Treatment Alternatives for Substance Use Disorders

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Disclosure

- The speaker has no conflict of interest, financial agreement, or working affiliation with any group or organization.
- This session will include discussion of unapproved or investigation uses of products or devices.

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Learning Objectives

- Understand Medication Assisted Treatment options for treatment of opioid use disorder
- Learn the medication options for relapse prevention in alcohol use disorder
- Understand the necessity for comprehensive treatment of substance use disorders.

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Medication Assisted Treatment for Opioid Use Disorder

- **Medication-Assisted Treatment (MAT)** is the use of medications, in combination with counseling and behavioral therapies, to provide a "whole-patient" approach to the treatment of substance use disorders. (SAMHSA)
- **Medication assisted Recovery (MAR)** is a transitional term to help the general public, recipients of health care services, and professional health care service providers understand that pharmacotherapy can be helpful in supporting recovery. (ASAM)
- **Medication Assisted Treatment (MAT)**, another variation on the concept of MAR, may involve pharmacotherapy alone. (ASAM)

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Medication Assisted Treatment for Opioid Use Disorder

- **Medication Assisted Treatment (MAT)** (cont.)…It is essential that addiction treatment and recovery approaches address the various aspects of biological, psychological, social and spiritual dimensions for optimum health and wellness. It is hoped that as the public and professionals recognize that recovery and treatment need to be holistic, appropriate pharmacotherapy would be well accepted as part of treatment and recovery, ***such that the terms MAR and MAT would be deemed unnecessary.*** (Italics added)

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Pharmacotherapy Options for OUD

- Methadone
- Buprenorphine
- Naltrexone
- Naloxone
- N.B. – The α-adrenergic agonist clonidine is not FDA approved for treatment of opioid withdrawal per se, but is widely accepted as a pharmacotherapy for opioid withdrawal.

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Goals of MAT

- Improve patient survival
- Increase retention in treatment
- Decrease illicit opiate use and other criminal activity among people with substance use disorders
- Increase patients' ability to gain and maintain employment
- Improve birth outcomes among women who have substance use disorders and are pregnant

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Methadone

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Methadone

August 23, 1965

A Medical Treatment for Diacetylmorphine (Heroin) AddictionA Clinical Trial With Methadone Hydrochloride

Vincent P. Dole, MD; Marie Nyswander, MD
Author Affiliations

From the Rockefeller Institute, and Manhattan General Division of Beth Israel Hospital, New York.

JAMA. 1965;193(8):646-650. doi:10.1001/jama.1965.03090080008002
Full Text

Abstract

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.

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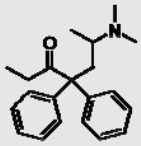
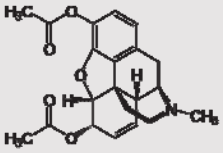
Methadone

- Full agonist at μ-opioid receptor



Methadone



Heroin

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Methadone

- Slow acting oral formulation
- Available through Opioid Treatment Programs (OTPs)
  - Methadone is the most highly regulated drug in existence
- Goals of methadone treatment
  - (1) To suppress opioid withdrawal.
  - (2) To block the effects of illicit opioids.
  - (3) To reduce opioid craving and stop or reduce the use of illicit opioids.
  - (4) To promote and facilitate patient engagement in recovery oriented activities including psychosocial intervention.

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Methadone

- Induction
  - Federal law limits first day's dose to 30mg.
- Dose escalation
  - No faster than 5 mg every 2nd day
    - Due to drug accumulation and AE risk
    - ***Start low; Go slow***
- Maintenance dose usually 60-120mg/day

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Methadone

- Split dosing may be necessary for rapid metabolizers
- Higher doses associated with QT prolongation and possible arrhythmia (Torsade de Pointes).
- Half-life 8-59 hours (or longer).
- Hepatic metabolism. Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, and CYP2C19 and to a lesser extent CYP2C9 and CYP2D6.
- Multiple drug interactions and pharmacogenomic determinants of effectiveness.

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Methadone

- Initial doses must be observed. Take-home doses earned by negative UDS and participation in programming.
- "A narcotic treatment program may permit a patient to reduce attendance at the narcotic treatment program for observation to one time weekly and receive no more than a 6-day take-home supply of medication when in the reasonable clinical judgment of the narcotic treatment physician, which is documented in the patient record." [28 PA Code 715.16]
- If weaning: reduce dose by 5-10% every 2 weeks.

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Buprenorphine

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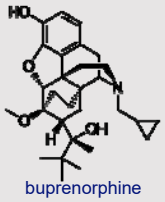
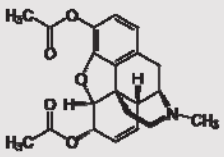
Buprenorphine

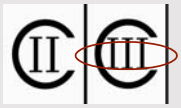
- Partial μ-opioid receptor agonist


buprenorphine

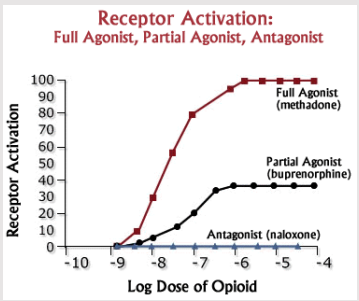

heroin

Buprenorphine

- High affinity for the MOR.
  - First dose usually >12 hours after short-acting opioid (heroin, fentanyl), >24 hours after other (or unknown) opioid.
  - May cause precipitated withdrawal.
  - Ceiling effect enhances "user friendliness'

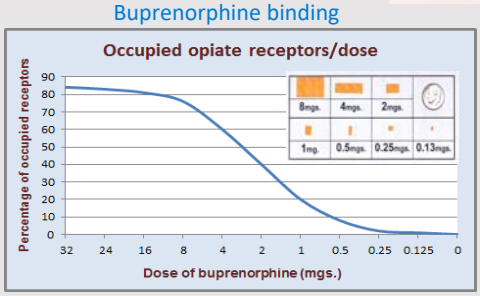


Full vs. Partial MOR Agonists



"Ceiling Effect"

Buprenorphine binding



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Buprenorphine

- Induction: 2-4mg day 1
  - Mono- or combination product (Suboxone)
    - Concern for misuse (IV administration)
- Increase dose 4-8mg/day to eliminate withdrawal symptoms and minimize cravings.
- Well tolerated.
  - Few adverse reactions
  - Few drug-drug interactions
  - Well-suited to out-patient management

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Buprenorphine

- Diversion is a concern
- Duration of treatment is not standardized
- Implantable formulation
  - Probuphine approved May 2016
  - Indicated for patients stable on sublingual buprenorphine
  - 80 mg per 4 implants.
  - Duration of action = 6 months, then remove.
  - Can be supplemented with s.l. formulation.

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Buprenorphine regulations

- To prescribe or dispense buprenorphine, providers must qualify and apply for a waiver under DATA 2000.
- Nurse practitioners (NPs) and physician assistants (PAs) can now train and apply to become DATA waivered practitioners.
- Prescribing limits: 30 patients year 1, 100 patients year 2, then some providers are eligible for 275 if criteria are met.

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Agonists Compared

Buprenorphine	Methadone
Partial mu agonist	Full mu agonist
36–48 hour half-life	24–36 hour half-life
Daily or alternate day dose frequency	Daily dose frequency
Less abuse potential	More abuse potential
Ceiling effect limits overdose risk	No protective overdose factors
Limited to mild–moderate dependence	More effective for severe dependence
Mild withdrawal symptoms	Moderate/severe protracted withdrawal
Tablet preparation—risk of injection	Oral liquid[a]—less risk of injection
	Tablet preparation is available
Moderately expensive	Inexpensive

[a]Methadone is sometimes prescribed as an intravenous preparation

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XR-Naltrexone

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XR-Naltrexone

- Vivitrol FDA approved 2010 for "the prevention of relapse to opioid dependence following opioid detoxification."
  - Was approved for AUD 2006
- μ-opioid receptor antagonist (No intrinsic activity at MOR)
- Reduces cravings for opioids and alcohol.
- Monthly IM injection, 380mg dose.
- No special training or licensure required.

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XR-Naltrexone-Adverse Reactions

- Hepatotoxicity – avoid in advanced liver disease
- Injection site reactions
- Depression and suicidality
- Precipitated withdrawal
- Potential opioid overdose risk
- Opioid ineffectiveness

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Candidates for XR-Naltrexone

- Those with occupational considerations, e.g. HCPs
- Failed agonist therapy or opposed to agonist therapy
- High motivation for abstinence-based recovery model
- Currently abstinent with high relapse risk
- Do not want physical dependence
- Stigma, regulations, family concerns
- ? Younger +/- shorter duration of use

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XR-Naltrexone

JAMA Psychiatry | Original Investigation

Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence
A Randomized Clinical Noninferiority Trial

Lars Tanum, MD, DMSci; Kristin Klemmetsby Solli, MSc; Zill-e-Huma Latif, MD; Jūratė Šaltytė Benth, PhD; Arild Opheim, MSc; Kamni Sharma-Haase, MD; Peter Krajci, MD, PhD; Nikolaj Kunøe, MSc, PhD

- First head to head study of XR-naltrexone vs. buprenorphine-naloxone published online October 18, 2017.

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Exhibit 1: Key Differences Between Medications Used To Treat Patients With Opioid Dependence

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

Sources: Adapted from [15, 18, 19]

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Pharmacotherapy for AUD

- Naltrexone (oral or IM) (ReVia, Vivitrol)
- Acamprosate (Campral)
- Topiramate (Topamax)
- Baclofen (Lioresal)
- Disulfiram (Antabuse)

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Naltrexone
(μ-opioid antagonist)

- Oral formulation
  - Once daily, dosage 50-200mg
  - Transient AEs - typically nausea, dysphoria x < 5 days
  - Witnessed dosing probably helpful
  - Duration of therapy – 6-12 months?
- IM formulation (Vivitrol)
  - 380mg IM every 4 weeks
  - Minimal G-I side effects
  - Ongoing therapy challenging

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Naltrexone for AUD

- The Sinclair Method
  - Take 50mg oral naltrexone prior to drinking alcohol on every drinking occasion
  - Diminishes the enjoyment of alcohol
  - Modeled on classical conditioning
  - 80% abstinence or moderate drinking at 4-6 months reported

Sinclair, J.D. Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. *Alcohol and Alcoholism*, 36: 2-10, 2001.

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Acamprosate (Campral)

- Partial NMDA agonist
- Not hepatically metabolized
- Minimal AEs reported; well tolerated
- Dose: 2x333mg tabs TID
- Dose adjust for renal impairment
- Neuroprotective effect?
- Decreases relapse to alcohol
- Effectiveness comparable to naltrexone

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Topiramate (Topamax)

- Na-channel blocker, NMDA antagonist, GABA enhancer
- Clinical trials show decrease alcohol intake and more days abstinent compared to placebo
- Not FDA approved for treatment of AUD
- Dose: 75-300mg/day in divided doses
- AEs include cognitive impairment

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Baclofen

- Skeletal muscle relaxant
- Mixed results in clinical trials
- Not FDA approved for AUD
- AEs include nausea, vertigo, drowsiness, abdominal pain
- More popular in EU than in US

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Disulfiram (Antabuse)

- Acetaldehyde dehydrogenase antagonist
- N,V, flushing, tachycardia, diaphoresis, anxiety ensue when ethanol is ingested
- Clinical trials show effectiveness in some studies, insufficient evidence in others
- Compliance is a limitation; ingestion under supervision most effective

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Duration of treatment

- Large individual variation
  - More is usually better!
- <90 days treatment is ineffective.
- Treatment outcomes are similar between those remanded to treatment and those who willingly engage, given a similar duration of participation.

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Duration of treatment

- Minimum of 12 months methadone maintenance appears to necessary for successful outcome.
- Duration of buprenorphine therapy for OUD:
  - ***UNKNOWN!***
- Duration of XR-naltrexone therapy for OUD:
  - ***UNKNOWN!***
- Duration of pharmacotherapy for AUD:
  - Minimum 6 months, probably 1 year is better.

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Common co-occurring disorders

- Chronic pain
- Mood Disorders
- ADHD
  - The psychostimulant problem
- Eating Disorders
- Other “process addictions.”
- Sleep Disorders

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Self Help/Peer Support

- 12-step programs
  - Pros:
    - Widely available
    - Free
    - Peer Credibility
  - Cons:
    - Unsupervised
    - Limited accountability
    - Highly opinionated!

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Comprehensive treatment

- Individual and group counseling
- Inpatient and residential treatment
- Intensive outpatient treatment
- Partial hospital programs
- Case or care management
- Medication
- Recovery support services
- 12-Step fellowship
- Peer supports

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Comprehensive treatment

- A person accessing treatment may not need to access every one of these components, but each plays an important role.
- These systems are embedded in a broader community and the support provided by various parts of that community also play an important role in supporting the recovery of people with substance use disorders.

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Comprehensive treatment

- Recovery Oriented Systems of Care
  - *"A ROSC is a coordinated network of community-based services and supports that is person-centered and builds on the strengths and resiliencies of individuals, families, and communities to achieve abstinence and improved health, wellness, and quality of life for those with or at risk of alcohol and drug problems."* - William White, PhD
  - This includes primary care medicine.

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Recovery Oriented Systems of Care

Where Do PCPs fit?

	Prevention	Intervention	Treatment	Post-Treatment
Examples of Recovery-Oriented Activities	• Early screening before onset • Collaborate with other systems, e.g., Child welfare, VA. • Stigma reduction activities • Refer to intervention treatment services	• Screening • Early intervention • Pre-treatment • Recovery support services • Outreach services	• Menu of treatment services • Recovery Support services • Alternative services and therapies • Prevention for families and siblings of individuals in treatment	• Continuing care • Recovery support services • Check-ups • Self-monitoring

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THANK YOU!
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