Pharmacotherapy of Alcohol Dependence

St. Louis, MO

May 28, 2009
9:00 AM to 10:15 AM
Session 2: Pharmacotherapy of Alcohol Dependence

Learning Objectives

- List 3 currently available pharmacologic treatments for alcohol addiction.
- Describe the mechanism of action of naltrexone and acamprosate.

Faculty

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Petros Levounis, MD, MA, is the director of The Addiction Institute of New York (formerly Smithers) and chief of addiction psychiatry at St. Luke’s and Roosevelt Hospitals in New York City. Dr Levounis is a board-certified addiction psychiatrist and fellow of the American Psychiatric Association (APA). He currently teaches at Columbia University College of Physicians and Surgeons, New York University School of Medicine and School of Nursing, and John Jay College of Criminal Justice in New York. His academic interests include the psychotherapy and psychopharmacology of addiction, the teaching of psychiatry, gay and lesbian mental health, crystal methamphetamine, and the behavioral addictions.

Dr Levounis is a Phi Beta Kappa graduate of Stanford University, where he studied chemistry and biophysics as a combined BS/MS student, before receiving his medical education at Stanford and the Medical College of Pennsylvania. In 1994, he moved to New York City to train in psychiatry at the New York State Psychiatric Institute of Columbia University. He graduated from Columbia, receiving the National Institute of Mental Health Outstanding Resident Award before completing a 2-year clinical and research fellowship in addiction psychiatry at New York University. Dr Levounis received the APA/Center for Mental Health Services Minority Fellowship and studied HIV risk factors in homeless men who suffer from severe mental illness and substance use disorders.

Dr Levounis has authored several articles, has lectured extensively on addiction topics throughout the United States and abroad, and has been interviewed by ABC, CBS, CNN, NBC, WB, The Martha Stewart Radio Show, the New York Times, the Daily News, TimeOut New York, the Washington Post, and Jornal do Brasil, among others.

Dr Levounis serves as chair of the Committee on Addiction Treatment of the APA, president-elect of the APA New York County District Branch, and co-chair of the Public Policy Committee of the American Society of Addiction Medicine.

Dr Levounis is currently editing a textbook on co-occurring substance use and other psychiatric disorders and writing a book on siblings of alcoholics.

Faculty Financial Disclosure Statement

The presenting faculty reported the following:
Dr Levounis serves on the speakers bureau for AstraZeneca LP; Cephalon, Inc; Forest Pharmaceuticals, Inc; Pfizer, Inc.; and Takeda Pharmaceuticals North America, Inc.

Drug List

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<th>Generic</th>
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<td>Campral</td>
<td>naltrexone</td>
<td>ReVia, Vivitrol</td>
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<td>Kemstro, Lioresal</td>
<td>ondansetron</td>
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<td>valproate</td>
<td>Depacon</td>
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<td>Depakote</td>
<td>valproic acid</td>
<td>Depakene</td>
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<tr>
<td>escitalopram</td>
<td>Lexapro</td>
<td>zolpidem</td>
<td>Ambien</td>
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</table>
Suggested Reading List


THE ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT)

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest.

<table>
<thead>
<tr>
<th>Questions</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often do you have a drink containing alcohol?</td>
<td>Never</td>
<td>Monthly or less</td>
<td>2 to 4 times a month</td>
<td>2 to 3 times a week</td>
<td>4 or more times a week</td>
</tr>
<tr>
<td>2. How many drinks containing alcohol do you have on a typical day when you are drinking?</td>
<td>1 or 2</td>
<td>3 or 4</td>
<td>5 or 6</td>
<td>7 to 9</td>
<td>10 or more</td>
</tr>
<tr>
<td>3. How often do you have five or more drinks on one occasion?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>4. How often during the last year have you found that you were not able to stop drinking once you had started?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>5. How often during the last year have you failed to do what was normally expected of you because of drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>7. How often during the last year have you had a feeling of guilt or remorse after drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>8. How often during the last year have you been unable to remember what happened the night before because of your drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>9. Have you or someone else been injured because of your drinking?</td>
<td>No</td>
<td>Yes, but not in the last year</td>
<td>Yes, during the last year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?</td>
<td>No</td>
<td>Yes, but not in the last year</td>
<td>Yes, during the last year</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total

**Note:** This questionnaire (the AUDIT) is reprinted from the National Institute of Alcohol Abuse and Alcoholism’s “Helping Patients Who Drink Too Much: A Clinician’s Guide 2005” at [www.niaaa.nih.gov](http://www.niaaa.nih.gov). To reflect standard drink sizes in the United States, the number of drinks in question 3 was changed from 6 to 5. A free AUDIT manual with guidelines for use in primary care is available online at [www.who.org](http://www.who.org).

**Scoring the AUDIT:** A minimum score (for nondrinkers) is 0 and the maximum possible score is 40. Scores of 8 or more for men (up to age 60) or 4 or more for women, adolescents, and men over the age of 60 are considered positive screens. For patients who have scores near the cut-points, clinicians may wish to examine individual responses to questions and clarify them during the clinical examination.
**Pharmacotherapy of Alcohol Dependence**

PMU-St. Louis  
Thursday, May 28, 2009  
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**Petros Levounis, MD, MA**  
Director, Addiction Institute of New York  
Chief, Division of Addiction Psychiatry at St. Luke's and Roosevelt Hospitals, New York  
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**INTRODUCTION**

Which one of the following is the least severe illness?

1. Alcohol Abuse  
2. Alcohol Dependence  
3. Alcohol Addiction  
4. Alcoholism  
5. They are all the same


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**Alcohol Abuse**

- In the past 12 months, drinking has repeatedly caused:
  - Role failure  
  - Risk of bodily harm  
  - Run-ins with the law  
  - Relationship trouble
- One or more = Alcohol Abuse


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**Alcohol Dependence**

- In the past 12 months, patient has:
  1. Tolerance  
  2. Withdrawal  
  3. Not been able to stick to drinking limits  
  4. Not been able to cut down or stop  
  5. Spent a lot a time drinking  
  6. Spent less time on other matters  
  7. Kept drinking despite problems
- Three or more = Alcohol Dependence

**Annual Societal Costs of Alcohol Dependence**

- Specialty alcohol services: $16,982 (9%)
- Medical consequences of FAS: $11,962 (7%)
- Lost future earnings due to premature deaths: $13,909 (8%)
- Lost earnings due to alcohol-related illness: $2,909 (2%)
- Lost earnings due to crime/victims: $6,499 (4%)
- Crashes, fires, criminal justice, etc: $7,466* (4%)

Total Cost: 184.6 Billion

*Cost in millions of US dollars.
FAS = fetal alcohol syndrome.
Key definitions correspond to pie chart sections in clockwise order beginning “specialty alcohol services” at the 12 o'clock position.

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**Screening 1**

- Physicians are often reluctant to assess for Alcohol Use Disorders.
- Adolescents:
  - The omnipotence of the peer group
- Elderly patients:
  - The absence of the peer group

**Screening 2**

- The CAGE Questionnaire
  - Cut Down
  - Annoyed
  - Guilty
  - Eye-Opener

- National Institute on Alcohol Abuse and Alcoholism (NIAAA):
  “Helping Patients Who Drink Too Much”

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**How much is “too much”?**

- **MEN:**
  - 5 or more standard drinks in a day, or
  - 15 or more per week
- **WOMEN:**
  - 4 or more standard drinks in a day, or
  - 8 or more per week.

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**Brief Intervention**

1. Be empathic and curious.
2. State your medical findings.
3. Educate about alcohol abuse and dependence.
4. Advise.
5. Follow up.
6. Refer, if absolutely necessary.

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**What is a Standard Drink?**

1 Standard Drink = 14 gr. (0.6 oz.) of pure alcohol.

The average person metabolizes about 1 Standard Drink per hour.

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Adapted from [www.niaaa.nih.gov](http://www.niaaa.nih.gov)
**Neurotransmitter Systems**

- GABA → CNS Inhibition
- Glutamate → CNS Excitation
- Opioid → Euphoria
- Dopamine → Addiction
- Serotonin → Impulsivity
- Cannabinoid → Pleasant Feeling

**DISULFIRAM**

Introduced in 1954

**Mechanism of Action**

- Alcohol → Acetaldehyde → Acetate
- Disulfiram irreversibly binds to acetaldehyde dehydrogenase inhibiting the metabolism of acetaldehyde to acetate.
- Acetaldehyde accumulates resulting in a violent reaction (nausea, vomiting, flushing).

**Effectiveness**

- Double-blind, placebo-control study design is not helpful as both the medication and the placebo pills may (or may not) result in fear of drinking.
- Most studies are negative, but disulfiram may be helpful in highly structured settings.

**Dosing and Safety**

- 250-500 mg daily.
- Medication costs approximately $106 a month.
- Some liver toxicity; liver function should monitored closely.
- Inhibits hepatic microsomal enzymes and increases drug levels (phenytoin, warfarin, isoniazid).

Medications for alcohol dependence have a small but appreciable addictive potential.

1. True
2. False


NALTREXONE
Oral - Introduced in 1995
Injectable - Introduced in 2006

Mechanism of Action
- Reduces positive reinforcement (reward craving).
- The patient does not experience the full euphorogenic/reinforcing effect of alcohol.
- Prevents a slip from becoming a full-blown relapse.

Effectiveness
- Effective in reducing relapse to heavy drinking (>5 drinks/day in men, >4 drinks/day in women).
- The Bouza et al (2005) meta-analysis found a 38% reduction in the rate of relapse to heavy drinking.
- Medication compliance may be a limiting factor in oral treatment.

Dosing and Safety - Oral
- 50 mg daily.
- Medication costs $248 ($104 generic) a month.
- Liver toxicity; liver function should be monitored closely.
- Antagonizes opioid-containing agents, but no other significant drug-drug interactions.

Dosing and Safety – Inj.
- 380 mg a month.
- Long-acting naltrexone injection: 100 μm diameter microspheres composed of naltrexone and PLG polymeric matrix.
- Wholesale price is $695 a month.
- Nausea, headache, injection site reactions, and fatigue are the prominent adverse effects.
ACAMPROSATE
Introduced in 2005

Mechanism of Action
- Reduces negative reinforcement (abstinence craving).
- Neuroadaptation and upregulation of the glutamate system in alcoholism.
- Acamprosate interferes with the glutamatergic system.

Effectiveness
- Effective in improving abstinence.
- The Mann et al (2004) meta-analysis found a 50% improvement in 6-month abstinence (36% drug vs. 23% placebo).
- The US trial (August 2006) showed efficacy only in patients motivated for abstinence.

Dosing and Safety
- 666 mg three times a day.
- Medication costs $150 a month.
- Excreted by the kidneys - No liver metabolism.
- Mild diarrhea (16% acamprosate vs. 10% placebo).
- No drug-drug interactions.

CO-OCCLUDING PSYCHIATRIC DISORDERS


Low tolerance for alcohol (i.e., getting drunk easily) is associated with a higher risk for alcoholism.

1. True
2. False

Which of the following agents is indicated for the treatment of Generalized Anxiety Disorder?

1. Quetiapine
2. Naltrexone
3. Es-Citalopram
4. Valproate
5. Zolpidem

In General

- Co-occurring alcohol dependence and other psychiatric disorders typically require treatment for both.
- Treating patients under one roof improves both addiction and mental health outcomes.

Depression and Anxiety

- Antidepressants are the first-line treatments for co-occurring alcohol and depressive and/or anxiety disorders.
- Benzodiazepines have been shown to be particularly problematic in the treatment of PTSD.
- Quetiapine shows some promise.

Most alcoholism treatment facilities in the United States offer medications approved to treat alcohol dependence.

1. True
2. False

Combinations

- Naltrexone and acamprosate have different mechanisms of action and may work synergistically.
  - Naltrexone on reward cravings (positive reinforcement)
  - Acamprosate on abstinence cravings (negative reinforcement)
- Medications and psychotherapy.
Naltrexone/Acamprosate

- Abstinence rates during a 12-week trial with:
  - Naltrexone 50 mg QD,
  - Acamprosate 666 mg TID.
- The combination of the two medications helped alcoholics stay abstinent ($P<0.002$) better than each drug alone.

Placebo  Naltrexone  Acamprosate  Combination

The COMBINE Study

- Percentage of abinent days per month during a 16-week treatment trial with:
  - Naltrexone 100 mg QD,
  - Acamprosate 1 g TID.
- All treatment groups had an increase in % days abstinent. Overall effect was from 25% to 73%.

New Pharmacological Agents

- Anticonvulsants
  - Topiramate
  - Carbamazepine
  - Valproic Acid
- GABA agonist
  - Baclofen
- Serotonin (5-HT$_3$) antagonists
  - Ondansetron
  - Mirtazapine
- Selective Serotonin Reuptake Inhibitors

Topiramate

- Percentage of heavy drinking days during a 14-week treatment trial with topiramate up to 300 mg QD.
- Topiramate significantly decreased ($P=.002$) heavy drinking.
  - Pre-Study 82%
  - Placebo 52%
  - Topiramate 44%

Sertraline

- Abstinence rates during a 14-week treatment trial with sertraline 200 mg QD.
- Sertraline helped Late-Onset alcoholics stay abstinent ($P<0.004$), but not Early-Onset.

Sertraline

Please note: This agent is not approved by the FDA for use in alcohol dependence.

Adapted from Kiefer F et al. Arch Gen Psychiatry. 2003;60:96.


Adapted from Johnson et al. JAMA. 2007;298:1641-1651.

CONCLUSIONS

1. Screening and Brief Interventions are effective in the initial management of alcohol use disorders.
2. We now have safe and effective medications that can help us treat Alcohol Dependence.
3. Antidepressants are the first-line pharmacological treatments of co-occurring anxiety disorders.
APPENDIX

ALCOHOL INTOXICATION

Characteristics
- 0-100 mg/dL: Well-being
- 100-200 mg/dL: Incoordination
- 200-300 mg/dL: Ataxia
- 300-400 mg/dL: Stage I Anesthesia
- 400-600 mg/dL: Coma
- 600-800 mg/dL: Death

Pharmacotherapy
- Use IV thiamine and glucose.
- Do not use ipecac, activated charcoal, caffeine, amphetamines, or flumazenil.
- Treatment is supportive.

ALCOHOL WITHDRAWAL

Characteristics
- Following the last drink:
  - 6 to 24 hours: Autonomic Hyperactivity
  - 24 to 48 hours: Seizures
  - 48 to 96 hours: Delirium tremens
- Autonomic Hyperactivity with:
  - Reduced GABA activity and
  - Enhanced glutamate activity
- Typically mild, occasionally severe, rarely fatal.

Pharmacotherapy

- Use the Clinical Institute Withdrawal Assessment for Alcohol revised (CIWA-Ar) where available.
- Long-acting benzodiazepines (e.g., chlordiazepoxide) are the treatment of choice except in significant liver failure or the elderly.
- Anticonvulsants are being studied.

Anticonvulsants are being studied.

Adapted from Mayo-Smith MF. JAMA. 1997;278:144-51.

Practice Guidelines

CIWA-Ar Categories

<table>
<thead>
<tr>
<th>CIWA-Ar Score</th>
<th>Neurpsych Symptoms</th>
<th>Physical Symptoms</th>
<th>Perceptual Disturbances</th>
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<tbody>
<tr>
<td>&lt; 8 Mild Withdrawal</td>
<td>No Medications Supportive Treatment</td>
<td>NAUSEA/VOMITING</td>
<td>AUDITORY</td>
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<tr>
<td>9 - 15 Moderate Withdrawal</td>
<td>PRN Medications Symptomatic Treatment</td>
<td>HEADACHE</td>
<td>VISUAL</td>
</tr>
<tr>
<td>&gt; 15 Severe Withdrawal</td>
<td>Standing Medications Inpatient Medical Treatment</td>
<td>TACTILE</td>
<td>SWEATS</td>
</tr>
</tbody>
</table>

* except 0-4 for sensorium

Adapted from Mayo-Smith MF. JAMA. 1997;278:144-51.