Long-acting depot buprenorphine
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Brian Grahan, MD, PhD, FACP, FASAM
Medical Director, Addiction Medicine office-based services
Director, Integrated Opioid & Addiction ECHO

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Disclosures

• I have no financial conflicts of interest.

• I will not be discussing off-label use of medications
Learner objectives

1. Describe pharmacology of subcutaneous depot buprenorphine (Sublocade)

2. Apply clinical pharmacology to prescribing practice

3. Describe clinical situations when depot buprenorphine may be indicated and contraindicated
Pharmacology Review: Buprenorphine

• Buprenorphine:
  • High MOR affinity (but similar to methadone, fentanyl, hydromorphone)
  • Partial agonism: reduced signal activation per receptor binding event
  • Slow dissociation
  • Long half-life

• Action at the mu-opioid receptor (MOR)
  • Competitive with high affinity opioid agonists at the MOR
  • Decreased downstream signaling per MOR binding event relative to full opioid agonists
Therapeutic goals & the mu opioid receptor

- Withdrawal suppression and some cravings: 40-50% saturation
  - ≥1 ng/mL serum buprenorphine
- Euphoria blockade from oral opioid agonists: 70-80% mOR saturation
  - ~2-3 ng/mL serum buprenorphine
- Blockade for high affinity opioids: 90% mOR saturation

Whole brain mOR availability reduction

- 2mg SL bup: 41%
- 16mg SL bup: 85-92%
- 32mg SL bup: 94-98%

Greenwald et al, 2003
Inter-individual variability

mOR availability at 8mg SL bup (inverse of graph)

<table>
<thead>
<tr>
<th>Region</th>
<th>mOR Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefrontal cortex</td>
<td>10-40%</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>10-40%</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>20-50%</td>
</tr>
<tr>
<td>Amygdala</td>
<td>25-50%</td>
</tr>
</tbody>
</table>

Variability narrows at higher buprenorphine doses

Greenwald et al., 2003
Time since administration matters

Buprenorphine

Plasma Concentration (ng/ml)

Time since buprenorphine (hrs)

- 32 mg
- 16 mg
- 2 mg
- 0 mg

Mean (±SEM) Buprenorphine Concentration (ng/ml)

Time of Sample

-24 hr -15 min -30 min -60 min +120 min +180 min +240 min +360 min +24 hr

Greenwald et al., 2003
Schuh & Johanson, 1999
Buprenorphine level reduces euphoria

<table>
<thead>
<tr>
<th>Measure</th>
<th>BUP 0 mg</th>
<th>BUP 2 mg</th>
<th>BUP 16 mg</th>
<th>BUP 32 mg</th>
<th>Dose–effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal (day 1)</td>
<td>17.1 (1.8)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.0 (1.5)&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>4.0 (0.9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.6 (0.7)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>F(3.12) = 5.01, p &lt; 0.02</td>
</tr>
<tr>
<td>Agonist (days 1–2)</td>
<td>6.1 (0.4)</td>
<td>7.5 (0.5)</td>
<td>8.1 (0.6)</td>
<td>9.2 (0.6)</td>
<td>F(3.12) = 3.31, p &lt; 0.08</td>
</tr>
<tr>
<td>Δ Agonist</td>
<td>14.8 (2.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.0 (1.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.5 (1.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.0 (1.7)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>F(3.9) = 8.77, p &lt; 0.005</td>
</tr>
<tr>
<td>Δ High</td>
<td>57.0 (8.3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69.0 (10.3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19.0 (10.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37.3 (9.5)&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>F(3.9) = 5.14, p &lt; 0.03</td>
</tr>
<tr>
<td>Δ Good Effect</td>
<td>55.8 (15.0)</td>
<td>49.0 (20.0)</td>
<td>15.8 (9.5)</td>
<td>9.8 (6.5)</td>
<td>F(3.9) = 3.41, p &lt; 0.07</td>
</tr>
</tbody>
</table>
Sublocade (RBP-6000)

Serial 100mg dose administrations
• 1\textsuperscript{st} dose ~2-4mg SL bup
• 2\textsuperscript{nd} dose ~4-6mg SL bup

Serial 300mg dose administrations
• 1\textsuperscript{st} dose ~8-12mg SL bup
• 2\textsuperscript{nd} dose ~16-24mg SL bup
Stability increased retention in care

Haight et al, 2019
Illicit opioid use improved, often intermittent

Haight et al., 2019
Results independent of other drug use

<table>
<thead>
<tr>
<th></th>
<th>BUP-XR 300 mg/300 mg plus individual drug counselling (n=196)</th>
<th>BUP-XR 300 mg/100 mg plus individual drug counselling (n=194)</th>
<th>Placebo plus individual drug counselling (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening</td>
<td>Weeks 5–24</td>
<td>Screening</td>
</tr>
<tr>
<td>Amphetamines*</td>
<td>15%</td>
<td>7–12%</td>
<td>25%</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>1%</td>
<td>0–1%</td>
<td>2%</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>10%</td>
<td>4–9%</td>
<td>12%</td>
</tr>
<tr>
<td>Cocaine†</td>
<td>40%</td>
<td>27–39%</td>
<td>47%</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>47%</td>
<td>30–38%</td>
<td>55%</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>1%</td>
<td>1–4%</td>
<td>0</td>
</tr>
</tbody>
</table>

Use of other substances at weeks 5–24 is shown as the range of observed values for percentage of participants with positive urine drug screen, positive self-report in timeline follow-back interviews, or concomitant medication per visit during weeks 5–24. Confirmatory testing was not done. Numbers of participants in each group reflect the number in the intent-to-treat population; this number fluctuated between weeks 5 and 24. *Defined as amphetamines and methamphetamines. †Based on assay for benzoylecgonine, a cocaine metabolite.

Haight et al, 2019
No significant increase in adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>BUP-XR 300/300 mg plus individual drug counselling (n=201)</th>
<th>BUP-XR 300/100 mg plus individual drug counselling (n=203)</th>
<th>Placebo plus individual drug counselling (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-emergent adverse event</td>
<td>134 (67%)</td>
<td>155 (76%)</td>
<td>56 (56%)</td>
</tr>
<tr>
<td>Any serious treatment-emergent adverse event</td>
<td>7 (3%)</td>
<td>4 (2%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Any severe treatment-emergent adverse event</td>
<td>13 (6%)</td>
<td>15 (7%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Any treatment-emergent adverse event leading to discontinuation</td>
<td>10 (5%)</td>
<td>7 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Any treatment-emergent adverse event leading to death</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Haight et al, 2019
Clinical exceptions

- Some people remain below 2 ng/mL after two (2) 300mg q4 week injections

- None remained below therapeutic level after 4th 300mg injection

Jones et al, 2021
Areas of exploration

- Pregnancy
  - Case reports exist of people maintained on Sublocade for duration of pregnancy and through either vaginal or cesarean section delivery without complication

- Adolescence and emerging adulthood
  - Nonadherence is commonplace

- Management of Sublocade for people with other moderate-severe SUDs
  - Loss of contingency management
  - Loss of medication safety monitoring

- Acute pain management in people on stable high dose (≥2 doses 300mg Sublocade) depot buprenorphine

- Buprenorphine taper/cessation approach
Taper option?

Anecdotally, some people who have wanted to taper off, but struggled with SL stepoffs below 2mg total daily, have successfully* tapered using Sublocade

*Long-term abstinence unknown
Considerations

- Sublocade may be indicated in these settings:
  - Medication non-adherence
    - Cognitive impairment
    - Psychosocial instability
  - Difficulty scheduling clinic follow-up
  - Convenience

- Questions
  - Given loss of contingency management, appropriate for people with active stimulant, sedative, or severe alcohol use disorders?
  - In what situations is counseling more important than medication adherence?
Questions?

Brian.Grahan@hcmed.org
www.HennepinHealthcare.org/ECHO
Office: 612-873-5597
Clinic: 612-873-5500
References


