Evidence-Based Treatment of Alcohol Use Disorder: A Focused Examination of Naltrexone’s Role

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Treatment of Alcoholism in the United States

- How to prescribe oral naltrexone
- Very low dose to begin
- Try to convince patient to continue at least 3 to 4 months before giving up
- Duration depends on results – years
- Slow release depot, Q 30 days
- Most success, few side effects
- Best continuity of care
- This is a chronic disease


FDA Approved Medications

- Disulfiram
- Naltrexone (generic)
- Acamprosate
- Depot Naltrexone
- Nalmefene (approved in Europe)
- Topiramate (used off-label)

DETOXIFICATION and referral to AA IS NOT TREATMENT!!

Hypothesis: Alcohol Releases Endogenous Opioids

**In vivo evidence:** Only indirect evidence in brain, direct evidence in plasma

**In vitro evidence:** Direct measures in lymphocyte cultures, HIV effects of alcohol blocked by naltrexone


Molecular mechanism unknown

Naltrexone: Investigational New Drug License 1983

- Open studies
- Range of doses
- Minimal side effects
- Institutional review board approval

Protocol 1986

- Self report + breathalyzer 5× per week
- Endpoint = Relapse to heavy drinking
- “Slips” recorded, not as endpoint
- Craving recorded
- RECRUITMENT OBSTRUCTIONS (counselors against medication)
- Joe Volpicelli started fellowship

Naltrexone Decreases Alcohol Preference

% Change from Saline Pretreatment Response Levels (10-day mean)

Naltrexone 1.0 mg/kg
Naltrexone 3.0 mg/kg
Naltrexone 5.0 mg/kg


Post-Shock Drinking

Change in % Ethanol Consumption

Placebo
Naltrexone


Series of Lucky Coincidences

1. Altshuler poster at College on Problems of Drug Dependence
2. Joe Volpicelli decides on Fellowship


Any Alcohol Drinking

Participants (%)

Naltrexone Placebo


Days Drinking

Average Drinking Days per Week

Naltrexone Placebo


Subjective “High” in Naltrexone and Placebo Participants

Mean “High” Rating

Naltrexone Placebo

* P < .05
Pharmacologic Treatments for Alcoholism

Alcohol Relapse

A. Coming to treatment appointment with a blood alcohol concentration > 100 mg%

OR

B. Self-report of drinking ≥ 5 days within 1 week

OR

C. Self-report of ≥ 5 drinks during 1 drinking occasion


No. of Weeks Receiving Medication

Naltrexone HCL (n = 35)

Placebo (n = 35)

Non-Relapse “Survival”

Cumulative Proportion with No Relapse

Naltrexone HCL (n = 35)

Placebo (n = 35)

Studies Supporting Efficacy

Studies Not Supporting Efficacy

Study\nNotes\nStudy\nNotes
Morin, et al (2001) 111 None
Hendricks, et al (2001) [Finland]

Studies Supporting Efficacy

Studies Not Supporting Efficacy

Study\nNotes\nStudy\nNotes
Morin, et al (2013) 604 Nalmefene (II), > 7000 patients

Rates of Never Relapsing According to Treatment Group


Adherence Improved

• Extended-release depot preparation
• Injection q 30 to 40 days
• Pharma sets price at $800 per injection
• Capitated systems (Kaiser, Aetna)

Side Effects

For alcohol dependence (ie, those occurring in ≥5% and at least twice as frequently with Depot Naltrexone than placebo):

- Nausea
- Vomiting
- Injection site reactions (including induration, pruritus, nodules, and swelling)
- Muscle cramps
- Dizziness or syncope
- Somnolence or sedation
- Anorexia
- Decreased appetite or other appetite disorders


Results: Heavy Drinking Days


Europe 2012

• 3 large clinical trials
• ~1000 alcoholics each
• Nalmefene vs placebo PRN
• All positive
• Approved 2013: European Medicine Agencies


Effect size “moderate” based on heavy drinking days outcome measure

NNT 7 to 12

Assumption: Alcohol causes the release of endogenous opioids that are “required” for dopamine release in response to alcohol?
Naltrexone Concurrently Antagonizes EtOH-Induced Accumbal Dopamine Release and EtOH Self-Administration

Gonzales RA, et al.

Brain Reward System


Prefrontal Cortex
Nucleus Accumbens
Arcuate Nucleus
Ventral Tegmental Area

Dopamine
GABA
β-Endorphin Neuron
Arcuate Nucleus
Ventral Tegmental Area

Long Loop

Nucleus Accumbens

Dopamine
GABA
β-Endorphin Neuron
Arcuate Nucleus
Ventral Tegmental Area

Opioid Antagonism


Alcohol effects become conditioned to environmental cues
Naltrexone blocks cue induced relapse better than stress induced

Examples of the Various Visual Cues from Normative Appetitive Picture System (NAPS)

Time Course of the Presentation of Stimuli During fMRI


*Craving rated after each block
Comparisons: Alcohol - Beverage - Vis Ctrl
Alcohol - Vis Ctrl - Beverage - Rest
Vis Ctrl - Rest

Alcohol – Beverage Condition


Alcoholics (n = 10) Controls (n = 10)

Z = 1.645 Ex .05


Drugs to Aid Alcoholics See Little Use, Study Finds

- Less than one-third of alcoholics receive any treatment
- Less than 10% are prescribed medications
- Data from 23,000 patients, 122 randomized trials. For acamprosate and naltrexone, 12 to 20 patients to prevent return to heavy drinking. For statins, 25 to 100 patients to prevent one cardiac event.


Why do many alcoholics respond to naltrexone, but others show no response?

Baseline Craving Scores

PACS = Penn Alcohol Craving Scale.
Family History and Naltrexone Efficacy


Baseline β-Endorphin Levels in Low- and High-Risk, and Abstinent Alcoholic Patients


Change in β-Endorphin Levels after Alcohol Consumption


BAES Stimulation Scores Among FH+ and FH Participants

BAES = Biphasic Alcohol Effects Scale.

Key effect: Sensitivity of endogenous opioid system to alcohol

One source of individual variability in response to ethyl alcohol

OPRM1 Protein Structure

LIGAND BINDING

EXTRACELLULAR
NH_TERMINUS
A118G

N460C N is an
N-glycosylation site

COOH TERMINUS
Human μ-Opioid Receptor Gene

PROMOTER 5' UTR EXON 1 EXON 2 EXON 3 EXON 4 3' UTR

10 variants
2 SNPs
1 SNP
1 INTRON
3 SNP
1 3' UTR SNP

4 5' UTR SNPs
6 INTRON 2 SNPs

6.6 kb of OPRM1 gene sequence was determined in ~200 persons; 25 variants occurred at a frequency > 1%.

The 118 A > G exon 1 SNP increases OPRM1 affinity for β-endorphin. The functional significance of other variants remains unknown.

SNP = single-nucleotide polymorphism.

Functional Allele

Increase
and
Decrease

Alcohol Effects by Genotype

Breath Alcohol Concentration

SHAS = Subjective High Assessment Scale.

Cortisol Responses by Naloxone by μ-Opioid Receptor Genotype

P1 = time of placebo (saline) administration; N = times of incremental naloxone administration.

Ethnicity and A118G Allele Frequency

Based on multiple studies, allele frequencies differ markedly across ethnicities for the A118G SNP in the μ-opioid receptor gene. It arose after the out-of-Africa migration.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>f(G)</th>
<th>Ethnicity</th>
<th>f(G)</th>
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<tbody>
<tr>
<td>African</td>
<td>1%</td>
<td>Koreans</td>
<td>31%</td>
</tr>
<tr>
<td>African-American</td>
<td>3%</td>
<td>Chinese</td>
<td>35%</td>
</tr>
<tr>
<td>Swedish</td>
<td>17%</td>
<td>Malaysian</td>
<td>45%</td>
</tr>
<tr>
<td>European-origin US</td>
<td>15%</td>
<td>Indian</td>
<td>47%</td>
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OPRM1 A118G Allele Frequency of Ethnic Group Migration of Humans on Planet Earth

There was a significant (Chi squared = 7.2, P = .007) increase in A/G, G/G genotype among alcoholics. In this study the attributable risk for the G allele is ~11%, suggesting that ~11% of Swedish alcoholics have disease in part due to the G allele.

**OPRM1 A118G and Alcoholism**

**Relapse Rate by Genotype**

**COMBINE Study**

- N = 1383; 9 randomized groups
  - MM + Placebo
  - MM + Naltrexone
  - MM + Acamprosate
  - MM + Naltrexone + Acamprosate
  - CBI only
  - At least 4 days abstinence at baseline
  - Endpoints
    - Percent days abstinent
    - Time to first heavy drinking day

**COMBINE: NIAAA Good Outcome**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Genotype</th>
<th>Relapse Rate</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone</td>
<td>A/G, GG</td>
<td>95%</td>
<td>N = 28</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>A/A</td>
<td>73%</td>
<td>N = 86</td>
</tr>
<tr>
<td>Placebo</td>
<td>A/G, GG</td>
<td>63%</td>
<td>N = 60</td>
</tr>
<tr>
<td>Placebo</td>
<td>A/A</td>
<td>65%</td>
<td>N = 205</td>
</tr>
</tbody>
</table>

Odds ratio, naltrexone good results, GVA = 10.25 (95% CI 1.31 – 80.0, P = .03)

*VA multi-site study: sample size with G allele small

**Rhesus model**

Ortholog of A118G allele in humans (OPRM1C77G)

- Increased sensitivity to alcohol
- Increased alcohol preference
- Greater effect in males

**Sub-sample of VA Cooperative Study**

Those who gave blood for DNA
Naltrexone significantly better than placebo, but no genetic association
Finnish study with nalmefene—naltrexone superior to placebo, but no genetic association

PROSPECTIVE study in progress
Slow release version of naltrexone

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Alcohol-Induced Dopamine Release in Ventral Striatum is Restricted to OPRM1 - 118G Carriers

AVS = anterior ventral striatum; PVS = posterior ventral striatum.

Animal Models for A118G: Mouse

OPRM 118 AA and GG mice were given ethanol 2 g/kg, during in vivo microdialysis. GG mice showed a significant dopamine elevation in striatum after the ethanol, while AA mice did not. The 5-HT levels in striatum showed no difference between genotypes.

Increased Alcohol-Induced Dopamine-Release in 118GG Mice is Associated with Increased Voluntary Alcohol Intake


CNN Special
Addiction: Life on the Edge

5 patients followed for 1 year
Different parts of country
• Admissions
• Graduations
• Relapses
• Interviews with counselors at famous programs

Addiction: Life on the Edge

GUPTA: And so he tried again. He checked himself into an experimental program run by Brown University. This time he got counseling once a week and a daily pill, a medicine called naltrexone. About 2 months into it, Walter Kent suddenly noticed the world around him looked and felt different.

KENT: And I had just turned around and I said, this is really something for the first time in my life that I never had this sensation where I didn’t want a drink. And this, to me, was like a godsend because of the fact that for someone who had to have a drink, now all of a sudden I don’t need that—I don’t have that feeling anymore.

GUPTA: He hasn’t had a drink in more than 8 years. Even after his doctor stopped the medication. He’s healthy, back at work, fixing up carburetors. And now he’s part of a running debate. Is addiction an illness you can treat with a pill or a character flaw to be tackled with therapy and self-help?

GUPTA: Despite the evidence, most fancy rehab centers use medication only rarely, if at all. The focus is much more on therapy.

Head Counselor Minnesota: With the health care professional staff here at Hazelden, our experience tells us having that network of support in recovery is what really makes the difference.

GUPTA: More so than medication?

CLARK: More so than just medication, exactly.

GUPTA: And that’s the conventional wisdom.
**Addiction: Life on the Edge**

California Program

GUPTA: What about medications?

Head Counselor California Program: We do not use them at the Betty Ford Center.

No comment from the interviewer, no follow-up questions.

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**Comorbidity**

2 new placebo controlled trials

- Alcoholism + Depression
- Naltrexone + Sertraline
- Alcoholism + PTSD
- Naltrexone + Exposure Therapy

PTSD = posttraumatic stress disorder.


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**Time to First Heavy Drinking Day and Time to First Drinking Day in Depressed Alcohol-Dependent Patients Randomly Assigned to Medication Treatment or Placebo**


**HAM-D Score Change from Baseline**

HAM-D = Hamilton Rating Scale for Depression.


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**Arguments Against Medications**

- They are just a “crutch”
- You have to work the program yourself – no chemical aids
- They get in the way of the 12 steps
- I’ve been sober for 10 years and I never took medication
- They have side effects
- You’ll become addicted to them
- Etc...