Medications for Alcohol and Drug Dependence Treatment

Robert P. Schwartz, M.D.
Medical Director
Rschwartz@friendsresearch.org

Friends Research Institute
Medications for Alcohol Dependence Treatment

- Disulfiram (Antabuse®)
- Naltrexone
  - Oral tablets (Revia®)
  - Extended-release injection (Vivitrol®)
- Acamprosate (Campral®)
Rationale for Using Medications to Treat Alcohol Dependence

• Many patients do not reduce or stop risky drinking with existing psychosocial treatment and AA alone

• Medications can help some patients improve their chances of reducing risky drinking

• These medications exert their effects in different ways
How Does Disulfiram Help Reduce Risky Drinking?

- Disulfiram interferes with the metabolism of alcohol
- Acetaldehyde builds up and causes aversive symptoms including:
  - Dizziness, hypotension, sweating, facial flushing, shortness of breath, nausea, and vomiting
In What Formulation is Disulfiram available?

Tablet (Antabuse ®)

- FDA-approved for the treatment of alcohol dependence over 50 years ago
- 250 mgs taken orally once per day
- Should not be taken within 12 hours (at least) of any alcohol
- Patient should not drink for up to 2 weeks after last drink
What is the Evidence of Disulfiram’s Effectiveness?

- 11 Randomized Clinical Trials with a total of 1,527 participants were reviewed (Jorgensen et al., 2011)
- Supervised treatment with disulfiram compared to placebo had some effect on short-term abstinence and days until relapse
- Unsupervised treatment had mixed results
How Does Naltrexone Help Reduce Risky Drinking?

- Mu opioid receptor activation is in part responsible for the “buzz” from alcohol
- Naltrexone is a mu opioid antagonist (i.e., blocker)
- Patients drinking while taking naltrexone report a reduced “buzz” from alcohol
- There is evidence that a genetic variant of the opioid receptor called OPRM1 may influence the response to naltrexone
In What Formulation is Naltrexone available?

Tablet (Revia®)
- FDA-approved in 1994 for the treatment of alcohol dependence

Long-acting injection (Vivitrol®)
- FDA-approved in 2006 for the treatment of alcohol dependence
  - Helpful for non-compliant patients
  - Lasts about 30 days
  - Intramuscular injection in the buttock
What is the Evidence of Naltrexone’s Effectiveness?

- 50 Randomized Clinical Trials with 7,793 patients were included in a recent Cochrane Review (Rossner et al., 2010)
  - Naltrexone reduced the risk to return to heavy drinking by 83% compared to placebo
  - It reduced the number of drinking days by 4%
  - It did not reduce the return to any drinking
  - Main side effects: GI symptoms & sedation
How Does Acamprosate Help Reduce Risky Drinking?

• Precise mechanism of action is not known

• Acamprosate acts on the glutamate receptor
  - it inhibits the neurons which may be involved in alcohol craving

• It also may reduce conditioned responses to alcohol-related cues

• These mechanisms may explain acamprosate’s ability to reduce the risk of relapse
In What Formulation is Acamprosate Available?

Tablet (Campral®)

- FDA-approved in 2004 for the maintenance of abstinence in alcohol dependent patients
- 2 tablets (333mg each) three times per day
What is the Evidence of Acamprosate’s Effectiveness?

• 24 Randomized Clinical Trials with 6,915 patients were including in a recent Cochrane Review (Rossner et al., 2011)
• Acamprosate reduced the risk of any drinking after detoxification by 86% compared to placebo
• It increased cumulative abstinence by 11% compared to placebo
• It did not reduce the risk of return to heavy drinking
• Main side effects: Diarrhea
Medications for Cocaine & Methamphetamine Addiction Treatment

- None are approved by the FDA for cocaine or methamphetamine dependence treatment
- Several have shown promising results
- Several compounds are under development
Medications for Opioid Dependence Treatment

- Methadone
- Buprenorphine
  - Sublingual mono-product (Subutex®)
  - Sublingual combination product of Buprenorphine/Naloxone (Suboxone®)
- Naltrexone
  - Oral tablet (Revia)
  - Extended-release injection (Vivitrol)
FDA-approved Medications for Opioid Addiction Treatment

**Opioid Agonists**

1) Full agonist: Methadone (oral)
2) Partial agonist: Buprenorphine (sublingual)

**Opioid Antagonist**

3) Naltrexone (oral)
4) Naltrexone (extended-release injection)
What is the difference between opioid agonists & antagonists?

Dose of Opioid

Opioid Effect

Methadone
Buprenorphine
Naltrexone
I. Opioid Agonists
How Do Methadone and Buprenorphine Reduce Opioid Use?

- Both activate the opioid receptors
- Buprenorphine’s (unlike methadone’s) effect plateaus at higher doses which accounts for its better safety profile [less likely to cause overdose]
- Reduce heroin craving
- Alleviate withdrawal
- Block heroin’s euphoric effects
Effects of Buprenorphine Dose on µ-Opioid Receptor Availability

MRI

Bup 0 mg

Bup 2 mg

Bup 16 mg

Bup 32 mg

Binding Potential (Bmax/Kd)
What is the difference between heroin addiction and opioid agonist treatment?

<table>
<thead>
<tr>
<th></th>
<th>Heroin Addiction</th>
<th>Opioid Agonist Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Injected or Snorted</td>
<td>Oral or Sublingual</td>
</tr>
<tr>
<td>Onset</td>
<td>Immediate</td>
<td>Slow</td>
</tr>
<tr>
<td>Euphoria</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dose</td>
<td>Unknown</td>
<td>Known</td>
</tr>
<tr>
<td>Cost</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Duration</td>
<td>4 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Legal</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>Chaotic</td>
<td>Normal</td>
</tr>
</tbody>
</table>
In What Formulation is Buprenorphine Available?

Combination of buprenorphine with naloxone (Suboxone®)

- Sublingual buprenorphine is well absorbed
- Naloxone (a potent, short-acting opioid antagonist) is not well absorbed sublingually
- Injection of suboxone will precipitate opioid withdrawal

Buprenorphine Alone (Subutex®)

- Rare indications for use
- Several generics available at lower price
What is the Evidence of Methadone’s Effectiveness?

- 11 Randomized Clinical Trials with a total of 1,969 participants were included in a Cochrane Review (Mattick et al., 2009)
- Methadone was more effective than placebo in reducing heroin use and in retaining patients in treatment
- There was inadequate evidence that it reduced criminal behavior
  - Although many longitudinal studies show an association between methadone treatment and reduced criminal behavior
What are the characteristics of effective maintenance treatment?

- Higher doses (individualized to patients’ needs)
- Longer time in treatment
- Psychosocial services of appropriate intensity & duration
What is the Evidence of Buprenorphine’s Effectiveness?

• 24 Randomized Clinical Trials with a total of 4,497 participants were included in a Cochrane Review (Mattick et al., 2008)

• Buprenorphine was more effective than placebo in reducing heroin use and in retaining patients in treatment

• Buprenorphine was less effective than medium dose methadone in reducing heroin use
How are buprenorphine & methadone provided?

Shorter-term: Detoxification

Longer-term: Maintenance

Length of time on these medications should be individually determined by patient and physician together.
Is Opioid Detoxification Effective?

- Effective at reducing withdrawal symptoms
- Helps some patients detoxify
- By itself, it is most often not successful in maintaining abstinence
- Most patients relapse quickly after detoxification
  
  29% success at 2 weeks post-detox (Ling et al, 2009)
Is Opioid Detoxification Effective?

• Low success rate is true for both inpatient & outpatient detoxification

• Relapse is associated with increased risk of overdose death and recidivism
Agonist Treatment in Criminal Justice System

- These medications can be used in probation, parole and drug courts
- Although not uniformly available
- Probationers respond to methadone (Kelly et al., 2013) and to buprenorphine (Mitchell et al., In press) as well as non-probationers
- Agonist treatments often are not continued upon incarceration
Agonist Treatment in Jails

Inmates

• Awaiting trial
• Short sentences (< 1 year)

Uses of Agonist Treatment

• Detoxification from heroin (if desired/indicated)
• Initiate in jail and continued upon release
• Continue in jail for arrested patients
Prisons

Prisoners

- Long sentences (> 1 year)

Treatment Issues

- Initiate treatment for in-prison heroin users
- Initiate treatment for in-prison abstainers who wish to avoid release upon release
II. Opioid Antagonists
In What Formulation is Opioid Antagonist Treatment Available?

Oral Naltrexone (Revia ®)

• Highly effective pharmacologically
• Hampered by poor patient adherence
• Useful for highly motivated patients

Injectable formulation (Vivitrol ®)

• FDA-approved for opioid dependence in 2010
• Effective for about 30 days
• FDA-approved medications for alcohol and opioid dependence have proven effectiveness

• These medications can reduce the use of alcohol and opioids

• However, they are underutilized in criminal justice settings, presenting an opportunity to improve outcomes by making them more widely available