Pharmacotherapy Works for Opioid Use Disorders in CJ Populations

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Roadmap

- Terminology
- Epidemics of incarceration and opioids
- Incarceration doesn’t treat the chronic, relapsing disorder of addiction
- Opioid use disorders harmful in CJ populations
- Pharmacotherapy works for opioid use disorders in CJ populations
Terminology

• Physiological dependence
  – Adaptation to chronic use of substance
  – Tolerance
    • Decreased effect of substance after repeated use
    • Need for increased dose to achieve same effect
  – Withdrawal syndrome
    • Characteristic symptoms on cessation of use

• Addiction: chronic, relapsing brain disease characterized by
  • Compulsive use
  • Loss of Control
  • Use despite Consequences
Abuse Potential

• Route of administration
  – Faster route has a greater abuse potential
    • Injecting IV ➤ Injecting SQ ➤ Oral

• Drug Half life
  – Briefer half-life has a greater abuse potential
    • Heroin ➤ Methadone

• Lipophilicity (faster into the brain)
  – Higher lipophilicity ➔ greater abuse potential
    • Heroin ➤ Morphine ➤ Methadone

• Agonist activity
  • Full ➤ partial
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"Opioid Epidemic": Sales, Overdose Deaths and Treatment Admissions, U.S. 1999–2010

CDC. MMWR 2011. [Link to CDC report]
Opioid Use Disorders Common in CJ Populations

- 20-23% U.S. inmates h/o opioid use
- ~5-15% U.S. arrestees u tox+ for opioids
- Jail inmates 12% regular use of opioids

The Revolving Door...

- >12 million jail releases per year
- >700,000 prison releases per year
  - >200,000 opioid-addicted adults cycle thru CJ system annually (Nunn et al. 2009)
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Repeated exposure to reinforcing agents $\rightarrow$ Long-Lasting Brain Effects
Neuronal Changes ➔ Substance Use Disorder (DSM-V) (2-3: mild; 4-5: moderate; six or more: severe)

Impaired Control
1. Larger amounts/longer than intended
2. Inability to cut down or control
3. Much time spent
4. Craving and urges

Social Impairment
5. Not able to function
6. Continued use despite interpersonal problems
7. Reduced activities

Risky Use
8. Use in dangerous circumstances
9. Continued use despite physical or psych. problems

Physiological Dependence
10. Tolerance
11. Withdrawal
Abstinence via incarceration

- Does not address substance use disorder
- Still vulnerable to triggers on reentry
- Decreases tolerance but not craving
  - increased risk of overdose death
Incarceration does not extinguish addiction

- Opioids are immediate and reliable reinforcers
- Learned associations (expectancies) are not unlearned with coerced detention
- Expectancies and responses re-triggered with return to community environment
• >½ relapse within 1 year  (Martin et al. 1999)
• 2/3rd return to custody within 3 years  
  (Langan & Levin, 2002)
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Post Release Dangers

- Relapse
- Recidivism
- Overdose
- Communicable diseases
- Other morbidity
Release from Prison - High Risk of Death

Causes of Death Post-Prison
Adjusted for Age, Sex, and Race

Relative Risk of Death

- Overdose
- Homicide
- Liver Disease
- MVA
- Suicide
- CVD
- Cancer

Overdose deaths are the tip of the iceberg

For every 1 opioid overdose death in 2010 there were...

- 15 abuse treatment admissions
- 26 emergency room visits
- 115 who abuse/are dependent
- 733 nonmedical users
- $4,350,000 in healthcare-related costs

Slide courtesy of Colleen Labelle
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- Opioid use disorders harmful in CJ populations
- **Pharmacotherapy works for opioid use disorders in CJ populations**
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.
‘Dope Sick’

- sweating
- aches
- diarrhoea
- shaking
- weakness
- muscular spasm
- feeling of chill
- craving for the drug
- feeling depressed
Medication Attenuates Reinforcement

- ↓ positive reward
- ↓ negative reinforcement
- Extinguishes expectancies associated w/use

Greenwald et al, Neuropsychopharmacol 28, 2003
MAT replaces a highly addictive, unsafe drug with a less addictive, safer one

Methadone, buprenorphine

- Lower abuse potential
  - Slower acting
  - Long half-life
  - Mild reinforcing/rewarding effect
- Block effects of short-acting opiate
- Eliminate withdrawal

- Decrease craving
  - Rewarding enough that people will take it
- Return to work, school, family, etc
- Facilitate counseling
- Prevent overdose deaths, HIV, viral hepatitis
What Does It Feel Like to Be on Opioid Replacement Therapy?

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.
Impact of Methadone Maintenance Treatment

- 7 trials → 4-fold ↑ stay in treatment
- 6 trials → 1/3rd ↓ opioid use
- ↓ death rates (Grondblah, ‘90)
- ↓ IDU (Ball & Ross, ’91; others)
- ↓ crime days (Ball & Ross, others)
- ↓ HIV seroconversion
- ↑ employment, health, social function

Mattick et al., Cochrane Review, 2009
Methadone Effectiveness
Gunne & Gronbladh, 1984

Baseline

Methadone

Regular Outpatient Rx.
Methadone Effectiveness
Gunne & Gronbladh, 1984

After 2 Years

Methadone

No Methadone

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

After 5 Years

Methadone

No Methadone

Baystate Health
Function at Receptors: Antagonists

1. occupies without activating
2. no abuse potential
3. blocks abused agonist opioid types
4. includes naloxone and naltrexone
Opioid antagonists bind and occupy mu opioid receptors but result in no specific intrinsic activity regardless of dose. Antagonist (e.g. naloxone)
Oral Naltrexone Treatment

• No reinforcement $\rightarrow$ poor adherence

• 6 trials $\rightarrow$ $\emptyset$ effect stay in treatment

• 3 trials $\rightarrow$ $\emptyset$ effect on opioid use

Minozzi et al Cochrane Review, 2011
Function at Receptors: Partial Agonists

- **Mu receptor**
- **Partial agonist binding ...**

1. activates the receptor at lower levels
2. is less reinforcing than full agonist
3. has less abuse potential than full agonist
4. includes buprenorphine
Partial Agonist Activity Levels

Like full agonists, partial agonist drugs increase mu activity at lower doses. At higher doses, even when partial agonist binds all mu receptors, maximal agonist effect is never achieved.

Partial Agonist Effect Reinforces Adherence

Full Agonist (e.g. heroin)

Partial Agonist (e.g. buprenorphine)
Buprenorphine Properties

- Opiate: derivative of thebaine
- Partial-agonist
  - Less reinforcing than a full agonist—milder effects
  - Safety — overdose ceiling effect
- Poor oral bioavailability — given sublingually
- High affinity to the opiate receptor
- Long duration of action (24-72hr)
- Strong safety profile
  - Little respiratory depression
  - Little overdose potential
Impact of Buprenorphine Maintenance Treatment

- 4 trials → 74% ↑ stay in treatment
- 6 trials → 23% ↓ opioid use

Mattick et al., Cochrane Review, 2009
RCT: Bup Detox vs. Maintenance
Kakko et al., Lancet 2003

All Patients: Group CBT Relapse Prevention, Weekly Individual Counseling, 3x Weekly Urine Screens

N=20 per group
### Bup RCT: Mortality
Kakko et al., Lancet 2003

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Buprenorphine</th>
<th>Cox regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>4/20 (20%)</td>
<td>0/20 (0%)</td>
<td>$\chi^2=5.9$; $P=0.015$</td>
</tr>
</tbody>
</table>
Opiate Agonist Treatment in Jails & Prisons

• **Outside the US**
  – Methadone: Australia, Canada, Europe, Iran and elsewhere (EMCDDA, 2009; Farnia et al, 2010)
  – Bup: France & Australia (Marzo et al., 2009)
  – Considered a best practice (WHO, 2009)

• **In the US**
  – Methadone: not widely used (Nunn et al., 2009)
  – Bup: used less frequently than methadone
RCT of Forced Withdrawal in Jail If Sentence ≤ 6 mos

Continued MMT (N=114)    Forced withdrawal (N=109)

Logrank P<.001

RCT of Pre-Release MMT: Baltimore

Percentage at 12-months

- Methadone Referral (N=64)
  - % in Comm-Based Tx. 0.0%
  - % Opioid + 65.6%

- Methadone Transfer Post-Release (N=69)
  - % in Comm-Based Tx. 17.3%
  - % Opioid + 48.7%

- Methadone Pre-and Post-Release (N=71)
  - % in Comm-Based Tx. 36.7%
  - % Opioid + 25.0%

RCT of Pre-Release MMT: Rhode Island

- Arm 1 (N=29)
  - MMT 30 days before release
  - MMT linkage in community (financial assistance)
  - 4 not treated before release
- Arm 2 (N=29)
  - MMT linkage in community (financial assistance)
- Arm 3 (N=30)
  - MMT referral
  - No financial assistance for MMT
  - 15 given ATR on release → as-treated crossed to Arm 2

McKenzie et al. Substance Abuse 2009.
NYC Jail-to-Community Buprenorphine

- More randomized participants continued bup-nx at jail re-entry vs. methadone
  - 48% vs. 23% (p<0.005)
- Once in office-based bup-nx treatment, no differences vs. non-jail patients

Lee 2009; Magura 2008
Bup Initiation Pre-Release → ↑ Treatment Retention Post-Release

- N= 44
- 73% postrelease; –27% pre-release
- Similar at baseline
- 82% 6 month f/u
- Median community rx 9 vs 24 wks (p=.007)
- IDU 26% vs. 0% (p=.05)
- Arrest 17% vs. 0 (p=.14)

Zaller, McKenzie, Friedmann et al. JSAT 2013
Pre-, Post-Release MMT, Bup $\rightarrow$ ↓ post-release mortality

- Pre-release MAT lowered mortality by reducing overdose in Week 1
Agonist Rx: Limited Uptake in CJ Settings

• Regulations and liability
• Mission
  – Security concerns
  – Lack of qualified staff
  – Budgets prioritize safety, not health care
• Stigma
• ‘Drug-free’ treatment predominates
  – Medication treatment “available in the community”
  – ↓tolerance → ↑overdose post-release

Agonist medications underutilized in CJ Settings

• Illicit opiate use in detention
  – Corruption and violence
  – HIV and hepatitis outbreaks

• Untreated opiate withdrawal in detention
  – Cruel and punitive
  – Morbidity
  – Reduces willingness to resume OAT post-release

Extended-Release Naltrexone

• Monthly IM injection
• Must be completely opioid-free

Cumulative % confirmed opioid-free weeks:
- Median of 90% for XR-TNX vs. 35% for placebo

RCT of XR-NTX for Opioid Dependence in Parole/Probation

• 5 site RCT
• Eligibility criteria
  – Adults with DSM-IV opioid dependence
  – Parole, probation, incarceration in past 12 mo.
  – Not seeking agonist treatment
• 6 month in-treatment phase
• Interviews, urine toxicology
  – In-treatment every 2 weeks
  – End-of-treatment (27 weeks)
  – 12 and 18 mos
• Relapse, rearrest/reincarceration, cost

Lee, Friedmann, Kinlock et al. Contemp Clin Trials 2015
Study Flow

1. Pre-screened, n=2753;
2. Screened, n=437

Ineligible, n=129
- Incomplete screen: 57
- Opioids+: 25
- Med/psyche/LFT: 19
- Recent overdose: 3
- BMI>35: 2

Randomization, N=308

XR-NTX, n=153

TAU, n=155

FU every 2 weeks

End of Treatment Phase, 6 months, N=308

1° outcome: N=308

Final FU at 12, 18 months: on-going
Time-to-Relapse

- Relapse = self-report or urine tox evidence of $\geq 10$ days of opioid use in a 4 week period, with a positive or missing urine test counted as 5 days of opioid use.

<table>
<thead>
<tr>
<th>Time-to-relapse (median weeks)</th>
<th>10.5</th>
<th>5.0</th>
<th>&lt;0.0001</th>
<th>HR .48 (.35, .66)</th>
</tr>
</thead>
</table>

![Product-Limit Survival Estimates](image)
XR-NTX Adherence and Attendance

• Of planned XR-NTX injections received:
  – 1\textsuperscript{st}: 97% (1 declined; 2 failed narcan)
  – 2\textsuperscript{nd}: 88%
  – 3\textsuperscript{rd}: 79%
  – 4\textsuperscript{th}: 73%
  – 5\textsuperscript{th}: 67%
  – 6\textsuperscript{th}: 61% (1 had allergic reaction after 5\textsuperscript{th})

• Mean 11 of 14 bi-weekly visits completed
  – No difference between arms
  – 75% had week 27 end-of-treatment assessment
## Results at 6 months: TAU Sought More Agonist Treatment

<table>
<thead>
<tr>
<th></th>
<th>XR-NTX</th>
<th>TAU</th>
<th>P value</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Participating in outpatient program for drug/alcohol</td>
<td>62.33%</td>
<td>65.03%</td>
<td>0.63</td>
<td>0.96 (0.81, 1.14)</td>
</tr>
<tr>
<td>% Entering hospital for detox</td>
<td>2.74%</td>
<td>2.11%</td>
<td>0.73</td>
<td>1.30 (0.30, 5.69)</td>
</tr>
<tr>
<td>% Entering residential program for detox or SA services</td>
<td>8.90%</td>
<td>10.56%</td>
<td>0.63</td>
<td>0.84 (0.42, 1.71)</td>
</tr>
<tr>
<td>% Reported suboxone treatment month 1-6</td>
<td>7.53%</td>
<td>25.35%</td>
<td>&lt;0.001</td>
<td>0.30 (0.16, 0.56)</td>
</tr>
<tr>
<td>% Reported methadone treatment month 1-6</td>
<td>3.42%</td>
<td>11.27%</td>
<td>0.01</td>
<td>0.30 (0.11, 0.81)</td>
</tr>
</tbody>
</table>

Lee, Friedmann, Kinlock et al. Submitted.
## Results at 6 months:
**No Differences in Secondary Outcomes**

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<th>P value</th>
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<tbody>
<tr>
<td>Cocaine use days %</td>
<td>3.32%</td>
<td>3.87%</td>
<td>0.70</td>
<td>0.89 (0.42, 1.58)</td>
</tr>
<tr>
<td>Avg # drinks/week</td>
<td>1.59, CI (0.73, 2.46)</td>
<td>1.23, CI (0.76, 1.70)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>% injection drug use</td>
<td>5.93%</td>
<td>8.62%</td>
<td>0.43</td>
<td>RR 0.69 (0.27, 1.75)</td>
</tr>
<tr>
<td>RAB Sex Risk Scores at 6 mo (mean)</td>
<td>2.75</td>
<td>2.86</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Self-reported re-incarceration</td>
<td>30 (19.61%)</td>
<td>27 (17.42%)</td>
<td>0.62</td>
<td>RR 1.13 (0.70, 1.80)</td>
</tr>
</tbody>
</table>

Lee, Friedmann, Kinlock et al. Submitted
Effect attenuated but still significant 6-month post-treatment (12-mo f/u)

P=0.0006 Van der Waerden 2 sided test
No increase in overdose during 6 months post-treatment

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<th>TAU</th>
<th>P value</th>
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<tbody>
<tr>
<td>Overdose (death or hospitalization)</td>
<td>0</td>
<td>7</td>
<td>0.015</td>
</tr>
<tr>
<td>Overdose deaths</td>
<td>0</td>
<td>3</td>
<td>0.248</td>
</tr>
<tr>
<td>Death, all cause</td>
<td>2</td>
<td>5</td>
<td>0.448</td>
</tr>
</tbody>
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Lee, Friedmann, Kinlock et al. Submitted
XR-NTX in Parole/Probation

• All had high rates of outpt counseling
• Over ¼ of controls reported agonist rx
• XR-NTX → ↓ opioid misuse & relapse.
  – ↑ Time-to-relapse and the % of weeks abstinent
  – ↓ overdoses out to 12 months
  – No differences in secondary outcomes
    • cocaine and alcohol use, HIV risk, CJ outcomes

Lee, Friedmann, Kinlock et al. Submitted
XR-NTX in Community CJ

- Well-tolerated, feasible and safe
- Effective at preventing relapse & overdose
- Likely effective in populations not seeking or able to access agonist therapies
- Like other meds, no detected effect on cocaine, CJ outcomes
Discussion

• Incarceration does not treat chronic, relapsing disorder of addiction
  – Significant prevalence of opioid use in CJ population
  – Community reentry is the rule
  – High risk for relapse and overdose

• Methadone, Bup, XR-NTX effective
  – ↓ opioid use in CJ populations
  – ↓ overdose short-term
Discussion

• Expand agonist tx. in jail/prison with linkage to community rx.
  – continued or initiated
  – humane
  – ↑ post-release linkage to effective treatment
  – ↓ post-release opioid use, overdose

• Need more studies to examine how best to implement in CJ settings
THANK YOU!

Colleagues who’ve shared slides
• Josh Lee, NYU
• Robert Schwartz, Friends
• Josiah Rich, Brown
• David Farabee, UCLA

Collaborators
• CJDATS collaborative
• XR-NTX collaborative R01s

NIDA esp. DESPR, Services Research Branch

Questions?? Comments??
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