Opioid Substitution Therapy – Pro/Con Debate
EAPCCT 2016 Madrid, Spain

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Disclosures:

No financial disclosures to make
Pro side of medication assisted treatment

“I medicate first and ask questions later.”
1960’s epidemic of heroin OD in New York, US

• 1960’s experienced a pronounced increase in heroin-related overdoses primarily in New York City and other urban centers
  – Heroin overdose is #1 cause of death ages 15-35
  – Hepatitis C transmission increasing
  – Criminality associated with addiction rising

• Panic in Needle Park -Life 1965
  – Photo essay –Bill Eppridge

• Panic in Needle Park.”

In response to OD epidemic - Dole and Nyswander

• Rockefeller University
• A internist specializing in metabolic disorders.
• A psychiatrist working with NY street “addicts”
• Theory -- the only way to account for the poor treatment outcome (relapse) was that narcotic addiction is a metabolic disorder…

Courtesy Dr. Vincent Dole
Dr. Vincent Dole and Dr. Marie Nyswander
Methadone Pioneers
The metabolic theory of addiction

• Dole hypothesized that there was a metabolic deficiency caused by repetitive use of short-acting opioids (e.g. heroin).

• Relapse occurred because heroin made up for this deficiency, or ‘imbalance’ in the addicted brain.

• *Endogenous opioids (endorphins) discovered and chemically elucidated years later.*
• SNP & other genetic variation


Opioid receptor polymorphism A118G associated with clinical severity in a drug overdose population.

Manini AF, Jacobs MM, Vlahov D, Hurd YL.

• Opioids modulate a variety of disease states


OPRM1 rs1799971 polymorphism and opioid dependence: evidence from a meta-analysis.

Haerian BS, Haerian MS.

Author information


Buprenorphine for the treatment of depression?

Balon R1.

Psychotherapeutic Benefits of Opioid Agonist Therapy

Peter L. Tenore, MD, FASAM

ABSTRACT. Opioids have been used for centuries to treat a variety of psychiatric conditions with much success. The so-called “opium cure” lost popularity in the early 1950s with the development of non-addictive tri cyclic antidepressants and monoamine oxidase inhibitors. Nonetheless, recent literature supports the potent role of methadone, buprenorphine, tramadol, morphine, and other opioids as effective, durable, and rapid therapeutic agents for anxiety and depression. This article reviews the medical literature on the treatment of psychiatric disorders with opioids (notably, methadone and buprenorphine) in both the non-opioid-dependent population and the opioid-dependent methadone maintenance population. The most recent neurotransmitter theories on the origin of depression and anxiety will be reviewed, including current information on the role of serotonin, N-Methyl-D-Aspartate, glutamate, cortisol, catecholamine, and dopamine in psychiatric disorders. The observation that methadone maintenance patients with co-existing psychiatric morbidity (so called dual diagnosis patients) require substantially higher methadone dosages by between 20% and 50% will be explored and qualified. The role of methadone and other opioids as beneficial psychiatric medications that are independent of their drug abuse mitigating properties will be discussed. The mechanisms by which methadone and other opioids can favorably modulate the neurotransmitter systems controlling mood will also be discussed.

Journal of Addictive Diseases, Vol.27(3) 2008
A Medical Treatment for Diacetylmorphine (Heroin) Addiction

A Clinical Trial With Methadone Hydrochloride

Vincent P. Dole, MD, and Marie Nyswander, MD

A group of 22 patients, previously addicted to diacetylmorphine (heroin), have been stabilized with oral methadone hydrochloride. This medication appears to have two useful effects: (1) relief of narcotic hunger, and (2) induction of sufficient tolerance to block the euphoric effect of an average illegal dose of diacetylmorphine. With this medication, and a comprehensive program of rehabilitation, patients have shown marked improvement; they have returned to school, obtained jobs, and have become reconciled with their families. Medical and psychometric tests have disclosed no signs of toxicity, apart from constipation. This treatment requires careful medical supervision and many social services. In our opinion, both the medication and the supporting program are essential.

JAMA Classics: Celebrating 125 Years Methadone Maintenance 4 Decades Later Thousands of Lives Saved But Still Controversial

Commentary by Herbert D. Kleber, MD

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

JAMA. 1965;193(8):646-650
## Maintenance Therapy of Ex-Addicts With Methadone Hydrochloride, Summary of First 15 Months (February 1964 to May 1965)

<table>
<thead>
<tr>
<th>Ethnic Group*</th>
<th>Age,† Years</th>
<th>Previous Treatments‡</th>
<th>Arrests</th>
<th>Education</th>
<th>Best Job.§</th>
<th>Military Service∥ Years</th>
<th>Time on Program, Months</th>
<th>D†</th>
<th>P‡</th>
<th>HS**</th>
<th>Present Activity</th>
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<td>E</td>
<td>16 22</td>
<td>F S M P</td>
<td></td>
<td>6 8th grade</td>
<td>Truck driver</td>
<td></td>
<td>15</td>
<td>150</td>
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<td>Odd jobs (few months each)</td>
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<td>15</td>
<td>180</td>
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<td>Cert</td>
<td>Horticulture school</td>
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<tr>
<td>P</td>
<td>21 32</td>
<td>2 4</td>
<td>14 2 years high school</td>
<td>Office clerk</td>
<td></td>
<td>10</td>
<td>100</td>
<td>1a</td>
<td>Cert</td>
<td>Employed (rehabilitation work)</td>
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<td>1 2 3 1</td>
<td>1 Graduated high school</td>
<td>Store manager</td>
<td>A 3</td>
<td>10</td>
<td>180</td>
<td>1a</td>
<td></td>
<td>Employed (usher, cashier in theater)</td>
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<tr>
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<td>80</td>
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<tr>
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<td>Head usher</td>
<td>A 3</td>
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<td>90</td>
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<td>Cert Army</td>
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<tr>
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<td>A 5</td>
<td>1½</td>
<td>130</td>
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<tr>
<td>P</td>
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<td>1</td>
<td>3 1 year high school</td>
<td>Paint sprayer</td>
<td></td>
<td>½</td>
<td>110</td>
<td>1</td>
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<td>4</td>
<td>9 2 years high school</td>
<td>Supervisor of shipping department</td>
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<td>100</td>
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<tr>
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<td>0 8th grade</td>
<td>Installing window screens</td>
<td></td>
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<tr>
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<td>2</td>
<td>2 2 years high school</td>
<td>Office clerk</td>
<td>M 3</td>
<td>3</td>
<td>70</td>
<td>2</td>
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<td>Welfare (seeking employment)</td>
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<tr>
<td>P</td>
<td>19 25</td>
<td>16</td>
<td>10 2 years high school</td>
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<td>110</td>
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<td>Employed (hospital record room)</td>
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<td>None</td>
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<td>2</td>
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<td>Vocational school (barber)</td>
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<td>1 2 3</td>
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<td>2</td>
<td>8 2 years high school</td>
<td>Construction laborer</td>
<td></td>
<td>1½</td>
<td>100</td>
<td>2</td>
<td>NS</td>
<td>Seeking employment</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>14 30</td>
<td>2</td>
<td>8 8th grade</td>
<td>Shipping clerk</td>
<td>AF 4</td>
<td>1½</td>
<td>10</td>
<td>2</td>
<td>Cert</td>
<td>Leather goods company interpreter</td>
<td></td>
</tr>
</tbody>
</table>
The Federal Narcotic Farm – Lexington Kentucky

• “Patients tilled the ground, harvested crops, milked cows, and raised pigs and female patients cooked, sewed, and laundered. Food was produced and cooked on site....”

• Goal was rehabilitation.

• Methadone first used for opioid detoxification 1950’s.

• Methadone was effective.

• >80% relapse after return to home city from the Farm.
Outcomes in Addictions Treatment

• Use of illicit drugs decreases
• Attendance in program
• Decreases in criminal activity
• Health improvement
• Normalization of function
• Lack of transmission of viral illness (HIV, HCV)
• Death rates decrease
Arrests for Men in MMT (O) vs controls (X)
MMT vs controls by arrests $X_{axis} = \text{LOS}$

- Methadone Maintenance Program Group
- Contrast Group from Detoxification Unit

**Period of Observation**

- Start in Program: n=473 (6%)
- 3-5 Months: n=353 (11%)
- 6-11 Months: n=326 (8%)
- 12-18 Months: n=185 (3%)
- 19-24 Months: n=101 (22%)
- 24+ Months: n=101 (22%)
Methadone maintenance (14 months) vs transition to abstinence

- Abstinence arm received methadone over 4 months then 2 month taper.
- Other cohort received stable dose x 14 months.
- Psychosocial support.

Methadone Maintenance vs 180-Day Psychosocially Enriched Detoxification for Treatment of Opioid Dependence
A Randomized Controlled Trial

Karen L. Sees, DO
Kevin L. Delucchi, PhD
Carmen Masson, PhD
Amy Rosen, PsyD
H. Westley Clark, MD
Helen Robillard, RN, MSN, MA
Peter Banys, MD
Sharon M. Hall, PhD

Context: Despite evidence that methadone maintenance treatment (MMT) is effective for opioid dependence, it remains a controversial therapy because of its indefinite provision of a dependence-producing medication.

Objective: To compare outcomes of patients with opioid dependence treated with MMT vs an alternative treatment, psychosocially enriched 180-day methadone-assisted detoxification.

Design: Randomized controlled trial conducted from May 1995 to April 1999.

Setting: Research clinic in an established drug treatment service.

Patients: Of 858 volunteers screened, 179 adults with diagnosed opioid dependence were randomized into the study; 154 completed 12 weeks of follow-up.

Interventions: Patients were randomized to MMT (n = 91), which required 2 hours of psychosocial therapy per week during the first 6 months; or detoxification (n = 88), which required 3 hours of psychosocial therapy per week, 14 education sessions, and 1 hour of cocaine group therapy, if appropriate, for 6 months, and 6 months of (non-methadone) aftercare services.

Main Outcome Measures: Treatment retention, heroin and cocaine abstinence (by self-report and monthly urinalysis), human immunodeficiency virus (HIV) risk behaviors (Risk of AIDS Behavior scale score), and function in 5 problem areas: employment, family, psychiatric, legal, and alcohol use (Addiction Severity Index), compared

In 1997, the most recent year for which data are available, treatment program admissions for opioid dependence surpassed admissions for cocaine abuse in the United States. As heroin use resurfaces, evaluation and improvement of the treatment of opioid abuse are increasingly urgent needs. Methadone maintenance treatment (MMT) has been
Methadone taper = illicit use and treatment drop outs

- Methadone taper after 2 months is the solid line.
- Methadone maintenance x 14 months is the hashed line.
Methadone taper = illicit opioid use

• 12 months of study.
• Initial decreases in illicit opioid use
• After taper begins heroin use returns

Medication normalizes
Opioid dependent patients given heroin cues

• A.) heroin-related video exposure = limbic response

• B.) After methadone activation is less

*Am J Psychiatry 2008; 165:390-394*
Methadone’s effect --stroke model

- Phosphocreatine – marker of bioenergetic status related to ATP & cAMP.
- Measured phosphomonoester and diester related to cell membrane integrity.
- Stroke model
  - Phosphocreatine decreases
  - Phosphomono/di esters rise

- Longer methadone maintenance more closely matched controls

• A.) brief methadone maint
• B.) longer (137 weeks) methadone maint
• C.) controls

Longer methadone maintenance more closely matched controls

• Kaufman M. Cerebral phosphorous metabolite levels in opiate dependent polydrug abusers in methadone maintenance. Psychiatry Research: Neuroimaging June 1999; 90(3): 143-152.
### Treatment vs addiction*

<table>
<thead>
<tr>
<th></th>
<th>Methadone and buprenorphine</th>
<th>Heroin or prescription opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Oral or sublingual</td>
<td>Intravenous, intranasal, oral</td>
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<tr>
<td><strong>Onset</strong></td>
<td>30-60 minutes</td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Long -24 hours</td>
<td>Short 4-6 hours</td>
</tr>
<tr>
<td><strong>Euphoria</strong></td>
<td>Not present with stabilization</td>
<td>Present (rapid up/down) then wanes</td>
</tr>
</tbody>
</table>

*substitution therapy’ is a misnomer
Since 2002, buprenorphine, a partial opioid agonist, has been available in the United States as an office-based treatment for opioid dependence. Physicians who wish to prescribe the drug may undergo a training program and become certified through the Substance Abuse and Mental Health Services Administration (SAMHSA) to prescribe buprenorphine.

http://buprenorphine.samhsa.gov/
In the US OTPs are federally regulated.
Unevenly distributed some states only 1-2 clinics.
None in Dakotas, Wyoming or Montana.
In December of 2006, buprenorphine providers (SAMSHA certified) authorized to treat up to 100 patients at any one time.

- A.) Qualified under DATA 2000
- B.) At least one year since initial qualifications
- C.) Must certify their capacity for counseling and referral services
Dose Response – partial agonist and ‘ceiling effect’

- Agonist
- Partial Agonist
- Agonist & Antagonist
- Ceiling effect with partial agonist
- Antagonist
Buprenorphine and the mu receptor

- Controls – mu activation

- At 16 mg of buprenorphine nearly all of the mu receptors are bound

Buprenorphine blocks opioid full mu agonist binding
Buprenorphine maintenance vs taper

- Buprenorphine vs placebo
- 75% retention in treatment
- 75% urine drug tests negative for illicit drugs.
- Mortality 20% in placebo group.

Buprenorphine Maintenance vs Detox

75% retention
75% UTS negative
20% mortality in placebo group

Evidence of buprenorphine effectiveness

- Drug-related and sex-related risk behaviors in 166 buprenorphine-treated individuals at baseline, 12 weeks, and 24 weeks

- Reports of intravenous drug use among the individuals declined over time, from 37% at baseline to 12% at 12 weeks, to 7% at 24 weeks.

Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial

Evgeny Krupitsky, Edward V. Nunes, Walter Long, Arthur Herman, Donald G. Costerlund, Bernard L. Sherman

Summary
Background Opioid dependence is associated with low rates of treatment-seeking, poor adherence to treatment, frequent relapse, and major societal consequences. We aimed to assess the efficacy, safety, and patient-reported outcomes of an injectable, once monthly extended-release formulation of the opioid antagonist naltrexone (XR-NTX) for treatment of patients with opioid dependence after detoxification.

Methods We did a double-blind, placebo-controlled, randomised, 24-week trial of patients with opioid dependence disorder. Patients aged 18 years or over who had 30 days or less of ingoing detoxification and 7 days or more off all opioids were enrolled at 13 clinical sites in Russia. We randomly assigned patients (1:1) to either 380 mg XR-NTX or placebo by an interactive voice response system, stratified by site and gender in a centralised, permuted-block method. Participants also received 12 biweekly counselling sessions. Participants, investigators, staff, and the sponsor were masked to treatment allocation. The primary endpoint was the response profile for confirmed abstinence during weeks 5–24, assessed by urine drug tests and self-report of nonuse. Secondary endpoints were self-reported opioid-free days, opioid craving scores, number of days of retention, and relapse to any form of fearful dependence. Analyses were by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00679438.

Findings Between July 3, 2008, and Oct 5, 2009, 250 patients were randomly assigned to XR-NTX (n=125) or placebo (n=125). The median proportion of weeks of confirmed abstinence was 80.0% (95% CI 69.0–92.4) in the XR-NTX group compared with 35.0% (CI 63–62.4) in the placebo group (p=0.0002). Patients in the XR-NTX group self-reported a median of 99.2% (range 80.1–99.4) opioid-free days compared with 60.4% (46.2–78.3) for the placebo group (p=0.0004). The mean change in craving was −10.1 (95% CI −12.3 to −7.8) in the XR-NTX group compared with 0.7 (3.1 to 4.1) in the placebo group (p=0.0004). Median retention was over 168 days in the XR-NTX group compared with 96 days (95% CI 63.1–165) in the placebo group (p=0.004). Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the XR-NTX group (p=0.0003). XR-NTX was well tolerated. Two patients in each group discontinued owing to adverse events. No XR-NTX-treated patients died, overdosed, or discontinued owing to severe adverse events.


Opioid antagonist
Long-acting
Survival
Relapse 43% vs 64% (NNT = 5)
Opioid agonist effectiveness

- Reduction death rates (Grondblah, ‘90)
- Reduction IVDU (Ball & Ross, ‘91)
- Reduction crime days (Ball & Ross)
- Reduction rate of HIV seroconversion (Bourne, ‘88; Novick ‘90; Metzger ‘93)
- Reduction in relapse to IVDU (Ball & Ross)
- Improved employment, health, & social function
Methadone maintenance > 3 months

• Employment and school status increases

• Use of social supports decrease.
Prevalence HIV-1 in methadone vs untreated

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_
HIV transmission and IVDU

• In Eastern Europe and Central Asia, for example, the Joint United Nations Programme on HIV/AIDS estimates that more than 80% of all HIV infections are caused by contaminated injection equipment (http://www.unaids.org/en/PolicyAndPractice/KeyPopulations/InjectDrugUsers/).
• An addict who was law-abiding before admission to the program and who had no alcohol problem had a 95.8 percent chance of staying on the program two years.

• A patient with seven or more criminal convictions on his record before admission and no employment skill to market had only a 55.6 percent chance.

• Overrepresentation of poverty in maintenance programs
Medication Assisted Treatment - Factors

- Ed Salsitz, MD
Methadone stigma

$R\ (l)$-methadone--$\mu$ agonist
SM: You must be excited to see him when he comes back?
Mrs. Claus: By the time he stumbles in at 6AM, Chris has eaten roughly 2 Billion cookies, so he pukes for a solid day! She continues-
THEN HE SPENDS A WEEK IN A METHADONE CLINIC TO COME DOWN FROM THE SUGAR HIGH.

Aidy Bryant, Seth Meyers. SNL, 12/8/12
Comedy Central ‘Roast’ of Courtney Love

• “Courtney Love looks like the girl next door…..If you happen to live next door to a methadone clinic.”
U.S. Drug Enforcement Administrative Agent Joanne Masur, one of the last government witnesses in the case against Shinderman, took the stand Friday in U.S. District Court in Portland.

Masur, whose job is preventing the diversion of prescription drugs to the black market, said she consulted with Shinderman on at least two occasions. But she said she had no bias against him or his clients, although she said she may have referred to them as "dirt bags."

"That is a term I use," she said. "But it's not necessarily derogatory."

Portland Press Herald, 7/15/06
Buprenorphine stigma much less although…
Buprenorphine diversion

- CESAR fax
- Other sources

Vincent Dole on a ‘substitution’ for alcohol?

• “He [Bill W.] suggested that in my future research, I should look for an analogue of a medication that would relieve the alcoholic's sometimes irresistible craving and enable him to progress in AA toward social and emotional recovery.

Methadone Maintenance 4 Decades Later
Commentary, Herbert Kleber, M.D. JAMA, 2008
• Among Nobel Prizes and Lasker awards sits methadone maintenance.
Treatment flexibility

- Opioid Treatment Programs (OTPs) should offer choice/flexibility:
- Methadone
- Buprenorphine
- Injectable naltrexone

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
Summary

• “Substitution” medications (methadone, buprenorphine, naltrexone) for opiate addiction are effective.
• A variety of outcomes are enhanced.
• Increased retention and decreases in use reduce mortality and disease transmission.
• Maintenance improves social function, is associated with decreased drug use and improved quality of life.

Hazelden Introduces Antiaddiction Medications into Recovery for First Time
• Deaths from prescription opioid pain relievers

Source: National Center for Health Statistics, CDC Wonder
Thank you

• Ed Salsitz, MD
• Norm Wetterau, MD