FDA Approved Medications for Opioid Use Disorder

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Opioid Response Network
STR-TA
1. Addiction is a chronic, neurobehavioral disorder
2. Medication treatment attenuates positive and negative reinforcement
3. Agonist treatment is the most effective way to reduce overdose deaths
Chronic Neurobehavioral Disorder

Executive-function & decision-making

Conditioned learning, memory & emotion

Reward & motivation
Classical Conditioning, Triggers and Craving

WATCH WHAT I CAN MAKE PAVLOV DO. AS SOON AS I DROOL, HE'LL SMILE AND WRITE IN HIS LITTLE BOOK.
Chronic Changes to the Brain “Quasi-permanent”

Normal levels of brain activity in PET scans show up in yellow to red.

Reduced brain activity after regular use can be seen even after 10 days of abstinence.

After 100 days of abstinence, we can see brain activity “starting” to recover.

Opioid Withdrawal *aka* ‘Dope Sick’
Powerful Negative Reinforcer

- Excruciating symptoms on cessation
- Strong Negative Reinforcer
Addiction ≠ Dependence

✨ Addiction – 4 C’s:
- compulsive use, impaired control, continued use despite consequences, craving

✨ Physiological dependence
- Seen with appropriate use of med.
  - Tolerance:
    » ↓effect with chronic use
    » ↑dose to achieve same effect
  - Withdrawal
- Tolerance lost:
  » ↑effect at usual dose (overdose)
  » ↓dose to achieve same effect
Strong Reinforcers/Aversives

- Salient
- Immediate
  - Swift
- Reliable
  - Certain
- Properties lost → behavior extinguished
<table>
<thead>
<tr>
<th>Positive Consequences</th>
<th>Negative Consequences</th>
</tr>
</thead>
</table>
| **Immediate**
euphoria; $$
| **Delayed**
arrest; prison; HIV; OD |
| ** Reliable
everytime** | **Unreliable**
Vagaries of CJ system |
<table>
<thead>
<tr>
<th>Positive Consequences</th>
<th>Negative Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delayed</strong></td>
<td><strong>Immediate</strong></td>
</tr>
<tr>
<td>Job; housing;</td>
<td>Withdrawal/craving;</td>
</tr>
<tr>
<td>relationships; health</td>
<td>stress; dysphoria; no</td>
</tr>
<tr>
<td></td>
<td>friends.</td>
</tr>
<tr>
<td><strong>Unreliable</strong></td>
<td><strong>Reliable</strong></td>
</tr>
<tr>
<td>No guarantee</td>
<td>?manageable</td>
</tr>
</tbody>
</table>
1. Addiction is a chronic, neurobehavioral disorder
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What Does It Feel Like to have Opioid Use Disorder?

Diagrammatic summary of functional state of typical "mailine" heroin user. Arrows show the repetitive injection of heroin in uncertain dose, usually 10 to 30 mg but sometimes much more. Note that addict is hardly ever in a state of normal function ("straight").

From "Narcotic Blockade," by V. P. Dole, M. E. Nyswander, and M. J. Kreek, 1966, Archives of Internal Medicine, 118, p. 305.
MOUD Inhibits Opiate Receptor Activation

- **Mu Opiate receptor**
  - Full agonist binds & fully activates receptor
  - Partial agonist binds & activates to a ceiling
  - Antagonist binds but does not activate

Graph showing the relationship between drug dose and % Mu receptor activity:
- Full Agonist
- Partial Agonist
- Antagonist
How Does Medication Treatment Work?

- **↓’s reinforcement**
  - Reward: ↓ immediate, reliable
  - Stops negative reinforcement associated with withdrawal

- **Extinguishes expectancies and conditioned responses**

*Greenwald, MK et al, Neuropsychopharmacology 28, 2003*
What Does It Feel Like to Be on MOUD?

Stabilization of patient in state of normal function by blockade treatment. A single daily oral dose of methadone prevents him from feeling symptoms of abstinence ("sick") or euphoria ("high"), even if he takes a shot of heroin. Dotted line indicates course if methadone is omitted.

From "Narcotic Blockade," by V. P. Dole, M. E. Nyswander, and M. J. Kreek, 1966, Archives of Internal Medicine, 118, p. 305.
FDA Approved Forms of Medication for Opioid Use Disorder (MOUD)

<table>
<thead>
<tr>
<th>Action on Mu Receptor</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Naltrexone (IM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full Agonist</td>
<td>Partial Agonist</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Dosing</td>
<td>80 mg-120+ mg PO daily</td>
<td>4-32 mg SL daily 300 mg→100 mg IM Qmo.</td>
<td>380 mg IM monthly Qmo.</td>
</tr>
</tbody>
</table>

**Advantages**
- Proven ↓OD
- Highly structured supervised setting
- Additional services on-site & diversion unlikely
- For individuals who need structure and support
- Proven ↓OD
- Safer than full agonist
- Available in office settings
- No addictive potential or diversion risk
- Option for individuals seeking to avoid all opioids

**Barriers/Concerns**
- Stigma
- Highly regulated, often inflexible
- Daily, in-person dosing early in treatment
- QT prolongation
- Drug-drug interactions
- Daily adherence for SL
- Diversion of SL
- SL “Bridge” between illicit opioid use
- SL child ingestions
- Pain management
- Must be opioid-free
- Risk of overdose if stopped
- Pain management
Decades of Randomized Controlled Trials of Methadone Maintenance (MMT)

- 4x ↑ retention (Mattick, 2009; others)
- 1/3rd ↓ opioid use (Mattick, 2009; others)
- ↓ mortality (Gronbladh, 1990)
- ↓ IDU (Ball & Ross, 1991; others)
- ↓ crime days (Ball & Ross, others)
- ↓ HIV seroconversion (Metzger 1992; others)
- ↑ employment, health, social function

Methadone Effectiveness
Gunne & Gronbladh, 1984

Baseline
Methadone Effectiveness
Gunne & Gronbladh, 1984

After 2 Years

1- Sepsis & endocarditis
2- Leg amputation
3- Sepsis
Methadone Effectiveness
Gunne & Gronbladh, 1984

After 5 Years

P
H
H
P

P
P

P

P

P
Buprenorphine Saves Lives

- Highly effective in reducing illicit opioid use
- Reduces overdose death rate
- Very low risk for overdose
- Decreased risk of misuse compared to agonist
- Available in ambulatory care settings

Sordo et al. BMJ 2017
Extended-Release NTX

- Monthly gluteal IM injection
- Must be completely opioid-free
- No withdrawal when stopped
  - Concern about overdose after stopping

Opioid relapse: ≥10 days use

![Graph showing the probability of relapse-free survival over weeks for Extended-release naltrexone and Usual treatment.]

<table>
<thead>
<tr>
<th>Week</th>
<th>No. at Risk</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Extended-release naltrexone</td>
</tr>
<tr>
<td>1</td>
<td>153</td>
</tr>
<tr>
<td>3</td>
<td>144</td>
</tr>
<tr>
<td>5</td>
<td>139</td>
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<tr>
<td>23</td>
<td>87</td>
</tr>
<tr>
<td>25</td>
<td>87</td>
</tr>
</tbody>
</table>
What Actually Works?

![Graph showing relapses per 100 months of treatment vs. length of treatment episode in months for Buprenorphine, Methadone, and Non-OAT Behavioral Health.]
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Loss of Tolerance $\rightarrow$ Overdose

Clamp down on opioid prescribing since ~2010

Wider distribution of illicit opioids
- ↑availability, ↓price
  $\rightarrow$ more heroin

Poor access to MOUD

Abstinence-focus (jail/prison, detox & med-free tx.) $\rightarrow$ loss of tolerance

Riskier illicit opioid supply
- ↑potency, ↑variability

Overdose $\rightarrow$ Death
Opioid Agonist Therapy Saves Lives

The graph shows the hazard/probability of survival (before long term cessation) over years from the first injection. It illustrates the impact of different years of opiate substitution treatment. The lines represent different durations of treatment: None, 1-5, <1, and >5 years. The graph indicates that longer durations of treatment are associated with a higher probability of survival.
Community Access to Agonist Treatment

Overdose Deaths

Buprenorphine Maintenance vs “Detox”

All received weekly individual cognitive-behavioral counseling, and twice-per-week supervised urine toxicology.

- N=20 Control (6-day taper)
- N=20 Buprenorphine Maintained

**NO DEATHS IN MAINTAINED PATIENTS**

**4 DEATHS (20% OF SAMPLE) IN DETOXED PATIENTS (P=.015)**

Who is most likely to benefit from Methadone?

- Preference for agonist therapy
- At risk for overdose
- Would benefit from structure of observed dosing
- Prefer to have services in one location
- Complex comorbidity
- Unstable psychosocial situation and unable to ensure the security of buprenorphine
- Co-occurring pain that has not responded adequately to other treatments
- Unable to stabilize on buprenorphine
Who is most likely to benefit from Buprenorphine?

- Preference for agonist therapy in office setting
- At risk for overdose
- Want flexibility of scheduling
  - Working people
- Level of comorbidity able to be managed with periodic office visits
- Able to ensure the security of buprenorphine
- Low-level of co-occurring pain that does not require full agonists
Who is most likely to benefit from XR-Naltrexone

- Preference, i.e. do not want agonist therapy – but want some protection
- High degree of motivation
  - Who are committed and engaged in treatment will adhere to injection schedule
- Good therapeutic alliance
- Job stipulations that forbid use of agonist therapy
- Unable to access agonist therapy
- Able to “detox” to opioid-free state for ~1 week
- Tolerates oral naltrexone
Thank you!

Questions?

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