Medication Assisted Treatment of Opioid Use Disorders: Progresses and Challenges

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Dr. Nora Volkow, Disclosures

- Dr. Nora Volkow has no financial relationships to disclose.
Target Audience

• The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.
Opioid Addiction

Prescription Drug Misuse/Abuse is a Major Problem in the US

Current Drug Use Rates in Persons Ages 12+

- Any Illicit Drug: 27
- Marijuana: 22.2
- Psychotherapeutics: 6.5
- Cocaine: 1.5
- Hallucinogens: 1.1
- Inhalants: 0.5
- Heroin: 0.4

Past Year Nonmedical Use of Psychotherapeutic Drugs Persons Ages 12+

- Pain Relievers
- Tranquilizers
- Stimulants
- Sedatives

Analgesic Mechanisms of Mu Opiate Drugs (Heroin, Vicodin, Morphine)
High Levels of Opioid Prescriptions have Facilitated Diversion & Contributed to Overdose Deaths

**Oxycodone & Hydrocodone Prescriptions**

- Oxycodone (Schedule II)
- Hydrocodone (Schedule III)

**Rx Opioid Overdose Deaths**

- Total
- Female
- Male

Source: CDC Wonder

SDI Health, VONA_02-1-13_Opioids Schedule II & III

Providers’ Clinical Support System for Medication Assisted Treatment
Abuse of Opioid Medications has led to a Rise in Heroin Abuse and Associated Deaths from Overdoses
Respondents Who Endorsed Past-Month Use of OxyContin or Heroin Before and After Introduction of an Abuse-Deterrent Formulation (ADF)

Cicero TJ and Ellis MS  JAMA Psychiatry. Published Online March 11, 2015.
How Can Research Help?

- **Pain:** develop less abuseable analgesics and alternative therapeutics
- **Overdoses:** user friendly Naloxone
- **Addiction:** new mediations and immunotherapies
- **Implementation Science**
- **Pharmacogenomics** (Precision Medicine)
Develop Less Abusable Drugs: Prodrugs

- **Problem:** changing method of taking opioids – i.e., crushing, injecting – increases euphoria; abuse
- **Challenge:** develop drugs that resist tampering; abuse
- **Research response:** oxycodone prodrug
  - Inactive compounds metabolized in the body to produce active drug
Pain: Alternative Therapeutics
Non-Medication Strategies for the Treatment of Pain and Addiction

Transcranial Magnetic Stimulation (TMS)

Deep Brain Stimulation (DBS)
Stereotaxtic implantation of electrodes that emit electrical stimulation to a targeted neuronal region


High-Definition transcranial Direct Current Stimulation (HD-tDCS)

Improving OD Treatments: Naloxone for Overdose

• Lay-friendly administration: intranasal naloxone

• *AntiOp*, developing disposable naloxone nasal spray. Product could be on the market 2015

• *Lightlake Therapeutics*, conducting clinical trials with intranasal naloxone for binge eating disorder will test this for opioid overdose

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BMJ Published 31 January 2013

**RESEARCH**

Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis

Alexander Y Walleys assistant professor of medicine, medical director of Massachusetts opioid overdose prevention pilot*2, Ziming Xuan research assistant professor*2, H Holly Hackman epidemiologist*1, Emily Quinn statistical manager*1, Maya Doe-Simkins public health researcher*1, Amy Sorensen-Alawad program manager*1, Sarah Ruiz assistant director of planning and development*1, Al Ozonol director, design and analysis core*1
Full and Partial Agonists vs Antagonists

Treatment Strategies for Opioid Addiction

- **Agonist**: An agonist drug has an active site of similar shape to the endogenous ligand so binds to the receptor and produces the same effect.

- **Antagonist**: An antagonist drug is close enough in shape to bind to the receptor but not close enough to produce an effect. It also takes up receptor space and so prevents the endogenous ligand from binding.

- **Effect**:
  - **Full Agonist** (Methadone)
  - **Partial Agonist** (Buprenorphine)
  - **Antagonist** (Naloxone)

- **Graph**:
  - Log Dose vs Opioid Effect
Medications Assisted Therapies

Opioid Agonist Treatments
Decreased Heroin OD Deaths

Baltimore, Maryland, 1995-2009


Methadone Promotes Initiation Of Antiretroviral Therapy in IDU

Treatment for Addiction to Opioid Medications

*Brief and Extended Buprenorphine-Naloxone Tx for Rx Opioid Dependence*

<table>
<thead>
<tr>
<th>Phase</th>
<th>% of Patients with Successful Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 (Brief)</td>
<td>6.6</td>
</tr>
<tr>
<td>Phase 2 (Extended)</td>
<td>49.2</td>
</tr>
<tr>
<td>After Taper</td>
<td>8.6</td>
</tr>
</tbody>
</table>

*Retention In Methadone Maintenance Drug Tx*

**ODDS RATIO**

- PTOP: 1.2
- Heroin: 1.0

*Weiss RD et al., Arch Gen Psych 2011;68(12): 1238-1246.*

*Prescription Opioid Abusers can be treated at MMT facilities at least as effectively as heroin users in terms of treatment retention.*

Long-Acting Injectable Naltrexone

XR-NTX: Positive Phase 3 Results
Opioid Dependence

**Primary Endpoint**
Rates of opioid-free urine tests  
P=0.0002

**Secondary Endpoints: XR-NTX vs. Placebo**
- Improved study retention during 6-month study period  
P=0.004
- Lower opioid craving scores  
P<0.001
- Less incidence of relapse to physiologic opioid dependence  
P=0.017
- Less self-reported opioid use  
P=0.003

*Krupitzky et al., Lancet 2010*

**Post Prison-Release Outcomes**

IM Injection every 4 weeks for 24 weeks

**Opiate Neg Urine Tox**

Weeks 1-8

*Lee JD et al., Addiction 2015;100:1008-1014.*
Improving Implementation of Medication Assisted Treatments: Addiction

% Treatment Programs Offering FDA-approved SUD medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>25%</td>
</tr>
<tr>
<td>Methadone</td>
<td>9%</td>
</tr>
<tr>
<td>Tablet naltrexone</td>
<td>17%</td>
</tr>
<tr>
<td>Injectable naltrexone</td>
<td>9%</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>16%</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>19%</td>
</tr>
</tbody>
</table>

% OTP patients receiving methadone, buprenorphine, or vivitrol

- Methadone: 26.4%
- Buprenorphine: 3.9%
- Vivitrol: 0.3%
- Not receiving Methadone, Buprenorphine or Vivitrol: 69.4%


2012 N-SSATS Data, SAMHSA
ED-initiated Buprenorphine
Increased TX Engagement,
Reduced Opioid Use & Inpatient

% engaged in treatment 30th day

D’Onofrio JAMA. 2015.

Infectious Clinic’s-Based
Buprenorphine of Opioid-Dependent
HIV+ Patients vs Tx Referral

Participation in Opioid Agonist Therapy (%)

New Therapeutics for Opioid Use Disorders

- Extended release medications (improve compliance)
  IMPLANTABLE Buprenorphine Probuphine™ (6 months)

Retention of Patients

- Buprenorphine: 66%
- Placebo: 31%

Example to understand this cumulative graph:
About 56% of patients in the buprenorphine implant group and also in the sublingual buprenorphine group had 20% or fewer of their 72 urines negative for illicit opioids over 24 weeks (50% were more successful), and about 80% of those in the placebo group had 20% or fewer negative urines (20% were more successful).

Ling, W. et al. JAMA 2010
Treating Opioid Addiction: Vaccines

Antibodies reduce amount of drug in the brain

Targets drugs, not receptors
Strategies that Can Help Address the Dangers of Opioid Overdose and Addiction in the US

- Expand MAT
- Responsible prescribing and management of chronic pain, which requires enhanced education of pain and its treatment
- Availability of naloxone
- Mandatory addiction education in medical, nursing and pharmacy schools
- PDMP that are universal and in real time to minimize doctor shopping
Education on Pain in Medical Schools

USA (median: 7 hours)
Canada (median: 14 hours)
Veterinarian schools:
75 hours on pain

Number of Hours of Pain Education

Mezei, L and Murinson, BB., J Pain, 12, 1199 -1208, 2011.
NIH Pain Consortium Activities

• Centers of Excellence in Pain Education (12 CoEPE)

ICs Involved:

- ORWH
- NIA
- OBSSR
- NINR
- NIDA
- NICHD
- NIDCR
- NIAMS
- NINDS
- NCCAM

• Consensus Workshop on Opioids for Chronic Pain
Why Drug Abuse Education Is Critical to Comprehensive Medical Education and Patient Health

Drug use affects patient outcomes and has wide-ranging health and social consequences including:
- cardiovascular disease
- stroke
- cancer
- HIV/AIDS
- anxiety
- depression
- sleep problems
- financial difficulties
- legal, work, and family problems

Only a fraction of people who need treatment for addiction receive it.

In 2010, more than 23 million persons aged 12 or older needed specialized treatment for substance abuse, but 20.5 million did not receive it.*

*http://www.oas.samhsa.gov/nso/2k10nsduh/2k10Results.htm

Resources for Medical Students, Resident Physicians & Faculty

- NIDA CoEs were established in 2007 to help fill gaps in current medical education curricula related to both illicit drugs and Rx drug abuse

- Working with NIDA, medical school faculty at the CoEs have developed a diverse portfolio of innovative curriculum resources about how to identify and treat patients struggling with drug abuse and addiction

www.drugabuse.gov/coe
Key Questions:
1. Effectiveness & comparative effectiveness
2. Harms & adverse events
3. Dosing strategies
4. Risk assessment & risk mitigation strategies

Where studies were available, the strength of evidence was rated no higher than low, due to imprecision & methodological shortcomings

Recommendations for research

- which types of pain benefit from opioids
- development of multidisciplinary pain interventions
- tools for identification of patient risk and outcomes related to long-term opioid use for clinical settings
- Electronic health record vendors should incorporate decision support to identify patients who benefit or are harmed by opioids
- consider alternative designs in addition to RCT
- Risk identification and mitigation strategies
Education for Healthcare Providers

CME Courses developed by NIDA & Medscape Education, funded by ONDCP

Safe Prescribing for Pain

Skills and tools clinicians can use to screen for and prevent abuse in patients with pain

Managing Pain Patients Who Abuse Rx Drugs

Learn symptoms of opioid addiction & dependence in patients with chronic pain, & how to screen for, prevent, & treat such conditions
Adverse drug events (ADEs) are the largest contributor to hospital-related complications & account for more than 3.5 million physician office visits each year.

DHHS’s National Action Plan for Adverse Drug Event Prevention (ADE Action Plan) targets opioids as a significant contributor to ADEs.

**The Pathways to Safer Opioid Use**

- Interactive training tool on health literate chronic pain management
- Development led by DHHS Office of Disease Prevention (ODPHP); at least 14 government agencies helped with its creation
- Teaches health care providers how to implement opioid-related recommendations from the ADE Action Plan, and patient-centered strategies to communicate the safe use of opioids in managing chronic pain
- Continuing medical education (CME) is available to participants who complete the course

http://health.gov/hcq/training.asp#pathways
Specific Binding
$[^{18}F]cyclofoxy$ (μ ligand)

Specific Binding
$[^{11}C]carfentain$ (μ ligand)

Normal Control

Methadone Maintained Patient

30-35 % occupancy for methadone doses > 80 mg a day

Source: Kling et al., JPET, 2000.

27-47 % occupancy for 2mg Bup
85-92% occupancy for 16 mg Bup
94-98% occupancy for 32 mg Bup

Greenwald, MK et al., Neuropsychopharm. 2003.
Potential mHealth Interventions for Preventing Opiate Overdose

**Potential mHealth Interventions for Preventing Opiate Overdose**

- **Wireless SENSORS**
  - Respiration
  - Oxymeter
  - Arrythmias

- **NALOXONE DELIVERY**
  - Automatic Patient
  - Third party

- **ALARM**
  - Set up delivery
  - Alert Patient
  - Alert Third Party
Gaps in Treatment Capacity in Most States

Rate of OA-MAT capacity

Rate of past year opioid abuse or dependence

Rate of abuse/dependence exceeds capacity

PCSS-MAT Mentoring Program

- PCSS-MAT Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.

- PCSS-MAT Mentors comprise a national network of trained providers with expertise in medication-assisted treatment, addictions and clinical education.

- Our 3-tiered mentoring approach allows every mentor/mentee relationship to be unique and catered to the specific needs of both parties.

- The mentoring program is available, at no cost to providers.

For more information on requesting or becoming a mentor visit: pcssmat.org/mentoring
PCSSMAT is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with: American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA), American Society of Addiction Medicine (ASAM) and Association for Medical Education and Research in Substance Abuse (AMERSA).

For More Information: www.pcssmat.org

Twitter: @PCSSProjects

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