Treatment for Opioid Use Disorder: Evidence and Ongoing Research

Nadherny/Calciano Youth Symposium
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Deputy Branch Chief, Services Research Branch
National Institute on Drug Abuse

Disclaimer: These comments do not necessarily reflect the position of NIDA, NIH, DHHS or the US Government. No endorsement from these organizations is intended or should be inferred.
OUTLINE

• Opioids and opioid use disorder (OUD)
• Medications for the treatment OUD
• The role of behavioral therapies for OUD
• Current NIDA-funded research
None
OPIOIDS AND OPIOID USE DISORDER (OUD)
OPIOIDS: THE BASICS

• Derived from opium poppy (e.g. heroin), synthetic (e.g. fentanyl, methadone)
• Act through endogenous opioid system, mainly mu-opioid receptors
• Cause burst of dopamine (a neurotransmitter) in the shell of the nucleus acumens, critical area of reward circuitry
• Selectively modulate the perception of pain
• Used for 1,000s of years
  • Dysentery, cough, pain
PROBLEMS ASSOCIATED WITH OPIOID MISUSE

• Respiratory depression, death
• Interactions (especially benzodiazepines, alcohol)
• Elevated risk for disease through needle sharing, etc. (HIV, HCV, endocarditis)
• Problems with jobs, family
• Criminal behavior
• Dependence, addiction, opioid use disorder
OUD

Dependence
- Neurons adapt to repeated drug exposure. Only function normally when on drug
- Absence causes withdrawal syndrome

Addiction
- Compulsive use despite harmful consequences

OUD
- Mild, moderate, severe according to number of symptoms...
SYMPTOMS OF OUD

• Taking more than intended
• Wanting or trying to control use w/o success
• Spending a lot of time obtaining, taking, recovering
• Using when physically unsafe
• Failing to carry out important roles
• Continuing to use despite relationship or social problems
• Giving up or reducing other activities
• Developing tolerance
• Craving
• Withdrawal symptoms
Figure 38. Opioid Use Disorder in the Past Year among People Aged 12 or Older, by Age Group: 2017

Number of People (in Thousands)

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<th>Age Group</th>
<th>Number of People</th>
<th>Percent</th>
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<td>12 to 17</td>
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<td>18 to 25</td>
<td>445</td>
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<td>26 or Older</td>
<td>1,562</td>
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Note: Opioid use disorder is defined as meeting DSM-IV criteria for heroin use disorder or pain reliever use disorder in the past 12 months.

MEDICATIONS FOR THE TREATMENT OF OUD

Methadone
Buprenorphine
Naltrexone
RESOURCES FROM THE SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION

Medications for Opioid Use Disorder
For Healthcare and Addiction Professionals, Policymakers, Patients, and Families

TREATMENT IMPROVEMENT PROTOCOL
TIP 63

Discover the rewards of treating patients with Opioid Use Disorders

https://pcssnow.org/
WHAT I MEAN BY TREATMENT

• The use of interventions to reduce symptoms and consequences, and to help people regain their lives
  • Medications
  • Behavioral therapies, counseling, education, training, mutual help, etc., when needed/desired

• For many long-term and/or multiple episode

**NOT:** Overdose reversal (e.g. naloxone) or withdrawal management (AKA detox) *by themselves*
METHADONE

• Developed in the 1960s
• Full agonist - binds to opioid receptors
• Reduces opioid cravings
• Alleviates withdrawal symptoms
• Blunts or blocks the effects of illicit opioids
• Long-acting – at stable daily doses, serum levels allow for 24 hours without withdrawal or overmedication
METHADONE OUTCOMES

- Meta-analyses of 11 moderate to high-quality randomized controlled trials (RCTs)
- 1,969 heroin dependent participants (all adults)

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<th>Studies/Participants</th>
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<td>Retention in treatment</td>
<td>4 studies, 750 patients</td>
<td>RR = 4.44 (95% CI: 3.26-2.04)*</td>
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<td>Opioid use (urine or hair)</td>
<td>6 studies, 1,129 participants</td>
<td>RR = 0.66 (95% CI: 0.56-0.78)*</td>
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<td>Criminal activity</td>
<td>3 studies, 363 participants</td>
<td>RR = 0.39 (95% CI: 0.12-1.25)</td>
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<td>Mortality</td>
<td>4 studies, 576 participants</td>
<td>RR = 0.48 (95% CI: 0.10-2.39)</td>
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* Statistically significant

METHADONE CONSIDERATIONS

• Daily; in-person, observed dosing at least Initially

• Health issues
  • Respiratory depression, especially during initial dosing and dose titration, exacerbated by co-use of benzodiazepines, alcohol
  • Cardiac risks (QTc prolongation and cardiac arrhythmia)
  • Drug-drug interactions

• Accidental ingestion of take-home doses
• No trials on those younger than 18
• Per regulations, may be dispensed to those under the age of 18...
  • to treat resumption of use after 2 short-term detoxification or drug-free treatment attempts within the past year; and
  • if parent/guardian/responsible adult designated state consents in writing
WHERE TO RECEIVE TREATMENT WITH METHADONE

- Schedule II narcotic, regulated per 42 CFR 8.12
- Dispensed through Opioid Treatment Programs (OTP)
- SAMHSA, Drug Enforcement Administration, State Opioid Treatment Authorities regulate
  - Licensed physician medical director
  - Adequate medical, counseling, vocational, educational, assessment and treatment services
- 1,611 OTPs in the continental US, serving over 380,000 patients

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~150 OTPs in CA

https://dpt2.samhsa.gov/treatment/directory.aspx
BUPRENORPHINE

- FDA approved (2002) for age 16 years or older
- Partial agonist treatment
- Less likely to cause respiratory depression than methadone, (though still possible)
- Multiple formulations: Sublingual tablet, buccal film, sublingual film, implant (6 mo.), subcutaneous injection (1 mo.).
  - w/ or w/o naloxone (to deter misuse)
- Reduces opioid cravings
- Reduces withdrawal symptoms
- Blunts or blocks the effects of illicit opioids
# Buprenorphine Outcomes

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<td>Retention in treatment (5 moderate – high quality studies, 1001 participants)</td>
<td>RR=1.82*</td>
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<td>Use of opioids – urinalysis (3 moderate to high-quality studies, 729 participants)</td>
<td>SMD= -1.17*</td>
<td>-1.85 to -0.49</td>
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* Statistically Significant

Source: Mattick et al., 2014 Buprenorphine maintenance vs placebo or methadone maintenance for OUD, Cochrane Database of Systematic Reviews
One “low-quality” study, RCT
- 9 weeks buprenorphine treatment with 3 week taper compared with 14 day detox with buprenorphine
- 152 patients aged 15-21 years in 6 community programs

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<td>Treatment drop-out</td>
<td>0.37*</td>
<td>0.26-0.54</td>
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<td>Positive urine test at end of treatment</td>
<td>0.97</td>
<td>0.78-1.22</td>
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<td>Self-reported heroin use, 12 mo. follow-up</td>
<td>0.73*</td>
<td>0.57-0.95</td>
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<td>Enrollment in addiction treatment at 12 mo.</td>
<td>1.33</td>
<td>0.94-1.88</td>
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*Statistically significant

BUPRENORPHINE CONSIDERATIONS

• Respiratory depression, overdoses, especially when used with benzodiazepines, alcohol, other sedatives
• Hepatitis and liver failure, especially with predisposing risk factors
• Adrenal insufficiency
• Physical dependence, potential for misuse/diversion
• Sedating effects, cognition and psychomotor issues
• Drug-drug interactions – especially CYP450 3A4 enzyme inhibitors, others
• Side effects, e.g. oral numbness, constipation, tongue pain, vomiting, intoxication, palpitations, insomnia, excessive sweating, blurred vision

Source: SAMHSA TIP 63
WHERE TO RECEIVE BUPRENORPHINE

• Schedule III narcotic
• OTPs may offer
• Physician may prescribe (8 hr. training, special license, patient cap)
• NP, PA, if w/in scope of practice (24 hr. training, patient cap)
• Initial dose may be dispensed in ED
• Caveat: Many who can don’t prescribe

BUPRENORPHINE, METHADONE LONG-TERM EFFECTS

• 1,269 individuals with OUD entering methadone programs, randomized to buprenorphine or methadone
• 1,080 located, 797 interviewed (73.6% of randomized participants)
• 2-5 years
• Opioid use (yes/no) based on urinalysis

* Statistically significant.

Mortality

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<td>4%</td>
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Opioid Use

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<td>43%</td>
<td>32%</td>
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EXTENDED-RELEASE NALTREXONE (XR-NTX)

• FDA approved in 2010
• Intramuscular injection
• Antagonist: Blocks receptors
• Prevents relapse
• Patients must abstain from opioids for 7-10 days to avoid precipitated withdrawal
• No diversion potential
• Can be prescribed by any health care provider who is licensed to prescribe medications
• Also used for alcohol use disorder

Source: SAMHSA TIP 63: Medications for Opioid Use Disorder
• 250 patients with OUD
  • Completed inpatient withdrawal management
  • Were seeking treatment
  • Had someone to supervise compliance
  • In 13 sites in Russia
• Randomized to XR-NTX plus counseling or counseling alone
• 24 week double-blind RCT, intent to treat analysis
• Drug co. funded, participated in design, conduct of study

XR-NTX VS BUPRENORPHINE/NALOXONE

• 570 patients, 18 years+ recruited from inpatient withdrawal management at 8 sites
• Randomized to XR-NTX or bup/nal, both with medical management
• 24 week open label trial
• ITT: Intent to treat

XR-NTX, CONTINUED

• Adolescents: No trials, but some case reports
• Side effects include injection site reaction, hypersensitivity reactions, insomnia, hepatic enzyme abnormalities.
• Attempts to override blockade may result in overdose
• Can be prescribed, administered by any healthcare provider licensed to prescribe medications
THE ROLE OF PSYCHOSOCIAL TREATMENTS FOR OUD
PSYCHOSOCIAL TREATMENTS PLUS MOUDS

• Meta-analysis: Does adding psychosocial treatments to agonist medication plus standard counseling improve outcomes? (Minozzi et al. 2011, Cochrane Database of Systematic Reviews)
  • E.g. Acceptance and Commitment Therapy, Cognitive Behavioral Therapy, Short-term Interpersonal Therapy, Contingency Management Twelve Step Facilitation
  • 35 studies, 4,319 participants
  • Answer: No

• Literature review: The jury is still out (Carrol and Weiss, Am J. Psychiatry, 2016 https://doi.org/10.1176/appi.ajp.2016.16070792)
  • Need to consider comparator (medical management), power, other outcomes (functioning)
  • Trial participants may not be representative of real-world patients
  • More work needs to be done

• Compared patient-centered MMT with treatment as usual
• Encouraged, not required to attend counseling
• Counselors as therapists only
• No “administrative discharge” for rules infractions, pre-specified treatment length, failure to pay fees, etc.

• Findings
  • No significant differences in 12 mo. percentage opioid positive urine screens, cocaine-positive screens, drug risk score, retention
  • Significant improvement in Quality of Life (WHOQoL-BREF)

Counseling:
- Evaluate health and substance problem
- Identify issues, create goals and treatment plans
- Help with employment issues
- Lead group counseling
- Provide behavioral treatments
- Refer to support groups
- Set up after-care plans
INTERIM BUPRENORPHINE VS WAITING LIST FOR OPIOID DEPENDENCE

- Shortage of services for OUD - waitlists
- Can we provide medications in the meantime?
- Earlier studies exist for methadone, several European countries provide
- Does it work for buprenorphine?
- Pilot study randomized 50 patients to buprenorphine or control
- Received medication in secure, automatic pill dispenser
- % illicit-free urines at 4 week intervals

Sigmon et al., NEJM, 2016; Sigmon et Al., Addictive Behaviors, 2015
CONTINGENCY MANAGEMENT

• Based on principals of operant conditioning
• Gives rewards to patients to reinforce positive behaviors, e.g. abstinence
• Voucher-based
  • Patient receives voucher for every drug-free urine
  • Voucher can be exchanged for goods and services consistent with a drug-free lifestyle (e.g. food, movie passes).
• Prize-Based
  • Individuals providing drug-negative urine screens draw from a bowl for a chance to win a prize worth between $1-$100
  • Number of draws starts at one and increases with consecutive drug-negative urines. Resets to one if drug-positive urine screen provided.
  • Can also be used to reinforce other behaviors (e.g. clinic attendance)

CONTINGENCY MANAGEMENT FOR COCAINE USE AMONG INDIVIDUALS WITH CUD RECEIVING METHADONE FOR OUD

- Meta-analysis, 4 studies, 163 patients
- Only cocaine use incentivized

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<th>Effect</th>
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<td>Sustained cocaine abstinence</td>
<td>RR=3.11*</td>
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<td>Cocaine free urine analysis</td>
<td>SMD=0.85*</td>
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<tr>
<td>Heroin free UA</td>
<td>SMD=0.36*</td>
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Castells et al 2009, AM J Drug and Alcohol Abuse DOI: 10.1080/00952990903108215
COGNITIVE BEHAVIORAL THERAPY (CBT)

• Based on theory that learning processes play crucial role in development of maladaptive behavior patterns

• Helps patients identify likely problems, apply coping strategies

• Examples include
  • Exploring positive and negative consequences of continued drug use
  • Self-monitoring to recognize cravings early, identify situations that might lead to drug use
  • Developing strategies to cope with cravings, avoid high-risk situations

101 patients with CUD randomized to standard MMT or MMT + weekly access to computer-based training for cognitive behavioral therapy.

8 week trial

Effect sizes

Carroll et al., Am J Psychiatry, 2014
WHAT IF I WANT TO DISCONTINUE MOUDS?

• No universally agreed upon length of treatment

• Cohort studies suggest that many who discontinue MOUDs resume use, *e.g.* 87% within 18 months after MMT (Nosyk et al, 2012).

• Many patients benefit from very long-term, even lifetime treatment

• If you must, TIP 63 recommends:
  • Gradual taper, adjusted if necessary for return to use
  • Psychosocial treatment
  • Possible use of naltrexone once tapered off agonists for sufficient duration
CHALLENGE: PERCENTAGE RECEIVING MOUD AFTER NON-FATAL OVERDOSE, LENGTH OF TREATMENT

- Retrospective Cohort Analysis
- 17,586 persons in MA
- 30% received at least one mo. of MOUD in 12 mo. post OD

OUD DIAGNOSIS, MEDICATION RECEIPT FOR ADOLESCENTS AND YOUNG ADULTS

- Commercial claims, large insurer
- Individuals age 13-25 with OUD and 6 months continuous (n=20,822)
- 2001-2014
- 88% age 18+, 22% age 13-15

Source: Hadland et al, 2017 JAMA Pediatrics
ILLUSTRATIVE CURRENT RESEARCH PROJECTS
• 600+ active grants with opioid, opiate, methadone, buprenorphine, or naltrexone, in the title

• Contracts

• NIDA Intramural Research Program
**NIH RePORTER**

**Fiscal Year (FY):**
- Current FY is 2018

**Active Projects**
- SELECT

**RESEARCHER AND ORGANIZATION**

- Principal Investigator (PI) / Project Leader:
  - (Last Name, First Name)
  - Use % for wildcard in PI names
  - Enter several PI/Project Leader names OR PI Profile IDs

- Organization:
  - SELECT

- Department Type:
  - SELECT

- Organization Type:
  - SELECT

**TEXT SEARCH**

- Text Search (Logic):
  - Advanced

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**PROJECT DETAILS**

- Project Number/Application ID:
  - Format: BR01CA012345-04/851000
  - Use % for wildcard in project number, e.g., %R21%
  - Enter multiple project numbers/application IDs

- Agency/Institute/Center:
  - SELECT

- NIH Spending Category:
  - SELECT

- Funding Mechanism:
  - SELECT

- Award Type:
  - SELECT

**Search in**
- Projects
  - Publications
  - News

**Limit Project search to**
- Project Titles
  - Project Terms
  - Project Abstracts

**Limit Publication search to**
- Start Year: 2017
- End Year: 2018

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<td>DISCONTINUATION FROM CHRONIC OPIOID THERAPY FOR PAIN USING A SUPERNAPHTHYNE TAMER</td>
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• Goal: Produce antibodies that bind the targeted opioid in blood and extracellular fluid and stop it from getting to the brain
• May be safer, and longer lasting than current medications
• Recent animal studies show promise (Raleigh et al., 2018, J pharmacology and experimental therapeutics, DOI: 10.1124/jpet.117.247049)
• Human study underway 1UG3DA047711-01, Phase 1A/1B Clinical Trials of Multivalent Opioid Vaccine Components (PI Comer)
NEW, REPURPOSED COMPOUNDS, LONG-TERM EFFECTS

• Highly selective D3 receptor antagonists (e.g. VK4-116)
  • Animal studies suggest it inhibits oxycodone reward and reduces withdrawal effects (Yu et al, 2018, Neuropsychopharmacology https://doi.org/10.1038/s41386-018-0284-5)

• Nalmefene (antagonist) implants, 6 month + duration. Lower liver toxicity risk than current MOUDs (1UG3DA047707-01, NALMEFENE IMPLANT FOR THE LONG-TERM TREATMENT OF OPIOID USE DISORDER, PI BEEBE DEVARNEY)
ENHANCING PATIENT EXPERIENCE

• Peer-facilitated physical activity intervention for MMT patients (R33DA041553-03, PI Abrantes)

• Provider-Pharmacy Practice Agreements for the provision of buprenorphine and naltrexone (4R33DA045848-02, PI Green)

• Patient Decision Aid for Medication-Assisted Treatment (PtDAMAT), to help patients understand and choose the approach that meets their needs and values (4R33DA045844-02 PI Hser)

• A Smartphone App to Facilitate Buprenorphine Discontinuation (R21 DA 041153-01)
THANK YOU!