Buprenorphine Treatment for Opioid Use Disorder in the Fentanyl Era

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Assistant Professor Family Medicine
No Disclosures

I will not discuss off-label use of medication
Objectives

• Review the current landscape of the opioid epidemic
• Discuss the pharmacology of Buprenorphine and evolving ways of initiation and maintenance treatment
• Review aspects of harm reduction in opioid use disorder
What is the Opioid Epidemic?
U.S. drug overdose death rate per 100,000 people, by race and ethnicity (age-adjusted)
Compton, et al.

Diagram:
- **Host** (opioid user)
- **Agent** (specific substance)
- **Vector** (e.g., pharmaceutical industry, physicians, illicit drug sellers)
- **Environment** (e.g., family, neighborhood, media, workplace, laws and policies, culture, etc.)
What is Addiction???

• Chronic relapsing disorder characterized by compulsive drive to continue a substance or behavior despite adverse consequences, *loss of control over intake*, and the emergence of a negative emotional state during abstinence.

ASAM

• 3 C's CONTROL, CONSEQUENCES, CRAVING
<table>
<thead>
<tr>
<th>DSM 5 Criteria Substance Use Disorder</th>
</tr>
</thead>
</table>

**IMPAIRED CONTROL**
1. LARGER use than planned  
2. Inability to CUT BACK  
3. Great deal of TIME spent on use  
4. Intense desire to use CRAVE

**SOCIAL IMPAIRMENT**
5. Failure to fulfill OBLIGATIONS at home or work  
6. INTERPERSONAL struggles  
7. Giving up ACTIVITIES

**RISKY USE**
8. Hazardous situations  
9. Physical or Emotion Consequences

**DEPENDENCE**
10. Tolerance  
11. Withdrawal
Addiction is a Biopsychosocial Condition

- Biology (Genes/Development)
- Environment, Epigenetics, Social Determinants
- Drug/Alcohol Use
- Brain Mechanisms
- Substance Use Disorder
Opioid Use Disorder

• 2.7 million people in the United States had OUD in the past 12 months NIDA 2020
• 990,000 used fentanyl NSDUH 2022
• 90 million will use prescription opioid
• 8.9 million will misuse NSDUH 2022
Suicide Risk

• 13% of overdoses in 2021 were intentional, 83% were unintentional, and 4% were undetermined, and 0.07% were homicide.


• Risk of suicide at least twice as high with chronic pain.

• Risk of suicide with abrupt wean of prescribed opioids associated with 4-12 times risk depending on MME.

  *NEJM* 2/17/21
Comorbidities & Cost

- Hepatitis C present 30% PWUD in US \cite{Hagan}
- PWID accounted for 10% new HIV \cite{CDC}
- MRSA strain \cite{Jackson}
- Neonatal Morbidity \cite{Ko}
- Cost $550 billion/year
- PDD 17% OUD vs 1% no OUD \cite{Thakrar}
Prevention

Treatment

Harm Reduction
Historical Buprenorphine

• Harrison Narcotic Act of 1914
• Developed 1960-1970 studies from JHU
• Patented 1965
• FDA approved 1981 pain
• DATA 2000
• FDA approved 2002 for OUD
• CARA 2016
• Mainstreaming Addiction Treatment ACT 2022
• OBOT
• Schedule 3
• Home induction
• Prescription with extended take homes
• PDMP
• Optional counseling
• LAI option
What properties of Buprenorphine make it unique?

• High affinity for the opioid mu receptor
• Partial agonist at the opioid mu receptor
• Ceiling effect
• Long acting
• Opioid kappa receptor inverse agonist
• B-arrestin and G-protein balance at the mu receptor
• Preferential action on spinal receptors rather than CNS receptors
Ceiling Effect

- Full agonist (e.g. morphine, methadone)
- Partial agonist (buprenorphine)
- Antagonist (naloxone, naltrexone)
Formulations

1. Buprenorphine + Naloxone
   - Suboxone
   - Zubsolv

2. Buprenorphine mono-product- Subutex

3. Buccal Film- Belbuca

4. Transdermal – Butrans

5. Subcutaneous injection
   - Sublocade
   - Brixadi

6. IV
Benefits of MAT: Decreased Mortality

Death rates:

- General population
- MAT
- No treatment

Standardized Mortality Ratio

Dupouy et al., 2017
Evans et al., 2015
Sordo et al., 2017
• Affinity
• Lipophilicity
• Efficacy at the opioid mu Receptor
• Increased desensitization of the mu receptor
• Depo Effect
Treatment Stages of Buprenorphine

- Initiation/Induction
- Stabilization
- Maintenance
- Discontinuation
Buprenorphine Initiation

• Standard
• Low Dose Overlapping (Micro)
• High Dose
Standard Buprenorphine Induction

• require mild-moderate withdrawal
• Comfort medication
• Traditionally start 2-4 mg every 1-2 hours watching for symptoms of precipitated withdrawal until symptoms abated
• Total 24-hour dose = daily dose
Spontaneous Opioid Withdrawal Symptoms

- myalgias
- Anxiety
- Lacrimation, rhinorrhea
- Diaphoresis
- Insomnia
- Yawning and sneezing
- GI upset
- Hypertension/tachycardia
- Goosebumps
- Dilated pupils
COWS Score for Opiate Withdrawal
Quantifies severity of opiate withdrawal.

Resting Pulse Rate (BPM)
Measure pulse rate after patient is sitting or lying down for 1 minute

<table>
<thead>
<tr>
<th>Pulse Rate</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤80</td>
<td>0</td>
</tr>
<tr>
<td>81-100</td>
<td>+1</td>
</tr>
<tr>
<td>101-120</td>
<td>+2</td>
</tr>
<tr>
<td>&gt;120</td>
<td>+4</td>
</tr>
</tbody>
</table>

Sweating
Sweating not accounted for by room temperature or patient activity over the last 0.5 hours

<table>
<thead>
<tr>
<th>Report</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>No report of chills or flushing</td>
<td>0</td>
</tr>
<tr>
<td>Subjective report of chills or flushing</td>
<td>+1</td>
</tr>
<tr>
<td>Flushed or observable moistness on face</td>
<td>+2</td>
</tr>
</tbody>
</table>

0 points
No active withdrawal

Copy Results
Next Steps
Precipitated Withdrawal

- Full agonist (e.g., morphine, methadone)
- Partial agonist (buprenorphine)
- Antagonist (naloxone, naltrexone)
Low Dose Overlapping Induction

1. Continuing the full opioid agonist while you start very low doses of Buprenorphine
2. Gradually increasing the Buprenorphine dose until you get to a standard dose then stopping the full opioid agonist
3. DO NOT WEAN full agonist until Buprenorphine at least 12 mg
### Bridging at Molecular Level

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2-3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Day 1 Diagram" /></td>
<td><img src="image2.png" alt="Day 2-3 Diagram" /></td>
<td><img src="image3.png" alt="Day 4 Diagram" /></td>
</tr>
</tbody>
</table>

**Legend:**
- Yellow pentagon: Full agonist opioid
- Blue rectangle: Buprenorphine

**Net Effect:**
- **min:** Minimum
- **max:** Maximum

**Slow**
Utilizes Mu Receptor Availability

Estimated receptor availability based on buprenorphine dose:
- 1mg: 71-85%
- 2mg: 53-72%
- 4mg: 36-55%
- 8mg: 11-22%
- 12mg: 13-24%
- 16mg: 9-20%
- 24mg: 4-15%
- 32mg: 2-12%
<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buprenorphine</strong>&lt;br&gt;Dose</td>
<td>0.5mg daily</td>
<td>0.5mg BID</td>
<td>1mg BID, 0.5mg in&lt;br&gt;afternoon</td>
<td>2mg BID</td>
<td>4mg BID</td>
<td>4mg TID</td>
<td>8mg BID</td>
</tr>
<tr>
<td><strong>Pill size</strong></td>
<td>2mg</td>
<td>2mg</td>
<td>2mg</td>
<td>2mg</td>
<td>2mg</td>
<td>2mg</td>
<td>8mg</td>
</tr>
<tr>
<td><strong>Morning dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Afternoon Dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Night dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Full agonist</strong></td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>STOP</td>
</tr>
</tbody>
</table>

*BID: twice a day*
High Dose Induction/Macro-dosing

• Start at 16-24 mg Buprenorphine
• Addition 8-16 mg if patient gets symptoms of withdrawal after dosing
• Stabilization dose may be lower after receptor re-sensitization has occurred
High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder

Andrew A. Herring, MD; Aidan A. Vosooghi, MS; Joshua Luftig, PA; Erik S. Anderson, MD; Xiwen Zhao, MS; James Dziura, PhD; Kathryn F. Hawk, MD, MHS; Ryan P. McCormack, MD, MS; Andrew Saxon, MD; Gail D’Onofrio, MD, MS
Stabilization

• Marked by discontinuation (or marked reduction) of use
• Buprenorphine adjustment
• What is the correct dose of Buprenorphine?
• Consider LAI formulations
Original Investigation | Substance Use and Addiction

Buprenorphine Dose and Time to Discontinuation Among Patients With Opioid Use Disorder in the Era of Fentanyl

Laura C. Chambers, PhD, MPH; Benjamin D. Hallowell, PhD, MPH; Andrew R. Zullo, PharmD, PhD; Taylor J. Paiva, MPH; Justin Berk, MD, MPH, MBA; Rachel Gaither, BS; Aidan J. Hampson, PhD; Francesca L. Beaudoin, MD, PhD; Rachel S. Wightman, MD, FACMT
Maintenance

• Set patient up for successful treatment
• Longterm side-effects
• Important patient education
• Approach other aspects of recovery
Discontinuing Buprenorphine

• What is successful treatment?
• Evidence around discontinuation
• Recovery Capital
Harm Reduction

- Naloxone
- Safe injection
- Maintain tolerance
Summary

1. Buprenorphine is a highly effective life-saving medication
2. Buprenorphine has a novel mechanism of action that makes it safer than full opioid agonists
3. Treating patients with Buprenorphine is rewarding and straightforward
4. Fentanyl use makes it more challenging to start Buprenorphine BUT understanding of pharmacology and patient education make success possible
Thank YOU

Questions