The Treatment of Alcohol, Cocaine and Methamphetamine Use Disorders

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Outline

• Alcohol
  • Update on detoxification
  • Review approved medications
  • Discuss new medications
• Cocaine update
  • New medications and combinations
  • Psychosocial treatments
• Methamphetamine
  • Best medication options
  • Psychosocial treatments
Strategies in outpatient detox

- Careful patient selection
- Frequent visits
- Traditional benzodiazepine approach
- Gabapentin may be used as well
  - 400 tid x 3 Days then 400 bid


Gabapentin for alcohol withdrawal

CIWA Scores Comparing Lorazepam and Gabapentin

Gabapentin for alcohol withdrawal

CIWA Scores Comparing Phenobarb and Gabapentin

![Graph showing CIWA scores over days comparing Phenobarbital and Gabapentin.]

Am J Addict 2006;15:76–84)

Gabapentin for alcohol withdrawal

Gabapentin Reduces Craving and Has Less Sedation

Baseline CIWA 7.7 gabapentin 8.8 chlordiazepoxide
Retention 65% gabapentin; 67% chlordiazepoxide
CIWA declined in both groups, not significantly different

Penn Alcohol Craving Scale  
Epworth Sleepiness Scale

Medications for Alcohol Use Disorder

- Naltrexone (oral and injectable)
- Disulfiram
- Acamprosate
- Topiramate - Not FDA approved
- Gabapentin - Not FDA approved
- Varenicline - Not FDA approved
- Nalmefene – Not FDA approved

Naltrexone for AUD

- Naltrexone
  - Blocks opiate receptors
  - Effective in endorphin sensitive alcoholics
Naltrexone for AUD

Family History Predicts Naltrexone Response

Meta-Analysis: Oral Naltrexone Reduces Relapse

Outcome: Relapse Rate

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>Peto OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anton 1999</td>
<td>26/68</td>
<td>38/63</td>
<td>7.5</td>
<td>0.42 [0.21, 0.82]</td>
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<tr>
<td>Chick 2000</td>
<td>59/90</td>
<td>54/85</td>
<td>9.2</td>
<td>1.09 [0.59, 2.03]</td>
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<tr>
<td>Guardia 2002</td>
<td>8/101</td>
<td>19/101</td>
<td>5.4</td>
<td>0.39 [0.17, 0.88]</td>
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<tr>
<td>Heinala 2001</td>
<td>49/63</td>
<td>51/58</td>
<td>4.0</td>
<td>0.50 [0.19, 1.27]</td>
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<td>Hersch 1998</td>
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<td>15/33</td>
<td>3.7</td>
<td>1.12 [0.42, 2.98]</td>
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<tr>
<td>Kranzler 2000</td>
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<td>31/63</td>
<td>7.1</td>
<td>0.94 [0.46, 1.89]</td>
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<tr>
<td>Krystal 2001</td>
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<td>83/187</td>
<td>27.4</td>
<td>0.75 [0.53, 1.08]</td>
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<tr>
<td>Latt 2002</td>
<td>19/56</td>
<td>27/51</td>
<td>6.0</td>
<td>0.46 [0.22, 0.99]</td>
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<td>Monti 2001</td>
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<td>19/64</td>
<td>5.8</td>
<td>0.79 [0.36, 1.72]</td>
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<tr>
<td>Morris 2001</td>
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<td>26/56</td>
<td>6.1</td>
<td>0.61 [0.29, 1.30]</td>
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<tr>
<td>Oslin 1997</td>
<td>3/21</td>
<td>8/23</td>
<td>1.9</td>
<td>0.34 [0.09, 1.33]</td>
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<td>O'Malley 1992</td>
<td>16/52</td>
<td>31/52</td>
<td>5.9</td>
<td>0.32 [0.15, 0.68]</td>
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<tr>
<td>Volpicelli 1995</td>
<td>10/54</td>
<td>17/45</td>
<td>4.5</td>
<td>0.38 [0.16, 0.93]</td>
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<tr>
<td>Volpicelli 1997</td>
<td>17/48</td>
<td>26/49</td>
<td>5.5</td>
<td>0.49 [0.22, 1.09]</td>
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<tr>
<td>Total (95%CI)</td>
<td>428/1142</td>
<td>445/930</td>
<td>100.0</td>
<td>0.62 [0.52, 0.75]</td>
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</tr>
</tbody>
</table>

Test for heterogeneity: chi-square = 17.80; df =10; P = 0.0747

for overall effect: Z = 6.87; P < 0.0001

Favors Naltrexone

Favors Control

CI = confidence interval; OR = odds ratio

**Naltrexone for AUD**

- Oral 50 mg daily most common dose
- Injectable one dose only 380 mg every 4 weeks
- Detoxed patients do better
- Injectable eliminates adherence problems
- Contraindications
  - Opiates
  - Severe liver disease
  - Endorphin sensitive alcoholics: craving & family history

**Nalmefene for AUD**

- Nalmefene
  - Mu and delta opiate receptor antagonist and a kappa receptor partial agonist
  - Available in Europe and Japan
  - Used PRN for AUD
Nalmefene for AUD

PRN Nalmefene Reduces HDD

Acamprosate for AUD

Acamprosate mechanism of action

- Glutamate antagonist
- Reduces protracted withdrawal
- Reduces craving
Meta-Analysis of Acamprosate: Abstinence Improved

### Outcome: Abstinence Rate

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<tr>
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<th>Weight %</th>
<th>Peto OR (95% CI Fixed)</th>
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<tr>
<td>Besson 1998</td>
<td>14/55</td>
<td>3/55</td>
<td>3.1</td>
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<td>1.63, 12.76</td>
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<tr>
<td>Chick 2000</td>
<td>35/289</td>
<td>32/292</td>
<td>12.6</td>
<td>1.12</td>
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<td>Geerlings 1997</td>
<td>14/128</td>
<td>7/134</td>
<td>4.1</td>
<td>2.16</td>
<td>0.89, 5.27</td>
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<td>Gual 2001</td>
<td>49/141</td>
<td>38/147</td>
<td>12.9</td>
<td>1.52</td>
<td>0.92, 2.52</td>
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<tr>
<td>Ladewig 1993</td>
<td>12/29</td>
<td>7/32</td>
<td>2.8</td>
<td>2.45</td>
<td>0.83, 7.18</td>
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<td>Paille 1995</td>
<td>45/361</td>
<td>16/177</td>
<td>10.1</td>
<td>1.41</td>
<td>0.80, 2.48</td>
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<tr>
<td>Peic 1997</td>
<td>52/126</td>
<td>9/62</td>
<td>7.7</td>
<td>3.37</td>
<td>1.76, 6.44</td>
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<tr>
<td>Poldrugo 1997</td>
<td>53/122</td>
<td>37/124</td>
<td>12.1</td>
<td>1.70</td>
<td>1.07, 3.01</td>
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<tr>
<td>Sass 1996</td>
<td>54/136</td>
<td>23/136</td>
<td>11.7</td>
<td>3.06</td>
<td>1.81, 5.18</td>
</tr>
<tr>
<td>Tempesta 2000</td>
<td>62/164</td>
<td>48/166</td>
<td>15.5</td>
<td>1.49</td>
<td>0.94, 2.35</td>
</tr>
<tr>
<td>Whitworth 1996</td>
<td>27/224</td>
<td>11/224</td>
<td>7.4</td>
<td>2.50</td>
<td>1.29, 4.87</td>
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<tr>
<td>Total (95%CI)</td>
<td>417/1775</td>
<td>231/1549</td>
<td>100.00</td>
<td>1.88</td>
<td>1.57, 2.25</td>
</tr>
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Test for heterogeneity: chi-square = 17.00; df = 10; P = 0.074  
Test for overall effect: z = 6.87; P < 0.0001

**Acamprosate and naltrexone compared**

- Systematic literature search of acamprosate and naltrexone
- Acamprosate larger effect size for abstinence
- Naltrexone larger effect size for reducing heavy drinking
- Detoxification prior to starting medications improved outcomes for both medications


CI = confidence interval; OR = odds ratio

*Addiction 2013; 108(2): 275-293*
Acamprosate for AUD

- 666 mg TID
- Reduce to 333 mg TID in moderate renal disease
- Contraindicated in severe renal disease
- Mild side effects: “chicken soup”
- Must be detoxified
- If they slip and relapse move on to another medicine
- Other than detox no predictors of efficacy
  - Non-endorphin sensitive alcoholics likely target group

Disulfiram for AUD

Disulfiram

- First medication approved for alcoholism
- Blocks acetaldehyde dehydrogenase
- Works best if dose observed
Disulfiram Does Not Promote Abstinence

JAMA. 1986; 256(11):1449-55

Disulfiram Metanalysis Comparing Supervised to Unsupervised Trials

PLoS ONE 2014; 9(2): e87366
Disulfiram for AUD

- Effect sizes for supervised disulfiram (.53) twice those for naltrexone (av. 0.28) or acamprosate (av. 0.26)
  - Plos One 2014;9:e87366
- East Asians with ALDH2 deficiency rarely alcoholic
- Supervised dosing needs to be managed
- Disulfiram side effects rare but serious

Alcohol and Alcoholism 2017; 52(2) 213–219

Disulfiram for AUD

- Dose 250 mg daily
- Medically stable patients only
- Check lfts baseline, at 2 wks, 3mos and 6 mos
- No alcohol for 12 hours before and up to 2 weeks after
- Not a first line med
Topiramate for AUD

Topiramate
Multiple mechanisms of action

1. Na\(^+\) and CA\(^{++}\) channel blockade
2. GABA potentiation
3. Glutamate antagonism (AMPA and Kainate)
4. Carbonic anhydrase inhibitor

Topiramate was Superior to Other Treatments in This Meta-analysis

Addiction 2017; 113, 220–237
Topiramate for AUD

- Don’t need to be detoxed
- Titrate slowly to 200 mg daily generally divided
  - 25 wk 1, 50 wk 2, 100 wk 3, 150 wk 4, 200 wk 5
- Word finding deficits and general mental slowing
- Not in patients with kidney stones or glaucoma

Gabapentin for AUD

Gabapentin

- Effects on both GABA and glutamate
- Reduces alcohol withdrawal
- Prevents relapse
Gabapentin for AUD

Gabapentin Reduced Heavy Drinking and Promoted Abstinence


Gabapentin for AUD

Gabapentin More effective in Patients with More Severe Alcohol Withdrawal

Gabapentin for AUD

Gabapentin Encarbil Was not Efficacious for AUD

![Graph showing percentage of subjects no heavy drinking days across treatment periods.](image)


Gabapentin for AUD

Gabapentin Reduces Heavy Drinking Days

![Table 2: Meta-Analysis Results](image)

Addiction. 2019 Sep; 114(9): 1547–1555
**Gabapentin for AUD**

- Target dose 1800 mg daily with rapid titration
- Dose reduction in renal disease
- Few side effects, variable sedation
- 3+ days of abstinence at start predicts better outcome

**Varenicline for AUD**

- Varenicline has effect on nicotinic acetylcholine receptors
  - α2β4 nAChR partial agonist
  - Full agonist at the α7 receptors and a
    - Partial agonist at the α6β2 receptors.
- Reduces alcohol self-administration in preclinical trials
- Reduced alcohol use in pilot clinical trials
Varenicline for comorbid TUD and AUD

Varenicline Treated Subjects Have Fewer Heavy Drinking Days

JAMA Psychiatry. 2018 Feb; 75(2): 129–138

Varenicline for comorbid TUD and AUD

Varenicline Treated Have Sustained Reductions IN HDD

Alcohol Clin Exp Res. 2019 May ; 43(5): 937–944
<table>
<thead>
<tr>
<th>Summary - medications for alcohol dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• There are now 4 approved medications</td>
</tr>
<tr>
<td>• Disulfiram</td>
</tr>
<tr>
<td>• Acamprosate</td>
</tr>
<tr>
<td>• Naltrexone oral</td>
</tr>
<tr>
<td>• Naltrexone injectable</td>
</tr>
<tr>
<td>• Topiramate not approved but may be useful</td>
</tr>
<tr>
<td>• Gabapentin not approved but may be useful</td>
</tr>
<tr>
<td>• Interesting data regarding varenicline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment of cocaine use disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stimulant dependence is a public health problem</td>
</tr>
<tr>
<td>• Cocaine is making a comeback</td>
</tr>
<tr>
<td>• No medications approved for stimulant dependence</td>
</tr>
<tr>
<td>• Contingency management</td>
</tr>
<tr>
<td>• Topiramate +/- stimulants</td>
</tr>
<tr>
<td>• Metyrapone plus oxazepam being studied</td>
</tr>
</tbody>
</table>
Contingency Management for Cocaine Dependence

Voucher treatment improves short-term abstinence

Voucher treatment improves short-term abstinence.

Arch Gen Psychiatry. 1994 Jul;51(7):568-76

Contingency Management for Cocaine Dependence

Percent Stimulant Negative Urines

OR=1.91 (1.4-2.6)

Percent of stimulant negative urine samples

J Subst Abuse Treat. 2010;38 Suppl 1:S61-9
Cognitive Behavioral Therapy for Cocaine Dependence

CBT Often Has Delayed Effects

[Graph showing cocaine use across time by psychotherapy]

Arch Gen Psychiatry 1994; 51: 989-97

Dextroamphetamine for Cocaine Dependence

Long-Acting Dextroamphetamine Reduced Cocaine Use

[Bar graph showing proportion positive vs study period]

Methamphetamine for Cocaine Dependence

Long-Acting Methamphetamine Reduced Cocaine Use

Drug Alcohol Depend 2009; 101:34-41

Topiramate for Cocaine Dependence

Topiramate Promotes Cocaine Abstinence

Drug Alcohol Depend. (2004); 75(3): 233-40
Topiramate for cocaine dependence

Topiramate Associated with Greater End of Trial Abstinence

![Graph showing % of Patients Cocaine Abstinent](image)

Drug Alcohol Depend. (2013);133(1): 94-9

Topiramate for Cocaine Dependence

Topiramate Reduced Cocaine Use

![Graphs showing weekly mean proportions of cocaine normal days](image)

JAMA Psychiatry (2013); 70(12): 1338-46
MAS + Topiramate for Cocaine Use Disorder

The Combination of MAS and Topiramate Promoted Cocaine Abstinence

![Graph]

Biological Psychiatry 2012; 72(11): 950-6

MAS + Topiramate for Cocaine Use Disorder

The Combination of MAS and Topiramate Promoted Cocaine Abstinence

![Graph]

Drug Alcohol Depend 2020; 206:107700
Stress relief reduces cocaine self-administration

- Cortisol blocking agents reduce self-administration
- Benzodiazepines reduce self-administration
- Combining meds could allow for lower doses of benzos
- Metyrapone and oxazepam in a single capsule

Multicenter double blind placebo controlled trial

- 80 subjects 4 sites
- 14 week trial
- Metyrapone (720 mg) plus oxazepam (24 mg) in a single capsule
- Twice daily dosing vs. placebo for 12 weeks
- Primary outcome is cocaine abstinence during the last 3 weeks
Metyrapone and oxazepam for Cocaine Use Disorder

Metyrapone and Oxazepam Reduced Cocaine Use

J Psychopharmacology, 2012, 26(7) 973–981

Summary – treatment of Cocaine Use Disorder

- No medications approved
  - Topiramate has the best signal
  - The search continues…
- Contingency management is most effective
- CBT has evidence of efficacy as well
What's new for Methamphetamine Use Disorder?

- Contingency management and CBT best psychosocial treatments
- Topiramate has some evidence of efficacy
- Mirtazapine may have benefit

Contingency Management for Methamphetamine Use Disorder

Contingency Management is Effective for Methamphetamine Use Disorder

[Graph showing percent of negative samples over weeks for Incentive and Treatment as usual]

Addiction 2007, 102 (Suppl. 1), 114–120
Topiramate for Methamphetamine Dependence

Topiramate Helped Prevent Relapse

Mirtazapine for Methamphetamine Dependence

Mirtazapine Reduced Methamphetamine Use
Summary – treatment of Methamphetamine Use Disorder

• No medications approved
  • Topiramate has some evidence of efficacy
  • Mirtazapine has some evidence of efficacy
  • Contingency management has the best evidence
Discussion

Questions

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