Alcohol Use Disorder Pharmacotherapy: Traditional Approaches and New Strategies

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Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.
Objectives

1. Compare the diagnostic criteria, biomarkers, and screening tools used for detecting alcohol use disorder.
2. Appraise efficacy of medications used to treat alcohol use disorder.
3. Construct a pharmacotherapy plan for a patient with alcohol use disorder.
4. Design a medication-specific monitoring plan for patients with alcohol use disorder.
Background Information

- Alcohol use is among the top three risk factors for global disease burden, behind only high blood pressure and tobacco smoking.
- High prevalence of Alcohol Use Disorder (AUD) with low rates of treatment:
  - US Adults in 2013: 16.6 million (7%)
    - Men 10.8 million (9.4%)
    - Women 5.8 million (4.7%)
  - Only 1.3 million (7.8%) received specialty treatment.

SAMHSA, National Survey on Drug Use and Health. 2013
Alcohol-Related Risk of Death

- Nearly 88,000 people die from alcohol-related causes annually
- Third leading cause of preventable death
- Any use of alcohol exceeding the recommended daily or weekly limits is considered hazardous
  - Increase in morbidity and mortality
  - Automobile crashes (30.8% of overall driving fatalities)
  - Accidental and intentional injury
  - Social and legal problems

SAMHSA, National Survey on Drug Use and Health. 2013
DSM-5: Alcohol Use Disorder

- Problematic pattern of use that causes significant distress or harm with at least two of the following over 12 months
  - Larger amounts or longer duration than was intended
  - Unsuccessful efforts to cut down or control use
  - Large amount of time spent obtaining, using or recovering from alcohol
  - Craving
  - Continued use despite adverse consequences
  - Enjoyable activities given up or reduced
  - Use in physically hazardous situations
  - Use despite knowledge of condition that is exacerbated by alcohol
  - Tolerance
  - Withdrawal symptoms or alcohol or benzodiazepine is used to avoid symptoms

- Symptom severity: mild = 2-3; moderate = 4-5; severe = 6+

Alcohol Use and Psychiatric Disorders: Diagnostic Challenges

- Alcohol-related symptoms and signs
  - Mood lability, depression, sleep disturbances, disinhibition, aggressiveness, antisocial behaviors, social withdrawal, difficulty concentrating

- Alcohol-induced psychiatric syndromes
  - Persistent symptoms that resemble mental disorders but are temporary
  - Occur during or after severe intoxication or withdrawal
  - Improve (before 30 days) without formal treatment

- Independent psychiatric disorders that co-occur with alcohol use disorder
  - Bipolar disorder, anxiety disorders, schizophrenia, major depressive disorder

Shivani R et al. NIAAA. 2002
Definitions

- AUD: drinking that causes distress or harm, classified as mild, moderate, or severe

- Binge drinking: 5 or more alcoholic drinks on the same occasion at least 1 day in the past 30 days

- Heavy drinking: 5 or more alcoholic drinks on the same occasion for more than 5 days in the past 30 days

# Cutoffs for Concern for AUD

<table>
<thead>
<tr>
<th></th>
<th>Single-day Limit</th>
<th>Weekly Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td>≤ 4</td>
<td>≤ 14</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>≤ 3</td>
<td>≤ 7</td>
</tr>
<tr>
<td><strong>Age &gt; 65</strong></td>
<td>≤ 3</td>
<td>≤ 7</td>
</tr>
</tbody>
</table>

Standard sizes of alcoholic beverages:

- 12 oz. Beer
- 5 oz. Glass of wine
- 1.5 oz (shot) of liquor
Basic Approach to Differentiating Diagnoses

- Probe for alcohol-related problems
  - Frequent injuries (unintentional and intentional)
  - Work and/or relationship problems
- Talk to relatives/friends
- Review medical records
  - Evidence on physical exam
  - Review laboratory results
Alcohol Biomarkers - How Can They Be Used?

- **Screening tool**
  - Role of alcohol can be missed and misuse is high in certain medical contexts (psychiatry, emergency departments)
  - Biomarkers may assist in differential diagnosis

- **Motivating change in drinking behavior**
  - Can provide objective measures of the benefits of reducing or stopping alcohol use

- **Identifying relapse to drinking**
  - Carbohydrate-Deficient Transferrin (CDT) elevation can be an early marker
  - Addressing relapse early is important
# Laboratory Monitoring: Indirect Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Screen for Heavy Drinking</th>
<th>Time to Return to Normal with Abstinence</th>
<th>Possible Source of False Positive</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>✓</td>
<td>2-4 weeks</td>
<td>Excessive coffee consumption; medications</td>
<td>Ratio AST:ALT &gt; 2:1 suggests liver damage from alcohol</td>
</tr>
<tr>
<td>ALT</td>
<td>✓</td>
<td>2-4 weeks</td>
<td>Excessive coffee consumption; medications</td>
<td>Less sensitive than AST</td>
</tr>
<tr>
<td>MCV</td>
<td>✓</td>
<td>Up to several months</td>
<td>Hemolysis, bleeding disorders; anemia, folate deficiency; hypothyroidism; hyperglycemia</td>
<td>Poor biomarker for relapse; higher sensitivity in women versus men</td>
</tr>
<tr>
<td>GGT</td>
<td>✓</td>
<td>2-4 weeks</td>
<td>Liver and biliary disease; smoking; obesity; diabetes</td>
<td>Primarily reflects liver damage, often related to alcohol</td>
</tr>
<tr>
<td>CDT</td>
<td>✓</td>
<td>2-4 weeks</td>
<td>Rare genetic variant, biliary cirrhosis, end stage liver disease, smoking and obesity can alter values</td>
<td>Less sensitive for women and younger age; good biomarker for relapse to heavy drinking</td>
</tr>
</tbody>
</table>

AST = aspartate aminotransferase; ALT = alanine aminotransferase; MCV = mean corpuscular volume; GGT = gamma glutamyl transferase; CDT = carbohydrate-deficient transferrin

SAMHSA. The Role of Biomarkers in the Treatment of Alcohol Use Disorders. *Advisory.* 2012
## Laboratory Monitoring: Direct Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Screening for Heavy Drinking</th>
<th>Time to Return to Normal with Abstinence</th>
<th>Possible Source of False Positive</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtG, EtS</td>
<td></td>
<td>1-2 days</td>
<td>Alcohol in medications, hygiene products, etc.</td>
<td>Direct analytes of nonoxidative breakdown of alcohol; sensitive to as little as a single drink; highly sensitive; good indicator of relapse</td>
</tr>
<tr>
<td>PEth</td>
<td>✓</td>
<td>3 weeks</td>
<td>None likely but still need more data</td>
<td>Direct serum-based biomarker; linear dose-response relationship; more research is warranted</td>
</tr>
</tbody>
</table>

EtG = ethyl glucuronide; EtS ethyl sulfate; PEth = phosphatidyl ethanol

SAMHSA. The Role of Biomarkers in the Treatment of Alcohol Use Disorders. *Advisory.* 2012
Screening - TWEAK Questionnaire

- **Tolerance:**
  - How many drinks can you hold ("hold" version; ≥ 6 drinks indicates tolerance)
  - How many drinks does it take before you begin to feel the first effects of the alcohol? ("high" version; ≥ 3 indicates tolerance)

- **Worried:** Have close friends or relatives worried or complained about your drinking in the past year?

- **Eye openers:** Do you sometimes take a drink in the morning when you first get up?

- **Amnesia:** Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember?

- **Kut down:** Do you sometimes feel the need to cut down on your drinking?

Burge SK et al. Am Fam Physician 1999
Chan et al. Alcohol Clin Exp Res. 1993
Screening - Alcohol Use Disorders Identification Test (AUDIT-C)

<table>
<thead>
<tr>
<th>Question</th>
<th>0 points</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
<th>4 points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How often did you have a drink containing alcohol in the past year?</strong></td>
<td>Never</td>
<td>Monthly or less</td>
<td>2 – 4 times per month</td>
<td>2 – 3 times per week</td>
<td>4 or more times per week</td>
</tr>
<tr>
<td><strong>On days in the past year when you drank alcohol how many drinks did you typically drink?</strong></td>
<td>1 or 2</td>
<td>3 or 4</td>
<td>5 – 6</td>
<td>7 – 9</td>
<td>10 or more</td>
</tr>
<tr>
<td><strong>How often do you have 6 or more drinks on an occasion in the past year?</strong></td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
</tbody>
</table>

When the AUDIT-C is administered by self-report add a “0 drinks” response option to question #2 (0 points based on validations studies). In addition, it is valid to input responses of 0 points to questions #2-3 for patients who indicate “never” in response to question #1 (past year non-drinkers).

Barbor TF, et al. AUDIT 2nd ed. WHO. 2001
VA/DoD CPG for SUD. 2015
Use the AUDIT-C Score to Help Guide Treatment

**Severity**

- **Abstinence or low-risk drinking**
  - AUDIT-C = 0-3
  - Health promotion

- **Moderate-risk drinking**
  - AUDIT-C = 4-5
  - Brief intervention

- **High-risk drinking**
  - AUDIT-C = 6-7
  - Brief intervention +/- pharmacotherapy +/- psychosocial interventions

- **Severe-risk drinking**
  - AUDIT-C = 8-9
  - Pharmacotherapy +/- psychosocial interventions +/- specialty care management
  - AUDIT-C = 10-12
  - Specialty care management

**Health promotion**

**Brief intervention**

**Brief intervention +/- pharmacotherapy +/- psychosocial interventions**

<table>
<thead>
<tr>
<th>AUDIT-C</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>Health promotion</td>
</tr>
<tr>
<td>4-5</td>
<td>Brief intervention</td>
</tr>
<tr>
<td>6-7</td>
<td>Brief intervention +/- pharmacotherapy +/- psychosocial interventions</td>
</tr>
<tr>
<td>8-9</td>
<td>Pharmacotherapy +/- psychosocial interventions +/- specialty care management</td>
</tr>
<tr>
<td>10-12</td>
<td>Specialty care management</td>
</tr>
</tbody>
</table>

Alcohol Use Disorder. VA Academic Detailing provider piece. 2014
A Menu of Treatment Options

Unhealthy Alcohol Use

- Brief Intervention
- Specialty Care
- Mutual help groups
- Pharmacotherapy
**Brief Interventions**

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Express concern</strong> about patients' risk for drinking-related health problems</td>
</tr>
<tr>
<td><strong>Provide education</strong> on links between alcohol use and patients’ co-occurring health conditions (if present), such as diabetes, hypertension, depression, anxiety, insomnia, pain, gastrointestinal problems (GERD), fractures, obesity, sexual dysfunction, &amp; peripheral neuropathy</td>
</tr>
<tr>
<td><strong>Advise patient to abstain</strong> (if contraindications) or drink below the recommended limits</td>
</tr>
<tr>
<td><strong>Support</strong> patient in setting a drinking goal and arrive at a shared decision in treatment plan. Encourage specificity, e.g., cutting down to X number of drinks and documenting intended steps</td>
</tr>
<tr>
<td><strong>Suggest treatment referral</strong>, if appropriate (e.g., AUDIT-C $\geq$ 8)</td>
</tr>
</tbody>
</table>

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"I am concerned about your use of alcohol because you are drinking above the recommended limits."

"Because of your [Chronic or co-occurring condition], I am concerned that your alcohol use may impact your health by [relevant repercussion]."

"What do you see as the possible benefits to cutting down?"

If no desire to change, provide information handout. "What would be a sign to you that change would be worth considering?"

"What changes are you willing to make to meet this goal?"

"Would you be willing to talk to one of my colleagues to learn about options to support your changes?"

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VA/DoD SUD Guidelines. 2015
Mr. Jim Beam

- 58-year-old white male treated for depression for more years than he can recollect and has tried “every medication there is”
  - Reports duloxetine is the only thing that has helped
  - Adequate doses and durations of previous medications confirmed with chart review
- Struggles with depressed mood, memory problems, 3 a.m. awakenings, and minimal contact with friends and family
- Denies using substances but admits to “having a beer now and then”
- Patient Health Questionnaire-9 (PHQ-9) = 15
- Current medications: methadone 30 mg three times daily for pain; duloxetine 60 mg daily for depression; omeprazole 20 mg every morning for GERD
Mr. Jim Beam Continued...

- Over the next few months tries several sleeping aids/medication adjustments with inadequate response
- Declined psychotherapy and cognitive behavioral therapy for insomnia (CBT-I)
- Several falls have led to visits to the emergency department
- Reports making calls and leaving incoherent messages that he does not remember, which he attributes to lack of sleep
What next steps should be taken to rule out any substances that could be contributing to Mr. Beam’s presentation?

A. Obtain urine drug screen
B. Have him fill out the AUDIT-C
C. Call his family and ask about substance abuse
D. Obtain complete blood count and complete metabolic profile
What next steps should be taken to rule out any substances that could be contributing to Mr. Beam’s presentation?

✓ A. Obtain urine drug screen
✓ B. Have him fill out the AUDIT-C
✓ C. Call his family and ask about substance abuse
✓ D. Obtain complete blood count and complete metabolic profile
Pharmacotherapy
Naltrexone (NTX)

- Opioid antagonist - thought to block endorphins therefore reducing the reinforcing effects of drinking alcohol

- Efficacy
  - Reducing heavy drinking
  - Reducing cravings
  - Increasing abstinence
  - Easy to dose

- Available as intramuscular monthly injection for patients with poor medication adherence

- Contraindicated in patients receiving opioids

NTX Efficacy

The COMBINE study

• Reduced risk of heavy drinking days when combined with medical management (HR, 0.72 with 97.5% CI, 0.53-0.98; p=0.02)
• Improved abstinence rates (Effect size, 0.22 with 97.5% CI, 0.03-0.4; p=0.25)

Meta-analysis

• Reduces the risk for heavy drinking by 15-25% compared to placebo (NNT = 8.1)
• Increases abstinence from alcohol (RR, 0.93; 95% CI, 0.88-0.99; NNT = 17.4)

NTX Reduces Health Care Utilization

- Reductions seen in:
  - Inpatient detoxification
  - Emergency department visits
  - Inpatient admission
  - Healthcare costs
- More pronounced with the extended-release injection (XR-NTX) and with those who are persistent with therapy

- More likely to discontinue treatment if on acamprosate or disulfiram and oral NTX more likely to discontinue than XR-NTX


Acamprosate

- Glutamate antagonist
  - Modulates the glutamate system
  - Promotes abstinence by ‘re-setting’ balance between GABA and glutamate systems
- Improved abstinence rates when used in combination with psychotherapy (NNT=9)
  - May be more effective in patients abstinent for 4 or more days before initiation
- Can be used in patients with liver impairment and those on opioids
- Must be renally adjusted; contraindicated when CrCl ≤ 30 mL/min

Acamprosate and Rates of Abstinence

Rates of Abstinence Across Three Pivotal Studies

Patients treated with acamprosate are 2x more likely to remain completely abstinent for 48-52 weeks

NTX vs. Acamprosate

When are these medications most helpful?
Meta-analysis results

- Acamprosate prolongs time to first drink and drinking frequency but has limited effects on reducing heavy drinking
- NTX prolongs time to first drink but not to the extent of acamprosate and significantly reduces heavy drinking days

Disulfiram

- Inhibits acetaldehyde dehydrogenase
- FDA approved to treat AUD
  - Evidence is somewhat limited
  - More effective with monitored administration
- Several safety considerations
- Should only be used if the patient is committed to a goal of complete abstinence from alcohol and is highly motivated
- Because of significant toxicity risk and limited effectiveness, risk and benefits must be considered before initiation

<table>
<thead>
<tr>
<th></th>
<th><strong>NTX Oral</strong></th>
<th><strong>NTX Injection</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Pearls</strong></td>
<td>Effective at ↓drinking, ↓ cravings and ↑ abstinence</td>
<td>Same as oral; may benefit patients with adherence issues</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>- Concomitant opioids</td>
<td>- Concomitant opioids</td>
</tr>
<tr>
<td></td>
<td>- Opioid dependence</td>
<td>- Opioid dependence with use within past 7-10 days</td>
</tr>
<tr>
<td></td>
<td>with use within past 7 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Evaluation</strong></td>
<td>- Opioid free ≥ 7-10 days</td>
<td>- Opioid free ≥ 7-10 days</td>
</tr>
<tr>
<td></td>
<td>- LFTs, GGT</td>
<td>- LFTs</td>
</tr>
<tr>
<td></td>
<td>- Bilirubin</td>
<td>- Bilirubin</td>
</tr>
<tr>
<td></td>
<td>- Urine beta-HCG for females</td>
<td>- Urine beta-HCG for females</td>
</tr>
</tbody>
</table>

# FDA-Approved Medication Dosing and Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>NTX Oral</th>
<th>NTX Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong> <strong>Initiation</strong></td>
<td>25 mg po on the first day then increase to 50 mg po daily</td>
<td>380 mg IM monthly</td>
</tr>
<tr>
<td><strong>Dose</strong> <strong>Maintenance</strong></td>
<td>50 mg po daily</td>
<td>Same as above</td>
</tr>
<tr>
<td><strong>Common</strong> <strong>Adverse Events</strong></td>
<td>- Nausea</td>
<td>- Same as oral</td>
</tr>
<tr>
<td></td>
<td>- Vomiting</td>
<td>- Injection site reaction (pain, pruritus, tenderness, bruising, induration, swelling)</td>
</tr>
<tr>
<td></td>
<td>- Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Insomnia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Dizziness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Anxiety</td>
<td></td>
</tr>
</tbody>
</table>

## FDA Approved Pharmacotherapy

<table>
<thead>
<tr>
<th>Clinical Pearls</th>
<th>Acamprosate</th>
<th>Disulfiram</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More effective for patients with a goal of abstinence</td>
<td>-More effective for patients with a goal of abstinence and with monitored administration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Acamprosate</th>
<th>Disulfiram</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl ≤ 30 mL/min</td>
<td>- Severe myocardial disease</td>
<td>- Use of alcohol-containing products within 14 days of use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Concomitant or recent use of metronidazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Psychosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Evaluation</th>
<th>Acamprosate</th>
<th>Disulfiram</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CrCl</td>
<td>- Alcohol free ≥ 24 hrs and BAL = 0</td>
<td></td>
</tr>
<tr>
<td>-Urine beta-HCG for females</td>
<td>- LFTs</td>
<td></td>
</tr>
<tr>
<td>-abstinence x 4 days prior to initiation</td>
<td>- Medical and psychiatric assessment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- EKG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Urine beta-HCG for females</td>
<td></td>
</tr>
</tbody>
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## FDA-Approved Medication Dosing and Adverse Events

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<tr>
<th></th>
<th>Acamprosate</th>
<th>Disulfiram</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose Initiation</strong></td>
<td>666 mg po three times daily; 333 mg po three times daily if CrCl 30-50 mL/min</td>
<td>250 mg po daily</td>
</tr>
<tr>
<td><strong>Dose Maintenance</strong></td>
<td>Same as above</td>
<td>Average dose 250 mg po daily (range 150-500 mg po daily)</td>
</tr>
</tbody>
</table>
| **Common Adverse Events** | - **Diarrhea**  
- Insomnia  
- Anxiety  
- Depression  
- Weakness | - Drowsiness  
- Headache  
- Psychosis  
- Rash  
- **Metallic or garlic-like aftertaste**  
- Hepatitis |

Non-FDA Approved Medications

- Topiramate
- Gabapentin
- Baclofen
- Ondansetron
- Varenicline

These agents may be particularly useful in patients with comorbid AUD and disease states for which these agents are FDA approved.
Topiramate

- Evidence suggests
  - Reduced cravings
  - Reduced heavy drinking
  - Increased abstinence

- Doses studied range between 75-300 mg per day given in divided doses

- Appears to be at least as effective as NTX at reducing heavy drinking and cravings

• Topiramate (TOP) had 51% less drinking days (DD) compared to placebo (PLA)
• Trends found TOP to have 55% fewer drinks per week and 60% fewer drinks per drinking day compared to PLA
• Significant reduction ($p = 0.001$) within TOP in PTSD symptom severity
  • Total PTSD Check List (PCL) score (baseline mean 57.1 vs. average week 1-12 = 42.3)
  • All three subscales (re-experiencing, avoidance, arousal)
• Trends in total score reduction and arousal scores for TOP vs. PLA

Topiramate Effectiveness Potentially Moderated by GRIK1 Polymorphism

- TOP (N= 67) vs. PLA (N= 71) x 12 weeks
- TOP found superior to PLA
  - Odds of a heavy drinking day: PLA 5.33x of TOP
  - No heavy drinking days during last 4 treatment weeks: TOP 2x greater than PLA group (n=24, 38.5% and n=12, 16.9% respectively) (OR=2.75; CI=1.24-6.10)
  - Abstinent days: greater for TOP vs. PLA (P=0.03) with an odds of abstaining by week 12 being 2.57x greater than PLA
- GRIK1 CC genotype potential moderator for effectiveness
  - Heavy drinking days had significant group-by-genotype interaction (TOP > PLA) only in rs2832407 C-allele homozygotes

Gabapentin for AUD

- Significant linear dose effect with abstinence rate ($p=0.04$) and no heavy drinking ($p=0.02$)
- Gabapentin 1800 mg
  - Complete abstinence: NNT=8; OR=4.8 (CI 0.9-35)
  - No heavy drinking: NNT=5; OR=2.8 (CI 1.1-7.5)
- Significant linear dose effects were found with cravings, mood, and sleep
- Significant linear dose effects were maintained at 24 weeks for abstinence and reduced number of drinks/week

Mason BJ. *JAMA*. 2014
Gabapentin and NTX

- 150 subjects with AUD received medical management for 16 weeks
  - NTX (50 mg/day) + placebo
  - NTX (50 mg/day) + gabapentin (up to 1200 mg/day) for six weeks
  - Double placebo
- NTX + gabapentin
  - Longer delay to heavy drinking vs. NTX but not placebo (p=0.04)
  - Less heavy drinking days vs. NTX alone (p=0.0002)
  - Less drinks/drinking day vs. NTX (p=0.02) alone and placebo (p=0.01)
  - Results faded after gabapentin was discontinued
- Poor sleep associated with increased drinking in the NTX alone group
- Withdrawal history associated with better response in the gabapentin group

## Non-FDA Approved Pharmacotherapy

<table>
<thead>
<tr>
<th>Clinical Pearls</th>
<th>Topiramate</th>
<th>Gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Effective at ↓ drinking and ↑ abstinence</td>
<td>- May be effective alone or in combination with NTX: ↓ drinking, ↓ cravings, ↓ insomnia, ↑ abstinence</td>
<td></td>
</tr>
</tbody>
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<tr>
<th>Contraindications</th>
<th>Topiramate</th>
<th>Gabapentin</th>
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</thead>
<tbody>
<tr>
<td>- History of renal stones</td>
<td>- Hypersensitivity to gabapentin</td>
<td></td>
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<table>
<thead>
<tr>
<th>Baseline Evaluation</th>
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<tbody>
<tr>
<td>- Weight</td>
<td>- CrCl</td>
<td>- CrCl</td>
</tr>
<tr>
<td>- CrCl</td>
<td>- Serum bicarbonate</td>
<td>- Urine beta-HCG for females</td>
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# Non-FDA Approved Pharmacotherapy

## Dosing and Adverse Events

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<th>Dose Initiation</th>
<th>Topiramate</th>
<th>Gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 25 mg daily, increase dose by 25-50 mg/day divided BID at weekly intervals</td>
<td>- 300 mg po at bedtime</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintenance</th>
<th>Topiramate</th>
<th>Gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Doses studied range between 75-300 mg/day divided BID</td>
<td>- Doses studied range between 600-1800 mg po at bedtime or divided twice daily</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing in Special Populations</th>
<th>Topiramate</th>
<th>Gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>- CrCl &lt; 70 mL/min: Give 50% of dose and use slower titration</td>
<td>- CrCl &gt;15-29 mL/min: 200-700 mg po at bedtime</td>
<td></td>
</tr>
<tr>
<td>- Hepatic impairment: Clearance may be reduced</td>
<td>- CrCl = 15 mL/min: 100-300 mg po at bedtime</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Hemodialysis: reduce dose in proportion to CrCl</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Topiramate</th>
<th>Gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Dizziness/ataxia</td>
<td>- Somnolence/fatigue</td>
<td></td>
</tr>
<tr>
<td>- Somnolence</td>
<td>- Dizziness</td>
<td></td>
</tr>
<tr>
<td>- Psychomotor slowing</td>
<td>- Ataxia</td>
<td></td>
</tr>
<tr>
<td>- Difficulty concentrating</td>
<td>- Peripheral edema</td>
<td></td>
</tr>
<tr>
<td>- Depression</td>
<td>- Nystagmus</td>
<td></td>
</tr>
<tr>
<td>- Weight loss/anorexia</td>
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</tr>
</tbody>
</table>
Baclofen for AUD

- Not enough evidence to support as a first line treatment option
- European Association for the Study of the Liver (EASL) clinical practice guidelines recommend for patients with advanced alcoholic liver disease
- Baclofen may be a promising agent for patients with liver disease and may be effective at:
  - ↑ Abstinence
  - ↓ Relapse rates
  - ↓ Cravings and state anxiety

High Dose Baclofen Utilization and Possible Risks

- Increased sedation in a dose-dependent manner
- Case reports of other problems
  - Overdose with acute renal failure
  - Central sleep apnea
  - Suicide attempts
  - Mania
- Withdrawal

Trial found that high-dose baclofen may help patients maintain abstinence (mean = 180 mg/day (SD 86.9))

Perogamvros L, et al. Respiration. 2015
Rolland et al. Eur Neuropsychopharm. 2015

Ondansetron

- May reduce alcohol consumption; mixed results
  - Randomized controlled trials have found better response in early onset (< 25 years old) AUD
  - Initial evidence suggest that polymorphisms of serotonin transporter (5-HTT) gene and HTR3A, HTR3B genes (which encode the 5-HT₃ receptor subunits A and B) predicted the treatment response to ondansetron
- Dosing: 4 mcg/kg po twice daily most commonly studied dose with beneficial effects

# Non-FDA Approved Pharmacotherapy

<table>
<thead>
<tr>
<th>Clinical Pearls</th>
<th>Baclofen</th>
<th>Ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Can be used in patients with cirrhosis or liver impairment</td>
<td>- May be more effective for patients with early onset AUD (&lt;25 year old) when used alone or in combination with NTX for:</td>
<td></td>
</tr>
<tr>
<td>- May be effective at:</td>
<td>- drinking</td>
<td>- drinking</td>
</tr>
<tr>
<td>- ↓ drinking</td>
<td>- ↓ cravings</td>
<td>- ↓ cravings</td>
</tr>
<tr>
<td>- ↓ cravings</td>
<td>- ↑ abstinence</td>
<td>- ↑ abstinence</td>
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<tr>
<td>- ↑ abstinence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Baclofen</th>
<th>Ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hypersensitivity to baclofen</td>
<td>- Hypersensitivity to ondansetron or any other selective 5HT₃ antagonist</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Evaluation</th>
<th>Baclofen</th>
<th>Ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>- None needed</td>
<td>- Magnesium and potassium level (↑ risk of QT prolongation with low electrolyte levels) - probably not needed due to low dose used in AUD - EKG if patient high risk for prolonged QT interval – probably not needed due to low dose used in AUD</td>
<td></td>
</tr>
</tbody>
</table>
### Non-FDA Approved Pharmacotherapy

#### Dosing and Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Baclofen</th>
<th>Ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose Initiation</strong></td>
<td>- 5 mg po three times daily</td>
<td>- 4 mcg/kg po twice daily (~0.25 mg po twice daily – use liquid solution)</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>- Most commonly studied dose is 10-20 mg po three times daily but growing evidence that higher doses may be needed (up to 270 mg/day)</td>
<td>- 4 mcg/kg po twice daily (~0.25 mg po twice daily – use liquid solution)</td>
</tr>
<tr>
<td><strong>Dosing in Special Populations</strong></td>
<td>- Renal dysfunction: dose adjustments may be necessary (no specific recommendations)</td>
<td>- None</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>- Drowsiness</td>
<td>- Headache</td>
</tr>
<tr>
<td></td>
<td>- Dizziness</td>
<td>- Fatigue</td>
</tr>
<tr>
<td></td>
<td>- Ataxia</td>
<td>- Constipation</td>
</tr>
<tr>
<td></td>
<td>- Insomnia</td>
<td>- Dizziness</td>
</tr>
<tr>
<td></td>
<td>- Weakness</td>
<td>- Fever</td>
</tr>
</tbody>
</table>

Varenicline

- Recent investigations found decreased alcohol consumption in smokers following varenicline treatment

- Multisite clinical trial (n = 200)
  - Lower weekly percentage of heavy-drinking days (37.9% vs. 48.4%; P = 0.03)
  - Fewer drinks per drinking day (4.4 vs. 5.3; P = 0.03)
  - Reduced craving for alcohol
  - Results similar for both smokers and non-smokers
  - No difference in abstinence rates

## Non-FDA Approved Pharmacotherapy

<table>
<thead>
<tr>
<th>Clinical Pearls</th>
<th>Varenicline</th>
</tr>
</thead>
<tbody>
<tr>
<td>- May be effective at ↓ drinking and ↓ cravings</td>
<td></td>
</tr>
<tr>
<td>- Results are similar for smokers and non-smokers</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contraindications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hypersensitivity to varenicline</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Evaluation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- CrCl</td>
<td></td>
</tr>
<tr>
<td>- Suicidal intent</td>
<td></td>
</tr>
<tr>
<td>- Neuropsychiatric symptoms</td>
<td></td>
</tr>
</tbody>
</table>
# Varenicline

## Dosing and Adverse Events

<table>
<thead>
<tr>
<th>Varenicline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose initiation</strong></td>
<td></td>
</tr>
<tr>
<td>- Days 1 to 3: 0.5 mg once daily</td>
<td></td>
</tr>
<tr>
<td>- Days 4 to 7: 0.5 mg twice daily</td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td></td>
</tr>
<tr>
<td>- 1 mg twice daily</td>
<td></td>
</tr>
<tr>
<td><strong>Dosing in special populations</strong></td>
<td></td>
</tr>
<tr>
<td>- CrCl &lt; 30 mL/min: Maximum of 0.5 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>- Hemodialysis: Maximum of 0.5 mg daily if tolerated</td>
<td></td>
</tr>
<tr>
<td>- Hepatic impairment: No adjustments needed</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td></td>
</tr>
<tr>
<td>- Nausea/vomiting</td>
<td></td>
</tr>
<tr>
<td>- Constipation</td>
<td></td>
</tr>
<tr>
<td>- Headache</td>
<td></td>
</tr>
<tr>
<td>- Insomnia</td>
<td></td>
</tr>
<tr>
<td>- Abnormal dreams</td>
<td></td>
</tr>
<tr>
<td>- Irritability</td>
<td></td>
</tr>
<tr>
<td>- Suicidal ideation</td>
<td></td>
</tr>
<tr>
<td>- Depression</td>
<td></td>
</tr>
</tbody>
</table>

Combination Treatment

- Minimal support for using more than one AUD medication concomitantly
- Using any combination of NTX, acamprosate, and disulfiram may be considered as a short-term approach
- Candidates include those with poor response to adequate trials of monotherapy combined with psychosocial interventions

DHHS. NIH Pub 07-3769
Length of Treatment

- No consensus regarding optimal length of treatment
- Consider using pharmacotherapy for at least 3 months to reduce risk of relapse (highest during first 6-12 months)
- Literature supports the benefits of continuing pharmacotherapy up to and beyond one year

Mr. Jim Beam Continued

- At clinic appointment reports his family is concerned about his drinking
- Alcohol free for the last 4 days and feels that he is going to start drinking again “just so he can sleep at least a few hours”
- Inquiring if there are any medications that could help
- Current medications:
  - Methadone 30 mg three times daily
  - Duloxetine 60 mg daily
  - Omeprazole 20 mg every AM
  - Trazodone 200 mg at bedtime
Based on the evidence, which medication would you recommend for Mr. Beam?

A. Gabapentin
B. Baclofen
C. Ondansetron
D. Naltrexone
What dosing regimen of gabapentin would you design for Mr. Beam?

A. 100 mg at bedtime; target dose 300 mg
B. 300 mg at bedtime; target dose 1800 mg
C. 900 mg at bedtime; target dose 2100 mg
D. 1800 mg at bedtime; target dose 3600 mg
What lab values would be important to monitor for medication safety?

A. Creatinine clearance
B. Electrocardiogram
C. Liver function tests
D. Serum bicarbonate
Psychosocial Interventions

- Important to meet psychosocial need whether or not pharmacotherapy used
- Tailored to the patients’ needs
- Provides structure with regular treatment visits and contact with support system

Effective Psychosocial Interventions in Early Recovery (first 90 days)

- Motivational Enhancement Therapy
- Community Reinforcement Approach
- Behavioral Couples Therapy
- Cognitive Behavioral Coping Skills Training
- Twelve-Step Facilitation
- First Line Psychosocial Interventions

VA/DoD CPG SUD. 2009.
Witkiewitz K. Alc Res & Health. 2011
McKay JR. Alc Res & Health. 2011
Huebner RB. Alc Res & Health. 2011
Measurement-Based Care

Brief Addiction Monitor (BAM)
- Focuses on three main areas of patient functioning
- Can be obtained by
  - Patient self-report
  - In person
  - Over the telephone

Factors Measured by BAM

<table>
<thead>
<tr>
<th>Substance Use</th>
<th>Risk Factors</th>
<th>Protective Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Heavy alcohol use</td>
<td>• Anger</td>
<td>• Work, school</td>
</tr>
<tr>
<td>• Drug use</td>
<td>• Risky situations</td>
<td>• Income, housing</td>
</tr>
<tr>
<td>• Cravings</td>
<td>• Family/social conflicts</td>
<td>• Social support for recovery</td>
</tr>
</tbody>
</table>

Cacciola JS. *J Subst Abuse Treat.* 2012 VA/DoD CPG SUD. 2009
Quick Monitoring Tool

- Three questions from the BAM can be used to quickly monitor treatment effectiveness outside of Addiction Specialty Care settings.

1. In the past 30 days, how many days did you drink ANY alcohol?
2. How many days did you have at least (5-men, 4-women) drinks?
3. In the past 30 days, how much were you bothered by cravings or urges to drink alcohol or use drugs?

0 - Not at all  1 - Slightly  2 - Moderately  3 - Considerably  4 - Extremely
We Can’t Afford NOT to Treat AUD

- It’s an investment in our entire public’s health
- Excessive alcohol use costs the U.S. ~$185 billion each year in health care, criminal justice expenses, and lost productivity
- Pharmacotherapy for AUD
  - Associated with fewer hospital admissions of all types
  - Total healthcare costs were 30% lower for patients who received pharmacotherapy for AUD versus those who did not

Pharmacists have the opportunity to be advocates for our patients recovery from AUD. Identifying and encouraging patients to obtain treatment for AUD is the right investment of resources.

Baser O. Am J Manag Care. 2011
Key Takeaways

- Screen for unhealthy alcohol use in ALL patients
  - AUD can complicate or mimic most psychiatric disorders and increase suicide risk
  - Psychiatric disorders make it harder to maintain abstinence
  - Tools like the AUDIT-C can help identify patients with unhealthy alcohol use
- Offer evidence-based pharmacotherapy and psychosocial interventions
- Monitor pharmacotherapy for effectiveness and potential side effects
- Identify and encourage patients to obtain treatment for AUD—it’s worth the investment
Questions?