Medication Assisted Treatment for Opioid Dependence

Presented to Kitsap Substance Abuse Advisory Board

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September 25, 2012
ADDICTION

“Addiction is a brain disease shaped by behavioral and social context.”

Dr. Alan Leshner, Former Director
National Institute on Drug Abuse

“Drug addiction is associated with altered cortical activity and decision making that appears to overvalue reward, undervalue risk, and fail to learn from repeated errors.”

Dr. Nora Volkow, Director
National Institute on Drug Abuse

“Any disease that is treated as a mystery and acutely enough feared will be felt to be morally, if not literally, contagious.”

Susan Sontag, “Illness as Metaphor” 1978
Today’s Topics

• What is medication assisted treatment for opioid dependence?
• Does medication assisted treatment work?
• Is medication assisted treatment any better than “treatment as usual”?
• Is a person who is receiving medication assisted treatment really in recovery?
• What medications are available for medication assisted treatment of opioid dependence?
Addiction / Drug Dependence as a Brain Disease

- Prolonged drug use changes brain function
- Changes are pervasive and persist after drug use stops
- Brain changes have been demonstrated at many levels
  - Molecular
  - Cellular
  - Structural
  - Functional
Drug Dependence: A Chronic Medical Illness

- Genetic Heritability – twin studies
  - Hypertension – 25-50%
  - Diabetes – Type 1: 30-55%; Type 2: 80%
  - Asthma – 36-70%
  - Nicotine – 61% (both sexes)
  - Alcohol – 55% (males)
  - Marijuana – 52% (females)
  - Heroin – 34% (males)

- Voluntary Choice – shaped by personality and environment

- Pathophysiology – neurochemical adaptations

- Treatment Response
  - Medications – effectiveness and compliance
  - Behavioral interventions

“What’s the difference between being addicted to painkillers and just really, really liking them a lot?”
581 Male Heroin Addicts Followed for 33 Years

Hser et al., 2001
If addiction is a chronic disease:

Addiction treatment doesn’t cure the disease.

The goal of treatment is to:

- Provide patients the tools to help them manage their addiction – and medications are among those tools
- Teach patients how to use those tools to achieve and maintain recovery
Medication Assisted Treatment (MAT) for Opioid Dependence

MAT is any treatment for opioid addiction that includes a medication (e.g., methadone, buprenorphine, levo-alpha acetyl methadol [LAAM], naltrexone) approved by the U.S. Food and Drug Administration (FDA) for opioid addiction detoxification or maintenance treatment.

MAT may be provided in an OTP or an OTP medication unit (e.g., pharmacy, physician’s office) or, for buprenorphine, a physician’s office or other health care setting. Comprehensive maintenance, medical maintenance, interim maintenance, detoxification, and medically supervised withdrawal are types of MAT.
Medication Assisted Treatment (MAT) Approaches

- Full agonist therapy – methadone (Methadone Maintenance Treatment, MMT)
- Partial agonist therapy – buprenorphine
- Antagonist therapy – naltrexone
NIH Consensus Panel on Effective Medical Treatment of Opiate Addiction

- 12 member multi-disciplinary panel, Nov. 1997
- heard testimony from 25 experts
- reviewed 941 research reports published over the period Jan. 1994 - Sept. 1997

“Of the various treatments available, MMT, combined with attention to medical, psychiatric, and socioeconomic issues, as well as drug counseling, has the highest probability of being effective.”

Adapted from:
JAMA, Dec. 9, 1998,
280 (22), 1936-1943
## Comparing Two Opioid Agonists: Methadone and Heroin

<table>
<thead>
<tr>
<th>Methadone</th>
<th>Heroin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orally effective. No risk of infection.</td>
<td>Not orally effective. Injection use is a risk factor for transmission of infectious diseases.</td>
</tr>
<tr>
<td>Long acting. Administered once a day.</td>
<td>Short acting. Must be administered several times a day.</td>
</tr>
<tr>
<td>Causes no sedation or euphoria.</td>
<td>Can cause significant sedation and/or euphoria.</td>
</tr>
</tbody>
</table>
Opiate Substitution Treatment

Goals

**Primary Goals:**
- ✓ Reduction in illicit opiate use and licit opiate misuse.
- ✓ Retention in treatment for 1-2 years or more.

**Secondary Goals:**
- ✓ Reduction in cocaine, alcohol, and other drug abuse.
- ✓ Reduction in transmission of infectious diseases by unsterile injection equipment.
- ✓ Reduction in criminal activity.
- ✓ Increase in pro-social activity — employment, education, child care, etc.
Salience Shifting

But aren’t they still addicted?

• What is the definition of addiction?
  ✓ Is it simply physical dependence?

• How does the change of lifestyle and psychosocial stability associated with long-term methadone treatment fit with that definition?
Definition of Recovery

Betty Ford Institute Consensus Panel
working definition of recovery:

“Recovery from substance dependence is a voluntarily maintained lifestyle characterized by sobriety, personal health, and citizenship.”

The Consensus Panel comments in Section 5.1.2:
“To be explicit, formerly opioid-dependent individuals who take naltrexone, buprenorphine, or methadone as prescribed and are abstinent from alcohol and all other non-prescribed drugs would meet this consensus definition of sobriety.”

Journal of Substance Abuse Treatment 33 (2007) 221-228
“The problem was one of the rehabilitating people with a very complicated mixture of social problems on top of a specific medical problem, and that (practitioners) ought to tailor their programs to the kind of problem they were dealing with. The strength of the early programs as designed by Marie Nyswander was in their sensitivity to individual human problems. The stupidity of thinking that just giving methadone will solve a complicated problem seems to me beyond comprehension.”

Vincent P. Dole, M.D., 1989

Source: Courtwright, et. al. Addiction: Who Survived
Treatment Requirements

- Attendance for observed dosing 6 days a week for the first 90 days
- Take-home doses permitted after 90 days but only to those patients meeting a number of criteria
- At least once per month urinalysis
  - Some clinics observe collection; some don’t
  - Some clinics have contingencies (+ & -); some don’t
  - Some agencies administer alcohol breath tests; some don’t
- Assessment and counseling
- Additional education, i.e., HIV/HCV, family planning
Methadone & Pregnancy

- Fetal outcomes better on MMT than heroin
- Detoxification from opiates risky for fetus
- Methadone dose adjustments during pregnancy
  - May need “split” dosing to improve serum stability
- Attention to prenatal care during pregnancy
- Some infants have abstinence syndrome within 72 hrs. of birth; may require pharmacotherapy
  - NAS may be associated with mothers’ level of smoking during pregnancy (Choo, et.al., 2004)
- Breastfeeding OK with MMT unless otherwise contraindicated, e.g., blood-borne infections

For further information see TIP 43, Chapter 13
Methadone Maintenance vs. 180 Day Detoxification

12 month study of 179 opioid dependent patients randomly assigned to:

➡ **Methadone Maintenance**
  ✓ mean dose=85.3mg
  ✓ for 14 months

➡ **180 Day Methadone Detoxification**
  ✓ mean dose=86.3 mg prior to taper at 120 days
  ✓ followed by psychosocial Tx for 8 months

“Methadone maintenance therapy resulted in greater treatment retention and lower heroin use rates than did detoxification.”

K.L. Sees et al., JAMA 2000
Return to I.V. Drug Use Following Premature Termination of Treatment

Adapted from: Ball & Ross, 1991.
Objectives and Methods

- To examine predictors of long-term mortality, researchers in Australia conducted a 10-year follow-up study of 405 heroin-dependent patients.
Results

- People who are opioid dependent are 13 times more likely to die than age- and sex-matched peers.
- Overall mortality was 8.8 deaths per 1000 person-years of follow-up (0.66 during opioid maintenance treatment [OMT] and 14.3 while out of OMT).
- Participation in additional OMTs lasting >7 days decreased mortality by 28%.
- Subjects using more heroin at baseline had a 12% lower mortality rate overall.
Swedish Methadone Study

Experimental Group (Methadone)

Before

Control Group (No Methadone)

Gunne & Gronbladh, 1981. Controlled study of 34 drug addicts, aged 20-24 years with a history of 4-8 years of IV heroin use.
Swedish Methadone Study

Experimental Group (Methadone)

After 2 Years

Control Group (No Methadone)

- d) In Prison

Gunne & Gronbladh, 1981

a) Sepsis
b) Sepsis and Endocarditis
c) Leg Amputation
d) Ongoing daily drug abuse
Dead
Swedish Methadone Study

Experimental Group (Methadone)  After 4.5 Years  Control Group (No Methadone)

- Chronic Heart Condition
- Leg Amputation
- In Prison

No drug abuse  Ongoing daily drug abuse  Dead

Admitted to MMT

Gunne & Gronbladh, 1981
Retention-enhancing

- Opioid dependent patients stay in methadone treatment significantly longer than outpatient psychosocial
  - In King County study, retention for primary opioid dependent patients at 90 days in psychosocial was 45%; in MMT it was 78%
- Longer retention in treatment is associated with improved treatment outcomes.
Drug Use and Length of Time in Methadone Treatment

Evergreen Treatment Services - 3/09

% of Time Cohort with a positive U.A. during month

- Red: < 90 days
- Green: 91 - 180 days
- Orange: 181 days - 1 year
- Yellow: 1 - 2 years
- Pink: > 2 years

57.4% of the cohort used drugs within the first 90 days, 42.9% used drugs between 91 and 180 days, 33.8% used drugs between 181 days and 1 year, 26.5% used drugs between 1 and 2 years, and 16.4% used drugs after 2 years.
Effectiveness:

Effect Size Matters

Most behavioral addiction treatment interventions have an effect size (d) of 0.2-0.4 (moderate):

- Recent meta-analysis described effect size for MMT of 0.90 for retention, 0.61 for opioid abuse and 0.35 for reduction of criminality (Johansson, Berglund & Lindgren, 2007)

- Another recent meta-analysis found that there was inadequate evidence to prove the effectiveness of psychosocial interventions alone for the treatment of opioid dependence or that they are superior to any other type of treatment. (Mayet, et. al. Cochrane Review 2004)
Review of Psychosocial Treatments

In a 2010 Cochrane Collaboration Review (Cochrane Library, 2010, issue 1):

5 trials, 389 participants studying Contingency Management, Brief Reinforcement Based Intensive Outpatient Therapy coupled with Contingency Management, Cue Exposure therapy, Alternative Program for Methadone Maintenance Treatment Program Drop-outs, and Enhanced Outreach-Counseling Program; all studied against a control condition.

Results: Some early differences. By 1- and 3- month followup, none were better than control.

“Evidence has low numbers and is heterogenous.”

“At present psychosocial treatments alone are not adequately proved treatment modalities or superior to any other type of treatment.”
The Effects of Methadone Treatment on Crime Days

Adapted from: Ball & Ross, 1991.

n= 617

70.8% Decline in Crime Days 94%

Years in Methadone Treatment

Crime Days Per Year

PreTx 0.33 1 2 3 4 5 6+
Methadone Treatment For Opiate Addiction Lowers Health Care Costs

Source: State of Washington, DSHS, Research & Data Analysis Division, Report 4.49fs, June, 2004
Characteristics of Successful Methadone Treatment Programs

✓ Adequate Dosing Policies
   ✦ Average Dose Between 60 & 120mg.
✓ Comprehensive Services
✓ Well-trained & Stable Staff
✓ Individualized Treatment
✓ Coordinated Services
   ✦ Medical, Counseling, & Administration

Adapted from: Ball & Ross, 1991.
BUPRENORPHINE

- Partial agonist at Mu-opiate receptor
  - Less subjective “high”
  - “Ceiling effect”
- Once-a-day dosing
- Sublingual administration
  - Compounded with naloxone (Suboxone®) which will precipitate abrupt withdrawal if injected
- Treatment outcomes approximately equivalent to methadone; retention in treatment seems to be less
BUPRENORPHINE

- In an OTP setting both medications equal at suppressing illicit opioid use.
- Initiating buprenorphine then switching poor responders to methadone is feasible.
- We need better predictors of who responds best to which medication.
- Office-based settings provide a less stigmatizing and much more convenient source of care but often suffer from much less structure.
- Diversion of buprenorphine can be a problem from some office settings.
Physician-Based vs. Clinic-Based Treatment

- In clinic-based treatment there are many rules (observed dosing, counseling, urinalysis), imposed by regulatory authorities (federal & state); physician-based treatment has no such rules, only guidelines.
- Physician-based perhaps more geographically available and certainly more private.
Naltrexone

- Pure opioid antagonist: blocks euphoric high of opioids.
- No psychotropic or reinforcing effects.
- Nonaddicting, with no withdrawal symptoms on cessation.
- No increased tolerance to opioid antagonist actions.
- Absence of serious adverse reactions or toxicity, even in long-term use.
- Essentially no abuse potential.
- No “black market” resale value or diversion potential.
- Easily available, may be administered in office settings.
Naltrexone Candidates

- Former opioid-addicted persons who have been drug-free and wish to remain abstinent (rehab centers, therapeutic communities, prison).
- Highly motivated persons in structured settings: Professionals - healthcare workers, lawyers, pilots, business, military people facing loss of employment or licensure due to opioid abuse.
- Opioid-dependent persons who prefer an alternative to methadone or buprenorphine.
- Individuals who have been drug-free but recently relapsed on opioids.
- Persons currently abstinent but concerned about possible stress-induced relapse.
- Younger persons at early stages of opioid dependence, especially if in structured environment.
Naltrexone Effectiveness

- Patients must be detoxified prior to initiation.
- If you don’t take it, it doesn’t work. This is particularly a problem with the oral form.
- Now available in a long-acting (monthly) injectable formulation that is expensive, but available for some.
- In a recent 24 wk RCT funded by the manufacturer, 36% abstinence in XR-NTX group 24% in placebo group. Retention 53% at 6 months in XR-NTX group.
- Safety concerns with relapse because of loss of tolerance.
- Even in the best studies, retention rates are less than half of those using buprenorphine or methadone.
- There are no studies comparing its effectiveness to methadone or buprenorphine.
Resources

- TIP 43, Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs – [www.health.org](http://www.health.org)
- Addiction Treatment Forum: [www.atforum.com](http://www.atforum.com)
- Web sites:
  - [kap.samhsa.gov](http://kap.samhsa.gov) – CSAT’s Knowledge Application Program
  - [www.aatod.org](http://www.aatod.org) – AATOD
  - [buprenorphine.samhsa.gov/index.html](http://buprenorphine.samhsa.gov/index.html) – CSAT’s buprenorphine Web site, including FAQs
  - [www.drugpolicy.org](http://www.drugpolicy.org) – Drug Policy Alliance
    - About Methadone
Spacer Slide
What about medication-free inpatient treatment or therapeutic communities?

Prospective study (prison setting) of 276 drug users admitted to 11 MFIT/TCs in Norway with a mean observation period of 8 years:

36 deaths, 24 overdoses. 7 violent deaths (including traffic accidents), and 5 unknown.

During first 4 weeks post discharge 6 persons died (excess mortality ratio of 15.7). All 6 were dropouts.

Deaths after discharge by time in inpatient treatment, risk per 100 person-years (N=276, n=36).

<table>
<thead>
<tr>
<th>Time in Tx</th>
<th>Number</th>
<th>Deaths</th>
<th>Years at risk</th>
<th>Risk of Death</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 1/2 yr.</td>
<td>169</td>
<td>25</td>
<td>1161.2</td>
<td>2.4</td>
<td>1.6-3.5</td>
</tr>
<tr>
<td>1/2 - 1 yr.</td>
<td>31</td>
<td>5</td>
<td>176.6</td>
<td>2.8</td>
<td>1.2-6.8</td>
</tr>
<tr>
<td>1 - 1.5 yr.</td>
<td>20</td>
<td>3</td>
<td>97.2</td>
<td>3.1</td>
<td>1.0-9.6</td>
</tr>
<tr>
<td>1.5-2 yr.</td>
<td>34</td>
<td>3</td>
<td>157.4</td>
<td>1.9</td>
<td>0.6-5.9</td>
</tr>
<tr>
<td>&gt; 2 yr.</td>
<td>22</td>
<td>0</td>
<td>101.7</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

What about medication-free inpatient treatment or therapeutic communities?

Deaths by time after discharge from inpatient treatment, risk per 100 person-years (n=36).

<table>
<thead>
<tr>
<th>Time after d/c</th>
<th>Deaths</th>
<th>Years at Risk</th>
<th>Risk of Death</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks</td>
<td>6</td>
<td>20.1</td>
<td>29.9</td>
<td>13.4-66.5</td>
</tr>
<tr>
<td>5 wks - 1/2 year</td>
<td>2</td>
<td>113.8</td>
<td>1.7</td>
<td>0.4-7.0</td>
</tr>
<tr>
<td>1/2 yr. - 1 yr.</td>
<td>2</td>
<td>133.5</td>
<td>1.5</td>
<td>0.4-6.0</td>
</tr>
<tr>
<td>Second year</td>
<td>7</td>
<td>263.4</td>
<td>2.7</td>
<td>1.3-5.6</td>
</tr>
<tr>
<td>Third year</td>
<td>5</td>
<td>256.3</td>
<td>2.0</td>
<td>0.8-4.7</td>
</tr>
<tr>
<td>Fourth year</td>
<td>7</td>
<td>250.6</td>
<td>2.8</td>
<td>1.3-5.9</td>
</tr>
<tr>
<td>Fifth Year</td>
<td>5</td>
<td>226.8</td>
<td>2.2</td>
<td>0.9-5.3</td>
</tr>
<tr>
<td>Sixth year +</td>
<td>2</td>
<td>329.0</td>
<td>0.6</td>
<td>0.2-2.4</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>1594.1</td>
<td>2.1</td>
<td>1.5-3.0</td>
</tr>
</tbody>
</table>