Biological Subtype of Alcoholism with specific treatment

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University of Pennsylvania
Consultant to

Embera (Research)
Alkermes (Depot Naltrexone)
Astra (drug development)
Alcohol: desired drink

• Common Disorder, 10-15% prevalence
• Barely covered in medical school
• 50-60% genetic
• Polygenic
• 223 Billion costs per year
• 90,000 deaths
• 30% of liver transplants
• Should be diagnosed and treated in PRIMARY CARE
Ethanol: a drug with complex effects on multiple neurotransmitter systems
Alcohol reward

Partial list

• GABA
• Serotonin
• AMPA, Glu-rec
• NMDA
• Neuropeptide Y
• Glycine
• Opioid- μ, k, δ
Treatment of Alcoholism in USA

<10% receive treatment

- Medications only for treatment of withdrawal
- Relapse prevention medication rare
- Relapses very common
FDA Approved Medications

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

DETOXIFICATION IS NOT TREATMENT
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…
True Translational Story: Naltrexone for Alcoholism

• Animal lab
to
• Randomized clinical trials
to
• FDA approval for clinical practice
to
?? Standard practice
Endogenous Opioid System

Opiate Receptors
Simon 1973
Pert & Snyder 1973
Terenius 1973

Enkephalin 1975 $\delta$
B-Endorphin $\mu$
Dynorphin $\kappa$
Nociceptin OFQ/NOC 1990s
Naltrexone decreases Alcohol preference*

* Altshuler 1980

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

Days Naltrexone

Naltrexone 1.0 mg/kg
Naltrexone 3.0 mg/kg
Naltrexone 5.0 mg/kg
Post-Shock Drinking

Change in % Ethanol Consumption

Days Post-Shock

Placebo

Naltrexone
Saline

Ethanol Responses

Time (min)

.25 mg/kg Naltrexone

Ethanol Responses

Time (min)

Baseline

Post-Deprivation (Day 1)

Post-Deprivation (Day 2)
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.

Wen Ze Ho et al, 2006

Molecular mechanism unknown
IND 1983

Open studies

Range of doses

Minimal side effects

IRB approval
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

Placebo
Naltrexone
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
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<td>Heavy drinkers</td>
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<td>O’ Malley et al 2002</td>
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<td>Gastpar et al 2002</td>
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<td>Neg. in self report</td>
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<td>Pos. GGT</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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<th>Group</th>
<th>Overall</th>
<th>Male</th>
<th>Female</th>
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<tr>
<td>Placebo</td>
<td>5.9</td>
<td>4.4</td>
<td>4.0</td>
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<tr>
<td>Vivitrol 190 mg</td>
<td>3.1</td>
<td>2.1</td>
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<td>Vivitrol 380 mg</td>
<td>5.6</td>
<td>4.9</td>
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Median Heavy Drinking Days per Month:

- Baseline: 19.3
- 25th Percentile: 7.0
- 75th Percentile: 21.5
Europe 2012

3 Large clinical trials
~1,000 alcoholics each
Nalmephene v placebo

prn

All positive

Approved 2013: EMA
Assumption: alcohol causes the release of endogenous opioids which are “required” for DA release in response to alcohol?
Naltrexone Concurrently Antagonizes EtOH-Induced Accumbal DA Release and EtOH Self-Administration

Assumption: alcohol causes the release of endogenous opioids which are “required” for DA release in response to alcohol?
Alcohol effects become conditioned to environmental cues

Naltrexone blocks cue induced relapse better than stress induced
Pre-Alcohol "Craving"

Dopamine (% baseline)

Time (minutes)

- Saline, N=13
- Naltrexone, N=16
**Examples of the various visual cues from Normative Appetitive Picture System (NAPS)**

**Alcohol (A)**  
**Beverage (B)**  
**Visual Control (C)**  
**Rest (R)**

### Time Course of the Presentation of Stimuli During fMRI

**Sip of Preferred Beverage**

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<th>C</th>
<th>A</th>
<th>B</th>
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<th>C</th>
<th>B</th>
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<td>10</td>
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<td>12</td>
<td>13</td>
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```

*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
Why do many alcoholics respond to naltrexone, but others show no response?
Baseline Craving Scores

PACS = Penn Alcohol Craving Scale

Days Heavy Drinking

Low Crave (PACS < 5)
Mod Crave (PACS 6-15)
High Crave (PACS > 15)

n = 44
n = 72
n = 57

NTX
PLA
Family History and Naltrexone Efficacy

Density of Familial Alcohol Problems

- < 25% Alc Problem
- 25%-50% Alc Problem
- > 50% Alc Problem

% Days Heavy Drinking

- n = 77
- n = 73
- n = 29

Comparison between Naltrexone (NXT) and Placebo (PLA)
Baseline $\beta$-Endorphin Levels in Low- and High-Risk, and Abstinent Alcoholic Patients

Minutes after alcohol consumption

Change in b-Endorphin Levels after Alcohol Consumption

- High Risk
- Low Risk

% change in plasma b-endorphin levels
BAES Stimulation Scores Among FH+ and FH Subjects

Placebo

Naltrexone
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 NH₂ 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
Alcohol effects by genotype

Self-reported Stimulation (SHAS)

Breath Alcohol Concentration

- AA allele
- AG allele
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.
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.

- Crowley et al, 2003
- Gelernter et al, 1999
- Tan et al, 2003
- Bart et al, 2004

<table>
<thead>
<tr>
<th>ETHNICITY</th>
<th>f(G)</th>
<th>ETHNICITY</th>
<th>f(G)</th>
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<tr>
<td>African</td>
<td>1%</td>
<td>Koreans</td>
<td>31%</td>
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<tr>
<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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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.
Relapse Rate by Genotype

Proportion Nonrelapsed vs. 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

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<tr>
<td>Nalt</td>
<td>A/G, GG</td>
<td>95%</td>
<td>N = 28</td>
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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*
Rhesus model
Ortholog of A118G allele in humans

*(OPRM1C77G)*

increased sensitivity to alcohol
increased alcohol preference
greater effect in males (Barr et al)
Sub-sample of VA coop. study

Those who gave blood for DNA
Naltrexone sig. 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
Alcohol-induced dopamine release in ventral striatum is restricted to OPRM1 - 118G carriers
(Ramchandani et al., Mol Psychiat 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.
OPRM 118 AA & 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. No change was seen in striatum for the 5HT levels. (Ramchandani et al Mol Psychiatry, 2010)
Increased alcohol-induced DA-release in 118GG mice is associated with increased voluntary alcohol intake (Thorsell et al, in preparation)

![Graph showing intake (g/kg/24hrs) against alcohol concentration for GG and AA genotypes.](image)
Treatment of Alcoholism in USA

How to prescribe oral natrexone
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.
Cost-Benefit studies

Cost of Treatment 6 months prior to admission compared to 6 months later

Fewer visits to Emergency Room
Co-Morbidity

2 new placebo controlled trials

Alcoholism + Depression (Pettinati 2010)
Naltrexone + Sertraline

Alcoholism + PTSD (Foa 2012)
Naltrexone + Exposure Therapy
Time to First Heavy Drinking Day and Time to First Drinking Day in Depressed Alcohol-Dependent Patients Randomly Assigned to Medication Treatment or Placebo
Hamilton Score Change From Baseline

Week in Treatment

Baseline 4 6 8 10 12 14

HAMD Score

-Baseline
-4
-6
-8
-10
-12
-14
-16
-18

- Placebo
- Sertraline
- Naltrexone
- Sert & NTX
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?

*Addiction: Life on the Edge – CNN Correspondent Dr. Sanjay Gupta aired April 19, 2009*
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 comment from the interviewer, no follow up questions.
http://www.med.upenn.edu/csa/or
obrien@upenn.edu
Endophenotype
Endorphin Dependent Alcoholism

- Alcohol ➔ Endogenous Opioids
- Euphoria/Stimulation
- Sensitive µ Receptors
- Family History
- Alcohol Craving
Best Treatment

- Medications
  Plus
- Psychosocial Intervention
Penn/VA Center Team

Joe Volpicelli
Wade Berrettini
John Cacciola
Anna Rose Childress
James Cornish
Charles Dackis
Ronald Ehrman
Teresa Franklin
Kyle Kampman
James McKay
A. Thomas McLellan
David Metzger
David Oslin
Helen Pettinati
Michael Stromberg
Elmer Yu
George Woody
Arthur Alterman
FOR MORE INFORMATION

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

obrien@mail.trc.upenn.edu
Possible Gender Effect

Males more responsive in only study with large number of women
Medications

- **Nicotine**
  - Nicotine patch, gum, nasal spray
  - Bupropion
  - Varenicline
  - Rimonabant*

- **Opiates**
  - Methadone
  - Buprenorphine
  - Naltrexone

- **Stimulants**
  - Modafinil
  - Topiramate
  - Baclofen
  - Disulfiram
  - Propranolol
  - Vigabatrin (clinical trials)

- **Alcohol**
  - Disulfiram
  - Naltrexone
  - Acamprosate
  - Topiramate
Effects of Drugs on Dopamine Levels

**AMPHEMATINE**
- Graph showing % of Basal Release over time (0-5 hr) after Amphetamine administration.
- % release peaks at 1 hr and drops over time.

**COCAINE**
- Graph showing % of Basal Release over time (0-5 hr) after Cocaine administration.
- % release peaks at 2 hr and drops over time.

**NICOTINE**
- Graph showing % of Basal Release over time (0-3 hr) after Nicotine administration.
- % release peaks at 1 hr and drops over time.

**MORPHINE**
- Graph showing % of Basal Release over time (0-5 hr) after Morphine administration.
- % release peaks at 2 hr for different doses (0.5, 1.0, 2.5, 10 mg/kg).

Source: Di Chiara and Imperato
Learning Objectives

• Describe the data supporting a new subtype or endophenotype of alcoholism.

• Describe the relative merits of the various medications available for the treatment of alcoholism.

• Describe the range of specific psychosocial treatments for alcoholism.
Use → Abuse (declarative) → Addiction (automatic)
Dependence (Addiction)

- Tolerance
- Withdrawal
- More use than intended
- Unsuccessful efforts to cut down
- Spends excessive time in acquisition
- Activities given up because of use
- Uses despite negative effects

DSM-IV
Possible Changes

- Addiction instead of Dependence?
- Abuse? necessary
- Severity?
- Substance and non-substance addictions
  - Gambling addiction
  - Internet gaming?
  - Food? Sex? Shopping?
## Risk of Addiction

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<th>Dependence (%)</th>
<th>Risk (%)</th>
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<td>75.6</td>
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<tr>
<td>Cocaine</td>
<td>16.2</td>
<td>2.7</td>
<td>16.7</td>
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<td>Heroin</td>
<td>1.5</td>
<td>0.4</td>
<td>23.1</td>
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<td>Alcohol</td>
<td>91.5</td>
<td>14.1</td>
<td>15.4</td>
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<tr>
<td>Cannabis</td>
<td>46.3</td>
<td>4.2</td>
<td>9.1</td>
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*Source: Anthony et al, 1994.*
Types of Genetic Studies

Family
Twin
Adoption
Large population: COGA
Candidate gene studies
Level Of Response To Alcohol

- Observe less response when tested with alcohol
- Self-report of more drinks for an effect
- IV alcohol clamp to control level
Response

- Genetically influenced (heritability $\geq 40\%$)
- Low LR in animals, twins, 1° relatives, 40% offspring of alcoholics
Low response Predicts Alcoholism 4-20 Years Later

- If response low at age 20
- And FH positive
- 60% men developed alcohol use disorder by age 30
Drugs of Abuse all Activate Reward System

- Cues associated with drugs become conditioned stimuli
Key Elements of the Neurocircuitry of Addiction

Key Elements of the Neurocircuitry of Addiction

[11C]Raclopride Binding In Cocaine Abusers (n=18) Viewing a Neutral and a Cocaine-Cue Video

Viewing a video of cocaine scenes decreased specific binding of [11C]raclopride presumably from DA increases

Volkow et al J Neuroscience 2006
Relationship between Cue-Induced Decreases in [11C]raclopride Binding and Cocaine Craving

Cue-induced increases in DA were associated with craving

Volkow et al J Neuroscience 2006
“Unseen” Cue Paradigm

33 msec targets (24 per category) followed by 467 msec neutral “masking” stimuli

Cocaine

Sexual

Neutral

Aversive

Null
“Unseen” Reward Cues activate amygdala v. striatum v. pallidum Insula
Baclofen blunts Amygdala Connectivity during 500 msec “SEEN” Cocaine Cues

Placebo

Baclofen

Second half of the task

[Drug 2; placebo n = 9; baclofen n = 10]
Pre-Alcohol “Craving”

Graph showing the change in dopamine (% baseline) over time (minutes) for two groups: Saline, N=13 and Naltrexone, N=16.
What is Transducer?

- Alcohol releases Beta endorphin in
  - Plasma (pituitary)
  - Lymphocyte cultures (HIV infectivity blocked by naltrexone)
  - ? CNS
Post-Docs

Tom Aronson, MD

☑ Joseph Volpicelli, MD, PhD
Any Alcohol Drinking

Percent of Subjects

Naltrexone

Placebo
Days Drinking

Average Drinking Days per week

Naltrexone

Placebo
Measures of Craving

- 100 mm Visual Analog Scale
- Anton’s Obsessive Compulsive Drinking Scale
- Alcohol Urge Questionnaire
- Penn Alcohol Craving Scale
OPRM1 A118G EFFECT ON TRANSLATION

Zhang et al, JBC, 2005
Lotsch et al, 2006
### Naltrexone Affinity at Opioid Receptor Subtypes

<table>
<thead>
<tr>
<th>Antagonist: Naltrexone</th>
<th>Receptor Binding Ki (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mu</td>
</tr>
<tr>
<td></td>
<td>0.37</td>
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</table>

<table>
<thead>
<tr>
<th>Agonists:</th>
<th>Receptor Binding Ki (nM)</th>
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<tbody>
<tr>
<td>Morphine (m)</td>
<td>Mu</td>
</tr>
<tr>
<td></td>
<td>38</td>
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<tr>
<td>DADL-enke (d)</td>
<td>150</td>
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<tr>
<td>(-)-EKC (k)</td>
<td>2.3</td>
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</table>

# Receptor Blockade with Naltrexone (50mg)

<table>
<thead>
<tr>
<th>Study</th>
<th>Naltrexone Dose</th>
<th>Time (hr)</th>
<th>Receptor Blockade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al, 1988*</td>
<td>50 mg</td>
<td>48</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>168</td>
<td>30</td>
</tr>
</tbody>
</table>

Receptor Blockade with Naltrexone in Alcoholics (50mg)

93% blockade of μ receptors, 24 hours, all SS C\textsuperscript{11} carfentanil

Variable (22.8 +/- 12%) blockade of δ receptors C\textsuperscript{11} N methyl naltrindole, 24 hrs.

* McCaul et al 2004
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
Possible Families of Risk Factors

• Level of response (LR)
• P3/disinhibition/ASPD/type 2/B
• Independent axis II disorders
• Endogenous Opioid System
• Alcohol metabolizing enzymes
Alcohol reward

Sedating drug, facilitates GABAergic meds, no specific receptor

“dirty” drug- affects numerous receptor systems, directly or indirectly
Variable response to alcohol

Alcohol seeking
10 of 22 Rhesus (Altshuler)
15% Vervets
10-15% H. sapiens

Less variable in rodents
µ receptor knock outs will not self administer alcohol
Addiction Therapy may be related to activation of Frontal Cortex

Orbital Frontal Cortex activation is increased by Naltrexone

(Boettiger, et.al. 2009)
(Crews and Boettiger et.al. 2009)
Alcohol - gene associations

- Genome scans
- Phenotype association

- Genotype
- Behavior, (DSM IV)
- 1940s categories
- Endophenotype – biological-

- Alcohol response, imaging
Propose an RCT of an opiate antagonist in human alcoholics because of animal data??

IND 1983

Begin open studies

50 mg dose based on experience with heroin

Philadelphia VA Hospital
### Opiate Receptors

![Diagram showing the post-synaptic neuron with Kappa, Mu, and Delta receptors and their affinity for Opiate Receptors.](image)

<table>
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<tr>
<th></th>
<th>Kappa</th>
<th>Mu</th>
<th>Delta</th>
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<tr>
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<td>406</td>
<td>108</td>
<td>54</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Double blind design

- 70 chronic alcoholics
- All received intensive day hospital, AA, psychotherapy
- Half received Naltrexone 50 mg/day
- Half received identical placebo
- Weekly craving scores
- “slips” measured (not a relapse)
- Relapse defined
Pharmacological Treatments for Alcoholism

Craving Scores by Week

Mean (SEM) Craving Score (0-9)

Weeks on Medication

Placebo
Naltrexone
Cue-induced increases in DA were associated with craving.

Volkow et al J Neuroscience 2006
Subjective “high” in Naltrexone and Placebo Subjects

mean “high” rating

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>0.1</td>
<td>* p&lt;.05</td>
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<tr>
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<tr>
<td>-0.1</td>
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<td></td>
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</tbody>
</table>

* * p<.05
Non-relapse “Survival”

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

Alcohol “PRIMING” in human, non-treatment seeking Alcoholics

O’ Malley et al

From the animal laboratory back to the clinic
Possible mechanisms of naltrexone effects

1. Block reward via endogenous opioid system
   - alcohol activates E.O.
   - Extinction of alcohol self-administration

2. Reduction in craving
   does not require extinction
   some treated alcoholics do not test by drinking

3. Direct effect of naltrexone on frontal executive fx
   Inc activity in r.lat.orbital gyrus during decision making (delay of reward) & decreased selection of immediate reward. (Boettiger et al 2009)
<table>
<thead>
<tr>
<th>Study</th>
<th># Ss</th>
<th>Notes</th>
<th>Study</th>
<th># Ss</th>
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<td>44</td>
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<td>Volpicelli, et al 1997</td>
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<td>Depot</td>
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<td>Anton, et al 2000</td>
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<td>Chick, et al 2000 (UK)</td>
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<td>Adherence</td>
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<td>Monterosso, et al 2001</td>
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<td>Kiefer et al 2003 (Germany)</td>
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<td>Balldin et al 2003</td>
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<td>Pos. GGT</td>
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<td>Gastpar et al 2002</td>
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<td>Neg. in self report</td>
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<td>Guardia et al 2002</td>
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<td>Kranzler et al 2003</td>
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<td>Heavy drinkers</td>
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<td>O’ Malley et al 2002</td>
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<tr>
<td>Anton et al 2006</td>
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<td>RCT, depot</td>
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</table>
Results: Heavy Drinking Days

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Placebo</th>
<th>Vivitrex 190 mg</th>
<th>Vivitrex 380 mg</th>
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<tbody>
<tr>
<td>Overall</td>
<td>19.3</td>
<td>7.0</td>
<td>4.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Male</td>
<td>5.9</td>
<td>4.4</td>
<td>3.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Female</td>
<td>5.6</td>
<td>4.0</td>
<td>5.4</td>
<td></td>
</tr>
</tbody>
</table>

Median Heavy Drinking Days per Month

- Overall: 19.3
- Male: 7.0
- Female: 21.5
Alcohol effects by genotype

Self-reported Stimulation (SHAS)

Breath Alcohol Concentration

AA allele
AG allele
Subjective “high” in Naltrexone and Placebo Subjects

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<thead>
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<tr>
<td>-0.5</td>
<td></td>
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</tbody>
</table>

* p<.05
OPRM1 A118G and Opioid Dependence

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 \( \sim 18\% \), suggesting that \( \sim 18\% \) of Swedish opioid addicts have disease in part due to the G allele.
## Genetic Variables

<table>
<thead>
<tr>
<th>Risk</th>
<th>Increase</th>
<th>Decrease</th>
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<tr>
<td>Low LR</td>
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<tr>
<td>High LR</td>
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<td>ASP</td>
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<tr>
<td>ALDH2</td>
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<tr>
<td>G-Allele-µ op. (Stimulation)</td>
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</tr>
<tr>
<td>Environment</td>
<td>+</td>
<td>-</td>
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</table>