Opioid Agonist Therapy: The Duration Dilemma

Edwin A. Salsitz, M.D., FASAM
Mount Sinai Beth Israel
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Presenter Disclosures

• Edwin A. Salsitz, M.D. has no financial relationships with an ACCME defined commercial interest.

The contents of this activity may include discussion of off label or investigational drug uses. The faculty is aware that is their responsibility to disclose this information.

OUTLINE

• History and Evolution of Opioid Agonist Therapy (OAT)
• Evidence of Effectiveness of Maintenance
• Safety Issues
• Methadone Medical Maintenance (OBOT)
• Stigma Issues
• Barriers to Long Term Maintenance
• Conclusions
• Discussion
Treatment of Opioid Addiction

- Medication Assisted: Therapy, Treatment, Recovery
- Opioid Full/Partial Agonist Therapy (OAT): Methadone, Buprenorphine, (LAAM)
- Opioid Antagonist Therapy: Naltrexone Tablets and Depot I.M. Injection
- Medication Plus Psychosocial--Optimal
- Drug Free Recovery-“Abstinence Based”
- Mutual Help, CBT, DBT, MI, etc.

MEDICATION ASSISTED ADDICTION TREATMENT

“All Treatments Work For Some People/Patients”
“No One Treatment Works for All People/Patients”

Alan I. Leshner, Ph.D
Former Director NIDA

MEDICATION ASSISTED ADDICTION TREATMENT

For Emphasis and Clarity,

Please Allow Me to Repeat:
MEDICATION ASSISTED ADDICTION TREATMENT

“All Treatments Work For Some People/Patients”
“No One Treatment Works for All People/Patients”

Alan I. Leshner, Ph.D
Former Director NIDA

My Treatment “Bias”

AGONIST

ANTAGONIST

Webinars; PCSS-MAT, PCSS-O

- Drs. Bisaga and Sullivan: Naltrexone, PCSS-MAT 7/21/14, 1/13/15
- Dr. David Fiellin: Buprenorphine, PCSS-O 12/15/14
- Dr. Judith Martin: Methadone, PCSS-O 1/21/15
- Dr. Kevin Sevarino: Neuroadaptations to Opioids, PCSS-MAT 10/9/14
- Dr. Daniel Alford: Managing Acute and Chronic Pain in Patients Maintained on OAT, PCSS-MAT 8/12/14
George Santayana 1863-1952

“Those who do not remember the past are condemned to repeat it.”

OPIOID AGONIST THERAPY (OAT)

The Lexington Narcotic Farm

The first facility opened on May 25, 1935, outside Lexington, Ky. The 1,050-acre site included a farm and dairy, working on which was considered therapeutic for patients. Morphine and methadone for w/d Rx. With the increased availability of state and local drug abuse treatment programs, The hospital was closed in February 1974.

Drs. Kolb, Himmelbach, Wikler, Jaffe, Kleber, Vaillant
JAMA. 1965;193(8):646-650

A Medical Treatment for Diacetylmorphine (Heroin) Addiction

A group of 22 patients, pregnant related to their behavioral phenomena, 12 patients, who had been addicted to heroin for 5 to 10 years, and 11 patients, who had been addicted to heroin for 10 to 20 years, were treated with methadone. The results of the treatment were evaluated using the criteria of withdrawal and craving for heroin. The patients were observed for 24 to 36 months post-treatment. The results showed a significant decrease in the craving for heroin and a significant decrease in the withdrawal symptoms. The patients were able to maintain their employment and relationships with family and friends. The treatment was well tolerated and had no significant side effects.

Commentary by Herbert D. Kleber, MD

Initial Publication

JAMA. 2008;300(19):2303-2305

Thousands of Lives Saved But Still Controversial

Distribution of Opioid Treatment Programs (OTPs) 2002

Copyright 2002

SAMHSA/CSAT
“The Effectiveness Of Methadone Maintenance Treatment,” Ball and Ross, 1991

Comprehensive Study of 6 Methadone Clinics in NYC, Philadelphia, and Baltimore
Objective: “Open the Black Box of Methadone Maintenance Treatment”
N=617 patients over 7 Years

Recent Heroin Use by Current Methadone Dose

Retention in Treatment Relative to Dose
Relative Risk of Leaving Treatment
Adapted from Caplehorn & Bell
Conclusions:

1. Inform the public that dependence is a medical disorder that can be effectively treated with significant benefits for the patient and society.

Expand Access to MMT:

CJS
Education of Providers
Regulations
Funding
Paternity with all medical/psych disorders
Minority Involvement

DATA 2000: Buprenorphine

- Major Paradigm Shift: OBOT vs MMTP
- Mechanism of Action: Similar to methadone
- Partial Agonist: Safety Implications
- 12 years of use in USA
- Now, more patients treated with Bupe than methadone
- Some of the same issues developing:
  1. Diversion, Misuse, Abuse
  2. Dosage
  3. Duration
  4. Other Drug Use Disorders
  5. Access
  6. Insurance Coverage, Prior Authorizations
Methadone Maintenance vs 180-Day Psychosocially Enriched Detoxification for Treatment of Opioid Dependence

Objective: To compare outcomes of patients with opioid dependence treated with methadone maintenance treatment, a pharmacologically assisted withdrawal. Patients: Randomized controlled trial conducted from May 1998 to April 1999. Setting: Research site in an inpatient drug treatment service. Methods: 156 patients (mean age, 37 years; predominantly male). Results: 20% mortality in placebo group. UTS indicate: Ugly Teeth Score.
POATS Study

Buprenorphine Maintenance vs Taper
Prescription Opioid Use Disorder

Methadone: Back to the Future

The Lesson - Sunday 8 September 1979

Results: Completeion of 14 week trial: taper 11% vs maintenance 66%

Mean percentage of urine negative for opioids: taper 35% vs maintenance 53%

Fiellin DA et al. JAMA Intern Med 2014
**Buprenorphine: Recurrent Relapse**

30 yo male. Buprenorphine was effective. Significant psychosocial problems, including high stress job, and many co-workers misusing prescription oxycodone. Unable or unwilling to access counseling, and dispute with wife over maintenance paradigm. Advised to return for treatment. Lost to F/U.

**Buprenorphine: Dosage Issue**

Drug and Alcohol Dependence, 144, 2014

**MesoLimbic Dopaminergic Circuit**

Pleasure/Reward Center

H2O, Food, Sex, Parenting, Social

E. Gardner
From these data, we conclude that polydrug abusers in MMT have 31P-MRS results consistent with abnormal brain metabolism and phospholipid balance. The nearly normal metabolite profile in long-term MMT subjects suggests that prolonged MMT may be associated with improved neurochemistry.
Methadone: Effectiveness/MOA

Figure 1. Activation Maps of Brain MRI Response to Heroin-Related Stimuli in Methadone Maintenance Patients Before and After Daily Methadone Dose.  
Am J Psychiatry 2008; 165:390-394

Duration: Potential “Pleiotropic” Benefits

Gavin Bart MD, FACP, FASAM  

Prevalence of HIV-1 (AIDS Virus)  
Infection in Intravenous Drug Users  

- 50 – 60% Untreated, street heroin addicts: Positive for HIV-1 antibody  
- 9% Methadone maintained since 1978 (beginning of AIDS epidemic): less than 10% positive for HIV-1 antibody

Kreek, 1984; Des Jarlais et al., 1984; 1989
581 Male Heroin Addicts Followed for 33yrs


- California cohort of heroin addicted males-CJS
- After 15 years of abstinence, 25% relapsed to heroin
- Participation rates in methadone maintenance were <10% in any given year

Relapses

- May be delayed and gradual
- ODs and OD death, e.g., fentanyl contamination
- Relationships
- Employment
- Child Custody
- Criminal Justice System
- New Infectious Agent
- Shame and guilt
- Etc.
As compared to active IV heroin users the methadone patients gained weight, and had less sexual dysfunction. Chronic liver disease was common, and antedated methadone treatment. “No clusters of unusual medical complications were observed.” *(EKGs not done)*

**OAT Duration: Safety**

- Avoid OD: Induction → Methadone Deaths → Pain Rx
- Drug/Drug Interactions: M>B
- Constipation
- Sweating
- Secondary Hypogonadism; ?M>B
- QTc Prolongation: M
- Other: Nausea, arousal, sedation, etc.
- No Organ Damage: Compare to Alcohol, Cocaine and Tobacco
- “Rots Teeth and Bones.” An enduring myth
Medical Maintenance

Admission Criteria

• At least 4 years in MMTP
• Negative urines for last 3 years
• Working/School etc.
• Adequate income for fees
• Recommendation from clinic
• Not in military reserves
• Stable and safe storage environment

Medical Maintenance

Procedures

• Patient given 28 day supply of methadone, by MD, in disket/tablet form, every 4 weeks.
• Medication prepared by hospital pharmacy in usual Rx type bottle and label
• Routine urine toxicology
• Patient returns before “run out” date
• Primary care provided

Medical Maintenance
Medical Maintenance MMTP/Medical Maintenance N=122 Years (%)

- MMTP
  - 5-10 yrs: 10%
  - 10-20 yrs: 44%
  - 20-30 yrs: 45%
  - 30-40 yrs: 18%

- Medical Maintenance
  - 5-10 yrs: 3%
  - 10-15 yrs: 22%
  - 15-20 yrs: 45%
  - 20-25 yrs: 20%
  - 25-33 yrs: 4%

Medical Maintenance Demographics: N=122

- Age
  - 18 yrs: 3%
  - 29 yrs: 10%
  - 39 yrs: 79

- Race
  - Caucasian: 29%
  - Latino: 10
  - African American: 14
  - Asian: 15

- Gender
  - Female: 39
  - Male: 63

Medical Maintenance: Dose N=122

- Average Dose = 68mg
- Range: 5mg–210mg

- 5-10mg: 2 (1.5%)
- 10-30mg: 17 (14%)
- 30-60mg: 41 (34%)
- 60-90mg: 37 (30%)
- 90-120mg: 15 (12%)
- 120-150mg: 18 (14%)
- 150-210mg: 2 (1.5%)
Medical Maintenance
1983 - Present

347 = Total Enrolled

Withdrawn: 25 (7.5%)
MMT/DISCH: 44 (13%)
Deaths: 79 (22%)
Active: 122 (35%)

Deaths
82 (22%)

<table>
<thead>
<tr>
<th># of Patients</th>
<th>Cause</th>
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<tr>
<td>31</td>
<td>Tobacco</td>
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<tr>
<td>19</td>
<td>Hepatitis C</td>
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<tr>
<td>5</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>4</td>
<td>Medical</td>
</tr>
<tr>
<td>1</td>
<td>Old Age</td>
</tr>
<tr>
<td>2</td>
<td>Homicide/Suicide</td>
</tr>
<tr>
<td>1</td>
<td>Prostate Cancer</td>
</tr>
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<td>1</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>1</td>
<td>Diabetes</td>
</tr>
<tr>
<td>1</td>
<td>Ovarian Cancer</td>
</tr>
</tbody>
</table>

Deaths: 1 Tobacco 1 Hep C

Methadone Medical Maintenance

Methadone Saved My Life
"I Never Thought I'd Get To Be __ Yrs Old"
Occupations of OBOT OAT Patients

- Teacher
- Electrician
- Plumber
- Social Worker
- Psychologist
- Chauffer
- Computer IT
- Drug Counselor
- Accountant
- Retail Manager
- Home Security Systems
- Restaurateur
- Food Dept Manager
- Movie Editing
- Student [PhD]
- HVAC Tech.
- Stamps
- School Principal
- Artist
- Advertising VP

* Safety Sensitive—Employer’s OK

Methadone → Buprenorphine

OAT: Stigma
STIGMA--METHADONE

- “My Wife’s Opinion Is that Methadone Maintenance Treatment Is As Close To Evil As You Can Get, Without Killing Someone.”

A “successful” methadone patient quoting his wife’s attitude toward methadone maintenance treatment.

OAT: Stigma

OAT: Stigma
OAT: Stigma

Quotation of the Day

A methadone patient is monitored more closely than a paroled murderer.

Dr. Edwin A. Salsitz, of Beth Israel Hospital in New York City.

OAT Barriers: Terminology

OAT Barriers: Terminology

OAT Barriers: Terminology
Duration Barriers: Terminology

- “Substitution Treatment” “OST”
- Standard terminology in Europe and Australia
- ?? Accurate ?? Helpful ?? Harmful
- “Aren’t you just substituting one drug or addiction for another??”
- Why not just call it “Treatment for Opioid Use Disorder?”

OAT: Terminology

Physical Dependence Does Not Necessarily Equal Addiction

Duration Barriers: Pregnancy

Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure

MOTHER Study, NEJM 2010
**Duration Barriers: Policy**

**Mayor Steps Up His Criticism Of Methadone**

One day after declaring his plan to use 2,000 heroin addicts of methadone at his hospital, Mayor Randolph W. Landry rejected his attacks on methadone treatment providers yesterday, saying there is no evidence that drug users instead of public service agencies care. He added: "The city's response to heroin addiction needs to be more like the treatment we offer."

**TURNDOWN RUDY PUTS $5M IN METHADONE CLINICS**

**CJS Barriers: Good News**

**SAMHSA Bans Drug Court Grantee from Ordering Patients off MAT**

"A great announcement issued by the Substance Abuse and Mental Health Services Administration (SAMHSA) last month to allow drug court participants an important new condition: drug court funds. This would no longer be allowed to prevent offenders to stop being prescribed to treat opioid use disorders. Many drug court judges have opposed reductions or the treatment of patients in drug court settings. The announcement is a significant step forward in the treatment of opioid use disorders."
Implication for Addiction Pharmacotherapy?

"Ass Backwards" Paradigm

- The patients who have responded well to OAT, are the patients who are urged to "get off" their medication. They are often not rewarded with the Federal and State regulations for which they are entitled.
- The patients doing well, feel the most stigmatized.
- Protracted Abstinence Syndrome
  Both Physiologic (RR, T) and Psychological s/sx
- No other chronic medical disease is viewed this way by providers—asthma, hypertension, diabetes, depression
- No acceptance by insurers of long term maintenance, no longer requiring weekly UDTs or documented counseling

What If There Were a Methadone or Buprenorphine for:

- Methamphetamine and Cocaine Addiction?
- Alcohol Addiction?
- Tobacco Addiction?
- Benzodiazepine Addiction?
- Food Addiction?
- Pathological Gambling?
Final Comments: OAT Duration

- The scientific evidence base, and 50 years of clinical experience overwhelmingly support maintenance in the OAT treatment paradigm.
- The goal of OAT maintenance is not to see how fast a patient can “get off” medication.
- The goal is normalization and stabilization of the brain, establishing durable and safe hedonic tone, and functioning at maximal potential at home and at work.
- Like most chronic medical therapies, the medication only works, when it is taken.
- “If It Ain’t Broke, Why Fix It?”

MEDICATION ASSISTED ADDICTION TREATMENT

“All Treatments Work For Some People/Patients”
“No One Treatment Works for All People/Patients”

If your treatment is working, keep doing the treatment
If your treatment is not working, change your treatment!!

Why Is This So Important?

Actor Philip Seymour Hoffman, who was found dead February 2, 2014 on the bathroom floor of his New York apartment with a syringe in his left arm, died of acute mixed drug intoxication, including heroin, cocaine, benzodiazepines and amphetamine, the New York medical examiner’s office said Friday.
Vincent Dole, Albert Lasker Award
JAMA, 1988
“27 Years Ago

• It is postulated that the high rate of relapse of addicts after
detoxification from heroin use is due to persistent derangement of
the endogenous ligand-narcotic receptor system and that
methadone in an adequate daily dose compensates for this
defect. Some patients with long histories of heroin
use and subsequent rehabilitation on a
maintenance program do well when the treatment
is terminated. The majority, unfortunately,
experience a return of symptoms after
maintenance is stopped. The treatment, therefore,
is corrective but not curative for severely addicted
persons. A major challenge for future research is to identify the
specific defect in receptor function and to repair it. Meanwhile,
methadone maintenance provides a safe and
effective way to normalize the function of
otherwise intractable narcotic addicted patients.”

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