...
# OPIOID RECEPTORS, REWARD, & ADDICTION

<table>
<thead>
<tr>
<th>Receptor class</th>
<th>Mu (μ)</th>
<th>Delta (δ)</th>
<th>Kappa (κ)</th>
</tr>
</thead>
</table>
| Activity      | Mu-1: analgesia  
Mu-2: sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, urinary retention, physical dependence | Analgesia, spinal analgesia | Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria |

OPIOID MISUSE AND ITS CONSEQUENCES

For every 1 death in 2010, there were:

- Past Year Nonmedical Users: 733
- People with abuse/dependence: 108
- ED visits for misuse or abuse: 26
- Abuse treatment admissions: 10

Figure 1. Age-Adjusted Rates of Death Related to Prescription Opioids and Heroin Drug Poisoning in the United States, 2000–2014.

Data are from the Centers for Disease Control and Prevention.5

Compton, WM et al. 2016. Relationship between nonmedical prescription-opioid use and heroin use. NEJM 374:154-63

https://dawninfo.samhsa.gov/default.asp
PHARMACOTHERAPY FOR OPIOID USE DISORDER

- Naloxone
- Naltrexone
- Buprenorphine
- Methadone
PHARMACOLOGIC TREATMENTS:
Agonists (Full & Partial Agonist) & Antagonist

- **Full Agonist (Methadone)**
- **Partial Agonist (Buprenorphine)**
- **Antagonist (Naloxone, Naltrexone)**

% Maximal Effect vs. Log Dose of Opioid
OPIOID ANTAGONISTS

• Naloxone (rescue)

• Naltrexone (abstinence maintenance)
NALOXONE (FOR ACUTE OVERDOSE RX)
NALOXONE, CONT.

**Use:** opioid reversal (e.g., rescue from opioid OD)

**MOA:** opioid receptor antagonist

**Route:** IM & intranasal (common in-field), nebulized (rare), IV (preferred if available)

**Pharmaco-dynamics/kinetics:**

- **Onset:**
  - IM, SubQ: 2-5min (Peak ~15min)
  - Intranasal: ~8-13min (Peak ~20-30min)

- **Duration & Half-life:** ~30-120min depending on ROA.

- **Metabolism:** Primarily hepatic via glucuronidation; metabolites excreted in urine
## Naloxone Product Comparison for Community Programs

<table>
<thead>
<tr>
<th></th>
<th>Intramuscular injection naloxone</th>
<th>Intranasal spray naloxone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product</strong></td>
<td><img src="image1.png" alt="Injectable Naloxone" /></td>
<td><img src="image2.png" alt="Spray Naloxone" /></td>
</tr>
<tr>
<td><strong>Packaging</strong></td>
<td>2 single use 1 mL vials. Requires 2 intramuscular syringes (23G, 3cc, 1-1.5), sold separately.</td>
<td>Two-pack of autoinjector devices. 2 Luer-Jet™ Luer-Lock 2mL needleless syringes. Requires assembly with 2 mucosal atomizer devices (MAD-300) sold separately.</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Inject 1 mL in shoulder or thigh.</td>
<td>Follow English voice prompt. Press black side firmly on outer thigh for 5 seconds.</td>
</tr>
<tr>
<td></td>
<td>Spray 1 mL (1/2 of vial) into each nostril.</td>
<td>Spray unit into one nostril.</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>0.4mg/mL</td>
<td>0.4mg/0.4mL</td>
</tr>
<tr>
<td></td>
<td>1mg/mL</td>
<td>4mg/0.1mL</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>68-77°F away from light, Fragile: Glass</td>
<td>59-77°F away from light, Fragile: Glass</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>$55*</td>
<td>$5</td>
</tr>
</tbody>
</table>

* Special pricing or donation programs available. See manufacturer website.

For all products, repeat administration if no or minimal response after 2-3 minutes.

NALOXONE, CONT.

Rescue Dosing and Administration:

– ‘Evzio’ IM/subQ (thigh) auto-injector (0.4 mg)
– ‘Narcan’ intranasal spray (4 mg)
– May repeat Q2-3min (but only 1 dose/device)

*** NOTE: repeat dosing may be required; EMS need to be involved ***

Significant Adverse Rx:

– precipitated w/d & analgesia reversal
NALOXONE, CONT.

Prescribe to anyone at risk of (1) OD or (2) witnessing OD

- Opioid Use DO (or even other hx of substance use DOs)
- Chronic high-dose pain management (>120mg Mes/day)
- Concurrent Benzodiazapine, EtOH (or other sedative) use
- Comorbid conditions that ↑ OD/medical risk (e.g. impaired respiratory function, OSA, smoker, fall risk, altered drug metabolism ~ age/renal/hepatic/cardiac/med interactions)
- Hx of OD (accidental or intentional)
- Significant psychiatric, neurocognitive DO
- At-risk/vulnerable pops (e.g., children or others at risk in home)

Educate pt, family, friends as available & appropriate

- ID possible OD, call 911, admin naloxone, rescue breathing

Resources: http://stopoverdose.org
MEDICATION ASSISTED TREATMENT (MAT):

**Indications & Conditions for Rx:**
- Opioid use DO
- Pt willing/able to consent to & engage in Rx

**Other Screening & Assessment:**
- Gen. Med:
  - Active conditions, med hx, rxvs
  - Evidence of intox/withdrawal
  - SU-assoc. conditions (abscesses, HIV, HepB/C, TB)
  - Cardio-pulmonary, hepatic, renal dysfunction
  - Labs: HCG, tox screen, BMP, LFTs, CBC, UA, Lipid, ID screens (HepB/C, HIV, TB, syphilis)
- Psych:
  - SU hx (substances, timecourse, severity, sequelae, prior tx/rx exp., check PDMP!)
    - Opioids: which, duration, frequ, recency, risk of relapse
    - Active sed/hypnotic, EtOH use DOs?
  - Other psych comorbidities, hx of self-harm & current risk
  - Social context: safety, stability, rx-barriers, etc

**MAT Options:**
- Opioid Substitution:
  - Buprenorphine
  - Methadone
- Abstinence Maint.
  - Naltrexone

**Treatment context:**
- Office-based
- Clinic-based
- Residential
## M.A.T. FOR OPIOID USE DISORDER

### Clinical Uses/Ideal Candidates

<table>
<thead>
<tr>
<th>Extended Release Injectable Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
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<tbody>
<tr>
<td>Prevention of relapse to opioid use disorder following opioid detoxification; studies suggest benefits for patients who are experiencing increased stress or other relapse risks (e.g., visiting places of previous drug use, loss of spouse, loss of job).</td>
<td>Detoxification and maintenance treatment of opioid addiction.</td>
<td>Treatment of opioid dependence. Patients who are motivated to adhere to the treatment plan and who have no contraindications to buprenorphine therapy. Buprenorphine should be part of a comprehensive management program that includes psychosocial support.</td>
</tr>
<tr>
<td>Appropriate for patients who have been detoxified from opioids and who are being treated for a co-occurring alcohol use disorder. Extended-release naltrexone should be part of a comprehensive management program that includes psychosocial support.</td>
<td>Patients who are motivated to adhere to the treatment plan and who have no contraindications to methadone therapy. Methadone should be part of a comprehensive management program that includes psychosocial support.</td>
<td></td>
</tr>
<tr>
<td>Other good candidates include persons with a short or less severe addiction history or who must demonstrate to professional licensing boards or criminal justice officials that their risk of opioid use is low.</td>
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</tbody>
</table>

http://store.samhsa.gov/shin/content//SMA16-4892PG/SMA16-4892PG.pdf
OPIOID ABSTINENCE MAINTENANCE: NALTREXONE
NALTREXONE, CONT.

**Use**: opioid-use relapse prevention (for non-OST candidates)

**MOA**: opioid receptor antagonist (high Mu affinity)

**Route**: IM  (Note: IM >>> PO in opioid use DO)

**Pharmacodynamics/kinetics:**

- Peak: biphasic w/ ~2hrs and then 2-3days
- Duration & Half-life: 4wks; 5-10 days.
- Metabolism: Primarily hepatic via non-cytochrome-mediated dehydrogenase (to 6-β-naltrexol); IM naltrexone ↓ 1st pass metab. Excreted in urine
NALTREXONE (VIVITROL): DOSING & ADMIN.

“Vivitrol” 380mg IM (gluteal, superior-lateral quadrant) Q4wks

Cautions:
- Pt should be opioid-free for 7-10 days before rx; consider naloxone challenge
- For active users, med-managed detox (outpt possible, depending on pt & context)
NALTREXONE: SPECIAL POPS

- Infant: Excreted in breast milk (avoid if possible)
- Geriatric: same as adult
- Hepatic & renal impairment:
  - no adjustment for mild impairment
  - caution w/mod-severe impairment (not studied)
- Pregnancy: not well studied (some development abnl in animal studies)
NALTREXONE: CAUTIONS & MONITORING

Potential SEs/Issues:

– Precipitated w/d
– Analgesia reversal/blockade
  • Provide med alert bracelet
– Hepatocellular injury (rare, dose-dependent)
– Risk of OD: if pt stops (loss of tolerance) or attempts to overcome blockade
– Acute/emergency pain management
– Injection site rxs (vivitrol)—rarely clinically signif.

Monitoring:

– LFTs at initiation, at 1 mo, then annually
Injectable Extended Release Naltrexone for Opioid Dependence


NIDA Notes Vol.21, No.3 - Research Findings
OPIOID SUBSTITUTION: BENEFITS

Studies have found:

• Reduced drug use
• Improved retention in treatment
• Improved health & functionality
• Public health gains (HIV, Hepatitis, etc.)
• Overall health care cost savings
• Reduced criminality (mixed results)
• Reduced mortality (mixed results)

Gunne & Gronbladh, 1981
Mattick, RP et al, 2009
Mattick, RP et al., 2014
Kimber, J et al, 2015
BUPRENORPHINE
(A PARTIAL $\mu$-OPIOID AGONIST)
Buprenorphine

**Use:** Opioid maintenance, medically supervised w/d

**MAO:** opioid receptor *partial* agonist (Mu), weak antagonist (Kappa)

**Formulations:**
- Bup. & bup/naloxone: SL tablets & films
- Buccal films
- Subdermal implant (Probuphine)

**Clinical context (OST, C-III):** office-based, clinic-based

**Pharmaco-dynamics/kinetics:**
- High receptor affinity, low intrinsic activity, slow dissociation
- Peak: ~30-60min
- Half-life (adults): ~16-38hrs
- Metabolism: Extensive 1st pass (poor PO.) Primarily hepatic N-dealkylation (CYP3A4) to norbuprenorphine (active)
- Excretion: feces (~70%) & urine (~30%)
BUPRENORPHINE: BENEFITS

Safety:

- Partial agonist:
  - Ceiling effect limits respiratory depression; less dangerous in OD or when combined w/benzos
  - Less: re-enforcing, physical dependence, w/d symptoms
- High affinity for Mu-receptor:
  - Limits OD-potential w/concurrent illicit use
  - Combination w/naloxone ("Suboxone") limits abuse/diversion

Access:

- Option of office-based treatment!
BUPRENORPHINE VS. PLACEBO FOR HEROIN DEPENDENCE

4 Subjects in Control Group Died

BUPRENORPHINE: PRE-INDUCTION

Assess hx of use:
– Duration & pattern of inappropriate opioid use (freq, quantity, time-course, last-use)

Discuss i/r/b/a to treatment
– Pay attention to pt’s hx, current risk-factors, goals/values, etc

Arrive at shared treatment goals
– Long-term maintenance vs. taper
– Buprenorphine vs. Methadone >>> Naltrexone
– Clinic vs. Office-based?
– Prescribe naloxone rescue kit
BUPRENOPHINE: DOSING (INDUCTION)

**Induction (Week 1):**

- Current opioid users:
  - Await COWS ≥ 13 (to avoid precip. w/d)
  - If on MMT, taper to <30mg/day and hold dose ≥ 2days

- Day#1 (in-office or home-based):
  - Begin w/2-4mg X 1 (2mg w/o ongoing opioid use)
  - If tolerated but w/cont w/d or urges/cravings, then repeat X1 at 60min
  - Can titrate by 2mg Q4hrs up to max 8-12mg over first 24hrs

- Day #2-5: titrate to max 16mg/day, PRN cravings -- monitoring SEs, SU
BUPRENORPHINE: DOSING (POST-INDUCTION)

Stabilization (1-2mo):
– C/w adjustment (+/- 2mg/day) for urges/cravings, SEs

Maintenance (thereafter):
– Avg dose range = 8-16mg Qday; range 4-32mg Qday (can split dose for OST + pain)

Taper:
– When: switch to MMT, SEs, non-compliance
– Approach: Very gradual
– Monitor: w/d, cravings/urges, relapse

** Note: High risk of relapse in pts w/opioid use DO taken off OST – consider Vivitrol post-taper **
BUPRENORPHINE: POTENTIAL SEs, CONCERNS

- **CNS & respiratory depression** (esp in children & w/benzos/other sedatives)
- **Precipitated w/d**
- QTc prolongation (in theory)
- Hypotension
- Hepatitis
- Hypogonadism (in theory – check T-level only w/clinical s/s)
- May lower sz threshold
- Multiple **med-med interactions** (anti-virals, AEs)
- **Acute pain management** (e.g., surgery)
  - Elective Surg.: dose-reduction vs. dc Bup 24-36 hrs before surgery. SA full agonist. opioids may be given during/after procedure.
  - Unplanned surg.: full agonists added to Bup (usually at higher doses.)
BUPRENORPHINE: SPECIAL POPS

**Pregnancy:** Increasingly a 1st line option for OST

**Neonates:** En utero exposure → risk of opioid w/d

**Infant:** Excreted in breast milk (<0.5% of maternal serum level)

**Geriatric:** same as adult dosing; use caution

**Hepatic:** no adjustment for mild impairment; caution w/mod-impairment, dose-reduction w/severe impairment (not well-studied)

**Renal impairment:** no adjustment

**Respiratory conditions** (OSA, resp ds): use w/caution

**QTc prolongation (in theory):** caution w/QTc > 450msec; if >500msec, ↓ other causes vs. ↓ Bup; weigh r:b & consider other tx options
BUPRENORPHINE: MONITORING

– Consider EKG in select pts (baseline and will titration; consider annual)
– LFTs (baseline & once in maintenance phase)
– Sedative effects
– Non-compliance, concurrent SU/med-med interactions
METHADONE
METHADONE: SOME BASICS

**Use:** opioid substitution; pain management

**Ideal Pts:** Opioid use DO, severe & chronic pain, tolerates/benefits from clinic structure, hx of successful rx w/MMT

**MOA:** opioid receptor *(full)* agonist; weak NMDA antagonist

**Route:** PO (tabs, syrup); inj

**Context (for OST, C-II):** licensed clinic; inpatient, emergency bridging (3-days)

**Pharmaco-dynamics/kinetics:**

- **Onset:** ~30-60min
- **Peak:** ~1-7.5hrs w/indiv dosing → **3-5days w/stacking**
- **Half-life (adults):** ~10-90hrs
- **Metabolism:** Primarily hepatic N-demethylation (multiple CYPs, esp p4503A4) → inactive metabolites; 2D6 polymorphism can Δ metab.; parent (10%) & metabolites excreted in urine
  - Lipophilic; may persist w/slow-release from liver, etc
METHADONE: INDUCTION & TITRATION

Induction & Titration:
- **Conservative** initiation & titration (*w/ stacking*)
- **Non-linear dose-potency** when considering morphine equiv (ranging 5-30% ME)

Maintenance:
- Usual range = **60-120mg/day** (some require high doses)
- **Daily clinic-based dosing** (*w/potential for earning carries over long-term*)

Taper: **High risk of relapse off OST**
- When: switch to suboxone, SEs, non-compliance,
- Approach: Very gradual
- Monitor: w/d, cravings/.urges, relapse
METHADONE: POTENTIAL SEs/ISSUES

- CNS & respiratory depression (w/risk of death, esp w/benzos & other sedatives)
- QTc prolongation (risk of Torsades)—in predisposed pts, dose-dependent
- Hypotension
- Hypogonadism (monitor & tx w/long-term Rx)
- Constipation
- Peripheral edema
- Hyperalgesia
- May lower sz threshold
- Multiple med-med interactions
METHADONE: SPECIAL POPULATIONS

Pregnancy: a 1st line Rx; clearance ↑ in 2nd/3rd Trimester

Neonates: En utero exposure → risk of severe w/d

Infant: Excreted in breast milk (2-3% of maternal serum level)

Geriatric: consider slower titration

Hepatic: no adjustment for mild-mod impairment; caution with severe (though not studied)

Renal impairment: for CrCl < 10 use 50-75% nl dose

Respiratory conditions (OSA, resp ds): use w/caution

QTc prolongation: caution in QTc > 450 if >500 msec, ↓ other causes vs. ↓ MMT; weigh r:b & consider other tx options
METHADONE: MONITORING

- EKG (baseline and will titration; consider annual f/u EKG)
- Sedative effects
- Non-compliance, concurrent SU/med-med interactions
OTHER POTENTIAL THERAPIES...

PHARMACOTHERAPIES

• Long acting Buprenorphine
  – “Probuphine”: Subcutaneous 74.2 mg buprenorphine implants (4 per Kit)
  – In-office under local anesthetic
  – Requires REMS training (http://probuphinerems.com/)

• Memantine (equivocal)
• Clonididine (equivocal)
QUESTIONS?

MANY THANKS!
-Andy Saxon, MD
-Mark Duncan, MD