Medication-Assisted Treatment for Opioid Dependence & Barriers to Implementation

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Disclosures

• None
NIDA CTN

Goals:
1. Bridge the gap between research and practice
2. Conduct clinical trials
3. Disseminating evidenced-based treatment to community treatment programs

• 13 Nodes across the country
• 6 active studies
• Enrolled 14,412 study participants
“The CTN has done a remarkable job translating our research and involving and integrating scientists from multiple backgrounds. It is flexible so as to engage the right people and facilitate their working together to hone research-based treatments and get our best science out to the field.”

—NIDA Director Nora Volkow, M.D. (address to NIDA Council, Feb. 2010)
Epidemiology

Opioid Dependence
Figure 5. Percentage of prescription drugs used most often, by drug type and age group: United States, 2007–2008

- **Children aged 0–11**
  - Penicillins (treat infections): 3.7%
  - Leukotriene modifiers (asthma, allergies): 3.9%
  - Bronchodilators (asthma): 5.7%
  - **Adolescents aged 12–19**
    - Antidepressants: 4.8%
    - Bronchodilators (asthma): 5.4%
    - CNS stimulants (attention deficit disorder): 6.1%
  - **Adults aged 20–59**
    - Cholesterol lowering drugs: 8.4%
    - Analgesics (pain relief): 10.1%
    - Antidepressants: 10.8%
  - **Older adults aged 60 and over**
    - Diuretics (high blood pressure, heart disease): 19.9%
    - β-blockers (high blood pressure, heart disease): 26.4%
    - Cholesterol lowering drugs: 44.9%

**Notes:** Primary indication for the use of the drug class is in parentheses. CNS is central nervous system.

**Source:** CDC/NCHS, National Health and Nutrition Examination Survey.
Prescription Drugs of Abuse

1. Opioids (for pain)
   a) Hydrocodone (Vicodin®)
   b) Oxycodone (OxyContin®)
   c) Propoxyphene (Darvon®)
   d) Hydromorphone (Dilaudid®)
   e) Meperidine (Demerol®)
   f) Diphenoxylate (Lomotil®)

2. Central nervous system depressants (for anxiety and sleep disorders)
   a) Pentobarbital sodium (Nembutal®)
   b) Diazepam (Valium®)
   c) Alprazolam (Xanax®)

3. Stimulants (for ADHD and narcolepsy)
   a) Dextroamphetamine (Dexedrine®)
   b) Methylphenidate (Ritalin® and Concerta®)
   c) Amphetamines (Adderall®)

SOURCE: NIDA Research Report, NIH Pub. #05-4881
National Data

**Prevalence**
- 20% (28 mil.) persons reported lifetime use
- 2.8% (7 mil.) persons reported past month use
- From 2002 to 2009, there was an increase (5.5% to 6.3%) among young adults aged 18 to 25 reports of current use

**Source of Drugs**
- Over half get their drugs from a friend or relative for FREE
- 17.6% report getting the drugs as a prescription from a doctor
- 4.8% got the drugs from a dealer or stranger

SOURCE: SAMHSA, NSDUH 2009 & NIDA Research Report, NIH Pub. #05-4881
Past Month Illicit Drug Use

Figure 2.1 Past Month Illicit Drug Use among Persons Aged 12 or Older: 2009

- Illicit Drugs: 21.8 million
- Marijuana: 16.7 million
- Psychotherapeutics: 7.0 million
- Cocaine: 1.6 million
- Hallucinogens: 1.3 million
- Inhalants: 0.6 million
- Heroin: 0.2 million

SOURCE: SAMHSA, NSDUH 2009
Treating Opioid Dependence
Who Needs Treatment?

- USE
- MISUSE
- ABUSE
- DEPENDENCE

Primary prevention
Secondary prevention
TREATMENT

DSM Criteria
Defining Addiction

American Society of Addiction Medicine (ASAM)’s Definition:

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry.

Addiction is characterized by:

• Inability to consistently abstain;
• Impairment in behavioral control;
• Craving; or increased “hunger” for drugs or rewarding experiences;
• Diminished recognition of significant problems with one’s behaviors and interpersonal relationships; and
• A dysfunctional emotional response.

Source: www.asam.org
Pharmacotherapy should be a standard component of treatment for SUD when effective drugs exist

- American Medical Association (AMA)
- American Psychiatric Association
- National Institute on Drug Abuse (NIDA)
- National Quality Forum
- Substance Abuse and Mental Health Services Administration (SAMHSA)
- Veteran’s Administration

SUD = substance use disorders
Purpose of Medications

Medications can be used to/for:

- Detoxification
- Decrease withdrawal symptoms/cravings
- Decrease reinforcing effects of drugs
- Prevent relapse
- Prevent overdose deaths
- Treat co-occurring psychiatric disorders
Why Provide MAT?

- Better outcomes
  - Less substance use, less criminal problems, less health problems, better employment & reduced mortality
- Cost-effective
- Evidence-based practice
- Provision of MAT as a quality indicator

Giving patients access to all of the tools that may improve the probability of recovery
Why Medications Work

DRUGS OF ABUSE TARGET THE BRAIN’S PLEASURE CENTER

Brain reward (dopamine) pathways

These brain circuits are important for natural rewards such as food, music, and sex.

Drugs of abuse increase dopamine

Typically, dopamine increases in response to natural rewards such as food. When cocaine is taken, dopamine increases are exaggerated, and communication is altered.

SOURCE: NIDA
EBPs for Opioid Dependence?

**Medication (detox):**
- Methadone
- Clonidine
- Benzodiazepines
- Buprenorphine (Suboxone)

**Medication (maintenance):**
- Methadone
- Buprenorphine
- Naltrexone (ReVia/Vivitrol)

**Psychosocial:**
- Cognitive Behavioral Therapy
- Contingency Management
- Brief Medication Management
- Individual & group counseling

**Detox Meds + Maint. Meds + Psychosocial**
Methadone

• Mu opioid agonist with long half-life, prevents withdrawal, craving, and high

• Dose: Typically 60 – 120 mg, highly regulated and only provided by licensed narcotic treatment programs

• Side effects: sedation, constipation, sweating, arrhythmia; can cause QTc interval prolongation

• Results: Highly effective – reduces illicit opioid use, criminal activity, spread of HIV, death due to overdose
Naltrexone

- **Mu-opioid antagonist prevents high**

- **Dosing:** 50 mg everyday or 380 mg IM

- **Side effects:** nausea, anxiety, dysphoria, insomnia, sedative effects, can have hepatic effects (increased LFTs); used with caution in patients with liver disease, contraindicated for acute hepatitis or liver failure

- **Effectiveness:** Decreases opioid use in compliant patients, reduces craving (Vivitrol study)
Buprenorphine

- High affinity partial mu opioid agonist and kappa-opioid antagonist prevents withdrawal, high, reduces craving; advantage: very low risk from overdose
  - Has effects of typical opioid agonists at lower doses
  - Produces a ceiling effect at higher doses
  - Binds to opioid receptors and is long-acting

- Dose: Typically 12-16 mg/day, initiated while patient is in mild to moderate withdrawal, prescribed by physicians who have completed a certification process
  - Slow to dissociate from receptors so effects last even if one daily dose is missed.
MAT in North Dakota

• 57 Substance abuse treatment facilities, 33.3% provide medications:
  • 33.3% provide meds for psychiatric disorders
  • 15.8% nicotine replacement
  • 17.5% Campral
  • 24.6% Anatabuse
  • 24.6% Naltrexone
  • 5.3% Buprenorphine
  • 5.3% Methadone

• 14 Physicians certified to provide buprenorphine

Source: SAMHSA’s 2010 National Survey of Substance Abuse Treatment Services (N-SSATS)
Buprenorphine

- Formulations: Buprenorphine only (Subutex), combined with naloxone (4:1; Suboxone); film
  - Each 8 mg tablet contains 2 mg of naloxone
  - Each 2 mg tablet contains 0.5 mg of naloxone
- Results: Very effective in reducing illicit opioid use
- FDA approved for use with opioid dependent persons aged 16 and older
- Side effects: Constipation, drowsiness, headache
Buprenorphine

- Buprenorphine is as effective as moderate doses of methadone (Fischer et al., 1999; Johnson, Jaffee, & Fudula, 1992; Ling et al., 1996; Schottenfield et al., 1997; Strain et al., 1994)

- Buprenorphine's partial agonist effects make it mildly reinforcing, encouraging medication compliance (Ling et al., 1998)

- After a year of buprenorphine plus counseling, 75% of patients retained in treatment compared to 0% in a placebo-plus-counseling condition (Kakko et al., 2003)
NIDA CTN: POATS

- Multi-site, two-phase adaptive, sequential treatment design
- 10 Community-based treatment programs
- Prescription opioid dependence, excluded prominent heroin use
- Included subjects with chronic pain
- Psychiatrically stable
- All subjects received bup/nx (8mg-32mg)

Online First
Adjunctive Counseling During Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence
A 2-Phase Randomized Controlled Trial
# POATS: Dosing

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
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<tbody>
<tr>
<td>8 mg</td>
<td>8 mg</td>
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<tr>
<td>12 mg</td>
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<td>16 mg</td>
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<td>20 mg</td>
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<td>24 mg</td>
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<tr>
<td>32 mg</td>
<td>32 mg</td>
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<tr>
<td>Other</td>
<td>Other</td>
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<tbody>
<tr>
<td>8%</td>
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<tr>
<td>18%</td>
<td>14%</td>
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<td>38%</td>
<td>27%</td>
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<td>10%</td>
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<td>13%</td>
<td>16%</td>
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<tr>
<td>-</td>
<td>11%</td>
</tr>
<tr>
<td>13%</td>
<td>18%</td>
</tr>
</tbody>
</table>
**Intial Treatment Study**
- **Phase 1**
- **Maximum 3 months**

- **N=653**

  - Randomization
  - SMM
    - 1 month BUP/NX
    - 2 months follow-up
    - Success

  - Failure
    - 7% success

  - Randomization
  - EMM
    - 1 month BUP/NX
    - 2 months follow-up
    - Success

**Stabilizing Treatment Study**
- **Phase 2**
- **6 months**

- **N=360**

  - SMM
    - 3 month BUP/NX
    - 1 month taper
    - 2 months follow-up
    - Substantial improvement

  - No substantial improvement

  - Randomization
  - SMM
    - No substantial improvement

  - Randomization
  - EMM
    - Substantial improvement

  - No substantial improvement

  - 1 month taper
  - 2 months follow-up
Percent Opioid-Positive Urine Over Time

Phase 1

Phase 2

Note: SMM=Standard Medical Management; ODC=Opioid Drug Counseling; Bup/nx=Buprenorphine Treatment; FU=Follow-Up
**POATS: Chronic Pain**

- No more likely to drop-out or terminate from Phase 1
- Equally likely to enter Phase 2
- No more likely to have an adverse event (AE) or serious adverse event (SAE)

<table>
<thead>
<tr>
<th>Phase 2 Week 12 (end of stabilization)</th>
<th>Success</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pain</td>
<td>53.0%</td>
<td>0.22</td>
</tr>
<tr>
<td>No</td>
<td>46.5%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 2 Week 24 (8 weeks post-taper)</th>
<th>Success</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pain</td>
<td>9.4%</td>
<td>0.60</td>
</tr>
<tr>
<td>No</td>
<td>8.1%</td>
<td></td>
</tr>
</tbody>
</table>
## Exhibit 1: Key Differences Between Medications Used To Treat Patients With Opioid Dependence

<table>
<thead>
<tr>
<th>Prescribing Considerations</th>
<th>Extended-Release Injectable Naltrexone</th>
<th>Buprenorphine</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of Administration</td>
<td>Monthly</td>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Intramuscular injection in the gluteal muscle by healthcare professional.</td>
<td>Oral tablet or film is dissolved under the tongue. Can be taken at a physician’s office or at home.</td>
<td>Oral (liquid) consumption usually witnessed at an OTP, until the patient receives take-home doses.</td>
</tr>
<tr>
<td>Restrictions on Prescribing or Dispensing</td>
<td>Any individual who is licensed to prescribe medicine (e.g., physician, physician assistant, nurse practitioner) may prescribe and order administration by qualified staff.</td>
<td>Only licensed physicians who are DEA registered and either work at an OTP or have obtained a waiver to prescribe buprenorphine may do so.</td>
<td>Only licensed physicians who are DEA registered and who work at an OTP can order methadone for dispensing at the OTP.</td>
</tr>
<tr>
<td>Abuse and Diversion Potential</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Additional Requirements</td>
<td>None; any pharmacy can fill the prescription.</td>
<td>Physicians must complete limited special training to qualify for the DEA prescribing waiver. Any pharmacy can fill the prescription.</td>
<td>For opioid dependence treatment purposes, methadone can only be purchased by and dispensed at certified OTPs or hospitals.</td>
</tr>
</tbody>
</table>

Sources: Adapted from 16, 18, 19

Medications in the Pipeline: Probuphine

- Sublingual formulations of buprenorphine have been associated with diversion

- A subcutaneous implant that delivers buprenorphine for 6 months, reduces risk of diversion, improves compliance, and reduces buprenorphine dose; maintains opioid tolerance, protects against inadvertent opioid overdose for 6 months

- Phase-III trial revealed probuphine, relative to placebo, significantly improved treatment retention and reduced opioid use, craving, and withdrawal

- Implant procedure generally well tolerated and the adverse events were similar to placebo
SAMHSA’S Medication Recommendation for Adolescents with OUD

- Detox. = Buprenorphine
- Maintenance = Naltrexone
- Drug-free
- Relapse
- Maintenance = Buprenorphine

March & colleagues (2005) study:
• RTC, n=36, ages 13-18 years old (mean=17)
• Treatment retention 72% (bup.) vs. 39% (clonidine)
• Opiate negative urines 64% (bup.) vs. 32% (clonidine)
• Max dose 8mg

Woody & colleagues (2008) study:
• NIDA CTN study, RTC, n=152, ages 15-21 years old (mean=19)
• Compared bup. detoxification vs. bup. maintenance
• Bup. maintenance had less opioid use, better treatment retention & less IV use

SOURCE: March et al. (2005) Arch Gen Psychiatry; Woody et al. (2008) JAMA
Chakrabarti & colleagues (2010) study:
• Secondary analysis of NIDA CTN study, n=69
• Withdrawal & pain predicted dose
  - No pain = 12.8mg
  - Some pain = 15mg
  - Extreme pain = 19.7mg

Polsky & colleagues (2010) study:
• NIDA CTN study, n=152
• Cost to treat maintenance vs. detox. = $1514 and the societal cost savings = $31,264
Neonatal Abstinence Syndrome (NAS)

- Recommended that opioids be used to treat NAS
- No current standard uniform protocol for treatment
- Most common medication is morphine
- In 2009, the average hospitalization costs of NAS was $53,400; 78% costs paid by Medicaid

SOURCE: Patrick et al. (2012) JAMA
Buprenorphine Dosing:

- Day 1 = 2 mg; max of 4 mg in 24 hours based on symptom relief
- Discharged and seen outpatient every 24-72 hours until dose is stable and withdrawal symptoms improved
- Dose needs adjustment upwards, presumably due to similar pregnancy-induced changes
- Dose adequacy assessed weekly with CINA, urinalysis results

SOURCE: Slide borrowed from Dr. Heil
Buprenorphine During Pregnancy

SOURCE: Jones et al. (2010) NEJM
Barriers to Implementing MAT
Medications for MI

Safe
Effective
Patient-Centered
Timely
Efficient
Equitable

Percentage of Medicare Beneficiaries Hospitalized for Heart Attack Who Received a Beta-Blocker Prescription at Hospital Discharge, State Rates, 2003


Percent of AOD Facilities offering Medications

SOURCE: N-SSATS 2009
Environmental Barriers

- **Regulatory**
  - Medication not on the Medicaid formulary
  - Training requirements & prescribing limitations for buprenorphine
  - Methadone facilities

- **Requires buy-in at the:**
  - State
  - Community-level
  - Political
  - Police

- **Geographic distance to treatment facility & pharmacy**
Missouri Approved Medications

- Acamprosate
- Buprenorphine
- Disulfiram
- Naltrexone
- Suboxone
- Vivitrol

“Although not for everyone, it is an essential part of the comprehensive array of services available to people struggling with addiction to alcohol or other drugs. A paradox in our field is that although we recognize addiction as a chronic, relapsing disease, some substance abuse counselors and administrators have been reluctant to embrace new technologies for its treatment.”

-- Mark G. Stringer, Director
Organizational Barriers

- Organizational size
- Staffing
- Hospital affiliation
- Organizational leadership buy-in
- Urine drug screening
- Profit status
- Modalities offered
- Cost
- Participation in NIDA CTN & other pilot studies

Sources: Knudsen et al. (2009) JSAT; Ducharme & Roman (2009) JSAT
Clinician & Patient Barriers

Clinician
- MAT educational opportunities
- Fear of diversion & liability
- Experience treating patients with SUD

Patient
- Health insurance
- Income

- Knowledge & attitudes about medication
- Experience with medication

Sources: Knudsen et al. (2009) The American Journal on Addictions
Clinician & Patient Barriers

Attitudes + social norms/expectations = Intentions to use MAT

Source: Rieckmann et al. (2007) JSAT
Philosophical Barriers

“Cultural belief ..... That medications are not effective when interjected into therapy, in spite of the preponderance of evidence-based practice to the contrary”

--Anonymous SSA

- Drug addiction should not be treated with a drug
- Abstinence – only approach
- Inconsistent with 12-Step facilitation
MAT as a Barrier

- Patient compliance with medication (e.g., antabuse & oral naltrexone)
- Buprenorphine & Vivitrol induction process
- Sufficient dose
- Diversion
- Drug availability

“I think the dosage needs adjusting. I’m not nearly as happy as the people in the ads.”
Overcoming Barriers

Medications at a reduced cost ➔
- Partner with FQHC or 24B clinicians
- Become an FQHC look-alike
- Add addiction medications to state Medicaid formularies

Access to medical personnel ➔
- Coordinate with medical providers in your area
Overcoming Barriers

Medication compliance ➔
- switch medications or formulation (Vivitrol)
- use psychosocial treatment approaches or contingency management to improve compliance

Philosophical differences ➔
- Medication saves lives
- Provision of MAT as a quality indicator
- Adoption of evidence-based practices for addiction
- Reconcile use of medication as a treatment towards the ultimate goal of recovery from ADDICTION
Overcoming Barriers

**Education**

- Participate in clinical training on how to use medications
- Educate patients & the community regarding the benefits of medications
- Learn from clinicians & patients with medication experience
- Physicians can use the PCSS-B online course to receive training on buprenorphine
- ATTC provide 6-hour training on buprenorphine for clinicians
Overcoming Barriers

Participate in a medication study
• Gain experience with a medication as part of a study

Try new modalities
• Buprenorphine induction centers
• Coordinate services with an inpatient detoxification center

Adopt policies to address diversion
• Implement urine drug screening
Re-invention to improve access

2.6 billion people around the globe do not have access to toilets, which accounts for as many as half of the hospital admissions in some countries.

..... If they can re-invent the toilet, we can re-invent the addiction specialty treatment system.

Concluding Remarks

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry.

• Use evidence-based practices to give patients the best chance of recovery
• Medications + psychosocial therapy works & improves outcomes
• In the long term, patients may be able to achieve drug abstinence & those who cannot should be able to use medications as a treatment tool to sustain their recovery
Additional Resources

http://ctndisseminationlibrary.org/

http://buprenorphine.samhsa.gov/bwns_locator/
THANK YOU!

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