Buprenorphine as a Treatment Option for Opioid Use Disorder

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Outline

1. Waiver requirements
2. Evidence base for buprenorphine in treating opioid use disorders
3. Buprenorphine pharmacology
4. Clinical use of buprenorphine
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1800s and early 1900s: Rise of opioid addiction in the US

1914: Harrison Narcotics Act

1970: Controlled Substance Act

1974: Methadone maintenance approved

2000: DATA 2000 and waiver requirements

2016: Comprehensive Addiction Recovery Act (CARA)

“Waiver authority for physicians who dispense or prescribe certain narcotic drugs for maintenance treatment or detoxification treatment (H.R. 4365, Children’s Health Act)”
Practitioner requirements

- Physician completes 8 hours of training, and NP/PAs complete 24 hours of training
- Register with SAMHSA and DEA
- Treat no more than 30 patients (concurrently, not cumulatively)
- After 1 calendar year since initial approval, may increase to 100 patients (for MD/NP/PAs)
- As of 2016, qualifying physicians can further increase limit to 275.
- Have the capacity to refer patients to counseling and ancillary services

Medication requirements

- Only medications approved by the US FDA for opioid dependence treatment may be used
- Schedule III, IV, or V only
- Buprenorphine/naloxone or buprenorphine
- Sublingual and buccal
- Tablets or films
- Implantable buprenorphine
Number of MDs obtaining waiver each year in the US

Total of 22,290 physicians completed waiver training to prescribe to 30

Total of 10,888 physicians have applied to increase capacity to 100

*Partial data
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4. Clinical use of buprenorphine
Buprenorphine reduces the cravings for heroin, allowing individual to focus on longer-term goals

![Graph showing the percentage of heroin taken with different doses of buprenorphine. Placebo shows 100% of heroin taken, 4mg shows a significant decrease, and 8mg shows a further decrease.](image-url)
Treatment leads to reduced illicit opioid use, but relapse frequently occurs after taper.
Even with extensive psychosocial support, difficult to stay in treatment after detoxification compared to maintenance with buprenorphine.

All patients received group CBT Relapse Prevention, Weekly Individual Counseling, 3x Weekly Urine Screens, n=20 per group.

Kakko J, Lancet 2003
Review of 31 trials and 5,430 participants

Treatment retention:
- Buprenorphine superior to placebo at all dose ranges
- Buprenorphine no different than methadone, except methadone superior to buprenorphine at low doses

Suppression of illicit opioid use
- Only high dose (>16 mg) of buprenorphine superior to placebo
- Buprenorphine equally effective to methadone
### Long-term outcomes from POATS study (n=375)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 18</th>
<th>Month 30</th>
<th>Month 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current opioid dependence</td>
<td>100</td>
<td>27.9</td>
<td>11.5</td>
<td>7.8</td>
</tr>
<tr>
<td>Agonist treatment</td>
<td>16.3</td>
<td>51.2</td>
<td>38.1</td>
<td>36.9</td>
</tr>
<tr>
<td>Abstinent from illicit opioids</td>
<td>51.2</td>
<td>10.2</td>
<td>63.5</td>
<td>61.4</td>
</tr>
<tr>
<td>Days of illicit rx opioid use</td>
<td>0</td>
<td>31.8</td>
<td>7</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Weiss et al. 2015
Summary of evidence for buprenorphine treatment

- Suppression of illicit opioid use, especially at doses greater than 16 mg per day
- When sufficiently dosed, improved treatment retention comparable to methadone
- Maintenance treatment leads to superior outcomes compared to taper
- Taper leads to relapse in many patients despite high levels of motivation
- Longer-term study suggests some patients are able to maintain their abstinence without agonists while others continue to benefit from maintenance treatment
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<table>
<thead>
<tr>
<th>Chemical:</th>
<th>Semi-synthetic opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacodynamics:</td>
<td>Mu-opioid receptor partial agonist, kappa-opioid antagonist</td>
</tr>
<tr>
<td>Half-life:</td>
<td>3-44 hours</td>
</tr>
<tr>
<td>Active metabolites:</td>
<td>norbuprenorphine, buprenorphine-3-glucuronide, norbuprenorphine-3-glucuronide</td>
</tr>
<tr>
<td>Tmax:</td>
<td>40 minutes to 3.5 hours</td>
</tr>
<tr>
<td>Metabolism:</td>
<td>N-dealkylation to norbuprenorphine via CYP3A4</td>
</tr>
<tr>
<td>Elimination:</td>
<td>Feces, 10-30% in urine</td>
</tr>
<tr>
<td>Bioavailability:</td>
<td>IM 70%, sublingual solution 50%, sublingual tablet 30%, buccal 28%, oral 10%</td>
</tr>
</tbody>
</table>
Activation of the mu-opioid receptor by endorphins leads to opioid-like effects.

Endorphin

Opioid Receptor

Pain relief

Euphoria

Constipation

Slow breathing

CSAT TIP40 2004
Activation of the mu-opioid receptor by heroin leads to similar effects.
Activation of the mu-opioid receptor by methadone also leads to opioid-like effects.

- Pain relief
- Euphoria
- Constipation
- Slow breathing

Methadone

Opioid Receptor
Activation of the mu-opioid receptor by buprenorphine only leads to partial opioid-like effects.

Buprenorphine

Opioid Receptor

Pain relief  Euphoria  Constipation  Slow breathing

CSAT TIP40 2004
Activation of the mu-opioid receptor by naltrexone leads to no opioid-like effects
Buprenorphine, Methadone, and Naltrexone

- **Methadone**: Full Agonist
- **Buprenorphine**: Partial Agonist
- **Naltrexone**: Antagonist

The graph shows the receptor activation (%) in response to different doses of the drugs. The x-axis represents the dose, and the y-axis represents the receptor activation percentage. The graph indicates that as the dose increases, the receptor activation increases for both Methadone and Buprenorphine, while Naltrexone remains almost constant. The graph is from CSAT TIP40 2004.
Methadone blocks the effects of heroin.
Buprenorphine also blocks the effects of heroin

- Pain relief
- Euphoria
- Constipation
- Slow breathing
Naltrexone blocks the effects of heroin
High affinity + partial agonism = Potential for precipitated withdrawal
Precipitated withdrawal

Administering buprenorphine while full agonists are present leads to ANTAGONIST effects.

<table>
<thead>
<tr>
<th>Receptor activation (%)</th>
<th>Full Agonist</th>
<th>Partial Agonist</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>No drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td></td>
<td></td>
<td></td>
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CSAT TIP40 2004
Precipitated withdrawal

Administering buprenorphine while full agonists are NOT present leads to AGONIST effects.
<table>
<thead>
<tr>
<th></th>
<th>Opioid Use Disorder</th>
<th>Chronic Pain</th>
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</thead>
<tbody>
<tr>
<td>Sublingual Tablets</td>
<td>Buprenorphine/naloxone Buprenorphine</td>
<td>None</td>
</tr>
<tr>
<td>Sublingual Films</td>
<td>Buprenorphine/naloxone</td>
<td>None</td>
</tr>
<tr>
<td>Buccal Films</td>
<td>Buprenorphine/naloxone</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Transdermal</td>
<td>None</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Parenteral</td>
<td>None</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Implant</td>
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Johnson et al 2005; SAMHSA 2016; Rosenthal et al 2013
Combination tablet

- Buprenorphine and naloxone in a 4:1 ratio
- If taken as prescribed, naloxone is minimally absorbed
- If injected, naloxone will produce a short (30-60 min) withdrawal reaction
- Combination tablet should be used by default

Mono tablet

- Only buprenorphine
- Reserve for pregnant patients or for those with documented allergy to naloxone
- Has a higher misuse liability and street value
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- **Medication**
  - Control cravings
  - Block other opioids

- **Counseling**
  - Learn about addiction and recovery
  - Relapse prevention skills and managing cravings
  - Treatment of psychiatric co-morbidities

- **Community supports**
  - Peer supports
  - Sober social network
  - Family supports

*Edwards and Koob, 2010; CSAT TIP40 2004*
Medication

- Control cravings
- Block other opioids
Counseling

• Learn about addiction and recovery
• Relapse prevention skills and managing cravings
• Treatment of psychiatric co-morbidities
Medication treatment should not be withheld from patients even if specialized counseling is not offered or not available.

Several multi-site studies of CBT, contingency management, and manualized drug counseling showed no benefit of these interventions above and beyond standard medical management.
Community supports

- Peer supports
- Sober social network
- Family supports
There are still some meetings and members who are opposed to the use of medications to treat OUD.

- disclosing use of buprenorphine needs to be considered carefully
- patients should still utilize AA/NA if they find it useful.
Initial assessment and patient selection

Induction

Early recovery and stabilization

Maintenance
Initial assessment and patient selection

• Assess if outpatient treatment is appropriate
• Detoxification vs maintenance
Induction

- Eliminate withdrawal
- Avoid precipitated withdrawal
Clinical Opiate Withdrawal Scale
• The patient should be given comfort medications (such as clonidine, trazodone, loperamide).

• Patient is reminded that no opioid should be used after 8-10 pm, and the induction may be tried the next day.

However, prevention is the best policy.
Early recovery and stabilization

- Weekly visits
- Medication + psychosocial supports
- Reduce cravings and illicit opioid use
There should not be an expectation that all patients will be able to abstain from all drugs or illicit opiate use during the early treatment phase.
Maintenance

- Less frequent visits
- Sustained recovery
Summary (1)

- To prescribe Bup, prescriber must obtain waiver
- Bup is a partial agonist
- Bup has a high affinity at the Mu receptor
- Just as effective as methadone
- Potential to produce precipitated withdrawal
- Most commonly given as a combination tablet
Summary (2)

- Prescribe monotablet only in exceptions
- Treatment = medication, counseling, social supports
- 2-step initiation process
- Induction will follow initiation
- On-site induction is preferred
Unit Resources

- SAMHSA - Medication Assisted Treatment
- Drug Enforcement Administration - DEA Requirements for DATA Waived Physicians (DWPs)
- Buprenorphine suppresses heroin use by heroin addicts (Mello NK & Mendelson JH, 1980)
- 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial (Kakko et. al, 2003)
- SAMHSA - TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction
- Quick Guide For Physicians Based on TIP 40 (pdf)
- Clinical Opiate Withdrawal Scale
- Neurobiology of dysregulated motivational systems in drug addiction (Edwards and Koob, 2010)