Substitution Therapy for Opioid Use Disorder
The Role of Suboxone®

Methadone/Buprenorphine 101 Workshop, April 1, 2017
Mandy Manak, MD, ABAM, CCSAM
Objectives

- Recognize the options available in treating opioid dependencies with medically assisted therapies
- Understand pharmacology and pharmacokinetics of buprenorphine-naloxone
- Understand adverse effects and potential drug interactions
- Understand the process of induction and how to avoid precipitated withdrawal
Opioid dependence treatment goals

- Suppress withdrawal
- Minimize/eliminate craving for opioids
- Block or attenuate euphoric effect of exogenous opioids
- Improve functional status in all spheres of life through psychosocial intervention
Treatment options

- Abstinence
- Naltrexone
- Opioid agonists
  - Methadone
  - Suboxone® (buprenorphine-naloxone)
Indications

Suboxone® (buprenorphine-naloxone) is indicated for substitution treatment of opioid dependence in adults

• The intention of the naloxone component is to deter intravenous (IV) misuse

• Patients prescribed Suboxone® should be carefully monitored within a framework of medical, social and psychosocial support
Contraindications

• Patients with a known hypersensitivity to buprenorphine, naloxone or any other component of the drug
• *Women who are breastfeeding
• Patients with severe respiratory insufficiency, severe hepatic insufficiency, acute alcohol intoxication, or DTs
Precautions

- Caution in the elderly or debilitated
- Severe impairment of hepatic, pulmonary or renal function
- Myxedema or hypothyroidism, adrenal cortical insufficiency (Addison’s Disease), hypotension
- CNS depression or coma or patients receiving CNS/respiratory depressants
- Intracranial pressure and head injury
- Toxic psychosis, prostatic hypertrophy, urethral stricture, acute alcohol intoxication, DT’s
Opioid agonist options

• Methadone and buprenorphine-naloxone
  – These are not cures, but are a great way to stabilize physical symptoms so that patients can focus on the other areas of recovery.
  – Methadone has worked very well for many patients since its introduction
  – Buprenorphine-naloxone is one more treatment option for patients
Pharmacology of buprenorphine-naloxone
Suboxone®

- A novel approach
  - Synthetic opioid
  - 4:1 of buprenorphine and naloxone
- “Designer drug”
  - Partial agonist at mu-opioid receptor
  - Antagonist at kappa-opioid receptor
Suboxone® dosage forms

- Suboxone® (buprenorphine-naloxone) is available as a sublingual tablet, available in two 4:1 ratio formulations:
  - 2 mg buprenorphine + 0.5 mg naloxone
  - 8 mg buprenorphine + 2 mg naloxone
- Daily dosage range from 4 mg to 24 mg maximum per day
Buprenorphine mu-opioid receptor

- A synthetic partial opioid agonist
  - very high affinity for the mu-opioid receptor (up to 1,000 times greater than other opioids)
  - will displace morphine, methadone, and other full opioid agonists within a short time frame
  - Results in blockade of the mu-opioid receptors
  - [http://www.suboxonecme.ca/en/module3/m3_s1/m3_s1_p2/](http://www.suboxonecme.ca/en/module3/m3_s1/m3_s1_p2/)
Perfect Fit - Maximum Opioid Effect

Empty Receptor

No Withdrawal Pain

Euphoric Opioid Effect
Buprenorphine mu-opioid receptor

- Low intrinsic activity = limited opioid effect
  - Enough to reduce craving and stop withdrawal, but not enough to cause intense euphoria
    - Less dopamine released
  - Opioid effects are blunted (less euphoria, sedation, analgesia, less respiratory depression)
  - Greater safety in overdose over other full opioid agonists (ceiling effect)
Relationship of drug dose and opioid agonist effects

Full Agonists: Heroin, morphine, methadone, codeine

Partial Agonists: Buprenorphine

Antagonists: Naltrexone, naloxone

Threshold for respiratory depression

Adapted from reference 3

http://www.suboxonecme.ca/en/module3
Buprenorphine kappa-opioid receptor

• Acts as an antagonist at the kappa-opioid receptor, binding to but not stimulating it into activity
  – Kappa-opioid receptor blockade may have antipsychotic and antidepressant effects, but the clinical relevance is unclear
Naltrexone

- Opioid receptor antagonist
- Does not help with cravings
- No opioid effect
- Useful for patients in stable recovery but who are concerned about relapse
Pharmacokinetics
Bioavailability

- Oral – high first pass metabolism, low bioavailability
  - Buprenorphine 3%
  - Naloxone barely detectable
- Sublingual
  - Buprenorphine 55%
  - Naloxone < 5%
Bioavailability

- Snort/IVDU
  - Buprenorphine <5%
  - Naloxone 70%
  - Acute withdrawal within two minutes
- Overall mean elimination half-life of buprenorphine in the plasma is 37 hours
Naloxone’s contribution

- Naloxone prevents abuse and diversion
- Poor oral and sublingual bioavailability
- Rapid binding action precipitates a rapid opioid-withdrawal syndrome that deters IV abuse of Suboxone
- Is not the reason go into precipitated withdrawal with SL use (i.e. during induction)
Naloxone pharmacokinetics

- Poor oral and sublingual availability
- When injected: acts as an opioid antagonist with a distribution half-life of four minutes
  - Has an onset of action within two minutes
  - Has an elimination half-life of 1.3 hours
  - Has very high affinity for the mu-receptor
  - Rapid binding action precipitates a rapid opioid withdrawal syndrome and deters IV abuse
Suboxone® pharmacokinetics

- Rapid onset of action and long duration of action
- Starts to work within 30 to 60 minutes
- Peak action occurs within one to four hours
- Peak effect lasts between one to two hours
- Max. plasma concentration from 40 minutes to 3.5 hours
- Elimination half-life 24 to 36 hours (sublingual)
- Steady state equilibrium is reached after three to seven days
Duration of action

Duration of action is dose dependent

- Low doses: 4→12 hours
- Mod doses (8 - 12): 24 hours
- Higher doses (>16mg): 24 to 48 hours
- Dissociation of buprenorphine from the opioid receptor is slow, accounting for it’s long duration of action.
- The blocking effect is dose dependent, such that 16 mg is more effective in blocking full agonist opioids than an 8 mg dose.
Adverse events

- Precipitated withdrawal
- Headache is the most common adverse event reported in clinical trials
- Most common treatment adverse events are consistent with opioid withdrawal or agonist effects
- Most adverse events are attributed to improper dosing or precipitated withdrawal
Adverse events

- Headache, pain, withdrawal syndrome, infection, back pain, flu symptoms, abdominal pain, accidental injury, chills, fever
- Vasodilation
- Constipation, nausea, vomiting, diarrhea, dyspepsia, tooth disorder
- Insomnia, depression, anxiety, nervousness, somnolence, dizziness
- Sweating, myalgia, peripheral edema
General treatment guidelines

• Same rules apply to Suboxone® maintenance therapy (SMT) as to methadone maintenance therapy (MMT)

• Daily dispense at pharmacy until the patient has sufficient clinical stability and is able to safely store Suboxone® take-home doses
Process for treatment

- Assess
- Diagnose
- Consider treatment options
  - Methadone, Suboxone®, taper, detox, rehab
- Pre-induction
- Induction
- Stabilization/maintenance
- Taper when appropriate
Pre-induction

• Additional screening/precautions
  – UDS, liver enzymes, ECG, etc. as usual
  – Negative βhcg
  – Birth control
  – Discuss need for switch to methadone if pregnancy results
    • Subutex → Health Canada → time factor
Dosing considerations

• Plan induction for **early morning dosing**
• Prior to induction, consideration should be given to the type of opioid dependence (**long-acting or short-acting**)  
• **Time since last opioid use**
• **The degree of opioid dependence**
Suboxone® induction

Day 1

• Recommended starting dose of Suboxone is 4 mg
• An additional 4 mg x 2 may be administered, individualized for each patient
• Morning dosing is recommended for first dose
Monitored induction

• Assess the patient before and after the first dose
• If the patient has withdrawal symptoms, distinguish between under-dosing and precipitated withdrawal
• Reassess frequently during the first few days of induction
Induction: managing withdrawal

Acute withdrawal
• Reassess the patient
• Educate the patient
• Add a second dose of Suboxone® of 4 mg to alleviate acute withdrawal
• Continue daily until the patient is stable and no longer experiencing acute withdrawal
Induction: managing withdrawal

Precipitated withdrawal

• Reassure the patient
• Emphasize that opioid use may interfere with induction and stabilization
• Be prepared: have a contingency plan and coordinate with the pharmacy
• Gently push through the pw
• Offer short-term symptomatic relief (clonidine 100 to 150mcg q4h prn, anti-emetics, anti-diarrheals, NSAID)
Precipitated withdrawal

- Can precipitate an acute withdrawal syndrome if administered to an individual who has taken a sufficient dose of a full agonist
- Can displace full agonist opioids from the mu receptors
- Because it acts as a partial agonist, rapid loss of the agonist effects of the displaced opioid, and the acute onset of withdrawal symptoms
Precipitated withdrawal

In patients who have taken another opioid in the past few hours, symptoms of precipitated withdrawal are:

- Felt 30 to 60 minutes after the first dose
- Peak at one to four hours
- Subside over 12 hours, but lasts three to four days
- Symptoms vary in severity
- Difficult to reverse
Avoiding precipitated withdrawal

• Abstain from
  – Short-acting opioids for 24 hours (e.g. heroin)
  – Long-acting opioids for 36 hours (e.g. LA morphine and hydromorphone)
  – Methadone 72 hours (if under 30 mg/24 hrs)
• Delay first dose of Suboxone® until patient is in early stages of withdrawal (COWS scale >12)
• Start with a low first dose (4 mg)
• Warn patient about the risks
• Communicate with pharmacist
Remember

Concurrent use of alcohol or benzodiazepines with Suboxone® is not recommended because of synergistic, toxic and potentially fatal adverse effects.
Missed doses

<72 hours

• Physician or pharmacist must document the reason for the missed dose (s)
• Physician or pharmacist must assess the patient stability
• Patient may continue with usual dose of Suboxone®

>72 hours

• Pharmacist should refer the patient back to the physician for assessment
• Prescribing physician must reassess patient for signs of intoxication
• Document reason for missed doses
• Urine screen
• Follow induction guidelines
Drug interactions

- Concomitant use of sedating agents (CNS depressants, alcohol, benzodiazepines) creates an additive effect of the sedative properties of Suboxone® and should be avoided.
- Some cases of death due to respiratory depression have been reported, particularly when used in combination with benzos, alcohol or other opioids.
Additive effects of SUBOXONE and benzodiazepines

- **Buprenorphine + benzodiazepines**
- **Fatal threshold**
- **Benzodiazepine alone**
- **Buprenorphine alone**

**Respiratory depression** vs **Dose**
Other drug interactions

• The full analgesic effects of other opioid agonists prescribed for pain relief are partially blocked by Suboxone®

• Acute pain relief requires explaining to other healthcare professionals, but is actually simple to manage
Overdose

• The primary management is to re-establish adequate ventilation with mechanical assistance of respiration
• Higher doses of naloxone may be required
• Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine
<table>
<thead>
<tr>
<th><strong>Methadone</strong></th>
<th><strong>Suboxone</strong></th>
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<tbody>
<tr>
<td><strong>Ceiling effect</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Price</strong></td>
<td>Cheaper than Suboxone;</td>
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<tr>
<td><strong>Dosage</strong></td>
<td>Titrate slowly Average 60–120 mg/day</td>
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<tr>
<td><strong>Active ingredient</strong></td>
<td>Methadone</td>
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<tr>
<td><strong>Forms</strong></td>
<td>Available in the form of tablets, dispersible tablets, oral solution (liquid)</td>
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<tr>
<td><strong>Bioavailable</strong></td>
<td>70-80%</td>
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<tr>
<td><strong>Concerns</strong></td>
<td>Prolonged QTc Hypogonadism Over-Sedation Diversion Depression Interactions (QTc)</td>
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<td><strong>Special populations</strong></td>
<td>Methadone is the standard care for pregnant women and has been shown to reduce illicit opioid use.</td>
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Additional considerations

Opiate agonist treatment in remote communities

• Given its safety profile, buprenorphine/naloxone may be a more appropriate treatment option for those in rural regions who may not have adequate physician and/or pharmacy supports in their community
Suboxone®

Want more?

• Visit http://www.suboxonecme.ca
• Comprehensive educational training program open to all physicians and pharmacists