Medication Assisted Treatment Options for Substance Use Disorders

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No Financial Disclosures

Learning Objectives

1. Understand the basis for medication assisted treatment and how it fits into one model of addiction treatment
2. Describe options for opioid detoxification management with adjuvant therapies
3. Understand the unique properties of methadone, buprenorphine, and naltrexone for opioid use disorder treatment
4. Identify and understand the strengths and weaknesses of the medications indicated for alcohol use disorders
5. Provide resources for providers to begin implementing these tools in their practices
Different Treatment Philosophies

- Abstinence-based Behavioral Treatments
- Medication Assisted Treatment (MAT)
  - Medication plus behavioral treatments
- Barriers to MAT
  - Lack of understanding of the medications
  - Organizational philosophy/staff beliefs about use of medications;
  - Cost of medications
  - Lack of appropriate staffing in treatment centers

Substance Use Disorders: Chronic Illness versus Moral Failing

Asthma, Diabetes, HTN, HIV, etc.

Like other chronic illnesses...

- Genetics, personal-choice, and environmental factors
- Behavioral change is an important part of treatment
- Relapse and medication adherence issues
- Comply with treatment and medications = better outcomes
- No reliable cure
- Older, employed with stable families = better outcomes
- Reasonably predictable course
All of the following are criteria for the diagnosis of an opioid use disorder while *prescribed* opioids except...

- A. Tolerance
- B. Withdrawal
- C. Repeated attempts to quit
- D. Craving
- E. A and B

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2-3 = mild SUD, 4-5 = moderate SUD, >6 severe SUD
Physiologic Dependence Vs. Addiction

Physical Dependence
Physiologic adaptations to chronic opioid therapy

Tolerance

Addiction
Maladaptive behavior associated with opioid misuse


Addiction in clinical practice

• The 4 C’s
  • Loss of Control
  • Compulsive use
  • Continued use despite harms
  • Craving


34 yo female with a 5 year hx of IV heroin use

• Recently treated for 7 days in the hospital for a forearm abscess.
• She was discharged 5 days ago with 100 tablets of 5mg oral oxycodone IR and states she has run out.
• Her forearm abscess is well healed with no fluctuance, redness, or swelling.
• She is complaining of sweating, nausea, body aches, severe pain, and restless legs.
• VS HR 110, BP 150/90, T 99 F
• PE shows dilated pupils, gooseflesh, diffuse abdominal tenderness, restlessness, rhinorrhea, and anxious affect.
• WBC 7 with no bands, normal Hct
• She asks for a refill of the oxycodone.
What is her diagnosis?

a. Recurrent abscess
b. Hematoma
c. Opioid Withdrawal
d. Cotton Fever

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a. Recurrent abscess
b. Hematoma
c. Opioid Withdrawal
d. Cotton Fever

How do you manage her opioid withdrawal?

a. Prescribe 20 tabs of oxycodone IR
b. Prescribe clonidine, vistaril, and ibuprofen
c. Refer her to a methadone clinic
d. A and C
e. B and C
How do you manage her opioid withdrawal?

a. Prescribe 20 tabs of oxycodone IR  
b. Prescribe clonidine, vistaril, and ibuprofen  
c. Refer her to a methadone clinic  
d. A and C  
e. B and C

Opioid Withdrawal Assessment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms / Signs</th>
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<tbody>
<tr>
<td>0</td>
<td>Anxiety, Drug Craving</td>
</tr>
<tr>
<td>1</td>
<td>Yawning, Sweating, Runny nose, Tearing eyes, Restlessness Insomnia</td>
</tr>
<tr>
<td>2</td>
<td>Dilated pupils, Gooseflesh, Muscle twitching &amp; shaking, Muscle &amp; Joint aches, Loss of appetite</td>
</tr>
<tr>
<td>3</td>
<td>Nausea, Extreme restlessness, Elevated blood pressure, Heart rate &gt; 100, Fever</td>
</tr>
<tr>
<td>4</td>
<td>Vomiting / dehydration, Diarrhea, Abdominal cramps, Curled-up body position</td>
</tr>
</tbody>
</table>

Clinical Opiate Withdrawal Scale (COWS): pulse, sweating, restlessness & anxiety, pupil size, aches, runny nose & tearing, GI sx, tremor, yawning, gooseflesh (score 5-12 mild, 13-24 mod, 25-36 mod sev, 36-48 severe)

Outpatient Opioid Detox Options

- Adjuvant therapies
  + Clonidine (hyperadrenergic state) 0.1-0.2mg po TID-QID prn (up to 2.4mg/day)  
  + NSAIDS or Tylenol (muscle cramps and pain)  
  + Hydroxyzine (agitation/insomnia) 25-100mg po every 4-6 hours prn (NOT benzos!)  
  + Dicyclomine or Hyocosamine (abdominal cramps)  
  + Bismuth subsalicylate (diarrhea)  
  + Phenergan or Zofran  
  + FLUIDS  
- Suboxone (If waivered)  
- Methadone from a methadone clinic only
Why can’t you prescribe opioids?

- Harrison Act of 1914
  - Physicians can prescribe opioids to patients in the course of normal treatment, but not for the treatment of addiction.
- Narcotic Addict Treatment Act 1974
  - Treat addiction in regulated clinics that dispense methadone
- Drug Addiction Treatment Act (DATA) 2000
  - Office Based Opioid Treatment with suboxone with specific training

Inpatient Opioid Detox

- Methadone
  - No more than 40mg once daily*
  - Check QTc interval
- Suboxone
  - With specialty consultation
- Adjuvant meds (use liberally)
  - Clonidine, NSAIDS or Tylenol, Hydroyzine, Dicyclomine or Hykosamine, Zofran, Fluids

*Avoid higher doses without specialty consultation

Common Pitfalls in Primary Care

Outpatient:
- Communication difficulties
- No use of adjuvant therapies
- Using Immediate release (IR) opioids to treat opioid withdrawal
- Not following up or discharging from practice

Inpatient:
- Communication difficulties
- Using IV or IR opioids to treat opioid withdrawal
- No use of adjuvant therapies
- Failure to refer to treatment during hospitalization
- Not treating concomitant pain adequately
Treatment Options for Opioid Disorders

- Self-help groups
- Detoxification +/- Medication Assisted Treatment (MAT)
- Outpatient treatment +/- MAT
- Residential treatment +/- MAT

- MAT = Methadone, Suboxone, or Naltrexone

Opioid Activity Levels

Methadone Maintenance Therapy

- Full agonist with long elimination half-life
- Once daily dispensing in a federally-qualified methadone clinic
- Reduces euphoria of subsequent opioid abuse
- Typical effective dose range 60-90mg/day*
- Contingency management – Take home doses (NTE 28 days)

*higher for pregnant patients
Methadone: Pros/Cons

- **Pros**
  - Increased retention in treatment
  - Decreased opioid use
  - Decreased HIV transmission
  - Highly structured treatment
  - Psychiatric comorbidity
  - Polysubstance use
  - Frequent relapses
  - Gold standard tx for Pregnancy
  - Some analgesic benefit

- **Cons**
  - QTc prolongation
  - High overdose risk
  - Many drug-drug interactions
  - Benzodiazepines
  - HIV meds
  - Seizure medications
  - Polysubstance use
  - Daily dosing

Buprenorphine (subutex™) /naloxone (Suboxone™) (4:1 combination)

- Partial opioid agonist (plateau effect)
- Long half-life
- Typically once daily, but BID or TID is safe
- 24mg usually the highest effective dose
- Less euphoric effect than other opioids
- Paired with antagonist (naloxone) to prevent abuse through injection
- Office based prescribing with DEA waiver or “X license”
  - One day or online training
  - Treat up to 30 patients first year, then up to 100 patients

Suboxone: Pros/Cons

- **Pros**
  - Effective for pain and addiction
  - Increased retention in treatment
  - Low overdose risk
  - Office-based prescribing (OBOT)
  - Minimal drug interactions
  - Except benzos, ethanol
  - No cardiac toxicity

- **Cons**
  - Training required to prescribe
  - Cost
  - Can complicate pain treatment
  - Potential for precipitated withdrawal
  - Can be diverted
Methadone Vs. Suboxone

- Low dose Buprenorphine (2-6mg) was less effective than methadone in retaining people in treatment.

- Buprenorphine (>7 mg/day) was not different from methadone (>40 mg/day) in retaining people in treatment or in suppression of illicit opioid use.


Naltrexone: opioid antagonist

Two formulations approved in US
Oral Naltrexone (1984), 50mg once daily
Extended Release Naltrexone, Vivitrol® (2010) Q 28 days

Blocks all Opioid receptors
Not controlled
Blocks euphoric effects of opioids
Also treats alcohol dependence
Vivitrol ® has important use in criminal justice
Extended release naltrexone (Vivitrol®)

XR-Naltrexone for Opioid Use Disorder
- Intramuscular injection lasts 28d
- Efficacious compared to placebo:
  - Comer: 60 U.S. heroin users at 8 weeks\(^1\)
  - Krupitsky: 250 Russian heroin users at 24 wks\(^2\)
- Potential for direct effects on HIV viral suppression & immune function
  - CD4 \(\kappa\) blockade increases HIV entry\(^3\) and viral killing\(^4\)
  - NTX is toll-like receptor (TLR-4) antagonist; may facilitate CD4 recovery\(^5\)

Naltrexone: pros/cons
- **Pros**
  - Not controlled
  - Mid-level providers can prescribe
  - Lasts 28 days
  - Treats etoh and opioid use disorders
  - No ability to feel effects of opioids
- **Cons**
  - Must be opioid free for 5-7 days
  - Can complicate pain treatment
  - May affect liver function
  - Pain at injection site
  - Cost
  - Theoretical overdose risk
Detox vs. Maintenance: Which is Better?

- Multi-site trial of buprenorphine/nx for 653 prescription opioid-dependent patients in 10 primary care clinics
- Detox phase followed by maintenance phase for those who relapse
- “Success” = minimal or no use on UDS & self-report

<table>
<thead>
<tr>
<th>Success at 12 Weeks:</th>
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<tbody>
<tr>
<td>Detox Phase:</td>
</tr>
<tr>
<td>Maintenance Phase:</td>
</tr>
</tbody>
</table>

Success at 12 Weeks: Detox Phase: 6.6% |
Maintenance Phase: 49.2%

Weiss Arch Gen Psych 2011

Treatment Retention: Buprenorphine Detox vs. Maintenance

<table>
<thead>
<tr>
<th>Treatment Retention</th>
<th>Opioid Misuse</th>
<th>Criminal Activity</th>
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</thead>
<tbody>
<tr>
<td>Detox</td>
<td>↑ (n=6)</td>
<td>No Effect (n=3)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>↓ (n=2)</td>
<td>No data</td>
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</table>

Weiss Arch Gen Psych 2011

Medication Efficacy For Opioid Dependence

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<tr>
<th>Treatment Program</th>
<th>Retention</th>
<th>Opioid Misuse</th>
<th>Criminal Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>↑ (n=3)</td>
<td>↓ (n=6)</td>
<td>No Effect (n=3)</td>
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<tr>
<td>Buprenorphine</td>
<td>↑ (n=4)</td>
<td>↓ (n=2)</td>
<td>No data</td>
</tr>
<tr>
<td>PO NTX</td>
<td>No effect (n=2)</td>
<td>↓ (n=4)</td>
<td>↓ (n=2)</td>
</tr>
<tr>
<td>XR NTX</td>
<td>↑ (n=2)</td>
<td>↓ (n=2)</td>
<td>No data</td>
</tr>
</tbody>
</table>

Mattick RP et al. Cochrane Database Syst Rev 2011;
Mattick RP et al. Cochrane Database Syst Rev 2011;
Minozzi S et al. Cochrane Database Syst Rev 2011;
Back to Arthur

• Chronic Pancreatitis causing chronic abdominal pain
• Frequent flares of pain requiring hospitalization
• Chronic alcoholism
• Frequent relapses
• Homelessness

What is the best medication option to treat Arthur’s opioid use disorder?

• A. Naltrexone
• B. Methadone
• C. Suboxone
• D. Methadone + Antabuse
• E. Methadone + Naltrexone
• F. None of the above

What is the best medication option to treat Arthur’s opioid use disorder?

• A. Naltrexone
• B. Methadone
• C. Suboxone
• D. Methadone + Antabuse
• E. Methadone + Naltrexone
• F. None of the above
Common Pitfalls in Primary Care

- Communication difficulties
- With patient and addictions providers
- Knowledge gaps about MAT
- Use of methadone to treat opioid dependence outside of a methadone clinic
- Referral to methadone clinics for patients with pain
- Prescribing drugs that interact with MAT

The three FDA approved medications for alcohol use disorder are...

- A. Acamprosate
- B. Naltrexone
- C. Disulfram
- D. Topamax
- E. Baclofen
- F. A, B, and C
The three FDA approved medications for alcohol use disorder are...

- A. Acamprosate
- B. Naltrexone
- C. Disulfiram
- D. Topamax
- E. Baclofen
- F. A, B, and C

Alcohol Use Disorder Medications

1. Naltrexone
2. Acamprosate
3. Disulfiram

(notice benzos are not on this list)

Naltrexone for Alcohol Dependence
50mg daily (oral)

- Approved for etoh treatment in 1994
- Endogenous opioid blockade reduces alcohol reward
- Potential liver toxicity
- Decreases alcohol drinking days, relapse, craving\(^1,2\)
- Poor adherence limits effectiveness
- XR-NTX achieves greater abstinence\(^3\)

O'Malley Arch Gen Psych 1992
Strain et al J Neuropsych 2005
Garbutt JAMA 2005
Lee JSAT 2012
Extended release Naltrexone (Vivitrol™); 380mg IM Q 4 wks
- Approved 2006
- Easy in office procedure by CMA or RN
- Greater pharmacokinetic stability and overall exposure relative to oral formulation
- Fewer subsequent detox days
- Fewer inpatient admissions for SUD
- Similar or lower overall costs
- CI in pregnancy or fulminant hepatic failure

Acamprosate
666mg TID oral dose
- Approved in 2004
- NMDA glutamate antagonist
- Increases glutamate and GABA neurotransmission
- Limited Effectiveness
  - Modestly effective in European trials
  - No effect compared to placebo for relapse in COMBINE study
- Poor adherence
- Renal excretion; avoid in CKD stage 4-5

Disulfiram (Antabuse):
250mg daily
- Approved 1951
- Inhibits aldehyde dehydrogenase
- Causes reaction when drinking alcohol:
  - Drowsiness, fatigue, nausea, vomiting, flushing, palpitations
  - Lasts about 30 minutes
  - Can occur 2 weeks after stopping disulfiram
- Must be fully detoxed first
- Modestly reduces # heavy drinking days
- Poor adherence
- Can worsen liver function
- Can be mixed with methadone
Medication Efficacy For Alcohol Dependence

<table>
<thead>
<tr>
<th></th>
<th>Abstinence</th>
<th>Drinking Days</th>
<th>Heavy Drinking Days</th>
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<tbody>
<tr>
<td>Disulfiram</td>
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<td>PO NTX</td>
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<td>(n=26)</td>
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<tr>
<td>Acamprosate</td>
<td>(n=15)</td>
<td>No Data</td>
<td>(n=5)</td>
</tr>
<tr>
<td>XR NTX</td>
<td>(n=3)</td>
<td>(n=3)</td>
<td>(n=3)</td>
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An Inpatient Treatment and Discharge Planning Protocol for Alcohol Dependence: Efficacy in Reducing 30-Day Readmissions and Emergency Department Visits

- Inpatients treated with naltrexone prior to discharge
- All cause 30 day readmissions decreased from 23% to 8% (p=0.04)
- All cause ED visits decreased from 19% to 6% (p=0.05)

JGIM, 2014

AUD Tx under investigation

- Varenicline
- Gabapentin
- Topiramate
- Valproate
- Nalmefene
- Nalmafen
- Baclofen
- Pyrrolopyrimidine compound
- Rimonabant
Common Pitfalls in Primary Care

- Communication difficulties
- Knowledge gaps about MAT
- Use of long term benzodiazepines to treat AUD
- Dangerous use of other sedative-hypnotics
- Drug interactions with etoh

Methamphetamines

- Oregon leads nation in meth treatment admissions
  - 22% of admissions in 2011
  - Prevalence 12-35% in Western U.S. HIV clinics
  - Neurotoxic
  - Longer duration of use associated with increased cognitive deficits, decreased brain volume

Medication Treatment Trials for ATS
(None currently FDA-Approved)

<table>
<thead>
<tr>
<th>Methamphetamine</th>
<th>Dextroamphetamine</th>
<th>Methylphenidate</th>
<th>Modafinil</th>
<th>Bupropion</th>
<th>Naltrexone</th>
<th>Mirtazapine</th>
<th>Topiramate</th>
<th>L-Dopa</th>
<th>Desipramine</th>
<th>Imipramine</th>
<th>Sertraline</th>
<th>Aripiprazole</th>
<th>Ondansetron</th>
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</table>
Medications Under Study as ATS Treatments

- Promising medications being studied
  - naltrexone, bupropion, mirtazapine
- Potential for use of amphetamines for treatment of withdrawal
- Immunotherapies are in early stages
- Contingency management may potentiate medication effect

Mirtazapine for Methamphetamine Dependence?

- Pilot trial in 60 MSM randomized to counseling with:
  - Mirtazapine 30mg/day
  - Placebo
  - 53% HIV-infected
- Mirtazapine decreased:
  - Methamphetamine use
  - Risky sexual behaviors
  - Well tolerated

Nicotine Use Disorders

- Nicotine Replacement Therapy
  - Gum, lozenge, inhaler, patch
- Varenicline
- Bupropion
No FDA approved medications for....

- Cocaine use disorders
  - Some promise using suboxone + vivitrol
- Marijuana use disorders
  - Trial of N-acetylcysteine
- Benzodiazepine use disorders
- Others....

What can I do as a PCP?

- Increase screening of substance use disorders
- Offer alcohol use disorder treatments
- Consider prescribing naltrexone and naltrexone ER
- Consider obtaining suboxone DEA waiver
- Get to know your local addiction provider and communicate with him/her about your patients

Questions? weimerm@ohsu.edu

FREE Substance Use Disorder Resources:

- www.coperems.org
- www.scopeofpain.com
- www.pcssso.org
- www.pcssmat.org