Pharmacotherapy for Opioid Use Disorder (OUD)

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PLEASE DIRECT ALL FEEDBACK FOR THE PRESENTATION TO COE@NJMS.RUTGERS.EDU. ALL FEEDBACK IS GREATLY APPRECIATED.
Objectives

• Review mortality data of the opioid crisis in New Jersey
• Review basic neurobiology of the addicted brain
• Provide an overview of medication-assisted treatment for OUD
• Discuss the evidence, pearls, and literature concerning MAT
• Identify adjunctive treatment for opioid withdrawal
• Identify potential future therapies for OUD
Mortality of OUD in New Jersey and Review of Neurobiology of OUD
Mortality in New Jersey

• Drug overdose deaths increased 29.3% from 2016 to 2017
• Opioids account for over 50% of deaths
• In 2018, Essex County had highest number of drug overdose deaths
  • About 12% of approximately 3,100 deaths
• 37% of adults in Essex county who required treatment for a substance use disorder were unable to access care

Addiction Neuroadaptation

Executive function disorder
FRONTAL CORTEX

Craving and Negative Affect

LONG-TERM

Neuroadaptations

Drug-Liking

Withdrawal and Negative Affect

Reward deficit disorder
REWARD PATHWAY

Stress Surfeit Disorder
ANTI-REWARD PATHWAY

Hedonic Tone

DA = dopamine
GABA = gamma-aminobutyric acid
CRF = corticotropin-releasing factor
NA = noradrenaline

Presence of a negative feedback system usually occurs until overpowered through neuroadaptations due to addiction.
MAT Pharmacology and Treatment Considerations
Opioid Receptor Subtypes

• Share common analgesic effect on brain circuitry
  • Distributed in the brain, spinal cord, skin, GI tract

<table>
<thead>
<tr>
<th>Location</th>
<th>Mu-Receptor</th>
<th>Kappa-Receptor</th>
<th>Delta-Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortex, nucleus accumbens</td>
<td>Hypothalamus</td>
<td>Basal ganglia</td>
<td></td>
</tr>
<tr>
<td>Physiologic Response</td>
<td>Stimulates euphoria</td>
<td>Stimulates dysphoria and sedation</td>
<td>Induces anxiolytic effects</td>
</tr>
<tr>
<td>Implications in OUD</td>
<td>Responsible for the homeostasis of the reward system</td>
<td>May promote relapse via CRF signaling and depressant effects</td>
<td>Increases levels of anxiety that may lead to relapse</td>
</tr>
</tbody>
</table>

Overview of MAT

• Shown to reduce substantial risk for all-cause and overdose mortality by 66% when patients retain in treatment with methadone
  • Meta-analysis of 19 cohorts of following ~123,000 people
• Has shown to improve treatment follow-up and retention among those started from an inpatient stay or emergency department to the outpatient.
  • Liebschutz, JM, et al RCT of 145 opioid-dependent patients
  • D’Onofrio G, et al – RCT of 329 opioid-dependent patients
  • ↓ in reduced self-reported illicit opioid use
  • ↓ use of inpatient addiction treatment services

• Studies ongoing to demonstrate treatment retention of MAT from prisons to outpatient


RCT = randomized clinical trial
Benefits of MAT

- Reduced opioid use
- Increased physical and mental health quality of life
- Reduced criminal behavior and incarceration
- Reduced emergency department use
- Increased employment
- Improved management of comorbid conditions

Comparison of Agonist Activity of MAT

Methadone

• Full opioid agonist with variable pharmacokinetics
  • Metabolized via N-demethylation via CYP3A4, 2D6, 2B6, 2C9, 2C10, etc to inactive metabolites
  • t1/2 = 24-36 hours

• Effects may not realized until approximately 5 days of therapy
  • Initial dose of 30-40mg daily
  • Maintenance dose of 80-120mg daily

• Risk for QTc prolongation and mortality when dose exceeds tolerance

• Most evidence for MAT is from methadone

• Requires enrollment in opioid treatment program (OTP)
Naltrexone ER (Vivitrol®)

• No special certification needed to prescribed
• Full μ-opioid antagonist with high affinity for the opioid receptor
  • Not metabolized by CYP enzymes
• Intramuscular depot formulation to prevent relapse particularly after detox
• Requires 7-10 days of opioid-free state
• Shown to reduce return to illicit opioid use, increased treatment retention, and craving vs. placebo
• Population that may benefit most from naltrexone ER?
• Risk of hepatotoxicity?

Buprenorphine

• Partial μ-receptor agonist of 40% intrinsic activity with more defined pharmacokinetics – t1/2 = 24-60 hours
  • Inhibited by 3A4 primarily – no major clinically significant interactions
• *Has a ceiling effect that reduces risk of respiratory depression and euphoria with greater doses
• *Initiate when patient develops period of moderate withdrawal symptoms
• Thomas CP, et al.
  • Buprenorphine is associated with improved outcomes compared to placebo in individuals and pregnant patients with OUD

Types of Buprenorphine Approved for OUD

- **Buprenorphine tablets (Subutex®)**
- **Buprenorphine/Naloxone tablets and films (Suboxone® and Zubsolv®)**
- **Extended-release injection (Sublocade®)**
  - Once-monthly formulation moderate-severe OUD
  - Need initiation with mucosal formulation of buprenorphine for at least a week and stable on doses of 8-24mg/day
  - Need to enroll in REMS program

- **Buccal film (Bunavail®)**
- **Intradermal implant (Probuphine®)**
  - 4 implants for 6 months of treatment
  - Indicated for those with daily doses of buprenorphine of \( \leq 8\)mg
  - Need to enroll in REMS program
Buprenorphine General Dosing

• Start with a dose of 2-4mg of buprenorphine when patient exhibits mild-moderate withdrawal
  • Take 2-4mg every 2 hours as needed for a maximum dose of 16mg on day 1

• On day 2, take the total daily dose of day 1 and may divide the dose. Patient can take up to a maximum dose of 24mg on day 2.

• Steady state may take 5-7 days

SAMHSA. Tip 63. Medications for opioid use disorder. 2018
Buprenorphine Dosing – Ceiling Effect

Most patients require <20% uOR availability to reduce the reinforcing effects of full opioids

Buprenorphine Treatment Duration

• There is no evidence and no defined time limit for treating OUD
  • Consider other diseases and their treatment.

• Studies show low rate of remaining abstinent when buprenorphine is tapered
  • Evidence of neurobiological disease vs. disease of “moral failing”

• Presence of a protracted withdrawal syndrome

Buprenorphine Microdosing

63 year old woman with history of multiple sclerosis and stage 4 decubitus ulcers

Table 1. Buprenorphine Microdosing Protocol Used by Our Team

<table>
<thead>
<tr>
<th>Day</th>
<th>Buprenorphine dosage</th>
<th>Methadone dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 mg\textsuperscript{a} SL once/day</td>
<td>Full dose</td>
</tr>
<tr>
<td>2</td>
<td>0.5 mg\textsuperscript{a} SL twice/day</td>
<td>Full dose</td>
</tr>
<tr>
<td>3</td>
<td>1 mg SL twice/day</td>
<td>Full dose</td>
</tr>
<tr>
<td>4</td>
<td>2 mg SL twice/day</td>
<td>Full dose</td>
</tr>
<tr>
<td>5</td>
<td>4 mg SL twice/day</td>
<td>Full dose</td>
</tr>
<tr>
<td>6</td>
<td>8 mg SL once/day</td>
<td>Full dose</td>
</tr>
<tr>
<td>7</td>
<td>8 mg SL in A.M. and 4 mg SL in P.M.</td>
<td>Full dose</td>
</tr>
<tr>
<td>8</td>
<td>12 mg SL/day</td>
<td>Stop</td>
</tr>
</tbody>
</table>

SL = sublingually.

\textsuperscript{a}For our buprenorphine formulation, one-quarter of a 2-mg sublingual strip was used.

Table 3. Protocol Use in Patient 2

<table>
<thead>
<tr>
<th>Protocol day</th>
<th>Buprenorphine total daily dose, mg</th>
<th>Methadone total daily dose, mg</th>
<th>Maximum pain score, 0–10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>1.0</td>
<td>100</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>100</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>100</td>
<td>8</td>
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<tr>
<td>6</td>
<td>8</td>
<td>100</td>
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<td>7</td>
<td>12</td>
<td>100</td>
<td>6</td>
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<td>8</td>
<td>16</td>
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<td>6</td>
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<td>9</td>
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<td>0</td>
<td>8</td>
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<tr>
<td>10</td>
<td>20</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

Are There Contraindications to MAT Therapy with Buprenorphine and Naltrexone?

• Generally, benefits >> risk – start low, go slow!
  • Pregnancy
  • Severe liver disease
  • Concurrent benzodiazepines and CNS depressants

• Concerns with treatment of acute pain on MAT
Approach to treatment of Acute Pain in OUD

• First-line: non-opioids $\rightarrow$ NSAIDs, APAP, topicals
• Dividing buprenorphine dose every 6-8 hours to potentiate analgesic effect
• Use opioids for shortest amount of time of 3-7 days
• Buprenorphine generally continued even during peri-operative period
  • 12mg dose or less due to receptor availability

# Summary of MAT Therapy

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine</th>
<th>Methadone</th>
<th>Naltrexone ER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Pharmacodynamic Property</strong></td>
<td>Partial µ - agonist Kappa - antagonist Delta - antagonist</td>
<td>Full µ - agonist</td>
<td>Full µ - antagonist</td>
</tr>
<tr>
<td><strong>Clinical Pearls</strong></td>
<td>Low risk of overdose and respiratory depression – “Ceiling Effect”</td>
<td>Risk of overdose/sedation and respiratory depression – “start low, go slow”</td>
<td>Must be opioid-free for 7-10 days to reduce risk of precipitated withdrawal</td>
</tr>
<tr>
<td><strong>Who may be a better candidate?</strong></td>
<td>Patients with low “hedonic tone” / concurrent psychiatric comorbidities?</td>
<td>Patients with concurrent OUD and chronic pain</td>
<td>Patients who have undergone a period of detoxification</td>
</tr>
</tbody>
</table>

**ALL ARE EFFECTIVE FOR REDUCING RISK OF RELAPSE**
So Why Does MAT Work?
# Adjunctive Therapies for Opioid Withdrawal

<table>
<thead>
<tr>
<th>Withdrawal Symptom</th>
<th>Therapy Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Loperamide</td>
</tr>
<tr>
<td>Nausea</td>
<td>Ondansetron, Metoclopramide</td>
</tr>
<tr>
<td>Anxiety, irritability, Diaphoresis</td>
<td>Clonidine $\rightarrow$ Lofexidine (Lucemyra®)*</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Diphenhydramine, Trazodone</td>
</tr>
<tr>
<td>Pain</td>
<td>APAP/ NSAIDs</td>
</tr>
</tbody>
</table>

*α-2 agonist blocking stress-induced response at doses lower than the starting dose

Future of OUD
Limitations of Current Therapy

• Continued
  • Stigma and access issues
    • “War on Drugs”
  • Federal laws concerning administration of MAT
  • Rigidity of prescription dosing vs. reality
  • Cravings
    • New targets in therapy?
  • Presence of protracted withdrawal despite long-term MAT
Potential Future Therapy

• Use of cannabinoids
  • Located in the VTA, nucleus accumbens, and PFC
  • Shown to reduce use of opioids – definite synergy with opioids
  • Possible use as a harm reduction tool as an adjunct?
  • NJ addition of cannabis in OUD treatment protocol

• Targeting the glutamatergic pathway

• Targeting the CRF and cortisol pathway to further restore the HPA axis


HPA = Hypothalamic-Pituitary-Adrenal
Conclusions

• MAT helps neurological recovery and reduces risk of addictive behaviors

• MAT has been shown to reduce risk of opioid overdose and death

• Most evidence for MAT has been with methadone but there has been a greater shift with buprenorphine and naltrexone

• Guidance is available to help prescribers with treating OUD patients
  • NJ Centers of Excellence are working on a manual
  • SAMSHA Tip Sheets (Tip 63)
  • ASAM National Guidelines
  • Provider Clinical Support System – www.pccsnow.org
Questions?
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