Injectable Extended-Release Buprenorphine Treatment in the Fentanyl Era

John J. Mariani, MD
Columbia University Irving Medical Center/
New York State Psychiatric Institute
Division on Substance Use Disorders
5/19/20
Disclosures

- John Mariani, MD, has a relevant financial relationship with Novartis and Indivior. He is a consultant in the area of medication treatment research.

*The content of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.*
Target Audience

- The overarching goal of PCSS is to train healthcare professionals in evidence-based practices for the prevention and treatment of opioid use disorders, particularly in prescribing medications, as well for the prevention and treatment of substance use disorders.
Educational Objectives

• At the conclusion of this activity participants should be able to:
  ▪ Review the data supporting the use of injectable extended-release buprenorphine treatment for opioid use disorder
  ▪ Identify special risks that fentanyl use presents and the possible role of injectable extended release buprenorphine treatment.
  ▪ Discuss the role of extended-release injectable buprenorphine in the treatment of OUD patients using fentanyl
Opioid Use Disorder Prevalence

People Aged 12 or Older with a Past Year Substance Use Disorder (SUD): 2018

- No Past Year SUD: 253.5 Million People (92.6%)
- Past Year SUD: 20.3 Million People (7.4%)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Number of People with Past Year SUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>14.8M</td>
</tr>
<tr>
<td>Illicit Drugs</td>
<td>8.1M</td>
</tr>
<tr>
<td>Marijuana</td>
<td>4.4M</td>
</tr>
<tr>
<td>Rx Pain Reliever Misuse</td>
<td>1.7M</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>1.1M</td>
</tr>
<tr>
<td>Cocaine</td>
<td>977,000</td>
</tr>
<tr>
<td>Rx Stimulant Misuse</td>
<td>561,000</td>
</tr>
<tr>
<td>Heroin</td>
<td>526,000</td>
</tr>
</tbody>
</table>

Rx = prescription.

Note: The estimated numbers of people with substance use disorders are not mutually exclusive because people could have use disorders for more than one substance.

(NSDUH, 2019)
Trends in US Opioid Prescribing

Rates for overall annual opioid prescriptions filled per 100 persons and for high-dosage prescriptions (≥ 90 morphine milligram equivalent [MME]/day) — United States, 2006-2018

(CDC, 2019)
US Overdose Death Trends

Age-adjusted rates\textsuperscript{a} per 100,000 population of drug overdose deaths\textsuperscript{b} by drug or drug class and year — United States, 1999-2017

(CDC, 2019)
Overall Overdose Death Rates

Age-adjusted drug overdose death rates, by sex: United States, 1999–2018

1Significant increasing trend from 1999 through 2016 with different rates of change over time, \( p < 0.05 \). Rate in 2018 was significantly lower than in 2017.
2Rates for males were significantly higher than rates for females for all years, \( p < 0.05 \).
3Significant increasing trend from 1999 through 2018 with different rates of change over time, \( p < 0.05 \). Rate in 2018 was significantly lower than in 2017.

NOTES: Deaths are classified using the International Classification of Diseases, 10th Revision. Drug poisoning (overdose) deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. The number of drug overdose deaths in 2018 was 67,367. Access data table for Figure 1 at: https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf#1.


(Hedegaard, 2020)
Overdose Death Rates By Opioid Type

Age-adjusted drug overdose death rates involving opioids, by type of opioid: United States, 1999–2018

1Significant increasing trend from 1999 through 2006 and 2013 through 2018, with different rates of change over time, p < 0.05.
2Significant increasing trend from 1999 through 2018, with different rates of change over time, p < 0.05.
3Significant increasing trend from 2005 through 2015, with different rates of change over time, p < 0.05.
4Significant increasing trend from 1999 through 2006, then significant decreasing trend from 2006 through 2018, with different rates of change over time, p < 0.05.
NOTES: Deaths are classified using the International Classification of Diseases, 10th Revision. Drug-poisoning (overdose) deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug overdose deaths involving selected drug categories are identified by specific multiple-cause-of-death codes: heroin, T40.1; natural and semisynthetic opioids, T40.2; methadone, T40.3; and synthetic opioids other than methadone, T40.4. Deaths involving more than one opioid category (e.g., a death involving both methadone and a natural or semisynthetic opioid) are counted in both categories. Deaths may involve multiple drugs. The percentage of drug overdose deaths that identified the specific drugs involved varied by year, with ranges of 75%–79% from 1999 through 2013 and 81%–92% from 2014 through 2018. Access data table for Figure 3 at: https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf#3.

(Hedegaard, 2020)
Overdose Death Rates Involving Opioids, by Type, United States, 1999-2018

- Any Opioid
- Other Synthetic Opioids (e.g., fentanyl, tramadol)
- Heroin
- Commonly Prescribed Opioids (Natural & Semi-Synthetic Opioids and Methadone)

U.S. Drug Overdose Death Count, by Year and Drug Category

![Bar charts showing the number of deaths by type of drug and presence of synthetic opioids.](image)

**SOURCE:** Data for this figure are from deidentified public-use MCOD certificate files produced by the National Center for Health Statistics, 2005–2017, shared with RAND researchers under a data use agreement.

**NOTE:** The “synthetic opioids only” panel excludes deaths that also mention cocaine, heroin, prescription opioids, or psychostimulants.
Timeline of Select Synthetic Opioid Events

1960: Fentanyl synthesized

1972: Fentanyl approved by FDA

1981: Fentanyl off patent, sales increase

1990: Fentanyl patches approved in US

1994: FDA warns about fentanyl patch misuse

2007: Fentanyl precursors scheduled by DEA

2013: Acetyl fentanyl outbreak

2013: Current fentanyl epidemic begins with rise in deaths

2015: Multiple fentanyl analog deaths in US

2015: China schedules 19 fentanyl, new analogs appear in 2 months

2017: US Senate resolution calling fentanyl public health crisis

2017: All synthetic opioid cases on the rise

1964: Fentanyl International Schedule I drug

1970’s-80’s: Fentanyl analog outbreaks

1980’s: First reports of fentanyl misuse by clinicians

1990’s: Reports of fentanyl patch misuse

2006: Fentanyl outbreak in heroin users; isolated to 1 lab in Mexico

2012: Synthetic Drug Abuse Prevention Act

2014: Counterfeit pills containing fentanyl enter market

2016: Counterfeit pills causing deaths due to fentanyl, U-47700

2016: Carfentanil outbreak in US

(Carmenian, 2018)
What are Highly Potent Synthetic Opioids (HPSO)?

- A class of full agonists at the μ-opioid receptor that include:
  - **Fentanyl**
    - Developed by Janssen in 1963
      - Purposefully seeking highly lipophilic opioid agonist
  - **Fentanyl analogues**
    - Sufentanil, alfentanil, remifentanil, carfentanil, lofentanil, thiofentanil
  - **Other novel synthetic opioids**
    - AH-7921, U-47700, and MT-45
- Diversity among agents for selectivity at mu receptors, some agents have delta and kappa receptor interactions

(Macguire, 1992)
## HPSO Legal Status

### DEA and UN scheduling of synthetic opioids.

<table>
<thead>
<tr>
<th>Synthetic Opioid</th>
<th>DEA (US)</th>
<th>Date (DEA)</th>
<th>UN</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha-methyhfentanyl</td>
<td>Schedule I</td>
<td>9/22/1981</td>
<td>Schedule I</td>
</tr>
<tr>
<td>sufentanil</td>
<td>Schedule II</td>
<td>5/25/1984</td>
<td>Schedule I</td>
</tr>
<tr>
<td>3-methylfentanyl</td>
<td>Schedule I</td>
<td>9/22/1986</td>
<td>Schedule I</td>
</tr>
<tr>
<td>alfentanil</td>
<td>Schedule II</td>
<td>1/23/1987</td>
<td>Schedule I</td>
</tr>
<tr>
<td>3-methylthiofentanyl</td>
<td>Schedule I</td>
<td>5/29/1987</td>
<td>Schedule I</td>
</tr>
<tr>
<td>alpha-methylthiofentanyl</td>
<td>Schedule I</td>
<td>5/29/1987</td>
<td>Schedule I</td>
</tr>
<tr>
<td>beta-hydroxyfentanyl</td>
<td>Schedule I</td>
<td>5/29/1987</td>
<td>Schedule I</td>
</tr>
<tr>
<td>para-fluorofentanyl</td>
<td>Schedule I</td>
<td>5/29/1987</td>
<td>Schedule I</td>
</tr>
<tr>
<td>thiofentanyl</td>
<td>Schedule I</td>
<td>5/29/1987</td>
<td>Schedule I</td>
</tr>
<tr>
<td>beta-hydroxy-3-methylfentanyl</td>
<td>Schedule I</td>
<td>1/8/1988</td>
<td>Schedule I</td>
</tr>
<tr>
<td>carfentanil</td>
<td>Schedule II</td>
<td>10/28/1988</td>
<td>NS</td>
</tr>
<tr>
<td>remifentanil</td>
<td>Schedule II</td>
<td>11/5/1996</td>
<td>Schedule I</td>
</tr>
<tr>
<td>acetyl fentanyl</td>
<td>Schedule I</td>
<td>7/17/2015</td>
<td>Schedule I</td>
</tr>
<tr>
<td>beta-hydroxythiofentanyl</td>
<td>Schedule I</td>
<td>5/12/2016</td>
<td>NS</td>
</tr>
<tr>
<td>butyryl fentanyl</td>
<td>Schedule I</td>
<td>5/12/2016</td>
<td>NS</td>
</tr>
<tr>
<td>AH-7921</td>
<td>Schedule I</td>
<td>5/15/2016</td>
<td>Schedule I</td>
</tr>
<tr>
<td>thiafentanil</td>
<td>Schedule II</td>
<td>8/26/2016</td>
<td>NS</td>
</tr>
<tr>
<td>U-47700</td>
<td>Schedule I</td>
<td>11/14/2016</td>
<td>NS</td>
</tr>
<tr>
<td>furanyl fentanyl</td>
<td>Schedule I</td>
<td>11/29/2016</td>
<td>NS</td>
</tr>
<tr>
<td>4-fluoroisobutyryl fentanyl</td>
<td>Schedule I</td>
<td>5/3/2017</td>
<td>NS</td>
</tr>
<tr>
<td>MT-45</td>
<td>NS</td>
<td></td>
<td>Schedule I</td>
</tr>
</tbody>
</table>

NS- not scheduled.

(Armenain, 2018)
Why are HPSO’s so Potent?

- Fentanyl and its analogues are highly lipophilic
- High lipophilicity results in:
  - Rapid crossing of the blood-brain barrier
  - Rapid distribution to the peripheral tissue and a slow return to the central compartment
- Highly efficacious μ-opioid receptor agonist
- Similar μ-opioid receptor affinity as morphine
  - Unclear why so much more potent than morphine
- Definitive human studies are lacking

Pharmacokinetic Consequences of High Lipophilicity

- Fentanyl is rapidly distributed from plasma into highly vascularized compartments, before redistribution to muscle and fat tissue occurs.
- After equilibration at these sites, fentanyl is released back into the plasma:
  - elimination half-life of 3–8 h
- Therefore, it has a short duration of action after single bolus administration, but the duration of effect is increased due to accumulation after multiple boluses or with a continuous infusion.
Fentanyl Metabolism

• Metabolised in the liver by the cytochrome P450 (CYP) 3A4 isoenzyme system
• Rapid and extensive first-pass metabolism via oxidative N-dealkylation to norfentanyl and other inactive metabolites
• Poor oral bioavailability (<30%), which is why there are no oral formulations

(Mystakidou 2006) (Labroo 1997)
Where does illicit Fentanyl come from?

- Historically, diverted from medical sources
  - Injectable formulations for anesthesia
  - Transmucosal formulations (lozenges, tablets, intranasal spray)
  - Transdermal patch
- In the current US epidemic, initially primarily from China, but now increasingly Mexico and India
  - Increasing enforcement in China
- It is estimated that a kilogram of fentanyl could generate $5–20 million in retail counterfeit sales
- Mixing with other illegal drugs (e.g., heroin) appears to be occurring in the US

(DEA, 2019)
How is Fentanyl used?

• Most fentanyl used in the US is thought to be via contaminated heroin, but pattern is changing
• Local variations as to whether fentanyl marketed directly as fentanyl or mixed with other drugs (e.g., heroin)
• Some reports of counterfeit oxycodone and alprazolam pills containing fentanyl, as well as cocaine
• Pure fentanyl or other HPSO less common in past, typically ordered on dark web, shipped directly from Asia, but now fentanyl street marketed
DEA Fentanyl Seizure
Clinical Experience: New York City

• September 2017
  ▪ Private patient using heroin able to override Naltrexone XR injection despite Q 3 week dosing
    - Was able to re-establish blockade with Q 2 week dosing
  ▪ 2 Private patients who are experienced with SL buprenorphine treatment report same story
    - Discontinued buprenorphine
    - Used heroin for several day period
    - Withdrawal symptoms did not start within usual time frame—delayed
    - Attempts to restart buprenorphine 48-72 hours after last use of heroin precipitated withdrawal
  ▪ Research clinic
    - Staff discussions noting difficulty with first day of buprenorphine treatment for a clinical trial
  ▪ Decision made to begin testing all patients in research clinic
New York City HPSO Overdoses

- From 2010 to 2017, unintentional overdose deaths increased from 8.2 per 100,000 residents to 21.2 per 100,000 residents.
- In 2017, 82% of overdoses involved an opioid, and for the first time, the most common substance (57%) associated with overdose deaths were a fentanyl analogue (Heroin 2nd most common at 52%).
- Prior to 2015, fentanyl analogues never accounted for more than 3% of the overdose fatalities in New York City.

(Nolan, 2018)
Challenges to Conducting OUD Pharmacotherapy Research with HPSO

- Most HPSO (in NYC) is being co-administered with heroin
- Illicit drug supply is non-standard
- Timelines for grants are multi-year
- Variability in drug supply characteristics by geography
- We will not have evidence-based recommendations for quite some time
What should clinicians do?

- We have essentially NO data to guide pharmacotherapy management decisions for the leading cause of fatal overdose deaths in the US
- In the absence of data to make evidenced-based recommendations, we still need to treat patients
- Need to take what we know about the properties of HPSO into account when making treatment decisions
- Need to educate patients, families, and other clinicians of this new risk of using opioids
  - And to a lesser degree, other illicit drugs (e.g., cocaine, BZDs)
- Need to adjust urine toxicology procedures
  - Major labs have MS/GC panels for HPSO
  - ELISA dip sticks for more rapid information
OUD Pharmacotherapy
Treatment Options

- Methadone
- Buprenorphine
  - Sublingual
  - Implant (Probuphine) (≤ 8 mg SL buprenorphine maintenance)
  - Extended release for injection (Sublocade, CAM2038)
- Naltrexone
  - Oral
  - Extended release for injection (Vivitrol)
- Overdose reversal: Naloxone
- Non-Opioid withdrawal treatments
  - Alpha-2 Agonists: Clonidine, lofexedine (Lucemyra)
  - Benzodiazepines
  - Antihistaminic (mirtazapine, quetiapine, trazodone)
  - Antinausea (ondansetron, prochlorperazine)
Naltrexone XR for Injection (Vivitrol)

• Advantages
  ▪ Injectable formulation ensures compliance for 1 month at a time
  ▪ No physical dependence on therapeutic agent (can also be a disadvantage)
  ▪ Provides some protection against overdose
    – Probably less so in HPSO-era

• Disadvantages
  ▪ Blocking effects may start to decay closer to 3 weeks
  ▪ Induction is difficult, need opioid-free period of abstinence, which is particularly difficult to accomplish as an outpatient
  ▪ Lowering of opioid tolerance MAY increase risk of opioid overdose when non-compliant or treatment discontinued
  ▪ Expensive
Naltrexone XR for Injection in the HPSO Era

- No clinical trial data
- Induction considerations:
  - Longer wait time to starting naltrexone
  - More difficult induction
    - Consider more aggressive adjunctive medication treatment
  - Inpatient > Outpatient?
- Maintenance considerations:
  - Consider more frequent administration
  - Closer monitoring for risk of override, blockade less effective
  - More urine toxicology testing
  - With repeated override attempts would switch to agonist treatment be safer?
  - Probably still a good choice for prescription pain killers, but not heroin/HPSO
Methadone

• Advantages
  ▪ Uncomplicated supervised induction
  ▪ Effective in reducing non-prescribed opioid use
  ▪ Inexpensive
  ▪ Full agonist effects protect against opioid overdose by raising tolerance out of reach

• Disadvantages
  ▪ Not available in most US counties
  ▪ Physical opioid dependence (can also be an advantage)
  ▪ Clinically used doses are lethal for non-tolerant individuals
  ▪ Must be administered in specialty clinics
    – Start off with daily clinic visits
    – Travel difficult
    – Unacceptable quality of life for many patients
Methadone in the HPSO Era

• No clinical trial data
• Induction considerations:
  ▪ May offer advantage over buprenorphine because no risk of precipitated withdrawal
• Maintenance considerations:
  ▪ Unknown if standard methadone doses are protective in raising tolerance out of reach of HPSO effects
  ▪ Urine drug testing for HPSO
Naloxone in the HPSO Era

- No clinical trial data
- There have been increasing reports of multiple doses of naloxone being required to reverse overdose
- Because the length of time between substance use and death is shorter with fentanyl, there have been more reports of unsuccessful attempts to revive with naloxone despite administration of multiple or escalating doses
- Some naloxone programs have begun providing more than the standard two doses of naloxone, and others have begun utilizing higher dose devices
  - It is not clear whether these approaches are effective
Sublingual Buprenorphine

- **Advantages**
  - Partial agonist properties
    - Maintain opioid tolerance—protects against overdose
  - High receptor affinity
    - Higher doses block other opioids from acting at the mu opioid receptor
  - Can start treatment rapidly after treatment contact in outpatient setting and stabilize patients

- **Disadvantages**
  - Some patients are non-compliant and continue to use non-prescribed opioids
  - Often difficult to maintain patients on therapeutic dose (>16 mg/daily)
  - Inductions have become more difficult in the HPSO era
  - Physical dependence on therapeutic agent (can also be an advantage)
Sublingual Buprenorphine in the HPSO Era

• No clinical trial data

• Induction considerations:
  ▪ Because of long effective half-life, may need to wait longer from last use to first dose of buprenorphine
    – But waiting longer may lower odds of successful induction
  ▪ Possible greater role for adjunctive medications to manage withdrawal during what can be a several day interval
  ▪ Greater role for inpatient setting?

• Maintenance treatment considerations:
  ▪ Consider higher doses to provide protection against HPSO override and maintain higher opioid tolerance
  ▪ More vigilant urine toxicology testing
Role for Injectable XR Buprenorphine in 2020

• Advantages
  - All the pharmacodynamic advantages of SL buprenorphine
  - Assured compliance for 4-6 weeks
  - Clinical effects >5 weeks
  - Maintains at higher serum level than patients would take sublingually
  - Induction may be easier than sublingual with HPSO users
  - Injection is logistically easier than Vivitrol
  - Diversion/compliance special populations (e.g., criminal justice system)

• Disadvantages
  - Cost
  - Accessibility (insurance prior authorization, shipping)
  - Nodules are noticeable on abdomen

• Two Formulations
  - Sublocade (on the market)
  - CAM2038 (under FDA review)
Sublocade Pivotal Trial

- Placebo-controlled 3-arm trial (n = 504) comparing
  - BUP-XR 300 mg/100 mg (2 x 300 then 4 x 100 mg)
  - BUP-XR 300 mg/300 mg (6 x 300 mg)
  - PBO
- Two week Open-Label run up with buprenorphine film
  - 8-24 mg SL daily
- Mean Participants % Abstinence
  (defined as percentage of negative urine samples and self-report from weeks 5 to week 24)
  - BUP-XR 300 mg/300 mg (41.3%)
  - BUP-XR 300 mg/100 mg (42.7%)
  - PBO (5 %)
- Labelling instructions recommends 7-days SL buprenorphine of at least 8 mg daily before injection
### Sublocade Pharmacokinetics

Comparison of Buprenorphine Mean Pharmacokinetic Parameters Between SUBUTEX and SUBLOCADE

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>SUBUTEX daily stabilization</th>
<th>SUBLOCADE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 mg (steady-state)</td>
<td>24 mg (steady-state)</td>
</tr>
<tr>
<td>Mean</td>
<td>1.71</td>
<td>2.91</td>
</tr>
<tr>
<td>C_{avg,ss} (ng/mL)</td>
<td>5.35</td>
<td>8.27</td>
</tr>
<tr>
<td>C_{max,ss} (ng/mL)</td>
<td>0.81</td>
<td>1.54</td>
</tr>
</tbody>
</table>

# Exposure after 1 injection of 300 mg SUBLOCADE following 24 mg SUBUTEX stabilization

†Mean plasma concentration of 1.86 ng/mL was observed on last day of the dosing interval (Day 29)

*Steady-state exposure after 4 injections of 100 mg or 300 mg SUBLOCADE, following 2 injections of 300 mg SUBLOCADE
Sublocade Blocking Study

300 mg Blocked Opioid Subjective Effects

[Graph showing LS Mean Drug Liking VAS Score [95% CI] over time (weeks) for different interventions including SUBOXONE, RBP-6000 Dose, Placebo, Hydromorphone 6 mg, and Hydromorphone 18 mg.]
Sublocade 300 mg Serum Level Time Course

(A) Buprenorphine
Sublocade 300 mg Dose Reaches Steady-State After Six Monthly Injections

Roll-over subjects who received 12 consecutive 300 mg doses.
Sublocade PK in Phase 3 Double-Blind Study

![Sublocade PK in Phase 3 Double-Blind Study](https://www.fda.gov/media/108382/download)
CAM 2038 Pivotal Trial

- Double-dummy design comparing injectable vs. SL buprenorphine formulations (n= 428)
  - Non-inferiority as primary outcome was met
- Phase 1: 12 weeks weekly injection
- Phase 2: 12 weeks monthly injection
- On day of randomization, received 4 mg SL buprenorphine, followed by randomization to either SL or injection treatment arms
  - 1st Injection weekly injection equivalent to 8 mg SL
  - 2nd injection on day 3-4 equivalent to 4 mg SL
- The response rates were (14.4%) for the SL-BPN/NX group and (17.4%) for the SC-BPN group (P < .001)
  - Response rate defined as abstinence at pre-defined study points
- The proportion of opioid-negative urine samples was (28.4%) for the SL-BPN/NX group and (35.1%) for the SC-BPN group, a 6.7% difference (P < .001)

(Lofwall, 2018)
Comparison of Sublocade and CAM-2038

- No direct efficacy comparisons available
  - CAM-2038 was “non-inferior” to SL buprenorphine
  - Sublocade was superior to placebo
- CAM-2038 available in weekly and monthly formulations in several formulations
  - Weekly (8, 16, 24 or 32 mg) or monthly (64, 96, 128 or 160 mg)
    - Good dosing flexibility
    - Unclear how weekly injection is an advantage
- Sublocade 300 mg and 100 mg monthly formulations available
  - Would be useful to have 200 mg dose, was studied, unclear why not produced commercially
- Great to have these options available, but much to be learned
  - Should all OUD patients being treated with buprenorphine be started on an injectable product?
  - No controlled studies on subgroups who would likely benefit from injectable formulation vs SL
- Many research questions remain to be answered to guide clinical decision making
Pilot Clinical Trial: Sublocade for HPSO

• Difficulty with buprenorphine and Vivitrol inductions in patients positive for HPSO
• Hypothesis that buprenorphine XR for injection would have utility for HPSO patients
• Open-label uncontrolled pilot study to demonstrate feasibility and have flexibility to develop optimal induction method
• 7-day stabilization period described in labelling was thought to be unnecessary
  ▪ Registry trial had 2 weeks open-label run up on SL buprenorphine prior to randomization
  ▪ What about patients who can’t tolerate SL induction?
# Phase 1 (2- or 3-day induction)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Current Status</th>
</tr>
</thead>
</table>
| 001     | • COWS = 10 at start of induction BUP-SL = 24 mg                     | • BUP-SL 16 mg BXR 300 mg injection | • COWS = 7             | • COWS = 4                                                           | • Received 3 BXR injections  
• Completed trial  
• No opioid use since day prior to start of induction |
| 003     | • COWS = 10 at start of induction BUP-SL = 10 mg                     | • BUP-SL 24 mg                | • BUP-SL 16 mg BXR 300 mg injection | • COWS = 0                                                           | • Received 3 BXR injections  
• Completed trial  
• No opioid use since receiving 1st BXR injection |
| 004     | • COWS = 16 at start of induction BUP-SL = 24 mg                     | • BUP-SL 16 mg BXR 300 mg injection | • COWS = 0             | • COWS = 0                                                           | • Received 3 BXR injections  
• Completed trial  
• No heroin use since second BXR injection |
| 005     | • COWS = 12 at start of induction BUP-SL = 24 mg                     | • BUP-SL 8 mg                 | • BUP-SL 16 mg BXR 300 mg injection | • COWS = 2                                                           | • Received 3 BXR injections  
• Completed trial  
• Intermittent heroin use after 3rd injection |
| 006     | • COWS = 10 at start of induction BUP-SL = 24 mg                     | • BUP-SL 8 mg                 | • BUP-SL 16 mg BXR 300 mg injection | • COWS = 0                                                           | • Received 1 BXR injection; refused 2nd injection  
• Retained in trial 5 weeks  
• No heroin use after 1st injection |

(Mariani, 2020)
### Phase 2 (One Day Induction)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| 007     | COWS = 11 at start of induction  
Total BUP-SL = 24 mg in divided doses  
BXR 300 mg injection | Missed visit | COWS = 0 | COWS = 1 | Received 3 BXR injections  
Completed trial  
Intermittent heroin use |
| 008     | COWS = 9 at start of induction  
Total BUP-SL = 24 mg in divided doses  
BXR 300 mg injection | COWS = 2 | COWS = 0 | COWS = 2 | Received 3 BXR injections  
Completed trial  
No heroin use since receiving 1st BXR injection |
| 009     | COWS = 8 at start of induction  
Total BUP-SL = 24 mg in divided doses  
BXR 300 mg injection | COWS = 7 | COWS = 5 | COWS = 0 | Received 3 BXR injections  
Completed trial  
No heroin use since second BXR injection |
| 010     | COWS = 18 at start of induction  
Total BUP-SL = 24 mg in divided doses  
BXR 300 mg injection | COWS = 3 | Missed visit | COWS = 7 | Received 3 BXR injections  
Completed trial  
Intermittent heroin use |
| 011     | COWS = 17 at start of induction  
Total BUP-SL = 24 mg in divided doses  
BXR 300 mg injection | COWS = 0 | COWS = 0 | Missed visit | Received 3 BXR injections  
Completed trial  
Intermittent heroin use |

(Mariani, in preparation)
Injectable Naltrexone (NXR) vs. Injectable Buprenorphine (BXR)

- No clinical trial data, but clinical experience suggests….
- Induction (favors BXR)
- Overdose Protection (likely favors BXR)
- Availability (at present likely favors NXR)
  - More clinicians familiar with NXR
  - Easier insurance approval
- HPSO/heroin users (likely favors BXR)
- Who is ideal NXR patient?
  - Prescription painkiller user with low opioid tolerance
- Who is ideal BXR patient?
  - Sublingual buprenorphine treatment failure
  - HPSO/heroin users (regardless of treatment history)
Collaborators

- Frances R. Levin, MD
- Edward V. Nunes, MD
- Nasir Naqvi, MD
- Christina Brezing, MD
- Sean Luo, MD
References

- Drug Enforcement Administration. 2019 national drug threat assessment. December 2019
PCSS Mentoring Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid use disorder.

- PCSS Mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medications for addiction treatment.

- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.

- No cost.

For more information visit: https://pcssNOW.org/mentoring/
PCSS Discussion Forum

Have a clinical question?

Ask a Colleague

A simple and direct way to receive an answer related to medication-assisted treatment. Designed to provide a prompt response to simple practice-related questions.

Ask Now

http://pcss.invisionzone.com/register
**PCSS** is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

<table>
<thead>
<tr>
<th>Addiction Technology Transfer Center</th>
<th>American Society of Addiction Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Family Physicians</td>
<td>American Society for Pain Management Nursing</td>
</tr>
<tr>
<td>American Academy of Pain Medicine</td>
<td>Association for Multidisciplinary Education and Research in Substance use and Addiction</td>
</tr>
<tr>
<td>American Academy of Pediatrics</td>
<td>Council on Social Work Education</td>
</tr>
<tr>
<td>American Pharmacists Association</td>
<td>International Nurses Society on Addictions</td>
</tr>
<tr>
<td>American College of Emergency Physicians</td>
<td>National Association for Community Health Centers</td>
</tr>
<tr>
<td>American Dental Association</td>
<td>National Association of Social Workers</td>
</tr>
<tr>
<td>American Medical Association</td>
<td>National Council for Behavioral Health</td>
</tr>
<tr>
<td>American Osteopathic Academy of Addiction Medicine</td>
<td>The National Judicial College</td>
</tr>
<tr>
<td>American Psychiatric Association</td>
<td>Physician Assistant Education Association</td>
</tr>
<tr>
<td>American Psychiatric Nurses Association</td>
<td>Society for Academic Emergency Medicine</td>
</tr>
</tbody>
</table>
Educate. Train. Mentor

Funding for this initiative was made possible (in part) by grant no. 1H79TI081968 from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.