Medication-Assisted Treatment (MAT) for Opioid Use Disorders

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Learning Objectives

- Following this presentation, participants will be able to:
  1. Describe the medical model of addiction
  2. Distinguish between the 3 types of Medication-Assisted Treatment (MAT)
  3. List strategies to integrate MAT into existing services

Explanatory Models of Addiction

- Moral → wrong
- Spiritual → empty
- Psychological → impulse control
- Behavioral → habit
- Medical → disease
Medical model of addiction

- Sick person seeking wellness
- SUDs as chronic diseases
  - Biological basis
  - Identifiable signs and symptoms
  - Predictable course and outcome
- Treatment improves outcomes
- Lack of treatment may lead to morbidity and mortality

The Human Brain

- Most complex organ in the body
- Brain areas affected by drugs:
  - Brain stem: critical life functions such as heart rate, breathing, sleeping, etc.
  - Limbic system: reward circuit (ability to feel pleasure), perception of emotions, motivation, etc.
  - Cerebral cortex: sensory processing, thinking, planning, solving problems, making decisions, etc.

Drugs and Pleasure: Dopamine

- All drugs of abuse directly or indirectly flood the brain’s reward circuit with dopamine
- Dopamine has many functions
  - Regulation of movement, emotion, cognition, motivation and feelings of pleasure
- Overstimulation of the reward system produces euphoria and teaches the repetition of using behavior

Natural Rewards

Food
Water
Sex
Nurturing
Why are drugs more addictive than natural rewards?

- Amount of dopamine release
  - Depending on the drug of abuse, 2 to 10 times the amount of dopamine can be released vs. natural rewards
- Onset and duration of dopamine release
  - Can happen immediately or very quickly and can last much longer than natural rewards
- Drug abuse is something the brain learns to do very very well!

Long-term effects of drug use on the brain

- Brain must adjust to overwhelming surges in dopamine by producing less dopamine and fewer receptors
- As a result, the ability to experience any pleasure is reduced
- Now, drugs are needed in larger amounts (tolerance) to feel high
- Eventually, drugs no longer make the individual high and are needed “just to feel normal”

DSM-5 Substance Use Disorder: 11 Criteria

- Taking the substance in larger amounts or for longer than intended
- Persistent desire or unsuccessful efforts to cut down or control use
- Great deal of time spent getting, using, or recovering from use
- Craving, or a strong desire or urge to use recurrent use resulting in a failure to fulfill major role obligations at work, school, or home
- Continued use despite persistent social/interpersonal problems caused or exacerbated by use
- Giving up important social, occupational or recreational activities because of substance use
- Recurrent use in situations in which it is physically hazardous
- Use despite knowledge of physical or psychological problems caused or exacerbated by use
- **Tolerance**
- **Withdrawal**

**This criterion is not considered to be met for those taking stimulants, inhalants, or sedative-hypnotics medication solely under appropriate medical supervision.

Substance Use Disorder (cont’d)

- 2-3/11 criteria = Mild SUD
  - will be coded with the DSM-IV Substance Abuse codes
- 4-5/11 criteria = Moderate SUD
- 6+/11 criteria = Severe SUD
  - will be coded with DSM-IV Substance Dependence codes

Treatment Options for Opioid-Addicted Individuals

- Behavioral treatments educate patients about the conditioning process and teach relapse prevention strategies.
- Medications such as naltrexone, methadone and buprenorphine operate on the opioid receptors to block heroin effects or relieve craving.

Combining the two types of treatment enables patients to stop using opioids and return to more stable and productive lives.
Treatment Options for Individuals with Opioid Use Disorders

- Medically-assisted withdrawal (‘detox’)
- Long-term residential treatment
- Outpatient psychosocial treatment
- Behavioral therapies
- Medication-Assisted Treatment (MAT) (‘relapse prevention/maintenance’)

Medication-Assisted Treatment

- Naltrexone—antagonist
  - Blocks the effects of opioids
- Methadone—agonist
  - Morphine-like effect
- Buprenorphine—partial agonist
  - Maximum effect is less than a full agonist

Partial vs. Full Opioid Agonist

<table>
<thead>
<tr>
<th>Opiate Effect</th>
<th>Dose of Drug</th>
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<tbody>
<tr>
<td>Full Agonist (e.g., methadone)</td>
<td>death</td>
</tr>
<tr>
<td>Partial Agonist (e.g., buprenorphine)</td>
<td></td>
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<tr>
<td>Antagonist (e.g., Naltrexone)</td>
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Oral Naltrexone = REVIA

- Blocks opioid receptors that are involved in the rewarding effects of drinking & alcohol craving
- Blocks effect of opiates
  - May precipitate opiate withdrawal in opiate abusers
  - Works best if you don’t drink 4-7 days before taking
  - May decrease anxiety
- Risk for hepatotoxicity
  - Baseline liver enzymes: don’t start if AST/ALT are more than 3X the upper limit of normal
  - Monitor liver enzymes regularly

Injectable Naltrexone = VIVITROL

- Given as a deep muscle gluteal injection Q 4 weeks
- Dosage = 380 mg IM
- May have increased efficacy for men vs. women, and those abstinent when medication is initiated vs. those still drinking

Naltrexone

- Opiate receptor blocker has no abuse potential
- Non-compliance is the main barrier to success
  - Most useful for highly motivated patients w/ external circumstances ➔ impaired professionals, parolees, probationers, etc
- Concerns:
  - Expensive
  - Logistics of giving the injection
  - Efficacy largely unproven
  - Increased risk for overdose and perhaps suicide
CAUTION with Naltrexone

- When clients have had opiate receptors blocked for some time, their tolerance is “reset.”
- Returning to drug use at the same levels they were previously using [prior to blockade] puts the client at INCREASED RISK for OD/death due to lowered tolerance.
- This information needs to be shared with all clients.

MAT: Oral Naltrexone

- Six-month retention in treatment is between 20-30%.
- Percentage of those remaining in treatment after 8 weeks:
  - 68% of those receiving 384 mg
  - 60% of those receiving 192 mg
  - 39% of those receiving placebo
- Meta-analysis of several studies involving oral naltrexone did not support its use in opiate-dependent patients
  - (Comer SD et al., 2006)
  - (Minozzi S et al., 2006)

MAT: Oral Naltrexone

- Increased risk of OD & suicide?
- In a 12-month study of 81 patients treated with naltrexone, there were 13 overdoses (4 fatal, representing almost 5% of the study population)
- One of the fatalities and four of the non-fatalities were intentional overdoses.
- 11 out of the 13 patients who overdosed had completed or dropped out of treatment prior to the event

Miotto K et al. Drug Alcohol Dep 1997; 45: 131-134.

MAT: oral Naltrexone

- Longitudinal study of 12 trials (N=1,244) showed 3 times greater risk of overdose with those on naltrexone vs those on opioid agonists while in treatment.
- Naltrexone patients were 8 times more likely than opioid agonist patients to overdose after treatment


Naltrexone and overdose risk

- The ability of naltrexone to suppress the subjective effects of heroin outlasts the ability of the medication to suppress the physiologic response 1
- Supersensitivity to opioid agonists following chronic opioid antagonist treatment has been observed in laboratory studies 2


MAT: Depot-Naltrexone (Vivitrol®)

- FDA based approval on a 24-week study of 250 patients in Russia who were randomized to XR-NTX 380 mg (N=126) or placebo (N=124)
  - Primary outcome: confirmed abstinence in wks 5-24
  - 54% of patients didn’t finish the study
  - Only slightly more than a half of those in the naltrexone arm finished the full course
  - Primary outcome: 36% of XR-NTX group reported total abstinence vs 23% in placebo group (p<0.022)

Narcotic Farms:
- U.S. Public Health Service, authorized by Congress in 1929 to establish 2 narcotic farms
- Lexington Narcotic Farm opened May 25, 1935
- First intramural research branch of NIMH
- Closed in February, 1974


Patient population consisted of both involuntary inmates and “voluntary” patients
- Lengths of stay varied from 2-10 years for involuntary inmates
- Variable, often short, length of stay for voluntary patients prompted passage of the “Blue Grass” law that made “habitual narcotic use” a crime that carried a sentence of one year of treatment at Lexington


Narcotic Farms: Outcomes
- Several outcome studies showed that 90-96% of addicts relapsed after being treated at Lexington
- The majority of relapses occurred within the first six months
- Similar results were seen at Ft. Worth, where at least 9 out of 10 patients reportedly relapsed on narcotics within five years of discharge
- In 1971, Dr. Vincent Dole noted that after an in-hospital detoxification from opiates: “human addicts almost always return to use narcotics.”

2 Himmelsbach CK., Arch Intern Med 1942;69:766-772

Protracted Abstinence Syndrome:
- Abnormalities in sleep
- Body temperature
- Weight
- Respiration
- BMR
- BP
- Decreased HR
- Myosis
- Increased sed rates
- <sens of resp ctrs
- EEG
- Hct

2 Himmelsbach CK., Arch Intern Med 1942;69:766-772
3 Martin WR, Jasinski DR., J Psychiatr Res 1969;7:9-17

Protracted Abstinence (PA) Syndrome:
- The concept of methadone maintenance was born, in part, out of the notion of PA and its proposed relationship to relapse
- Dole felt that the problem of PA could be better dealt with at a later time

Drs. Vincent Dole and Marie Nyswander


Maintenance Treatment:
- Methadone (50-120mg) or Buprenorphine (12-16mg)
- No withdrawal symptoms
- Receptors blocked in case of “slip”
Opioid Maintenance Treatment (OMT):
- Initially conceived of as a stepping stone toward abstinence
- This has not, however, been the reality
- Only 10-20% of those who discontinue methadone are able to remain abstinent

Methadone
- Opiate agonist to treat opiate dependence
- Well-studied and effective treatment
  - Normalizes function/return to work, decreases crime/violence, reduces HIV exposure
- Doses > 70mg/day generally better than low doses
- Enhanced services = improved outcomes
  - Counseling, medical, social/vocational services, etc
- No contraindication in SMI, though not well studied

Methadone
- Usually taken once a day to suppress withdrawal for 24 to 36 hours
- Usually given in liquid form by Opiate Treatment Programs
- Induction phase—no more than 30 to 40 mg on the first day of treatment
- Dosage changes usually occur once a week
  - More rapid dosage increases can cause overdose
- Maintenance phase—usually 80-120mg daily

Methadone: “Addicting patients to another drug?”
- Difference between PHYSICAL DEPENDENCE vs. ADDICTION (or Substance Use Disorder in DSM-5)
- Pharmacology of methadone prevents highs and lows common with short-acting drugs and normalizes patient functioning
- The patient is PHYSICALLY DEPENDENT on methadone but is no longer displaying the behaviors associated with addiction

Methadone
- Common side effects
  - Sweating, constipation, abnormal libido, sleep abnormalities, mild anorexia, weight gain, water retention
- Adverse effects
  - Prolongation of QTc (usually seen with very high doses, mean of 350mg daily)

Methadone

![Figure 1. Methadone Dosage-Response Curve](image)
**Buprenorphine**

- Opioid partial agonist
  - ↓ risk of overdose and ↓ abuse potential

- Approved in U.S. (2002) as office-based treatment for opioid use disorder vs. OTPs
  - Additional training required: addiction medicine certified OR addiction psychiatry certified OR complete 8-hr course
  - X-DEA Number allows treatment of 30 patients in first year; 100 patients in subsequent years
  - As of August 2016, buprenorphine limit increased to 275 patients/year for certain prescribers only

- May precipitate withdrawal in individuals using opioids regularly → MUST BE IN MILD OPIOID WITHDRAWAL (“dope-sick”) before starting it!!

- What about the naloxone?
  - Sometimes mixed with naloxone to prevent abuse by intravenous injection
  - When taking sublingually, the naloxone is INACTIVE

- Multiple formulations
  - Buprenorphine only = oral tablets, SUBUTEX
    - Suggested use in pregnant patients
  - Buprenorphine/Naloxone combination = oral tablets, ZUBSOLV tablets, SUBOXONE FILM, BUNAVAIL BUCCAL FILM
  - Buprenorphine subdermal implant = PROBUPHINE
    - 4 rods [26 mm x 2.5mm] in upper arm q 6 months;
    - ONLY for patients stable on 8mg or less buprenorphine (oral) daily

- Maintenance phase: usually 8 to 16 mg daily of SUBOXONE; FDA max dose = 24 mg

- Varies in clinical practice, but realize that 16mg dose covers ~95% of opiate receptors

- Adverse side effects: Increased LFTs, cytolytic hepatitis

- Common side effects: generally mild
  - Constipation; dizziness; drowsiness; headache; nausea; sweating; vomiting;

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**Buprenorphine and MAT:**

- Numerous studies have proven efficacy in retaining patients in treatment and decreasing positive urine drug screens

- Studies of buprenorphine in primary care settings have shown the following retention rates:
  - 12-13 wk studies: 52-79%
  - 6 mo studies: 43-100%
  - 5yr study: 38%

- A nearly 20-year review of buprenorphine published this year clearly demonstrated that buprenorphine:
  - Improves treatment retention
  - Reduces illicit opioid use
  - Associated with improved outcomes during pregnancy
  - May afford fewer adverse outcomes than methadone in certain populations
  - Clearly provides greater access to care than methadone

- A study conducted in Baltimore between 1995-2009 revealed an association between increased availability of MAT (both methadone and buprenorphine) and a roughly 50% drop in fatal overdoses

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Feldman et al., 2008
Crommings et al., 2010
Fiellin et al., 2002
Fiellin et al., 2007
O'Connor et al., 1996

Jerry JM and Collins GB. CCJM 2013; 80(6): 345-349

Thomas CP, Psychiatric Services 2014
Mortality (per 100,000/yr)

- Prescription Opioids: 4.8
- Illicit Drugs: 2.8
- Methadone Maint: 0.4-0.5
- Buprenorphine: 0.1

(1) Clausen et al., Drug and Alcohol Dependence 2008; 94: 151-157
(3) Bell JR, et al. Drug and Alcohol Dep 2009; 104: 73-77

Does relapse = treatment failure?

- NO! Relapse is likely, and is a part of the chronic nature of the disease
- Relapse rates for drug addiction are similar to relapse rates in other chronic diseases
  - 40-60% relapse rate for addiction in 1 yr period
- Relapse often indicates that treatment needs to be reinstated, adjusted, or changed to an alternate form

Comparison of Addiction to Other Chronic Diseases

<table>
<thead>
<tr>
<th></th>
<th>Med compliance</th>
<th>Required hospital stay annually</th>
<th>Follow diet &amp; behavior change</th>
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<tbody>
<tr>
<td>DM I</td>
<td>&lt;60 %</td>
<td>~40 %</td>
<td>&lt;30 %</td>
</tr>
<tr>
<td>HTN</td>
<td>&lt;40 %</td>
<td>~60 %</td>
<td>&lt;30 %</td>
</tr>
<tr>
<td>Asthma</td>
<td>&lt;40 %</td>
<td>~60 %</td>
<td>&lt;30 %</td>
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Addressing Barriers to MAT

- Philosophical
  - “harm reduction” vs. “abstinence-only”
- Logistical
  - Access (limited slot availability)
  - Clinics may not be set up to provide MAT
- Financial
  - Insurance coverage, prior authorizations
- Regulatory
  - State laws, Recovery housing practices

Possible Strategies

1) Consensus building re: agency philosophy
2) Agency-wide needs assessment (infrastructure?)
3) Staff training and/or adding new staff
4) Consultation with MAT experts
5) Partnerships with local providers (i.e. detox, induction, IOP, primary care, sober housing, etc.)
6) Collaboration with insurance companies
7) Advocacy with regulatory bodies

Discussion

- What (other) strategies can your setting use to more fully integrate all three types of MAT?
- Can you think of short-term goals (3 to 6 months) and long-term goals (12 to 24 months) which would improve integration?
- What assistance might you need in meeting these goals?
Resources

- SAMHSA Medication-Assisted Treatment Brochure (Facts for Families and Friends)

- [http://pcss-o.org/](http://pcss-o.org/) Providers’ Clinical Support System for Opioid Therapies

- [http://www.samhsa.gov/medication-assisted-treatment](http://www.samhsa.gov/medication-assisted-treatment)

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