Buprenorphine LAI: Two Many Options

Samrat Shrestha, Pharm.D.
PGY-1 Pharmacy Resident
Central Texas Veterans Health Care System
Disclosure

Nothing to disclose
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUD</td>
<td>opioid use disorder</td>
</tr>
<tr>
<td>OD</td>
<td>overdose</td>
</tr>
<tr>
<td>S/x</td>
<td>symptoms</td>
</tr>
<tr>
<td>LAI</td>
<td>long acting injection</td>
</tr>
<tr>
<td>SL</td>
<td>sublingual</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>BUP</td>
<td>buprenorphine</td>
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<tr>
<td>BPN-NX</td>
<td>buprenorphine/naloxone</td>
</tr>
<tr>
<td>COWS</td>
<td>clinical opioid withdrawal scale</td>
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<tr>
<td>SOWS</td>
<td>subjective opioid withdrawal scale</td>
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</table>
Objectives

• Identify guideline recommendations for BUP treatment of OUD
• Analyze the effectiveness of two different BUP LAI formulations
• Construct patient criteria for use for the formulations discussed
Outline

• Introduction to OUD
  • Diagnostic criteria
  • Etiology and pathophysiology
  • Treatment and standard of care

• Clinical controversy
  • Evaluate two different trials on similar formulations of BUP LAI
  • Create patient criteria for each formulation based on the literature

• Final Conclusion
Preface

• Buprenorphine Physician-Pharmacist Collaboration in the Management of Patients With Opioid Use Disorder: CTN 0075 (Pharm-OUD-Care)

https://clinicaltrials.gov/ct2/show/NCT03248947
Background: Opioid Use Disorder
• OUD: a problematic pattern of opioid use, leading to clinically significant impairment or distress
  • Use of diverted opioids
  • Use of heroin
  • Misuse of opioid medications
Diagnosis: DSM V

- Mild: 2-3 symptoms
- Moderate: 4-5 symptoms
- Severe: 6+ symptoms
Etiology and Pathophysiology

- Acute vs. Chronic Opioid Use

<table>
<thead>
<tr>
<th>1996 Conventional Name</th>
<th>Important Clinical Effects of Receptor Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu_1 )</td>
<td>Supraspinal analgesia</td>
</tr>
<tr>
<td></td>
<td>Peripheral analgesia</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
</tr>
<tr>
<td></td>
<td>Euphoria</td>
</tr>
<tr>
<td></td>
<td>Prolactin release</td>
</tr>
<tr>
<td>( \mu_2 )</td>
<td>Spinal analgesia</td>
</tr>
<tr>
<td></td>
<td>Respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Physical dependence</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal dysmotility</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Growth hormone release</td>
</tr>
</tbody>
</table>
Acute Use

• Inhibition of adenylate cyclase
• Results in suppression of downstream excitatory actions

Acute Use

- Opening of K efflux channels
- Resulting in hyperpolarization

Acute and Chronic use

- Close Ca influx channels

Chronic Use

• Production of cAMP response element binding (CREB) proteins
  • Results in opening of Na influx channels, preventing hyperpolarization

Chronic Use

- Reduced efficacy of opioids actions on K efflux channels
  - Preventing hyperpolarization

Etiology and Pathophysiology

• Results in the misbalance of neuronal excitatory and inhibitory actions
• With sudden cessation of opioids, rebound hyperexcitability can occur

• Results in the clinical withdrawal symptoms seen:
  • Craving
  • Anxiety
  • Dysphoria
  • Insomnia
  • Sweating, Piloerection (gooseflesh)
  • Lacrimation, Rhinorrhea
  • Nausea, Vomiting, Diarrhea
  • Cramp, Muscle aches
  • Fever
Treatment Options

• Standard of care:
  • Psychosocial treatment with medication assisted therapy

• 3 FDA approved medications for treatment of OUD (at the time)
  • Methadone
  • Buprenorphine (+/- Naloxone)
  • Naltrexone

• 1 off label medication for OUD withdrawal management
  • Clonidine

Treatment Options

• New medications approved for OUD since then:
  • Buprenorphine depot implant (Probuphine®)
  • Buprenorphine SC injection (Sublocade®)
  • Buprenorphine SC injection (Brixadi®)
  • Lofexadine (Lucemyra®)
Pharmacotherapy Review

• Methadone: full mu-agonist
• Buprenorphine: partial mu-agonist, acts as an antagonist at high doses
• Naloxone: opioid receptor antagonist
• Naltrexone: mu opioid receptor antagonist
• Lofexadine: alpha-2-agonist
• Clonidine: alpha-2-agonist
Buprenorphine Treatment Initiation

- Initially weekly visits with psychosocial treatment
- Urine drug tests to assess compliance and illicit opioid use
- Validated scales used for withdrawal assessment:
  - COWS, SOWS, and OCVAS
- Induction:
  - Start after last dose of opioids in physicians office
  - Start BUP therapy if COWS score >11-12
  - Start with low doses (2-4 mg) and increase by 2-4 mg per hour until withdrawal symptoms are controlled
- Post-Induction – titrate dose down to maintain opioid abstinence
- Patient directed treatment duration: can be done slowly over many months to many years
Treatment Goals

- Block effects of illicit opioids
- Suppress opioid withdrawal
- Reduce opioid craving and reduce/stop the use of illicit opioids
- Promote patient engagement in recovery-oriented activities
Treatment Concerns

- Diversion
- Unintended exposure
- Adherence
- Physiologically dependent
Which of the following is a symptom of opioid withdrawal?

A. Polyphagia  
B. Drowsiness  
C. Seizures  
D. Nausea/Vomiting/Diarrhea
Question!

Which of the following is an opioid that patients with OUD will be treated for?

A. Crank
B. Cocaine
C. Methamphetamine
D. Heroin
Clinical Controversy
Three New BUP Formulations

- Buprenorphine (Probuphine®)
  - 6-month BUP implant
- Buprenorphine-XR (Sublocade®)
  - Once monthly BUP SC injection
- Buprenorphine (Brixadi®)
  - Weekly and/or monthly BUP SC injection
Controversy

What patient population should receive the new BUP LAI?

- The extent of patient criteria for use of BUP includes:
  - Consent to treatment
  - No contraindications to therapy
- There are no recommendations for selection between the different BUP injectable products
Trial #1; SC BUP XR (Sublocade®)


<table>
<thead>
<tr>
<th>Design</th>
<th>Multi-center, randomized, double-blind, placebo-controlled trial</th>
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</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults w/ moderate-severe OUD</td>
</tr>
<tr>
<td>Intervention</td>
<td>SC BUP-XR 300 mg x 6 months or SC BUP-XR 300 mg x 2 months then 100 mg x 4 months + drug counseling</td>
</tr>
<tr>
<td>Control</td>
<td>Volume matched placebo + drug counseling</td>
</tr>
<tr>
<td>Outcome</td>
<td>Percentage of urine samples negative for illicit opioid use from week 5-24</td>
</tr>
</tbody>
</table>
Methods

Run-in-phase → Randomized 2:2:1 →

- BUP-XR 300 mg/300 mg + DC
  n = 196
- BUP-XR 300 mg/100 mg + DC
  n = 194
- Volume Matched Placebo + DC
  n = 99
Patient Population

Inclusion Criteria:

• Adults 18-65 years
• New diagnosis of moderate-severe OUD within the last 3 months

Exclusion Criteria:

• Contraindications to BUP therapy
• Concurrent non-opioid substance abuse diagnosis
• Moderate-severe alcohol use disorder
**Patient Population**

- No significant differences in baseline characteristics
- Mean opioid use of 11-12 years

<table>
<thead>
<tr>
<th></th>
<th>BUP-XR 300 mg + drug counseling (n = 196)</th>
<th>BUP-XR 300 mg/100 mg + drug counseling (n = 194)</th>
<th>Placebo + drug counseling (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWS</td>
<td>2.2 (2.56)</td>
<td>2.1 (2.31)</td>
<td>2.3 (2.5)</td>
</tr>
<tr>
<td>SOWS</td>
<td>4.4 (6.12)</td>
<td>3.6 (5.42)</td>
<td>4.5 (5.64)</td>
</tr>
<tr>
<td>Opiate Craving VAS</td>
<td>7.1 (13.29)</td>
<td>5.5 (10.97)</td>
<td>9.5 (16.94)</td>
</tr>
</tbody>
</table>
# Outcomes

<table>
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<tr>
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<th>BUP-XR 300 mg + drug counseling (n = 196)</th>
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</thead>
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<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean percent of negative urine tests weeks 4-24</td>
<td>41.3% (39.66%) p&lt; 0.0001</td>
<td>42.7% (38.5%) p&lt; 0.0001</td>
<td>5% (16.98%)</td>
</tr>
<tr>
<td><strong>Secondary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of participants with treatment success</td>
<td>57 (29%)</td>
<td>55 (28%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>
Safety

- Headache
- Constipation
- Nausea
- Injection Site Pruritis
Trial Conclusions

Monthly SC BUP-XR is more effective than placebo for treatment of mod-severe OUD at doses of 300 mg/300 mg and 300 mg/100 mg.

Patient criteria includes:

- Mod-Severe OUD
- History of opioid use for less than 10 years
- Stabilized on SL BUP-NX first
Presenter’s Conclusion

Pros
• RCT
• Similar baseline characteristics
• Intent to treat

Cons
• Placebo controlled
• Large rate of dropouts
• No mean doses of SL BUP-NX in the run-in phase given
• No mention of supplemental doses given
Presenter’s Conclusion

• Use Sublocade in patients whose symptoms are adequately controlled and the main concerns are adherence, ease of use and to minimize exposures

• Would not recommend use due to:
  • Unknown dosing comparisons to SL BUP-NX
  • Cost of therapy
Trial #2, SC BUP (Brixadi®)

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, randomized, double-blind, double-dummy, non-inferiority trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults w/ mod-severe OUD</td>
</tr>
<tr>
<td>Intervention</td>
<td>Weekly and monthly SC BUP + SL placebo + addiction counseling</td>
</tr>
<tr>
<td>Control</td>
<td>SL BUP-NX + SC volume-matched placebo + addiction counseling</td>
</tr>
<tr>
<td>Outcome</td>
<td>Percent of urine samples negative for opioids and the responder rate</td>
</tr>
</tbody>
</table>

Methods

Day 1: SC BUP + SL placebo + addiction counseling n = 213

Phase 1 Weeks 1-11: SL BUP-NX + placebo + addiction counseling n = 215

Phase 2 Weeks 12-24
Patient Population

Inclusion Criteria:
- Adults 18-65
- Mod-severe OUD

Exclusion Criteria:
- Contraindications to BUP therapy
- Chronic pain requiring opioids
- Received treatment for OUD within 60 days prior to enrollment
- Use of strong CYP3A4 inhibitors
- Suicidal ideations
- Pending legal action
Patient Population

- No significant differences in baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>SC-BPN + SL placebo + addiction counseling (n = 213)</th>
<th>SL-BPN/NX + SC placebo + addiction counseling (n = 215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration since OUD diagnosis (years)</td>
<td>4.7 (6)</td>
<td>4.3 (7.8)</td>
</tr>
<tr>
<td>COWS</td>
<td>12 (6)</td>
<td>12 (5.4)</td>
</tr>
<tr>
<td>SOWS</td>
<td>31 (16.1)</td>
<td>32 (15.4)</td>
</tr>
<tr>
<td>Opiate Craving VAS</td>
<td>76 (24.9)</td>
<td>77 (25.4)</td>
</tr>
</tbody>
</table>
Outcomes Evaluation

• Primary outcomes:
  • Mean percent of urine samples negative for opioids from weeks 1-24
  • Responder Rate: no illicit opioid use at:
    • Phase 1: 2/3 negative during weeks 9-11 and week 12
    • Phase 2: 5/6 in weeks 13-24
    • Total = 8/10 negative urine tests
Outcomes

• Primary outcome: SC BUP was non-inferior to SL BUP-NX

• Nonsignificant difference in supplemental doses used:
  • 17/215 in SL group
  • 14/213 in SC group
Outcomes

- Primary outcome: Responder Rate: SC BUP was non-inferior to SL BUP-NX
Outcomes

- Secondary outcomes: Significant difference favoring SC BUP in mean negative urine tests during phase 2
Safety

- Headache
- Constipation
- Nausea
- Injection Site Pruritis
- UTI
Patient criteria includes:

- Mod-Severe OUD
- Adherence issues
- Concerns with diversion

SC BUP is non-inferior to daily SL BUP-NX during both acute and maintenance phases of treatment
Presenter’s Conclusion

Pros
- Great study design for non-inferiority
- Used an active comparator arm
- Similar baseline characteristics
- Intent to treat
- Low dropout rate
- Ability to use in the acute phase to titrate to effect with flexible dosing
- Dose equivalence and included mean doses used

Cons
- $0-75 stipend provided to patients
- No assessment of adherence in SL group
Presenter’s Conclusion

• Agree with trials outcomes and patient criteria listed
• Would recommend use due to:
  • Flexibility of dosing
  • Ability to use in acute as well as maintenance phase
• Concerns for therapy:
  • Cost
  • 160 mg/month dose may not be necessary for most patients because it correlates to 32 mg/day and usually we do not see increased efficacy at doses greater than 24 mg/day
Final Conclusions
Drug comparison

**SC BUP-XR (Sublocade®)**
- Maintenance phase only
- Better than placebo
- 100 mg and 300 mg doses

**SC BUP (Brixadi®)**
- Acute and maintenance phase
- Non-inferior to current standard of care
- Available dose equivalencies to SL BUP-NX
- Weekly doses of 16-32 mg/week
- Monthly doses of 64-160 mg/month
Patient Criteria For Use

- For any SC BUP formulation:
  - Adults 18-65
  - Mod-severe OUD
  - Mean years of use does not matter
  - Not pregnant/lactating
  - No AST/ALT > 3x ULN or T. Billi > 1.5x ULN
  - No concurrent drug-drug interactions (3A4)
  - Normal cardiac function or stable disease without risk for QTc
  - Adherence issues
  - Presence of children or pets
  - At risk populations
Which one would you use?

• I would recommend using SC BUP (Brixadi®) over SC BUP-XR (Sublocade®) due to:
  • Flexibility of dosing
  • Ability to use in acute as well as maintenance phase
  • Consider using it as 1st line due to:
    • Eliminates adherence issues
    • Minimizes potential for diversion and unintended exposures
    • Significant difference favoring SC BUP in maintaining abstinence from illicit opioids during the maintenance phase
    • Avoid 160 mg/month dose
  • Recommendation of SC BUP-XR:
    • Use the 300 mg dose over the 100 mg dose
      • No difference in primary outcomes
      • Cheaper
ER physician has diagnosed the patient with severe OUD and wants to start something to treat his withdrawal symptoms immediately and then defer to outpatient for treatment. Which of the following is the best option to initiate in this patient?

a) SC BUP XR 300 mg monthly
b) SC BUP 16 mg weekly
c) Naltrexone 50 mg daily
d) Clonidine 0.1 mg QID
e) Methadone 20 mg daily
Opinion Question!

Based on these studies, and all other factors considered equal, which of these 3 medications would you prefer to use for the treatment of moderate-severe OUD?

a) SC BUP XR 300/100 monthly
b) SC BUP XR 300 mg/300 mg monthly
c) SC BUP weekly/monthly
d) SL BUP-NX
No Access!

Sublocade® vs. Brixadi® court case
Thank You!

• UT Mentor:
  • Dr. Kirk Evoy

• VA Mentors:
  • Dr. Erin Wunderlich
  • Dr. Sarah Norman