Anti-Craving Medications for Alcoholism and Drug Addiction

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Disclosure

• I have no relevant financial relationships to disclose concerning any topic in this presentation.
Objectives: Pharmacists

• Identify anti-craving drugs used in alcoholism and drug addiction

• Compare and contrast anti-craving drugs used in alcoholism and drug addiction

• Review key evidence-based research supporting use of anti-craving medications

• Recommend an anti-craving medication, given a patient case study
Objectives: Pharmacist Technicians

• Identify key anti-craving drugs used in alcoholism and drug addiction

• Categorize key anti-craving drugs used in either alcoholism or drug addiction

• Recognize regulations for dispensing specific anti-craving drugs
Overview of Addiction

Review Medications

Analyze Literature

Understand Clinical Application
Background: Why these dependencies?

• 24.6 million Americans used illicit drugs in 2013
  • 2/3 of those used ALCOHOL

• Top 3 drugs causing addiction
  • Cocaine
  • Opioids
  • Marijuana (controversial)

http://www.samhsa.gov/atod; Last accessed 2015 September 14
Treatment of Addiction

• Goals
  • Re-establishes normal brain function
  • Prevent lapse and diminish craving

• Behavioral Treatments
  • Outpatient behavioral treatment
  • Residential treatment

• Medications
Established Medications

**Alcohol Dependence**
- Acamprosate
- Naltrexone
- Disulfiram

**Cocaine Dependence**
- Still under investigation

**Opiate Dependence**
- Buprenorphine/Naloxone
- Methadone
- Naltrexone
“Novel” Medications

Alcohol Dependence
- Topiramate
- Gabapentin
- Baclofen

Cocaine Dependence
- Disulfiram
- Nepicastat

Opiate Dependence
- New Formulations
Literature Analysis
Alcohol Dependency

Cocaine Dependency

Opiate Dependency
<table>
<thead>
<tr>
<th>Alcohol Dependency Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disulfiram</td>
</tr>
<tr>
<td>Naltrexone</td>
</tr>
<tr>
<td>Acamprosate</td>
</tr>
<tr>
<td>Gabapentin</td>
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<tr>
<td>Baclofen</td>
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<tr>
<td>Topiramate</td>
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<td>Nalmefene</td>
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<td>Ondansetron</td>
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<td>Varenicline</td>
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</table>
Gabapentin

- Been used in alleviation of somatic symptoms of drug and alcohol withdrawal
- Protective effects on CNS hyperexcitability associated with alcohol withdrawal
- Alcohol Dependence
  - Found to have statistically significant positive effects on heavy drinking
Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial

- **Objective:** To determine if gabapentin increases rate of sustained abstinence and no heavy drinking and decreases alcohol-related insomnia, dysphoria and craving in a dose dependent manner.

- **Design:** 12 week double blind, placebo-controlled, single-site, outpatient facility, n=150 participants

- **Interventions:** Oral gabapentin (placebo vs. 900 mg vs. 1800 mg/day)

- **Main Outcome and Measures:**
  - Rate of complete abstinence and no heavy drinking (coprimary)
  - Change in mood, sleep and craving (secondary)
Gabapentin Treatment for Alcohol Dependence—Coprimary Outcomes: Figure 1

Gabapentin Treatment for Alcohol Dependence – Coprimary Outcomes: Figure 2

Gabapentin Treatment for Alcohol Dependence – Secondary Outcome on Craving: Figure 3

- Data based on Alcohol Craving Questionnaire

- Data showed significant linear dose effects on craving

- Data also showed significant linear dose effects on sleep and mood (not pictured)

Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial

- **Limitations**
  - Single site study
  - Dropout rate was significant

- **Strengths**
  - Could be used for co-occurring dependencies
  - Gabapentin is not appreciably metabolized in the liver

- **Concluding Thoughts**
  - Gabapentin 1800 mg effectively treated alcohol dependence and relapse associated symptoms.
  - Favorable safety profile
  - Sustained post treatment effect on drinking outcomes was found in those who responded well to gabapentin in the study
Baclofen

• FDA approved for spasticity associated with neurologic conditions

• May benefit in alcohol dependency
  • Activation of GABA$_B$ receptors in mesolimbic system may result in local inhibition of surrounding dopamine neurons
  • Result in decrease of alcohol-stimulated dopamine release
  • Decreasing positive reinforcement from alcohol consumption

Baclofen: A Review

- **Objective:** To assess the benefit of baclofen for alcohol dependence
- **Design:** Review of 6 randomized controlled trials (n=287) from inpatient and outpatient sites
- **Intervention:** Baclofen (30-60 mg) vs. placebo
- **Main Outcome and Measures**
  - % maintain abstinence
  - % heavy drinking
  - Time to relapse
  - Drinks per day

### Description of randomized controlled trials assessing Baclofen in alcohol dependency (modified according to Brennan et al.

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<tbody>
<tr>
<td>setting</td>
<td>single inpatient site</td>
<td>outpatients recruited from community</td>
<td>single inpatient site</td>
<td>single outpatient site</td>
<td>single inpatient site</td>
</tr>
<tr>
<td>number of subjects</td>
<td>84</td>
<td>80</td>
<td>39</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>age</td>
<td>49.0 (range 43.0–61.0)</td>
<td>47.5 ± 7.6</td>
<td>45.8 ± 10.6</td>
<td>placebo: 46.0 (39.5–52.5) baclofen 30 mg: 48.479 (42.2–53.5) baclofen 60 mg: 46.6 (39.8–53.5)</td>
<td>placebo: 43.1 (23–59) baclofen 30 mg: 45.6 (32–60) baclofen 60 mg: 43.1 (30–57)</td>
</tr>
<tr>
<td>male gender</td>
<td>76%</td>
<td>55%</td>
<td>n.a.</td>
<td>placebo: 64% baclofen 30 mg: 50% baclofen 60 mg: 21%</td>
<td>placebo: 78% baclofen 30mg: 86% baclofen 60mg: 64%</td>
</tr>
<tr>
<td>daily drinks</td>
<td>n.a.</td>
<td>7.3 ± 3.7 (baclofen group)</td>
<td>14.2 ± 7.9 (all subjects)</td>
<td>placebo: 14.3 (8.1–20.5) baclofen 30 mg: 15.6 (8.2–16.9) baclofen 60 mg: 15.1 (8.5–21.8)</td>
<td>placebo: 12.0 (9.1–14.9) baclofen 30mg: 13.9 (10.4–17.5) baclofen 60mg: 9.7 (7.3–12.0)</td>
</tr>
<tr>
<td>duration of use (y)</td>
<td>22.0 (range 17.0–27.0)</td>
<td>23.5 ± 9.9</td>
<td>12.6 ± 4.8</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>comorbidities</td>
<td>cirrhosis (Child-Pugh A, B, or C) no medical/psychiatric no medical/psychiatric no medical/no clinical relevant psychiatric (anxiety disorder according to Mini International Neuropsychiatric interview n = 17) no medical/psychiatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intervention</td>
<td>baclofen 3 × 10 mg for 12 weeks</td>
<td>baclofen 3 × 10 mg for 12 weeks</td>
<td>baclofen 3 × 10 mg for 4 weeks</td>
<td>baclofen 3 × 10 mg vs. 3 × 20 mg for 12 weeks</td>
<td>baclofen 3 × 10 mg vs. 3 × 20 mg for 12 weeks</td>
</tr>
<tr>
<td>primary outcome</td>
<td>percentage of patients maintaining abstinence: 71% vs. 29% (P = 0.0001) cumulative abstinent days: 62.8 ± 5.4 vs. 30.8 ± 5.5 (P = 0.001)</td>
<td>percentage of heavy drinking days: 19.3% vs. 24.7% (P = 0.73) percentage of abstinent days: 51.7% vs. 51.6% (P = 0.61)</td>
<td>percentage of patients maintaining abstinence: 70% vs. 21.2% (P = 0.005) cumulative abstinent days: 19.6 ± 2.6 vs. 6.3 ± 2.4 (P = 0.005)</td>
<td>time to lapse (days): placebo 3.1 (1.9–4.4) vs. baclofen 30 mg 13.1 (2.8–23.5) vs. baclofen 60 mg 17.6 (3.5–31.8) (Chi, treatment vs. placebo p = 0.18, n.s.) time to relapse (days): placebo 7.1 (2.4–11.8) vs. baclofen 30 mg 23.8 (9.6–38.0) vs. baclofen 60 mg 19.2 (4.9–34.5) (Chi, treatment vs. placebo p = 0.08, n.s) Drinks per drinking day Placebo 2.8 (0.0–5.6) vs. baclofen 30 mg 5.9 (2.8–8.9) vs. baclofen 60 mg 5.6 (3.2–8.1) (mixed model, p = 0.68, n.s.) heavy drinking days per week: placebo 1.4 (0.3–3.0) vs. Baclofen 30 mg 2.1 (0.3–3.9) vs. Baclofen 1.9 (0.4–3.3) (mixed model, p = 0.91 n.s.)</td>
<td>drinks per day placebo 0.55 (0.4–0.7) vs. baclofen 30 mg: 0.3 (0.21–0.4)(p&lt;0.0001) vs. baclofen 60mg: 0.14 (0.09–0.19) (p&lt;0.0001)</td>
</tr>
</tbody>
</table>
Baclofen

• Conflicting evidence

• Safe to use in patients with alcohol dependence including those with moderate to severe liver cirrhosis

• Randomized studies were less promising than the findings in case reports

• Baclofen doses may attribute to different responses
  • Majority of the RCTs used ¼ of the dose Ameisen used on himself

• Future studies
  • 3 major studies are currently being conducted in France and Germany

Topiramate

- FDA approved for epilepsy, migraine prophylaxis
- May benefit in alcohol dependency
  - Decreasing positive reinforcement from alcohol consumption by reducing craving through antagonizing the glutamate receptors and inhibiting dopamine release.
  - Earlier meta-analysis found support for topiramate; however, analysis was limited due to small sample of studies (k=3)
Topiramate: Meta-Analysis

- **Objective:** Review and highlight outcomes for the use of topiramate in Alcohol Use Disorders (AUDs)

- **Design:** Systemic review seven randomized controlled trials (n=1,125 participants)

- **Main Outcomes and Measures:**
  - Compared topiramate vs. placebo
    - Abstinence
    - Heavy drinking
    - Craving
    - γ-glutamyltranspeptidase (GGT)

## Topiramate-Meta-Analysis: Table 2

### Characteristics of Randomized, Placebo-Controlled Trials Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Medication groups (desired daily dosage)</th>
<th>N randomized</th>
<th>N completers</th>
<th>Months of planned treatment</th>
<th>Required initial abstinence?</th>
<th>Psychotherapy provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson (2003)</td>
<td>Topiramate (300 mg)</td>
<td>78</td>
<td>55</td>
<td>3</td>
<td>No</td>
<td>Weekly sessions of manual-guided brief behavioral enhancement therapy</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>80</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson (2007)</td>
<td>Topiramate (300 mg)</td>
<td>183</td>
<td>112</td>
<td>4</td>
<td>No</td>
<td>Weekly sessions of manual-guided Brief Behavioral Compliance Enhancement Treatment (BBCET)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>188</td>
<td>144</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baltieri (2008)</td>
<td>Topiramate (300 mg)</td>
<td>52</td>
<td>33</td>
<td>3</td>
<td>Yes</td>
<td>Weekly sessions of standardized relapse prevention counseling</td>
</tr>
<tr>
<td></td>
<td>Naltrexone (50 mg)</td>
<td>49</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>54</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubio (2009)</td>
<td>Topiramate (250 mg)</td>
<td>n/a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31</td>
<td>3</td>
<td>Yes</td>
<td>Weekly sessions of supportive group therapy</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>n/a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kampman (2013)</td>
<td>Topiramate (300 mg)</td>
<td>83</td>
<td>54</td>
<td>3</td>
<td>Yes</td>
<td>Weekly sessions of manual-guided CBT (adapted from MATCH manual)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>87</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likhitsathian (2013)</td>
<td>Topiramate (100 to 300 mg)</td>
<td>53</td>
<td>28</td>
<td>3</td>
<td>Yes</td>
<td>3 to 5 Sessions of motivational enhancement therapy&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>53</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kranzler (2014)</td>
<td>Topiramate (200 mg)</td>
<td>67</td>
<td>55</td>
<td>3</td>
<td>No</td>
<td>9 Sessions of manual-guided medical management</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>71</td>
<td>62</td>
<td></td>
<td></td>
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</tbody>
</table>

<sup>a</sup>Number of participants who continued to take their assigned pills throughout the planned medication period.

<sup>b</sup>Of 76 randomized overall, group sample size not specified.

<sup>c</sup>Participants were recruited from inpatient detoxification and residential treatment programs (mean length of stay: 25 days). Topiramate or placebo was initiated a mean of 3.7 days prior to discharge.
Topiramate-Meta-Analysis

Figure: 4

- **Overall Results**: Small to moderate effects of topiramate

- Largest effect was found on abstinence \( (g=0.468, p<0.01) \)

- Followed by heavy drinking \( (g=0.406, p<0.01) \) and GGT \( (g=0.324, p=0.02) \)

- Effects on cravings did not reach significance

Topiramate: Meta-Analysis

• **Limitations:**
  • Small number of studies
  • Target doses were higher than the most recent study (Paparrigopoulos et al.)

• **Strengths:**
  • Co-occurring conditions tested
  • Different types of settings (inpatient vs. residential treatment)

• **Concluding Thoughts:**
  • Topiramate is efficacious in AUDs
  • Significant benefits for abstinence and heavy drinking outcomes
  • Positive outcomes on GGT and alcohol cravings

Topiramate: Other Studies

• Batki et al.
  • Preliminary results indicate that topiramate is effective in reducing alcohol consumption, cravings and PTSD symptom severity in the veteran population

• Cochrane review by Pani et al.
  • Topiramate had fewer drinks/drinking days, fewer heaving drinking days, more abstinent days
  • Failed to show superiority in reducing cravings

### Cocaine Dependency Medications

<table>
<thead>
<tr>
<th>Medication</th>
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</thead>
<tbody>
<tr>
<td>Topiramate</td>
</tr>
<tr>
<td>Disulfiram</td>
</tr>
<tr>
<td>Nepicastat</td>
</tr>
<tr>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Buspirone</td>
</tr>
<tr>
<td>Modafinil</td>
</tr>
<tr>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Cocaine Vaccine</td>
</tr>
<tr>
<td>Butyrylcholinesterase</td>
</tr>
</tbody>
</table>
Topiramate: Cocaine Dependency

- **Objective:** To determine the efficacy of topiramate vs. placebo as a treatment for cocaine dependency

- **Design:** Double blind, randomized placebo controlled, 12 week trial of 142 cocaine-dependent individuals

- **Intervention:** Topiramate (n=71) vs. placebo (n=71) in escalating doses from 50 mg/day to the target maintenance dose of 300 mg/day in weeks 6-12, combined with weekly cognitive behavioral therapy (CBT).

- **Main Outcomes and Measures:**
  - Primary outcome: Weekly difference from baseline in the proportion of cocaine nonuse days
  - Secondary outcome: Urinary cocaine free weeks

Johnson B et al. JAMA Psychiatry. 2013; 70(12):1338-1346
Topiramate- Cocaine Dependency: Figure 5

Each symbol represents the mean proportion of cocaine nonuse days for each study week, and the error bars indicate standard error (SEM). Weekly mean proportion of cocaine nonuse days was analyzed (A) without imputing missing data and (B) imputing missing data using baseline values. Mean (SEM) values for the weekly proportion of cocaine nonuse days at baseline (ie, mean cocaine use during the 2-week baseline period) for the 2 groups receiving topiramate and placebo were 0.5775 (0.0294) and 0.5665 (0.0302), respectively. Participants were allocated to treatment groups at the end of the 2-week baseline period. Study medication was provided at week 0 and, therefore, week 1 contains those individuals who had received 1 or more weeks of double-blind treatment.

Johnson B et al. JAMA Psychiatry. 2013; 70(12):1338-1346
Disulfiram: Cocaine Dependency

- Aldehyde dehydrogenase inhibitor and dopamine-beta-hydroxylase (DβH) inhibitor

\[ \text{Dopamine } \rightarrow \rightarrow \rightarrow \text{Norepinephrine} \]

- Dopamine > Norepinephrine
Disulfiram for the treatment of cocaine dependence in methadone-stabilized patients

• **Objective:** This study examined the dose-related efficacy of disulfiram for treating cocaine dependence in methadone-stabilized cocaine dependent participants.

• **Design:** One hundred and sixty-one cocaine- and opioid-dependent volunteers were entered into a 14-week, double blind, randomized, placebo-controlled clinical trial at two sites.

• **Intervention:** Disulfiram (62.5 mg, 125 mg, 250 mg) vs. placebo

• **Main Outcome and Measures**
  • Positive urine drug screen for cocaine
Disulfiram for the treatment of cocaine dependence in methadone-stabilized patients: Table 3

The number of participants with urine samples that either tested all negative (neg) or had at least one positive (pos) test, respectively, for cocaine/cocaine metabolite within a given week.

<table>
<thead>
<tr>
<th>Study week</th>
<th>Placebo</th>
<th>Disulfiram 62.5</th>
<th>Disulfiram 125</th>
<th>Disulfiram 250</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neg</td>
<td>Pos</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>27</td>
<td>13</td>
<td>24</td>
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<tr>
<td>3</td>
<td>12</td>
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<td>14</td>
<td>12</td>
<td>17</td>
<td>8</td>
<td>18</td>
</tr>
</tbody>
</table>

Oliveto A et al Drug and Alcohol Dependence 113(2011)184-191
Disulfiram for the treatment of cocaine dependence in methadone-stabilized patients

- **Concluding Thoughts**
  - Groups receiving disulfiram 250 mg/day had a significant decrease in cocaine-positive urines over time compared to lower doses.
A Multi-Center Trial of Nepicastat for Cocaine Dependence

• **MOA:** Selective dopamine β hydroxylase inhibitor

• **Design:** Randomized, double-blind placebo-controlled trial in treatment-seeking cocaine-dependent subjects (n=179) using nepicastat

• **Intervention:** Nepicastat vs. placebo

• **Main Outcome and Measures**
  • Positive UDS for cocaine

• **Results:** When compared to placebo, nepicastat did not meet the primary efficacy endpoint of an increased proportion of subjects remaining abstinent from cocaine during the last two weeks of the treatment period.

https://clinicaltrials.gov/show/NCT01704196; Last accessed 2015 September 14
**Opioid Dependency**

- Opioid agonist treatment
  - Methadone
  - Buprenorphine/Naloxone

- Opioid antagonist treatment
  - Naltrexone

- Psychosocial treatment

**New Formulations**
- Bunavail™
- Depot Buprenorphine
- Buprenorphine Implant

**New opioid antagonist**
- Samidorphan (ALKS33)
Opioid Dependency: Bunavail™

• NDA approved on June, 6 2014
• Limited under the Drug Addiction Treatment Act (DATA)
• Maintenance treatment of opioid dependency
• Buccal film:
  • 2.1 mg Buprenorphine/ 0.3 mg Naloxone
  • 4.2 mg Buprenorphine/ 0.7 mg Naloxone
  • 6.3 mg Buprenorphine/ 1 mg Naloxone
• Small patch which adheres to the inside of the mouth with the drug being absorbed through the cheek
Samidorphan (ALKS33)

- Selective opioid antagonist u-opioid receptor
- Without affecting the delta-opioid or k-opioid R
- Similar to naltrexone but reduced side effects

- Indications
  - Opioid Dependency
  - Alcohol Dependency
  - Cocaine Dependency
  - Major Depressive Disorder
  - Binge Eating

Clinical Application
Safety Considerations

• Well tolerated medications across the board in all dependencies
• Saw some benefit in lower doses
• Safe in using with dependent agents

• When looking at cost/accessibility/prescribing barriers
  • “Novel” medications look promising
Financial Burdens

- Addiction-$600 billion annually
- Treatment less expensive than its alternatives
  - Incarceration addicted $24,000 per person/year
  - Methadone maintenance treatment ~$4,700 per person/year
- For every $1.00 spent on treatment $4.00-$7.00 ROI

http://www.drugabuse.gov/; Last accessed 2015 September 14
Anti-Craving Medications Concluding Thoughts

- FDA approved medications for opioid and alcohol
- No medications approved for cocaine
- Long-term success of medications is low
- “Novel” medications being investigated
- Difficult to interpret statistics
- Ongoing investigation
Anti-Craving Medications for Alcoholism and Drug Addiction

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