Ethical Issues in the Treatment of Addictions

Charles P. O’Brien, MD, PhD
University of Pennsylvania
Disclosure

Consultant to

Embera (Research)
Alkermes (Depot Naltrexone, no patent, no stock)
Reckitt (Suboxone)
Addiction = Brain Disorder

Strongly inherited
  adoption studies, twin studies
Polygenic

Treatments
  Psychotherapy, 12 Steps
Medications
  Opioids
  Alcohol
  Tobacco
Addiction ethics

Ethical questions involving addiction
Diminished responsibility for actions
Validity of confession during withdrawal
Treatment research in prisoners
Informed consent in parolees

Duties of treatment professionals
Qualifications
Philosophy on medications
12 Step doctrine (what “big book” says)
Alcoholism: Genetic Subtype

Diagnosis based on drinking behavior

Reasons for drinking

Learned behavior

  Conditioned response

Animal models

  Predict effects in humans
Naltrexone decreases Alcohol preference*

Days Naltrexone

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

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

* Altshuler 1980
Post-Shock Drinking

![Graph showing change in ethanol consumption during different days post-shock for Placebo and Naltrexone groups. The graph illustrates a significant increase in ethanol consumption for the Placebo group over the first 5-6 days post-shock, while the Naltrexone group shows a slight decrease.]
Saline

Ethanol Responses

Time (min)

0 5 10 15 20 25 30

0 10 20 30 40 50 60 70 80

.25 mg/kg Naltrexone

Ethanol Responses

Time (min)

0 5 10 15 20 25 30

0 10 20 30 40 50 60 70 80

Baseline

Post-Deprivation (Day 1)

Post-Deprivation (Day 2)
IND 1983

Open studies
Range of doses
Minimal side effects
IRB approval
Protocol 1986

70 male alcoholics, DSM III
Day hospital 27 hours per week,
12-step, AA groups
Self report + breathalyzer 5x per week
Endpoint = Relapse to heavy drinking
“Slips” recorded, not as endpoint
Craving recorded

RECRUITMET OBSTRUCTION
Protocol 1986

Self report + breathalyzer 5x per week

Endpoint = Relapse to heavy drinking

“Slips” recorded, not as endpoint

Craving recorded

RECRUITMENT OBSTRUCTIONS

Joe Volpicelli started fellowship
Series of Lucky Coincidences

- 1. Altshuler poster at CPDD
- 2. Joe Volpicelli decides on Fellowship
Any Alcohol Drinking

Percent of Subjects

Naltrexone    Placebo
Days Drinking

Average Drinking Days per week

Naltrexone  Placebo
Subjective “high” in Naltrexone and Placebo Subjects

* p<.05
Pharmacological Treatments for Alcoholism

Craving Scores by Week

Mean (SEM) Craving Score (0-9)

Weeks on Medication
Alcohol Relapse

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

B. self report of drinking five or more days within one week  
   or

C. self report of five or more drinks during one drinking occasion
Non-relapse “Survival”

Volpicelli et al, Arch Gen Psychiatry, 1992; 49: 876-880
Rates of Never Relapsing According to Treatment Group (n=97)

O’ Malley et al, Arch of Gen Psychiatry, Vol 49, Nov 1992
<table>
<thead>
<tr>
<th>Study</th>
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<td>Latt et al 2002</td>
<td>107</td>
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<td>153</td>
<td>Heavy drinkers</td>
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<td>O’ Malley et al 2002</td>
<td>18</td>
<td>Human lab</td>
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<td>Anton et al 2006</td>
<td>1383</td>
<td>RCT, depot</td>
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Compliance Improved

- Extended release depot preparation
- Injection q 30-40 days
- Pharma sets price at $800 per injection
Results: Heavy Drinking Days

<table>
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<tr>
<th></th>
<th>25th Percentile</th>
<th>75th Percentile</th>
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<tr>
<td>Placebo</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>Vivitrol 190 mg</td>
<td>19.3</td>
<td>21.5</td>
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<tr>
<td>Vivitrol 380 mg</td>
<td>5.9</td>
<td>5.4</td>
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Overall Median Heavy Drinking Days per Month: 19.3

Male Median Heavy Drinking Days per Month: 7.0
Female Median Heavy Drinking Days per Month: 5.6
Europe 2012

3 Large clinical trials

~1,000 alcoholics each

Nalmefene v placebo prn

All positive

Approved by EMA 2013
Assumption: alcohol causes the release of endogenous opioids which are “required” for DA release in response to alcohol?
Dopamine

Opioid Antagonism

– GABA

Ventral Tegmental Area

Arcuate Nucleus

– Endorphin Neuron

Nucleus Accumbens

Alcohol

GABA

Ventral Tegmental Area

Alcohol activates classical DA reward pathways through activation of μ-opioid (OPRM1) receptors in the VTA

(Spanagel et al., 1992; Johnson and North, 1992; Tanda & Di Chiara 1998)

- Local μ-opioid antagonism in the VTA blocks alcohol-induced DA release in the Nc. Accumbens

- Tonic inhibition onto VTA DA cells from GABA-ergic interneurons

- Activation of μ-opioid heteroceptors suppresses GABA release, produces disinhibition of DA cells
Rat & Human Studies: Alcohol effects become conditioned to environmental cues

Naltrexone blocks cue induced relapse better than stress induced (F. Weiss et al)
Examples of the various visual cues from Normative Appetitive Picture System (NAPS)

<table>
<thead>
<tr>
<th>Alcohol (A)</th>
<th>Beverage (B)</th>
<th>Visual Control (C)</th>
<th>Rest (R)</th>
</tr>
</thead>
</table>

Time Course of the Presentation of Stimuli During fMRI

Sip of Preferred Beverage

Time (min)

0    1    2    3    4    5    6    7    8    9    10   11   12   13

* Craving rated after each block

Comparisons:
Alcohol - Beverage
Alcohol - Vis Ctrl
Vis Ctrl - Rest
Beverage - Vis Ctrl
Beverage - Rest
Alcohol - Beverage Condition

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

Z=1.645 Ex .05
Alcohol - Beverage Condition

Ventral Tegmental Area

Cingulate

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

Z=1.645 Ex .05, Myrick et al, 2004
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

Density of Familial Alcohol Problems

- < 25% Alc Problem: n = 77
- 25%-50% Alc Problem: n = 73
- > 50% Alc Problem: n = 29
Minutes after alcohol consumption

Change in b-Endorphin Levels after Alcohol Consumption

% change in plasma b-endorphin levels

- High Risk
- Low Risk

Minutes after alcohol consumption

0 20 40 60 80 100 120
BAES Stimulation Scores Among FH+ and FH Subjects

**Placebo**

- FH+ (yellow line)
- FH- (green line)

**Naltrexone**

- FH+ (yellow line)
- FH- (green line)
OPRM1 PROTEIN STRUCTURE

LIGAND BINDING

EXTRACELLULAR NH$_2$ TERMINUS
A118G

N40D, N is an N-glycosylation site

COOH TERMINUS
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 beta-endorphin. The functional significance of other variants remains unknown.
Functional Allele

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

<table>
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<th>ETHNICITY</th>
<th>f(G)</th>
<th>ETHNICITY</th>
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<tr>
<td>African</td>
<td>1%</td>
<td>Koreans</td>
<td>31%</td>
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<td>African-American</td>
<td>3%</td>
<td>Chinese</td>
<td>35%</td>
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<tr>
<td>Swedish</td>
<td>17%</td>
<td>Malaysian</td>
<td>45%</td>
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<tr>
<td>European-origin US</td>
<td>15%</td>
<td>Indian</td>
<td>47%</td>
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- Crowley et al, 2003
- Gelernter et al, 1999
- Tan et al, 2003
- Bart et al, 2004
Figure 3. Cortisol responses to Naloxone by mu-opioid receptor genotype. PI denotes time of placebo (saline) administration. N denotes times of incremental Naloxone administration.
Bart et al (Mol Psychiatry 9:547, 2004) studied opioid addicts in Sweden for A118G. 

There was a significant (Chi squared = 13, p = 0.00025) increase in A/G, G/G genotype among opioid addicts. The attributable risk for the G allele is ~ 18%, suggesting that ~ 18% of Swedish opioid addicts have disease in part due to the G allele.
Bart et al (Neuropsychopharmacol, 2005) studied alcoholics in Sweden for the A118G.

There was a significant (Chi squared = 7.2, p = 0.007) 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.
Hunt for Candidate Genes!

David Oslin, MD

Wade Berrettini, MD, PhD
Relapse Rate by Genotype

Proportion No relapsed

Days

Naltrexone / Asp40 Allele (A/G, G/G)
Naltrexone Asn40 Allele (A/A)
Placebo / Asp40 Allele (A/G, G/G)
Placebo / Asn40 Allele (A/Al)
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


CBI = cognitive behavioral intervention; MM = medical management
### Combine: NIAAA Good Outcome

<table>
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<th>A/G, GG</th>
<th>95%</th>
<th>N = 28</th>
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<tr>
<td>Nalt</td>
<td>A/A</td>
<td>73%</td>
<td>N = 86</td>
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<tr>
<td>Plac.</td>
<td>A/G, GG</td>
<td>63%</td>
<td>N = 60</td>
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<tr>
<td>Plac.</td>
<td>A/A</td>
<td>65%</td>
<td>N = 205</td>
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Odds ratio, nalt good regs, GVA = 10.25 (95% CI 1.31 - 80.0 P= .03)

*VA multi-site study: sample size with G allele small
Alcohol effects by genotype

Breath Alcohol Concentration

Self-reported Stimulation (SHAS)

- AA allele
- AG allele

Levels: 0.02, 0.04, 0.06
Alcohol-induced dopamine release in ventral striatum is restricted to OPRM1 - 118G carriers
(Ramchandani et al., Mol Psychiatry 2010)
Mouse models: “knock-in” human OPRM-1
2 Labs A/A and G/G versions of μ receptor gene, 4x inc DA release in response to ethanol in G/G mice, increased ethanol Self Adm
Penn: Blendy inc DA response
• Rhesus, functionally equivalent allele (77G variant13) produces sensitivity to alcohol-induced psychomotor stimulation.
Increased alcohol-induced DA-release in 118GG mice is associated with increased voluntary alcohol intake (Thorsell et al, in preparation)
Cost of Treatment 6 months prior to admission compared to 6 months later

Fewer visits to Emergency Room
Treatment of Alcoholism in USA

<10% receive treatment

- Medications only for treatment of withdrawal
- Relapse prevention medication rare
- Relapses
- Interviews with counselors at famous programs
How to prescribe oral naltrexone
Very low dose to begin
Try to convince patient to continue at least 3-4 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.
CNN Special
Addiction: Life on the edge

5 patients followed for one year
Different parts of country

• Admissions
• Graduations
• Relapses
• Interviews with counselors at famous programs
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 two 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 eight 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.
California Program

Gupta: **What about medications?**

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

No sign of embarrassment from professional staff. No intention of trying medication that worked so well. No comment from the interviewer, no follow up questions.

Hazeldon now using Suboxone and naltrexone.

*Addiction: Life on the Edge – CNN Correspondent Dr. Sanjay Gupta aired April 19, 2009*
Anti-depressant med v. Psychoanalysis

Osheroff case, 1980s
Depressed pediatrician, unable to work
Chestnut Lodge, Maryland, in-patient
Intensive Psychoanalysis, (4x/wk.) no medication
No benefit
Funds exhausted in 6 mo.
Discharge
Family brought him to psychiatrist
Prescribed anti-depressant
6 wks. later, recovered, wants to work
Medical practice lost, lawsuit against Chestnut Lodge
Large settlement to patient
Ethics questions

Is it ethical to deprive a patient of a trial on an effective medication with no serious risk simply because of your philosophy?

Does a therapist have the ethical responsibility to learn about all effective treatments (naltrexone FDA approval 1995)
Ethics questions

Coercion of health care professionals using license suspension
Is it ethical to order physician doing well on medication to stop Suboxone or naltrexone?
Is it ethical to coerce physicians in State Programs to have extended residential care if therapist believes it to be not necessary
Health Care Reform

Cost-benefit data showing savings in treatment of alcoholics with meds. Aetna, Kaiser

Obama care will pay for meds as prevention

Other meds available for alcohol, opioids, nicotine
FOR MORE INFORMATION

http://www.med.upenn.edu/csa/or

obrien@upenn.edu