Buprenorphine Maintenance Therapy: A Primer

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Disclosures

- The speakers have no conflicts to disclose.
Objectives

- To learn the basic pharmacology, side-effects, and safety concerns for buprenorphine treatment.

- To be able to select appropriate patients for buprenorphine maintenance.

- To understand the process of induction and maintenance for buprenorphine, including take-home doses.
Outline

- Pharmacology
- Selecting Appropriate Patients
- Induction & Maintenance (including take-home doses)
- Special Populations
- Case Examples
- Additional Resources
Pharmacology
Historical Perspective

- 1937 – Methadone is first synthesized in Germany
- 1947 – FDA first approves Methadone for use
- 1963 – Robert Halliday sets up the first methadone maintenance clinic in the world in BC
Historical Perspective

- 1980s – Buprenorphine first marketed by Reckitt & Colman as an analgesic.

- 2003 – FDA approves office-based use of buprenorphine-naloxone for maintenance by primary care physicians

- 2007 – Suboxone approved by Health Canada
Partial Agonists

Partial Agonist $K_D = 3 \times 10^{-6}$
$e = 0.10$

Receptor Occupancy by Partial Agonist

Response to Partial Agonist

Log Dose of Partial Agonist

% Maximal Response

% Receptor Occupancy
Pharmacological Properties

- Partial agonist of mu-opioid receptor and kappa-opioid antagonist
- Half-life is 24-60 hours (mean 37 hours)
- Metabolized by CYP 3A4 in the liver, has active metabolite norbuprenorphine
Pharmacological Properties

- High affinity for mu-opioid receptor

- Can displace other opioids from receptor
  - E.g. 8mg of buprenorphine completely attenuates 4mg of hydromorphone

- This can lead to precipitated withdrawal
Bioavailability

- Sublingual
- Intramuscular
- Intravenous
Drug-drug Interactions

Inducers:

- Anticonvulsants: phenytoin, carbamazepine
- Barbituates (e.g. phenobarbital)
- Rifampin
- Most HIV medications (NNRTIs, PIs)
- St John’s Wort
- Cocaine / Chronic Alcohol Use
Drug-Drug Interactions

- Inhibitors
  - Antidepressants: Fluvoxamine, Paroxetine, Sertraline, Bupropion
  - Antibiotics: Erythromycin, Cipro, Clarithromycin
  - Calcium Channel Blockers: Diltiazem, Verapramil, Amiodarone
  - Some HIV medications: Ritonavir, Indinavir
  - Others: Fluconazole, Omeprazole, Disulfiram, Grapefruit juice
  - Acute Alcohol Use
Side-Effects

- Respiratory Depression
- Constipation
- Sweating
- Testosterone Deficiency
Buprenorphine and Naloxone

- Suboxone is Buprenorphine with a 4:1 ratio of Buprenorphine:Naloxone

- Naloxone has poor sublingual bioavailability, but is sufficiently absorbed when injected

Safety

- Because of ceiling effect, Buprenorphine is considered to be safer for use than methadone.
  - There seems to be a lower risk from OD, especially early in treatment.

- Only a few known reported cases of death from Buprenorphine use.

- Most of these cases involved the combination of Buprenorphine with Sedative/Hypnotics
  - Most occurred in France
  - Usually concurrent benzodiazepine injection, most commonly flunitrazepam.
Mortality of Methadone vs. Buprenorphine

<table>
<thead>
<tr>
<th>Year</th>
<th>Methadone</th>
<th></th>
<th></th>
<th>Buprenorphine</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Deaths</td>
<td>No. of Patients</td>
<td>Death Rate</td>
<td>No. of Deaths</td>
<td>No. of Patients</td>
<td>Death Rate</td>
</tr>
<tr>
<td>1994</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>1000</td>
<td>0</td>
</tr>
<tr>
<td>1995</td>
<td>5</td>
<td>400</td>
<td>0.0125</td>
<td>5</td>
<td>2900</td>
<td>0.0017</td>
</tr>
<tr>
<td>1996</td>
<td>3</td>
<td>1200</td>
<td>0.0025</td>
<td>3</td>
<td>25000</td>
<td>0.0001</td>
</tr>
<tr>
<td>1997</td>
<td>7</td>
<td>2350</td>
<td>0.0030</td>
<td>6</td>
<td>49000</td>
<td>0.0001</td>
</tr>
<tr>
<td>1998</td>
<td>4</td>
<td>5360</td>
<td>0.0007</td>
<td>13</td>
<td>55000</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Patient Selection
Preparation for OMT

- Meets Criteria for Opiate Dependence (DSM-IV)
- Urine Drug Screen positive for Opiates
  - Screen for Methadone and Buprenorphine as well
- Screen for pregnancy
- Treatment Agreement is Recommended (visit frequency, UDS frequency, take-home doses, approach to instability, etc.)
Caution With:

- Seizures (drug-drug interactions)
- HIV (drug-drug interactions)
- Impaired Hepatic Function (decreased metabolism)
- Pregnancy (possible fetal risk)
- Comorbid Sedative-Hypnotic or Alcohol Dependence (increased mortality risk)
Caution With:

- Paralytic Ileus
- Decreased LOC
- Respiratory Illness
- Allergy
Lab Tests

- Urine Drug Screen
- Beta-HCG
- If concerns of cirrhosis / hepatitis: LFTs
- If IVDU: HIV, Hep B, Hep C
First Line Buprenorphine Patients

- High Risk For Methadone Toxicity:
  - Prolonged QTc
  - Elderly Patients
  - Medication that interfere with methadone metabolism
  - Sedative/Hypnotic or Alcohol Dependence
  - Respiratory Illness (e.g. COPD)
  - Milder Opiate Addiction (e.g. codeine, less than daily opioid use)
  - History of Methadone Abuse
First Line Buprenorphine Patients

- Patients with good prognosis who may be able to taper off opioid agonist treatment after 6-12 months
  - As buprenorphine may be easier to discontinue than methadone
- Adolescents or Young Adult Patients
- Patients who may need early carries
Induction and Maintenance
Induction

- Select good candidate for induction

- Minimum moderate opiate withdrawal to begin induction
  - Use objective scale (e.g. COWS > 12)
  - Risk of precipitated withdrawal

- Initial dose of 2-4mg sl

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Precipitated Withdrawal

DEFINITION

Precipitated withdrawal

Precipitated withdrawal can occur when the patient is provided with their initial dose of buprenorphine/naloxone when they are not in satisfactory opioid withdrawal. In such a circumstance, the high affinity partial mu agonist buprenorphine will displace the full mu agonist opioid of abuse from the mu receptor causing a rapid decrease in receptor activity and the precipitation of opioid withdrawal symptoms.
### COWS

<table>
<thead>
<tr>
<th>Resting Pulse Rate:</th>
<th>GI Upset: over last ½ hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measures after patient is sitting or lying for one minute</td>
<td></td>
</tr>
<tr>
<td>0 pulse rate 80 or below</td>
<td></td>
</tr>
<tr>
<td>1 pulse rate 81–100</td>
<td></td>
</tr>
<tr>
<td>2 pulse rate 101–120</td>
<td></td>
</tr>
<tr>
<td>4 pulse rate greater than 120</td>
<td></td>
</tr>
<tr>
<td>0 no GI symptoms</td>
<td></td>
</tr>
<tr>
<td>1 stomach cramps</td>
<td></td>
</tr>
<tr>
<td>2 nausea or loose stool</td>
<td></td>
</tr>
<tr>
<td>3 vomiting or diarrhea</td>
<td></td>
</tr>
<tr>
<td>5 multiple episodes of diarrhea or vomiting</td>
<td></td>
</tr>
</tbody>
</table>

| Sweating: over past ½ hour not accounted for by room temperature or patient activity |
| 0 no report of chills or flushing |
| 1 subjective report of chills or flushing |
| 2 flush or observable moistness on face |
| 3 beads of sweat on brow or face |
| 4 sweat streaming off face |

| Tremor: observation of outstretched hands |
| 0 no tremor |
| 1 tremor can be felt, but not observed |
| 2 slight tremor observable |
| 4 gross tremor or muscle twitching |

| Restlessness: Observation during assessment |
| 0 able to sit still |
| 1 reports difficulty sitting still, but is able to do so |
| 3 frequent shifting or extraneous movements of legs/arms |
| 5 unable to sit still for more than a few seconds |

| Yawning: Observation during assessment |
| 0 no yawning |
| 1 yawning once or twice during assessment |
| 2 yawning three or more times during assessment |
| 4 yawning several times/minute |

**Score:** 5–12 = mild withdrawal; 13–24 = moderate withdrawal; 25–36 = moderately severe withdrawal; more than 36 = severe withdrawal
## COWS

<table>
<thead>
<tr>
<th>Pupil Size:</th>
<th>Anxiety or Irritability:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o pupils pinned or normal size for room light</td>
<td>o none</td>
</tr>
<tr>
<td>1 pupils possibly larger than normal for room light</td>
<td>1 patient reports increasing irritability or anxiousness</td>
</tr>
<tr>
<td>2 pupils moderately dilated</td>
<td>2 patient obviously irritable anxious</td>
</tr>
<tr>
<td>5 pupils so dilated that only the rim of the iris is visible</td>
<td>4 patient so irritable or anxious that participation in the assessment is difficult</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone or Joint Aches: if patient was having pain previously, only the additional component attributed to opiate withdrawal is scored</th>
<th>Gooseflesh Skin:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o not present</td>
<td>o skin is smooth</td>
</tr>
<tr>
<td>1 mild diffuse discomfort</td>
<td>3 piloerection of skin can be felt, or hairs standing up on arms</td>
</tr>
<tr>
<td>2 patient reports severe diffuse aching of joints/muscles</td>
<td>5 prominent piloerection</td>
</tr>
<tr>
<td>4 patient is rubbing joints or muscles and is unable to sit still because of discomfort</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Runny Nose or Tearing: not accounted for by cold symptoms or allergies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>o not present</td>
<td></td>
</tr>
<tr>
<td>1 nasal stuffiness or unusually moist eyes</td>
<td></td>
</tr>
<tr>
<td>2 nose running or tearing</td>
<td></td>
</tr>
<tr>
<td>4 nose constantly running or tears streaming down cheeks</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Score</th>
<th>The total score is the sum of all 11 items.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Initials of Person Completing Assessment:</th>
<th></th>
</tr>
</thead>
</table>

**Score:** 5–12 = mild withdrawal; 13–24 = moderate withdrawal; 25–36 = moderately severe withdrawal; more than 36 = severe withdrawal
Induction

- Consider reassessing patient in 1 hour for precipitated withdrawal.

- Can reassess patient 3 hours later for additional observed dose or can prescribe take home dose.

- Maximum dose in first day 8mg.
Induction

- Prescriber then prescribes total dose taken in first day as daily dose for the following days.

- Patient should be reassessed within 1-3 days of the induction phase. Observe for:
  - Withdrawal symptoms
  - Side-effects
  - Cravings
  - Intoxication
Induction → Maintenance

- Titrate dose upwards to maintenance dose.
  - Optimal maintenance dose:
    - No withdrawal symptoms for 24 hrs
    - No intoxication, sedation
    - Minimal side-effects
    - Significant improvement in cravings.
    - Cessation of opiate use (negative UDS)
    - No euphoria from opiate use

- Average maintenance dose is 8-12 mg, max dose in Canada is 24mg.

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Maintenance

- Once stable dose is achieved, decreased frequency of visits

- UDS should ideally be done weekly in first 4-8 weeks, depending on patient
  - Afterwards q2 weeks

- Follow up visits should evaluate substance use, cravings, side-effects, psychiatric symptoms, social factors

- Can consider less than daily dosing
## Missed Doses

<table>
<thead>
<tr>
<th>Buprenorphine Dose</th>
<th>Number of Consecutive Days Missed</th>
<th>New Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 8 mg</td>
<td>&gt; 7 days</td>
<td>4 mg</td>
</tr>
<tr>
<td>&gt; 8 mg</td>
<td>6–7 days</td>
<td>8 mg</td>
</tr>
<tr>
<td>6–8 mg</td>
<td>6 or more days</td>
<td>4 mg</td>
</tr>
<tr>
<td>2–4 mg</td>
<td>6 or more days</td>
<td>2–4 mg</td>
</tr>
</tbody>
</table>
Take-Home Doses

- In MMT programs, take-home doses contingent on drug-free UDS prevent the decline in treatment outcomes over time.

- Treatment retention rates are lower in clinics with restrictive take-home policies.
Take-Home Doses

- Therapeutic intervention with benefits and risks

- Better to gradually loosen tight boundaries rather than tighten looser boundaries.

- Health Canada recommends no more than weekend and holiday carries in the first two months of Suboxone use, but there is no evidence to support this.

- Individual risk assessment (Australia) is probably more beneficial to prescribe take-home doses.
Take-Home Doses

- **Individual Risk Assessment:**
  
  - Unstable patients (SI, psychosis, cognitive symptoms, ongoing drug use, comorbid substance use, unstable housing) not to receive early take home doses
  
  - Clinically stable (absence of unstable features above) – could receive weekend and holiday take home in the first 2 months
  
  - More clinically stable (working, particularly stable social situation, no psychiatric symptoms) can get more carries than just weekends and holidays in the first 2 months, but carries still to be increased gradually.
Take-Home Doses

- Patients should be asked how they will store medication before take home doses are given.

- Patients should be made aware of risks to family and the public.

- If clinically unstable and patient is diverting
  - Dose of buprenorphine should be reduced by 25-50% and consider discussing with an expert.

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Tapering

- Discuss safety of taper with patient prior to beginning. Ideally:
  - Drug-free
  - Stable
  - Higher functioning

- Rate of taper should be gradual to facilitate ongoing stability (e.g. 2mg / wk)
Early RCTs

- **1996 – Archives of General Psychiatry,**
  High dose methadone > (Buprenorphine = low dose methadone)


- **2000 – NEJM, Levomethadyl acetate >**
  (Buprenorphine = high dose methadone)


- **2003 – Addictions, Methadone > Buprenorphine**

Special Populations
Pregnancy

- Repeated cycles of intoxication and withdrawal lead to high risk pregnancies in opiate users.

- Methadone is still considered standard of care for pregnancy.
  - Buprenorphine can be considered in patients unsuitable for methadone.

- Buprenorphine is a Category C substance
  - Recommended to use Buprenorphine without Naloxone in pregnancy to reduce fetal risk.

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Pregnancy

- Risk of neonatal abstinence syndrome for mothers maintained on opiate maintenance.

- Refer for prenatal care
  - Consider high risk prenatal care in some cases.

- Buprenorphine is expressed in breast milk but poor oral bioavailability so infants would only be exposed to small amounts
  - Should be discussed with patient.
Management of Acute Pain

- Employ non-opioid alternatives when possible.
- If using opioid to treat pain, avoid using ones that patient has abuse.
- Options include:
  - Continue Buprenorphine – use higher doses of opiates at more frequent intervals.
  - Split dose of Buprenorphine – increase dose, treat both pain and opiate addiction (off-label)
  - Stop Buprenorphine – “opioid debt”, initially use higher doses of opiates, but may need to decrease dose of opiates as buprenorphine is cleared of the body.

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Case Studies
Patient A.M.
Patient A.M.

- 58 year old female, works in sales, full time
- Percocet, up to 30mg Oxycodone per day, oral use only
- No medical comorbidities, no psychiatric illness
- Alcohol 2 glasses of wine, 2-3 nights per week
Patient B.F.
Patient B.F.

- 50 year old male, retired
- Oxycontin 80-120mg per day, oral use only, was prescribed for chronic back pain, now buying from street
- No IVDU, no other opioid use
- Alcohol dependence, in remission x years
- Wife in AA x years and supportive
Patient C.S.
Patient C.S.

- 30 year old man, on ODSP, unemployed, under drug-treatment court

- Polysubstance dependence: IV Opiate Use, IV cocaine / methamphetamine Use, etc.

- History of IV methadone use.

- Possible diagnosis of schizophrenia
Additional Resources
Additional Resources

- Online Courses
  - CAMH
  - AAAP
  - ASAM
  - APA

- CAMH Guidelines (2011)