The Psychopharmacology of Alcohol Use Disorders: Current Status and New Developments

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Conflict of Interest

• None
• I will discuss off-label use of medications
Objectives

1) Gain awareness of the extent of alcohol use disorders and the low utilization of FDA approved medications in the treatment of these disorders.

2) Acquire knowledge of evidence base for FDA medications for alcohol dependence including efficacy and safety considerations.

3) Gain awareness of the efforts to identify predictors of response to medications and to develop new medications for alcohol dependence.
The United States is a drinking culture.

In 2013:
-70.7% of the adult population reported that they drank in the past year
-56.4% reported that they drank in the past month
-24.6% reported binge drinking in the past month
Alcohol: Third Leading Cause of Preventable Death

Prevalence of Alcohol Use Disorders in the United States 2013
SAMHSA. 2013 National Survey on Drug Use and Health (NSDUH).

About 17 million Americans affected by alcohol use disorders in 2013
Greater prevalence in clinical populations including those coming for psychiatric treatment

Only 25% of patients with alcohol use disorders receive treatment and of those only 10% or so receive an FDA approved medication
Given the Prevalence and Burden of Alcohol Use Disorders Why Aren’t FDA Approved Medications Used More Often?

Only about 13% of patients with alcoholism received naltrexone.

“The results of this study indicate that naltrexone is perceived by the average addiction physician as a costly medication, which yields a modest clinical effect and is associated with low compliance rates.”
The Big Issues

• Alcohol Use Disorders are common, affect many patients and are associated with significant morbidity and mortality
• We have FDA approved medications for alcohol dependence but they are minimally used.
• What should we expect medications to do for the alcohol use disordered patient?
• Clinicians need to consider the use of medications for treating the alcoholic patient and develop a level of comfort and experience in using these medications.
Using Medications to Reduce Drinking or Enhance Abstinence

What are appropriate outcomes?
- Abstinence clearly desirable but often a challenge to obtain
- Reduction in heavy drinking positive for health (harm reduction) and society

but what is meaningful? One less heavy drinking day is one less day something bad can happen.

-NIAAA Clinician Guidelines: “. . . The safest course is abstinence, and that would be the usual clinical recommendation. Still, it is best to determine individualized goals with each patient. Some patients may not be willing to endorse abstinence as a goal, especially at first. If an alcohol-dependent patient agrees to reduce drinking substantially, it is best to engage them in that goal while continuing to note that abstinence remains the optimal outcome.”
FDA Approved Medications for Alcoholism

- 1952 disulfiram (Antabuse)
- 1995 naltrexone (Revia)
- 2004 acamprosate (Campral)
- 2006 long-acting naltrexone (Vivitrol)
- All current meds are approved for alcohol dependence, effect on milder forms of alcohol use disorders not clear.
Naltrexone

- Synthesized 1963

- Opioid antagonist with greatest affinity for the \( \mu \)-receptor but with actions at \( \delta \)- and \( \kappa \)-receptor

- First clinical testing was in heroin addiction but oral formulation not well accepted in this population

- Approved by FDA in 1984, given orphan drug status in 1985

- One likely action is to counteract effect of alcohol-induced release of \( \beta \)-endorphin, reduces rewarding response
Naltrexone in the Treatment of Alcohol Dependence: Primary Outcome

Cumulative Relapse Rate*

Cumulative Proportion With No Relapse

Treatment Weeks

Naltrexone HCl (N=35)
Placebo (N=35)

*Time to first episode of heavy drinking; $P<.01$

Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings: A Systematic Review and Meta-analysis  Jonas et al, JAMA 311:1889, 2014

Naltrexone 50 mg/d, Return to Heavy Drinking

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Type</th>
<th>Heavy Drinking</th>
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Subtotal: $I^2 = 43.7\%$; $P = .02$

Number Needed to Treat = 12  WMD: $-4.1\%$ HDD ($-7.6$ to $-0.61$)
Naltrexone 50 mg/d, Return to Any Drinking

Number Needed to Treat = 20
How Does Naltrexone Work?

More effective on reducing heavy drinking than enhancing abstinence but can do both
Naltrexone vs. Placebo: Effect on Experience of Feeling “High” During Lapse
Volpicelli et al, 1995

The bar chart illustrates the comparison between Naltrexone and Placebo on the experience of feeling "High" during a lapse. The x-axis represents the type of treatment (Naltrexone or Placebo), while the y-axis shows the number of subjects. The chart categorizes the effect into three groups: Less Effect, Equal Effect, and More Effect.

- Naltrexone:
  - Less Effect: 6 subjects
  - Equal Effect: 4 subjects
  - More Effect: 2 subjects

- Placebo:
  - Less Effect: 2 subjects
  - Equal Effect: 12 subjects
  - More Effect: 0 subjects
Effects of Naltrexone on Cue-Induced Activation of Ventral Striatum (Craving?)

Myrick et al, Arch Gen Psychiatry. 2008;65(4):466-475

Figure 2. Brain regions with significantly increased activation in one task (alcohol) compared with another (beverage) are depicted in color on coronal structural magnetic resonance images (P≤.001). Ondansetron given as ondansetron hydrochloride.
Long-Acting Naltrexone

• Awareness that compliance with naltrexone very problematic in opioid addiction and compliance with medications an important factor in alcoholism.

• Multiyear effort by many parties to develop long-acting formulation.

• Technology is same as for long-acting risperidone—microspheres that degrade and release drug at therapeutic level over 30 days.
Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence: A Randomized Controlled Trial  Garbutt et al JAMA. 2005;293:1617-1625.

- 627 alcohol dependent patients randomized to placebo, 190 mg LA-NTX, or 380 mg LA-NTX
- 68% men, 50% were actively drinking at randomization
- Primary outcome measure was event rate of heavy drinking
- Gender, goal of abstinence and established abstinence for 7 days at first injection were randomization factors.
Results: Median Heavy Drinking Days

- Median Heavy Drinking Days per Month:
  - Baseline: 19.3
  - Placebo: 6.0
  - Long Acting Naltrexone 190 mg: 4.5
  - Long-Acting Naltrexone 380 mg: 3.1

- Sample size: n = 624
- Statistical significance: 48% decrease, p < 0.005

Garbutt et al, 2005
Heavy Drinking Events: Placebo Men

Days

Patients

-30  0  30  60  80  120  150  180  210  240

Initial Injection
Heavy Drinking Events: Long-Acting Naltrexone 380 mg Men

No significant effect in women

Initial Injection
Effect of Long-Acting Naltrexone in Maintenance of Abstinence

Subjects with 4 day lead in abstinence

Percent Abstinent

0 10 20 30 40 50 60 70 80 90 100

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

Weeks

Placebo (n = 28)  Long-Acting Naltrexone (n = 28)

p < 0.025

Acamprosate

- Early animal trials in early 1980s suggested could reduce voluntary ethanol intake
- Positive clinical trial in 1985 in 85 “severe alcoholics” revealed improved rates of total abstinence.
- Thought to reduce protracted withdrawal by possibly stabilizing hyperglutamatergic systems?
• 272 patients with alcohol dependence, ~80% male, mean of 40 years of age
• Alcohol free from 14-28 days and no overt withdrawal symptoms
• Randomized, double-blind placebo controlled trial
• Placebo or acamprosate 1998 mg/d or 1332 mg/d depending on weight for 48 weeks followed by 48 week follow up
Acamprosate Improves Abstinence in Alcohol Dependence

- Treatment Period: 43% for Acamprosate (N = 136), 21% for Placebo (N = 136)
- Follow-Up Period: 37% for Acamprosate, 17% for Placebo

*P = 0.001; †P = 0.003; 272 patients were entered into the study over 2 years.

Kaplan-Meier survival analysis (survival function estimate); abstinence for the treatment and follow-up periods.

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Acamprosate, Return to Any Drinking

<table>
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<tr>
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<th>Duration, wk</th>
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<th>Treatment Events, No.</th>
<th>Treatment No Events, No.</th>
<th>Control Events, No.</th>
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<th>Risk Difference (95% CI)</th>
<th>Favors Treatment</th>
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Number Needed to Treat=12
Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings: A Systematic Review and Meta-analysis
Jonas et al, JAMA 311:1889, 2014

Acamprosate, Return to Heavy Drinking

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<tr>
<th>Source</th>
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<th>Risk of Bias</th>
<th>Events, No.</th>
<th>No Events, No.</th>
<th>Events, No.</th>
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<th>Risk Difference (95% CI)</th>
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No Significant Effect of Acamprosate on Heavy Drinking
Where are we in 2016?

- Four FDA approved medications, each has value though overall effect size for any single medication modest.
- Active research ongoing to understand who responds to which medication and identifying new medications with new molecular/clinical targets.
Three Stories

1) Identifying responders to naltrexone

2) Baclofen, a potential new medication for alcohol use disorders?

3) Oxytocin, can it reduce alcohol withdrawal and improve drinking?
Alcoholism comes in many forms
How do we identify responders?

**Figure 2** Fishbone diagram of possible moderators of response to naltrexone in alcohol dependence. For each bone, we provide the number of studies that indicate a positive (+) or negative (−) association or mixed/neutral evidence (Ø) between the moderator and naltrexone response.
Naltrexone and the Asn40Asp Polymorphism of the u-opioid Receptor Gene

- A single nucleotide change leads to a shift from asparagine to aspartate at position 40 in the mu-opioid receptor.
- There is evidence that this change is functional, i.e. there are differences in opioid response between the Asn40 and the Asp40 receptors.
- Frequencies of AG/GG Genotype:
  - Caucasian 2.5-15%
  - African-American 0-5%
  - Asian 25-47%
Polymorphism of the \( \mu \)-Opioid Receptor and Response to Ethanol

- Asn40Asp or G allele, associated with *enhanced* DA response to ethanol:

\[
\text{N}=28 \ (12 \text{ AG; 16 AA})
\]

Dopamine response to ethanol assessed with PET scans.  
Ramchandani et al, Mol Psych 16: 809, 2011
Response to Naltrexone and AG/GG Allele
Oslin et al, Neuropsychopharmacology 28:1546, 2003

Figure 1. Survival analyses for time to relapse in subjects with one or two copies of the Asp40 allele vs those homozygous for the Asn40 allele by medication group.

<table>
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<th>Author, Year</th>
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<th>Type of Analysis</th>
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<td>Coller et al., 2011</td>
<td>Substudy of VA</td>
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<td>NTX-50mg/d</td>
<td>100</td>
<td>⊳ ↔ ○</td>
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<td>⊳ ↔ ○</td>
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<tr>
<td>Gelernter et al., 2007</td>
<td>Non-randomized</td>
<td></td>
<td>NTX-50mg/d</td>
<td>220</td>
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<td>⊳ ↔ ○</td>
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<tr>
<td>Kim et al., 2009</td>
<td>Non-randomized</td>
<td></td>
<td>NTX-50mg/d</td>
<td>320</td>
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<td>Olsson et al., 2003</td>
<td>Pooled analysis</td>
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<td>NTX-50-100mg/d</td>
<td>130</td>
<td>↑</td>
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All these findings came from secondary analyses.
Naltrexone vs Placebo for the Treatment of Alcohol Dependence: A Randomized Clinical Trial
Oslin et al, JAMA Psychiatry. 72:430, 2015

221 subjects, 5 sites, randomized to placebo or naltrexone (50 mg) for 12 weeks.
Randomization by Asn40 or Asp40 genotype.

No main effect of naltrexone found.

NO EFFECT of Asp40 genotype found.

“Negative” trials not uncommon in alcohol use disorders.
The biology of the hedonic response to sweets utilizes similar neural pathways that respond to alcohol and drugs—the opioidergic/dopaminergic reinforcement pathways.
Sweet-Liking/Sweet Disliking Phenotype

Figure 1. Hedonic response to varying concentrations of sucrose in SL and SD (adapted from Thompson et al., 1976)
Sweet Liking Phenotype, Alcohol Craving and Response to Naltrexone Treatment in Alcohol Dependence  Garbutt et al, Alc Alcohol 44:293, 2009

• Open label trial in 40 subjects (15 SL phenotype) of 50 mg naltrexone
Sweet Liking Phenotype and Craving for Alcohol Moderate Response to Naltrexone Treatment in Alcohol Dependence: A Randomized, Double-Blind, Placebo-Controlled Trial. Garbutt et al, in preparation

- N=80 (22 SL phenotype, 71% male, age 47 years) randomly assigned by SL/SDL status and level of craving to naltrexone 50 mg/d or placebo for 12 weeks
- Heavy drinking days and abstinent days over the trials were primary outcomes
Main Effects

• A marginal main effect of naltrexone on heavy drinking was noted (p=0.065).
• SL moderated the effect of naltrexone on heavy drinking (p=0.020) and abstinence (p=0.024)
• High craving moderated heavy drinking (p=0.008).
• The combination of SL and high craving was associated with a strong response to naltrexone (12.4 fewer heavy drinking days, p=0.024 and 43.6 more abstinent days, p<.0001, compared to placebo).
SL Phenotype and Craving for Alcohol Associated with Fewer Heavy Drinking Days with Naltrexone
Baclofen

-Baclofen is a GABA\textsubscript{B} agonist that, unlike GABA\textsubscript{A}, activates second messenger systems rather than ion channels. It modulates multiple systems including reward pathways and anxiety pathways.

-It is FDA approved for spasticity.

-Early clinical trials (Addolorato et al, 2002; 2007) showed evidence for efficacy in reducing drinking, craving and anxiety but later trials (Garbutt et al, 2010) did not show effects on drinking though an effect on anxiety. Dose was 30 mg. One explanation is greater physical dependence in Addolorato sample.
Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study

30 mg baclofen vs placebo, 12 weeks

84 alcohol dependent patients with cirrhosis, 88% Child-Pugh class B/C

71% of baclofen patients maintained abstinence vs 29% of placebo, P<.0001

The only medication to date shown in a clinical trial to have potential value for improving drinking behavior in alcohol dependent patients with cirrhosis
Baclofen Dose Considerations

Dr. Ameisen treated himself with baclofen based on Addolorado’s work. He increased his dose up to 270 mg/d and reported marked decrease in anxiety and thoughts of alcohol. Became sober and reduced baclofen dose.

Along with case reports of efficacy of high dose, 100-150 mg/d, baclofen for drinking interest developed in testing higher doses.

- 56 alcohol dependent subjects, all post-detox, ~14 drinks/drinking day. 20 week trial with 8 weeks at high dose (goal 270 mg/d, mean was 180 mg/d).

---baclofen superior to placebo in maintaining abstinence, p<.05
---In this population, 70% male, 45 years old, baclofen was well tolerated.
Side effects of high dose baclofen

- de Beaurepaire, Frontiers Psychiatry 3:1, 2012  
  n=100, open label, mean dose 147 mg/d for one year: substantial fatigue/sleepiness 64%, insomnia 31%, dizziness 21%, paresthesia 18%, nausea/vomiting 17%, sensory alterations 16%  
- Rigal et al, Alcohol Alcohol 47:439, 2012  
  n=181, mean dose 129 mg/d at one year, “Common” side-effects: fatigue or somnolence, insomnia, vertigo and digestive disorders. 6 subjects stopped drug.
Baclofen Status 2016

• Mixed evidence for efficacy at low-moderate dose. High dose trials, 90-300 mg/d, in Europe and U.S. ongoing.

• Suggestions that higher doses may be more effective but adverse effects need to be evaluated.

• May be a useful agent for managing anxiety/sleep in the alcoholic patient and no major addiction risk noted so far.

• Only agent to date shown to be safe and effective in alcoholic cirrhosis—but limited data.
Oxytocin

Nonapeptide released by posterior pituitary for uterine contraction, milk ejection. Oxytocin in brain associated with pro-social and anxiolytic properties and can counteract physical dependence to opiates and alcohol.
Oxytocin Blocks Development of Tolerance to Ethanol


Fig. 5. Effect of OXT on ethanol-induced hypothermia. Mice were injected with OXT 2 h before injection of ethanol. Rectal temperature was monitored 45 min after ethanol administration. Values represent mean ± SEM for 10–19 animals per group.
Intranasal Oxytocin Blocks Alcohol Withdrawal in Human Subjects
Pedersen et al, ACER 37:484, 2013

• Placebo-controlled clinical trial
• Hospitalized subjects at risk for alcohol withdrawal; CIWA-Ar triggered lorazepam
• Oxytocin 24 IU intranasally bid (n=7), PBO (n=4)
• Followed for 3 days with CIWA-Ar ratings
Intranasal Oxytocin Blocks Alcohol Withdrawal in Human Subjects
Pedersen et al, ACER 37:484, 2013

![Bar chart showing the comparison of CIWA-Ar Day 1 and Lorazepam total mg between Placebo and Oxytocin groups.](chart.png)
Summary in Broader Context of Recovery

• Medications for alcoholism are minimally utilized.
• Overall effect sizes are low but that is a group statistic--some patients have very positive responses.
• The use of medications should be considered when treating the patient with an alcohol use disorder.
• It makes sense to start with FDA approved medications:
  - disulfiram for the motivated patient who wants sobriety
  - naltrexone for most patients and can consider long-acting naltrexone if affordable
  - acamprosate may be considered for the patient with some established sobriety, may help with post-withdrawal sleep problems as well.
• Off-label medications
  - topiramate has strongest evidence for efficacy but tolerability problems
  - gabapentin emerging as promising agent and may help with sleep/anxiety/withdrawal.
  - baclofen has less certainty but only drug with evidence in patients with cirrhosis.
  - varenicline?
• Medications are one tool in recovery. Patients should be encouraged to engage in counseling, attend AA or other meetings and realize recovery is more than taking a pill.
“The Journey of a Thousand Miles begins with a Single Step”