Use of Opiate Antagonists in Treating Addiction and Mental Disorders

Steven Lamm, MD
Meeting medical conditions

• I have a pill for that
Pharmacotherapies for Opiate Dependence

- Methadone
- Buprenorphine
- Naltrexone
Naltrexone Uses

- Alcoholics
- Opiate addicts
- Weight loss
- Impulse control
The use of low dose naltraxone as a novel anti-inflammatory treatment for chronic pain (ie: fibromyalgia, Crohn's disease, multiple sclerosis)

These effects entirely independent from activity on opioid receptor possibly glial cell modulator
Naltrexone Pharmacology

- Similar structure to naloxone (Narcan)
- Potent inhibitor of Mu opioid receptor binding
  - may explain reduction of relapse
    - because endogenous opioids involved in the reinforcing (pleasure) effects of alcohol
  - May explain reduced craving for alcohol
    - because endogenous opioids may be involved in craving alcohol

Naltrexone Safety

Main Adverse Effects
- gastrointestinal upset
- abdominal pain
- nausea
- vomiting
- headache
- dizziness

Other Contraindications
- concomitant opioid analgesics (naltrexone will block analgesic effect)
- opioid dependence or withdrawal
- hypersensitivity to naltrexone
- Medical conditions requiring opioid analgesics
- pregnancy (Category C)
Naltrexone in Alcohol Dependence

The mechanism by which naltrexone exerts its effects in alcohol dependent patients is incompletely understood. However, involvement of the endogenous opioid system is suggested by preclinical data.
Ethanol

Dopamine

Beta endorphin release potentiated

prefrontal cortex

nucleus accumbens

VTA

Firing

Naltrexone: Reward Pathway

Ethanol
Extended Release Naltrexone (Vivitrol)

- Uses polymer-based microsphere injectable extended-release technology to deliver and maintain therapeutic medication levels in the body through just one injection every four weeks.
Pharmacotherapy of Alcohol Dependence: Naltrexone

• Oral Naltrexone Hydrochloride
  ▪ DOSE: 50 mg per day

• Extended-Release Injectable Naltrexone (Vivitrol) (Garbutt et al, JAMA 2005)
  ▪ 1 injection per month
Naltrexone Hepatic Effects

- Can cause hepatocellular injury in very high doses (e.g., 5-10 times higher than normal).
- Contraindicated in acute hepatitis or liver failure.
- Check liver function before, q1 month for 3 months, then q 3 months.
- Caution about ibuprofen (Motrin, Advil, etc) and other non-steroidal anti-inflammatory agents.
  - May have additive hepatic effects.

VA/DoD CPG SUDs, www.oqp.med.va.gov/cpg/SUD/SUD_Vase.htm
Cochrane Review of Naltrexone for Alcohol Dependence

- Decreased relapse to heavy drinking [RR = 0.64]
- Decreased return to any drinking [RR = 0.87]
- Increased the time to first drink
- Reduced craving
- Superior to acamprosate in reducing relapses, drinks and craving.

Naltrexone Delays the Onset of Relapse to Alcohol

Investigator: Stephanie O'Malley et al. 1992

Number of Days Until Relapse for All Patients
Naltrexone vs. Placebo

P < 0.001
Case Study

A 42 year old man with a 14 year history of alcohol dependence relapsed to alcohol abuse 3 months ago. He currently reports drinking 3-5 drinks 4-5 times/wk, but states that he when he abstains for a day or two occasionally he does not experience alcohol withdrawal symptoms. However, his spouse is upset with his drinking and he now wants medication to help him to abstain. He tried naltrexone in the past, but says it ‘didn’t help much.’ He takes no other medications and has no known allergies.

What of the following would you recommend?

- A. Liver function tests
- B. Acamprosate 666 mg three times daily
- C. Disulfiram 250 mg/d
Case Study: Answer

- A and C: This patient has a long and difficult history of struggling with alcoholism. He has failed naltrexone in the past and acamprosate is not likely to be helpful (the Combine Study showed it to be inferior to naltrexone). He has significant consequences of his drinking; is motivated to quit; therefore; if his liver functions indicate that he does not have significant impairment; a trial of disulfiram 250 mg daily might help.
Naltrexone

Block effects of a dose of opiate (Walsh et al. 1996)

Prevent impulsive use of drug

Relapse rates high (90%) following detoxification with no medication treatment

Dose (oral): 50 mg daily, 100 mg every 2 days, 150 mg every third day

Blocks agonist effects

Side effects: hepatotoxicity, monitor liver function tests every 3 months

Biggest issue is lack of compliance; but those who “test” naltrexone by taking a dose of opioid and experiencing no effect do better with the medication (Cornish JW, et al. 1997)

Injectable naltrexone
Who is a Candidate for Naltrexone?

- The patient is opioid free for 7-10 days
- The patient does not have severe or active liver or kidney problems (Typical guidelines suggest liver function tests no greater than 3 times the upper limits of normal, and bilirubin normal)
- The patient is not allergic to naltrexone, and no other contraindications are present (rarely would someone be allergic to naltrexone, but opioid addicted individuals sometimes may report an allergy as this is not a preferred treatment or they may have started naltrexone before being completely withdrawn from opioids and experienced precipitated withdrawal—ask patient about the time frame of adverse events when trying to evaluate)
Mental Illness in Substance Use Disorders

- Among those with an alcohol disorder, 37% had a comorbid mental disorder.
- Among those with non-alcohol drug disorders, more than half (53%) were found to have a mental disorder, with an odds ratio of 4.5

(Regier 1990 JAMA)
Among those with a mental disorder, the odds ratio of an addictive disorder was 2.7, with a lifetime prevalence of about 29% including an overlapping 22% with an alcohol use disorder, and 15% with another drug disorder.

(Regier 1990 JAMA)
How it works…

- Cuts down cravings
- Blocks receptors from opiates and alcohol
Naltrexone blocks these receptors to prevent any stimulation from opiate or alcohol use.
Naltrexone

- Oral or Injection
  - Oral: Administered over a three month period.
  - Injection: One per month for three months.
  - Studies have proven that the injected Naltrexone succeeds more often than the oral
Addictive and Co-Occurring Disorders in Late Life

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University of Pennsylvania, School of Medicine
And
Philadelphia, VAMC

Hazelden Research Co-Chair on Late Life Addictions
### Targets of Molecular Action: Alcohol and Opioids

<table>
<thead>
<tr>
<th>Opioid Targets</th>
<th>Alcohol Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptors</strong></td>
<td><strong>NMDA, Kainate, GABA, Cannabinoid</strong></td>
</tr>
<tr>
<td>Opioid Receptor</td>
<td>Glycine, Nicotinic Ach, Serotonin</td>
</tr>
<tr>
<td><strong>Channels</strong></td>
<td>Calcium, Potassium</td>
</tr>
<tr>
<td><strong>Transporters</strong></td>
<td>Dopamine, Adenosine</td>
</tr>
<tr>
<td><strong>Signaling systems</strong></td>
<td>PKA, PKC, CREB, G Proteins</td>
</tr>
<tr>
<td><strong>Neuromodulators</strong></td>
<td>Opioids, CRF, Neurosteroids, NPY</td>
</tr>
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Efficacy of Naltrexone Established Over a Decade Ago

- 14 studies

- Relapse to heavy drinking
  - Naltrexone 428/1142 (37%), Control 445/930 (48%)
    - \( p<0.00001 \)

- Odds Ratio (favoring naltrexone)
  - 0.62 (95% CI 0.52, 0.75)

Bouza C et al. *Addiction* 2004;99:811
Prescribing Naltrexone

Naltrexone 12.5 mg/d --> 25 mg/d --> 50 mg/d

- Main contraindication: opiates, pregnancy
- Main side effects: nausea, dizziness
Psychiatric Comorbidity and Drug/Alcohol Dependence in the Elderly

- Higher than expect rates in representative community samples
- Markedly higher rates in treatment seeking samples
- Increased morbidity and mortality particularly suicide
- Presents diagnostic difficulties
- Poor prognostic factor
- Call for integrated care system
Suicide in the Elderly

- Highest rates of suicide occur in late life among men.
- Depression causes a 5.8 fold increase in risk of suicide compared to death from other causes
- Heavy drinking (3+ drinks/day) causes a 8.9 fold increase in risk of suicide compared to death from other causes
- Moderate drinking (1-2 drinks/day) causes a 10.6 fold increase in risk of suicide compared to death from other causes

What is the Extent of the Issues? In the Community

<table>
<thead>
<tr>
<th>Issue</th>
<th>Current / Last 12 months</th>
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</thead>
<tbody>
<tr>
<td>Alcohol Dependence</td>
<td>2 - 4 %</td>
</tr>
<tr>
<td>Medication misuse</td>
<td>? Overall</td>
</tr>
<tr>
<td>Chronic Benzodiazepine use</td>
<td>5 - 20%</td>
</tr>
<tr>
<td>Nicotine dependence</td>
<td>10 - 15 %</td>
</tr>
<tr>
<td>Illicit Substance dependence</td>
<td>&lt; 1 %</td>
</tr>
<tr>
<td>Pathological Gambling</td>
<td>1 – 2 %</td>
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</tbody>
</table>
Depression Alcohol Aging Trial

• Hypotheses
  ▪ Among older adults with major depression and comorbid alcoholism, naltrexone combined with sertraline improves the outcomes of both drinking and mood.
    
    ▪ Reduction in alcohol consumption will be associated with improved mood regardless of randomization.
    
    ▪ Naltrexone will lead to a reduction in alcohol consumption independent of changes in mood.
Concurrent Treatment of Depression Complicated by Alcohol Dependence

- Current depressive syndrome
- Current alcohol dependence
- Age 55 and over
- 10 sessions of compliance enhancement therapy
- 1/2 of subjects are randomly assigned to receive naltrexone 50 mg
- All subjects receive sertraline 100 mg
- Outcomes at 3 months

(Oslin, 2004)
## Pre-Treatment Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Naltrexone</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDRS Score</td>
<td>23.4 (5.0)</td>
<td>20.1 (5.7)</td>
<td>0.011</td>
</tr>
<tr>
<td>Percent Days Heavy Drinking</td>
<td>75.8 (29.1)</td>
<td>59.2 (35.6)</td>
<td>0.032</td>
</tr>
<tr>
<td>Percent Days Drinking</td>
<td>82.4 (24.5)</td>
<td>75.5 (29.3)</td>
<td>0.270</td>
</tr>
<tr>
<td>Drinks/ Drinking Day</td>
<td>10.2 (6.8)</td>
<td>6.5 (3.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>ASI-Alcohol Score</td>
<td>0.67 (0.18)</td>
<td>0.64 (0.17)</td>
<td>0.433</td>
</tr>
<tr>
<td>PCS</td>
<td>43.8 (8.5)</td>
<td>46.1 (10.3)</td>
<td>0.325</td>
</tr>
<tr>
<td>MCS</td>
<td>33.2 (9.6)</td>
<td>38.1 (11.5)</td>
<td>0.061</td>
</tr>
<tr>
<td>% with Primary Depression</td>
<td>68.6</td>
<td>65.7</td>
<td>0.799</td>
</tr>
</tbody>
</table>
## Relationship between heavy drinking during the trial and depression outcomes

<table>
<thead>
<tr>
<th></th>
<th>No Relapse</th>
<th>Relapse</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed Research (%)</td>
<td>83.7</td>
<td>84.0</td>
<td>0.886</td>
</tr>
<tr>
<td>Depression Remitted</td>
<td>63.3</td>
<td>32.0</td>
<td>0.011</td>
</tr>
<tr>
<td>HDRS – end of trial</td>
<td>8.8 (6.7)</td>
<td>12.7 (8.2)</td>
<td>0.013</td>
</tr>
</tbody>
</table>
Overall Treatment Outcomes

- Well: 42%
- Depressed only: 24%
- Relapsed only: 11%
- Depressed and Relapsed: 23%
Substance Induced Depression in the elderly?

- Less than 50% resolution of symptoms early in treatment
- No relationship between clinical impression of primary vs. secondary depression and early response
What about moderate or abusive drinking (non-dependent drinking)

- Most common pattern of drinking among those with depression
- May be beneficial for heart disease
Sedative/Hypnotic Use

M:W p = 0.0393, Positive: Negative p=0.002