Pharmacotherapy for Alcohol Use Disorder

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Disclosures

Neither my spouse nor I have disclosures
Objectives

- Epidemiology of Alcohol Use Disorders
- FDA approved medications
- Off label medications
- Case examples
- Resources
High Cost Consequences of AUD

- > 88,000 deaths per year directly attributed to alcohol use
- 4th leading cause of death in US
- 30% of homicides, 22% suicides, 33% MVAs
- Annual estimated cost of alcohol use is up to $250 BILLION

CDC 2016
Prevalence of Alcohol Use Disorder

Center for Behavioral Health Statistics and Quality. (2016). *Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health* (HHS Publication No. SMA 16-4984, NSDUH Series H-51)
Recommendations vs. Reality

- Veterans Administration, NIAAA, SAMHSA
  - All recommend pharmacotherapy for alcohol use disorder
  - Yet...

- Fewer than 1 in 3 patients receive treatment for alcohol use disorder
- Fewer than 1 in 10 receive medication

- 70% relapse with psychosocial treatment alone

...90% do not receive treatment

FDA Approved Pharmacologic Treatments

Disulfiram (Antabuse)
1951

Naltrexone (Revia)
1994

Acamprosate (Campral)
2004

Naltrexone ER (Vivitrol)
2006

DSM 5
Heterogeneous disorder stemming from a complex interaction between neurobiological, genetic, and environmental factors
The presence of 2 or more criteria indicates an Alcohol Use Disorder*

<table>
<thead>
<tr>
<th>DSM-5 Criteria</th>
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<tbody>
<tr>
<td>Alcohol is taken in larger amounts or over a longer period than intended</td>
<td>Important social, occupational, or recreational activities are given up or reduced because of alcohol use</td>
</tr>
<tr>
<td>Persistent desire or unsuccessful efforts to cut down or control alcohol use</td>
<td>Recurrent alcohol use in situations in which it is physically hazardous</td>
</tr>
<tr>
<td>A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects</td>
<td>Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol</td>
</tr>
<tr>
<td>Craving</td>
<td>Tolerance</td>
</tr>
<tr>
<td>Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol</td>
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*Mild = 2-3 criteria, Moderate = 4-5 criteria, Severe 6 or more criteria*
Patient Selection

- Moderate and severe alcohol use disorder
- Mild use disorder PLUS risk, on case by case
- Desire to cut down or quit
- Able to participate in shared decision making
- Co-occurring medical illnesses
- No medical contraindications
- Patient preference
Naltrexone

• Mechanism of Action: Opioid receptor antagonist

• Dosing:
  – NTX Oral: 12.5 or 25 mg po x 3 days, then 50 mg daily
  – NTX Depot: 380 mg IM every 4 weeks
  – Baseline and monitor LFTs, wallet card or ID

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Warnings</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Hepatotoxicity</td>
<td>Opioid Use</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Depression</td>
<td>Transaminitis &gt;5 x normal</td>
</tr>
<tr>
<td>Headache</td>
<td>Suicidality</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>Injection Reaction</td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>Transaminitis</td>
<td></td>
</tr>
<tr>
<td>Transaminitis</td>
<td>Injection Reaction</td>
<td></td>
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<tr>
<td>Pain Blockage</td>
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Naltrexone Efficacy

• Meta-analysis of short RCT (<3 mo)
  - Improved outcomes in primary care settings
  - Reduced intensity, duration and frequency of relapse to heavy drinking from 48%-37%
  - Decreased drinking days by 4.5%
  - Increased days abstinent from 30—35%

• No head to head studies of oral vs depot ER naltrexone

• Two short term trials compared acamprosate to naltrexone
  • Both found naltrexone superior

Monterosso JR et al. Predicting treatment response to naltrexone: the influence of craving and family history. AmJAddict 2001; 10:258
# Naltrexone and Hepatotoxicity

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>NTX Dose</th>
<th>Hepatotoxicity Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volpicelli et al, 1992</td>
<td>77</td>
<td>50 mg daily</td>
<td>↓AST &amp; GGT in NTX group, insignificant</td>
</tr>
<tr>
<td>O’Malley et al, 1992</td>
<td>97</td>
<td>50 mg daily</td>
<td>↓AST in NTX (p &lt;0.05)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>↓ALT in NTX (p&lt;0.1)</td>
</tr>
<tr>
<td>Morris et al, 2001</td>
<td>111</td>
<td>50 mg daily</td>
<td>↓ALT &amp; GGT in both groups, insignificant</td>
</tr>
<tr>
<td>Garbutt et al, 2005</td>
<td>627</td>
<td>IM 190 mg qmth</td>
<td>No significant changes in AST/ALT from baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IM 380 mg qmth</td>
<td></td>
</tr>
<tr>
<td>Kiefer at al, 2003</td>
<td>160</td>
<td>50 mg daily</td>
<td>Significant ↓GGT in all groups from baseline</td>
</tr>
<tr>
<td>COMBINE Study, 2006</td>
<td>1383</td>
<td>100 mg daily</td>
<td>Pts with AST/ALT ≥5 times ULN: Pbo= 0, Acamprosate= 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NTX= 6, Acamprosate/NTX= 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p= 0.02</td>
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</table>
Naltrexone & Depression/Suicidality Risk

Zaaijer et al, 2015

- Theory: ↓ striatal DA transporter availability is cause of depression & anhedonia in patients with OUD
- Single photon emission CTs were performed at baseline and 2 weeks after the XR-NTX injection
- Beck Depression Inventory (BDI) scores were taken at baseline and 2 weeks after the XR-NTX injection
- Results:
  - No difference in DA transporter binding
  - Statistically significant ↓ BDI scores 2 weeks after XR-NTX injection

Naltrexone Wrap Up

- Monitor LFTs
- Opioid pain blockage – wallet card
- Can be used in people who are still drinking
- Decreases compulsivity
  - Strong cravings, positive family history are predictors of response
- Consider oral supplementation end of month
Acamprosate

Mechanism of action

- thought to inhibit glutamate, antagonize NMDA, stimulate GABA

Dosing:

- 666mg po TID
- No need to change in hepatic dysfunction

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<tr>
<td>• Diarrhea</td>
<td>• Half life increases with renal insufficiency</td>
<td>• Severe renal insufficiency (CrCl ≤30)</td>
</tr>
<tr>
<td>Nausea</td>
<td>• Adjust dose for Cr Cl</td>
<td></td>
</tr>
<tr>
<td>• Somnolence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acamprosate Efficacy

• 2006 meta-analysis naltrexone better for reducing drinking and acamprosate for abstinence

• Predictors of therapeutic response
  – Anxiety, physiologic dependence, late age of onset, female, negative FH

Improvements may be expected:
  – Time to first relapse (6 month vs 3)
  – Total number of days abstinent (270 vs 135)
  – Time to first drink
  – Craving may decrease

Length of treatment
  – One year whether drinking or not

48 week trial
  – 40% abstinent rate for Acamprosate vs. 17% placebo
  – Effect durable at 96 weeks

Verheul R et al. Predictors of acamprosate efficacy; Psychopharmacology 2005;178:167
Disulfiram

- **Mechanism of Action: Aversive**

- **Dosing:**
  - 250 mg daily → 500 mg daily
  - Abstain from EtOH >12-24 hours
  - Abstain from disulfiram >2 weeks prior to EtOH

### Adverse Effects
- Flushing
- Transaminitis
- Neuropathy
- Dysgeusia
- Dermatitis
- Headache

### Warnings
- Recent EtOH use
- Possible
- Hepatotoxicity (idiosyncratic)
- Warfarin, INH
- Pregnancy cat C
- Breastfeeding

### Contraindications
- Severe CAD
- Psychosis
- Varices
- Pregnancy
- Elder
- Rubber, Nickel, Cobalt allergies
Disulfiram Efficacy

– Evidence from RTCs does not support long term efficacy
– Efficacy in supervised trial
– Who then?
  • Patients with goal of abstinence but either intolerant of or not interested in daily medication
  • High risk situations
  • Expect double abstinent rate if monitored (23% vs. 15% at one year)

Topiramate

• Mechanism of Action:
  – Enhances GABA A (non-benzodiazepine site) activity
  – Glutamate receptor antagonist

• Dosing:
  – 25-50 mg/day
  – Titrate up by 25 mg per day week, to max dose 150mg BID

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<tr>
<th>Adverse Effects</th>
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<th>Contraindications</th>
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</thead>
<tbody>
<tr>
<td>• Weight loss</td>
<td>• Cognitive Delay</td>
<td>• Nephrolithiasis</td>
</tr>
<tr>
<td>• Paresthesias</td>
<td>• “Dope-a-max”</td>
<td>• Breastfeeding</td>
</tr>
<tr>
<td>• Change in taste</td>
<td>• Fatigue</td>
<td>• Nephrolithiasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pregnancy</td>
</tr>
</tbody>
</table>
Topiramate Reduces Heavy Drinking Days

Topiramate Increases Days Abstinent

Topiramate Increases Mean Abstinent Days per Week

**Gabapentin**

**Mechanism of Action:**
- Enhances GABA activity
- Glutamate receptor antagonist

**Dosing:**
- 900-1800 mg by mouth daily (divided 3 times a day)
- Response appears dose-related

**Adverse Effects**
- Fatigue
- Headache
- Sedation
- Insomnia
- Nervousness
- Depression

**Warnings**
- Seizure with abrupt cessation
- Misuse Potential
- renal insufficiency

**Contraindications**
- Known allergy to Gabapentin
Gabapentin & Misuse Potential

• Wilens et al, 2015
  – n= 162 opioid dependent patients
  – Pt self-report of psychotropic medication use
  – 22% reported gabapentin misuse

• Drug Abuse Warning Network data show that ED visits involving the nonmedical use of gabapentin ↑ 90% in the US since 2008

• Prescribing information not accessible through PMP

SAMHSA. Emergency Department Data. June 10, 2014
## Summary of Potential Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacy</th>
<th>Next Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalmefene</td>
<td>Small effect size in 3 recent European trials</td>
<td>• No plans for FDA approval for AUD</td>
</tr>
<tr>
<td></td>
<td>↓ Heavy drinking, ↓ Cravings</td>
<td></td>
</tr>
<tr>
<td>Varenicline</td>
<td>Multisite RCT ↓ Heavy drinking in AUD</td>
<td>• No plans for FDA approval for AUD</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Single site RCT ↓ Cravings, ↓ Heavy drinking, ↑ Abstinence</td>
<td>• Ongoing multi-site trials</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Several RCTs and one multi-site RCT ↓ Cravings, ↓ Heavy drinking, ↑ Abstinence</td>
<td>• Ongoing multi-site trials to reproduce findings</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>2 single site RCTs ↓ Heavy drinking</td>
<td>• Several ongoing trials</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Several RCTs with mixed results</td>
<td>• Several large ongoing studies (higher doses)</td>
</tr>
<tr>
<td></td>
<td>↑ Abstinence, ↓ Cravings (?)</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>2 large RCTs ↓ Heavy drinking in early onset AUD and genetic polymorph</td>
<td>• Ongoing multisite RCTs</td>
</tr>
</tbody>
</table>
How to Choose?
Case 1

• Mark is a 35 yo businessman with mild AUD, a few ER visits for alcohol related accidents and altercations, now s/p MVA while OUI.

• Admitted to hospital x 7 days and plan for DC home.
  – LFTs 2 x normal but trending down from 10 x normal
  – Normal renal function

• He is interested in medication
Case 1

• Starts oral naltrexone
• Transitions to IM pre-discharge from hospital
• Pain at injection site, but resolved after 1 week
• Continues to drink 3-4 EtOH/day, but no binges
• What do you do/recommend?
  A) DC naltrexone as he is not abstinent
  B) Continue naltrexone but only if he agrees to full abstinence
  C) Continue naltrexone and assess his level of support/other treatment
Case 2

• Richard is a 60 yom with severe AUD, cirrhosis, esophageal varices s/p UGI, s/p TIPS, DM, nephrolithiasis, admitted to your facility for the 5th time this year with complicated alcohol withdrawal, now stable and ready for discharge.

• Normal LFTs, normal renal function

• Highly motivated to stop drinking

• What medication would you recommend?
  A) Naltrexone
  B) Acamprosate
  C) Disulfiram
  D) Topiramate
Case 3

• Sandra is a 45 yr old nurse with moderate AUD, fatty liver disease, anxiety, insomnia, and worsening migraines. Alcohol relaxes her. She would like to lose weight, sleep better and control her migraines and anxiety. She would like to cut back on drinking after speaking with you.

• What medication would you recommend?
  A) Naltrexone
  B) Acamprosate
  C) Topiramate
  D) Clonazepam 0.5-1 mg po qHS
Case 4

• James is a 28 yr old jazz musician on probation, in early remission from severe AUD, on Acamprosate. He has a big gig he’s thrilled about coming up, where he knows there will be lots of alcohol and would like something to provide added “protection” against drinking.

• No other medical issues.

• You suggest:
  A. Don’t go to this event – too triggering
  B. D/C Acamprosate and give him Naltrexone ER 380 mg one day prior to the event
  C. He needs a higher level of care
  D. Continue Acamprosate and add Disulfiram daily for the days of the event
Bottom Line

• AUD is prevalent and vastly under-treated
• Goals of therapy = abstinence or reduction of heavy drinking
• Primary care/outpatient settings optimal
• Medications for AUD are not controlled substances and not addictive
• Medications are another “tool in the shed”
• Patient-centered care most effective
• Recall other chronic disease management and treatment options
  ...this is no different
Moving Forward...
Want to Learn More?

lgkehoe@partners.org
Case Answers

• Case 1: C) Continue naltrexone and assess his level of support/other treatment
• Case 2: B) Acamprosate
• Case 3: C) Topiramate
• Case 4: D) Continue acamprosate and add disulfiram 250 mg po daily for the days of the event