Pharmacotherapy for Alcohol Use Disorder

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Objectives

- Epidemiology of Alcohol Use Disorders
- FDA approved medications
- Off label medications
- Cases
- Resources
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)
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
Recommendations vs. Reality

- Veterans Administration, NIAAA, SAMHSA
  - All recommend pharmacotherapy for alcohol use disorder
- 70% relapse with psychosocial treatment alone

Yet...

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

...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.
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
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, symptoms, 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 as start</td>
</tr>
<tr>
<td>Headache</td>
<td>Suicidality</td>
<td>Stop if &gt;10X nl</td>
</tr>
<tr>
<td></td>
<td>Injection Reaction</td>
<td></td>
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<tr>
<td></td>
<td>Pain Blockage</td>
<td></td>
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<tr>
<td></td>
<td>Transaminitis</td>
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</table>

Naltrexone Efficacy

**Oral Naltrexone (Meta-analysis of 11 short RCT, <3 mo)**

- improved outcomes in primary care settings
- reduced intensity, duration and frequency of relapse to heavy drinking (38% ntx vs. 60% placebo)
- fewer return to drinking (61% ntx vs. 69% placebo)
- increased days abstinent

**Depot NTX (Meta-analysis, 6 months)**

- reduced risk of heavy drinking to 83% of risk in placebo group
- decreased drinking days by about 4%

**Acamprosate to naltrexone (two short term trials compared)**

- Both found naltrexone superior

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Oral Naltrexone

Cumulative Relapse Rate
Naltrexone vs. Placebo

Decreased Drinking and Increased Abstinence

Impact of Long-Acting Naltrexone on Median Heavy Drinking Days per Month

# 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) ✅ 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 IM 380 mg qmth</td>
<td>No significant changes in AST/ALT from baseline</td>
</tr>
<tr>
<td>Kiefer et 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 NTX= 6, Acamprosate/NTX= 5 p= 0.02</td>
</tr>
</tbody>
</table>
Naltrexone & Depression/Suicidality Risk

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

Zaaijer et al, 2015

How to Do a Gluteal Injection

Youtube Naltrexone ER Gluteal Injection
Naltrexone ER Injection

https://www.youtube.com/watch?v=lZBaDClWSwg

https://pcssmat.org/overview-of-mat/naltrexone/
Total time spent...

Preparation  2 minutes, 10 seconds
+            |
Administration 1 minute, 25 seconds

________________________________________

Total Time Spent  =  3 minutes, 35 seconds
## Compare to Other Primary Care Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exam</td>
<td>15-25 minutes</td>
</tr>
<tr>
<td>Pap smear</td>
<td>10-20 minutes</td>
</tr>
<tr>
<td>Incision and Drainage</td>
<td>15-30 minutes</td>
</tr>
<tr>
<td>Joint Injections</td>
<td>15-30 minutes</td>
</tr>
<tr>
<td>Ear irrigations</td>
<td>10-15 minutes</td>
</tr>
<tr>
<td>Manual Vital Signs</td>
<td>2-4 minutes</td>
</tr>
<tr>
<td>Immunizations</td>
<td>2-5 minutes</td>
</tr>
</tbody>
</table>
Naltrexone Wrap Up

- Can be used in people who are still drinking
- For abstinence and to decrease use/consequences
- No empirical evidence on frequency of LFT monitoring
- Transaminitis usually other cause (EtOH, Hep C)
- Opioid pain blockage – wallet card, IM vs. oral
- Many do well with oral
- Naltrexone ER not difficult, aides adherence
Acamprosate

Mechanism of action

- thought to inhibit glutamate, antagonize NMDA, stimulate GABA

Dosing:

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

### Adverse Effects

- Diarrhea
- Nausea
- Somnolence

### Warnings

- Half life increases with renal insufficiency
- Adjust dose for Cr Cl

### Contraindications

- Severe renal insufficiency (CrCl \(\leq 30\))
Acamprosate Efficacy

Naltrexone better for reducing drinking and acamprosate for abstinence, (2006 meta-analysis)

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

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

Compared efficacy of 9 different treatment combinations

- Acamprosate, naltrexone, or combination of both

Behavioral interventions included medical management (MM) and combined behavioral intervention (CBI)

Placebo conditions included pills and no med

Patients receiving medical management with naltrexone, CBI, or both showed substantial reduction in drinking.

Acamprosate showed no evidence of efficacy, with or without CBI.

No combination produced better efficacy than naltrexone or CBI alone.
Acamprosate Wrap Up

- Consider in patient with decompensated liver disease
- Consider in patient intolerant of Naltrexone
- Consider in patient on chronic opioids
- TID dosing tough for anyone
- Best outcomes for abstinence post detox
- No need to taper
Disulfiram

• Mechanism of Action: Aversive

• Dosing:
  – 500 mg daily x 1 week → 250 mg daily
  – Abstain from EtOH >12-24 hours
  – Abstain from disulfiram >2 weeks prior to EtOH

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<tr>
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<tr>
<td>• Flushing</td>
<td>• Recent EtOH use</td>
<td>• Severe CAD</td>
</tr>
<tr>
<td>• Transaminitis</td>
<td>• Possible</td>
<td>• Psychosis</td>
</tr>
<tr>
<td>• Neuropathy</td>
<td>• Hepatotoxicity (idiosyncratic)</td>
<td>• Varices</td>
</tr>
<tr>
<td>• Dysgeusia</td>
<td>• Warfarin, INH</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Dermatitis</td>
<td>• Pregnancy cat C</td>
<td>• Elder</td>
</tr>
<tr>
<td>• Headache</td>
<td>• Breastfeeding</td>
<td>• Rubber, Nickel, Cobalt allergies</td>
</tr>
</tbody>
</table>
Disulfiram Efficacy

Evidence from RCTs does not support long term efficacy

Efficacy in supervised trial

Expect double abstinent rate if monitored (23% vs. 15% at one year)

Disulfiram Wrap Up

- Aversive only
- Consider for patients with goal of abstinence but either intolerant of or not interested in daily medication
- Consider as add on for others in high risk situations
- No need to taper
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>
<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>
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<td></td>
<td></td>
<td>Pregnancy</td>
</tr>
</tbody>
</table>
Topiramate Reduces Heavy Drinking Days

Topiramate Increases Days Abstinent

Topiramate Wrap Up

- Off label use
- Consider in patient intolerant of Naltrexone or Acamprosate
- Consider in patient with co-occurring other indication (neuropathic pain, migraines, seizure disorder, obesity, insomnia, cocaine use disorder)
- Slow titration up
- Need to taper
• **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

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<tr>
<td>Fatigue</td>
<td>Insomnia</td>
<td>Seizure with abrupt cessation</td>
</tr>
<tr>
<td>Headache</td>
<td>Nervousness</td>
<td>Misuse Potential</td>
</tr>
<tr>
<td>Sedation</td>
<td>Depression</td>
<td>renal insufficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Known allergy to</td>
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<tr>
<td></td>
<td></td>
<td>Gabapentin</td>
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</tbody>
</table>
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:

- ED visits involving the nonmedical use of gabapentin ↑ 90% in the US since 2008

Prescribing information now accessible through PMP

- Individualize care, weigh risks and benefits

SAMHSA. Emergency Department Data. June 10, 2014
Gabapentin Wrap Up

- Consider in patients immediately post detox
- Consider in patients with ongoing use/cravings/post acute withdrawal symptoms
- Consider in patients with co-occurring indications (neuropathic pain, seizure disorder)
- Caution misuse potential
- Needs to be tapered
## 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&lt;br&gt;↓Heavy drinking&lt;br&gt;↓Cravings</td>
<td>• No plans for FDA approval for AUD</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&lt;br&gt;↓Cravings&lt;br&gt;↓Heavy drinking&lt;br&gt;↑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&lt;br&gt;↑Abstinence&lt;br&gt;↓Cravings (?)</td>
<td>• Several large ongoing studies (higher doses)</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?
Mark

• 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
Mark

- 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
Richard

- 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 totally
- Good support system, has done numerous inpatient and outpatient treatment programs, 12 step support
- What medication would you recommend?
  A) Naltrexone
  B) Acamprosate
  C) Disulfiram
  D) Topiramate
Richard

• Richard returns for follow up 1 week later
• Notes Acamprosate causing GI upset, and he cannot tolerate 2 tabs TID dosing. Adamant he can’t take it
• He had a drink last night and is terrified he will go on a binge again. His goal is abstinence.
• He has insomnia, but denies other depressive symptoms
• He starts an intensive outpatient program next week and has a sponsor from AA
Richard

You recommend:

A) Start IOP and follow up in one week, prescribe Alprazolam (Xanax) 0.5 mg HS prn for insomnia, journal EtOH intake

B) Rx Gabapentin 300 mg TID with up-titration as needed and tolerated

C) Encourage him to give Acamprosate another try

D) All of the above
Sandra

• 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
Sandra

- 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 (Klonopin) 0.5-1 mg po qHS
James

- James is a 28 yr old rock 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.
- Goal is abstinence.
- 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
Monica

- 40 yof mother of 3 high school kids, VP of local bank
- Tells you she is distraught because her husband gave her an ultimatum that she stop drinking or he will leave her
- She requests to see a therapist for stress reduction
- Her kids have told her she embarrasses them when she drinks because she gets loud, says inappropriate things, falls asleep when guests are over, and sometimes picks fights for no reason
- Drinks 1.5-2 bottles of wine daily, occasionally a “cosmo” or two on weekends too
Monica

• Drinking relaxes her after stressful day
• Enjoys it
• Usually drinks with others, and recently has started drinking earlier in the day, alone, at lunch
• Has tried numerous times to cut back or control her drinking, but only lasts a few weeks max
• She went to AA and could not relate to the people there
• She has hangovers after she drinks, but no withdrawal sx
• Does not want to stop completely
• BP elevated and mild transaminitis (1.5x normal)
You refer to a therapist and recommend:

• A) Refer to inpatient detox
• B) Naltrexone (Revia), 50 mg daily
• C) Refer to AA
• D) A and C
Monica

• You check in with her by phone after one week
• She notes she is doing well with the Naltrexone, no side effects, no trouble with adherence
• Notes instead of 2 bottles a day, she stops after one. Finds she just doesn’t want more and feels less out of control
• She’s excited but admits she worries she won’t take the tabs and will put herself at risk of increased drinking
• Starts therapy next week
• Husband upset she is still drinking, despite decrease
Monica

You suggest:

A) Naltrexone ER (Vivitrol) injection
B) Encourage her to bring husband to next visit if she is comfortable so doing
C) Encourage her to stick with the oral Naltrexone and add Acamprosate
D) A and B
Monica

- Accepted Naltrexone ER injection and tolerated it well
- You met with couple together
- Drinking now down to 2 glasses of wine a day and engaged in therapy
- BP normalized
- Notes uptick in cravings EtOH and end of third week/beginning of 4th before next injection
You recommend:

A) DC Naltrexone ER and switch to Acamprosate
B) DC Naltrexone ER and switch to Topiramate
C) DC Naltrexone ER and revert to oral Naltrexone
D) Continue Naltrexone ER and supplement with oral naltrexone at the end of the month
Justin

- 35 yom with severe OUD and chronic pain due to crush injury with neuropathic LE pain, in sustained remission on buprenorphine/naloxone 20 mg daily, severe AUD who was recently admitted to the hospital with uncomplicated EtOH withdrawal.
- Because of his AUD, his buprenorphine provider has DC’d his buprenorphine citing risk too high, and recommends detox and residential treatment
- Never offered Rx for AUD but has done numerous short term detoxes, residential and repeated intensive outpatient programs
- Not interested /cannot afford more intensive treatment
You recommend:

A) transition to Naltrexone ER for dual treatment of AUD and OUD
B) resume buprenorphine/naloxone and add Acamprosate
C) resume buprenorphine/naloxone and add Gabapentin
D) resume buprenorphine/naloxone and add Topiramate
E) any of the above
Jim

- Jim is a 64 yo homeless man with hx MDD, severe AUD, DM, well known to the ED, hx of uncomplicated withdrawal
- Admitted for SDH after fall while intoxicated and hypoglycemic
- Frequently leaves the hospital AMA, spotty attendance in primary care
- Numerous involuntary commitments to detox
- Notes “I’m tired of living like this”
- Ambivalent about abstinence, but asks if you can help control his use
- LFTs 3x normal
You recommend:

A) Close interval fu as an outpatient, repeat LFTs, if drop to normal, start oral naltrexone

B) Start oral naltrexone in hospital and transition to naltrexone ER IM prior to DC

C) Start Acamprosate

D) Section him to 30 day program if presents to ED again. Too risky as an outpatient
Jim

You and Jim decide to try Naltrexone, but he needs to leave within 3 hours to secure a bed at the shelter.

Can you give him the injection today?

A) Yes
B) No
Jim

• You give him a dose of oral naltrexone 25-50 mg
• After 60-90 minutes, he has tolerated it, no reaction
• You administer 380 mg naltrexone ER into his LVOQ buttock and plan to see him for close interval follow up
• Give him wallet card, necklace or bracelet
• Educated him about opioid blockade and other risks
But what about his LFTs...!? And homelessness?

- Screen for symptoms
- Recheck LFTs within a few weeks
- LFTs usually drop/normalize
- Recall risk/benefit
- Homelessness does not preclude treatment
Bottom Line

• AUD is prevalent and vastly under-treated
• Goals of therapy = abstinence or reduction of heavy drinking
• Outpatient settings optimal
• Medications for AUD are not controlled substances and not addictive
• Medications are another “tool in the shed”
• Patient-centered, individualized care most effective
• Recall other chronic disease management and treatment options

...this is no different