PERSONALIZED APPROACHES TO THE TREATMENT OF ALCOHOL ADDICTION

Markus Heilig MD PhD
Laboratory of Clinical and Translational Studies
NIAAA

Why might pharmacotherapy of alcohol addiction be of interest to you?

- Alcohol addiction is a major public health problem
- Interesting (but complicated!) pharmacology
- Illustrates principles of personalized medicine

Alcohol is a major cause of death and disability


- Tobacco
- Blood pressure
- Alcohol
- Cholesterol
- Overweight
- Low fruit and vegetable intake
- Physical inactivity
- Illicit drugs
- Unsafe sex
- Iron deficiency

% Total Number of Health Years Lost to Death/Disability
Or expressed differently:

- Appr. 88,000 deaths are attributable to excessive alcohol use each year in the United States
- Excessive alcohol use is responsible for 2.5 million years of potential life lost annually
- About 30 years of potential life lost for each death
- Costs of excessive alcohol consumption estimated at $223.5 billion annually

http://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm

Alcohol-related harm is closely related to total consumption in the population

Rehm et al. The Lancet 2009

What about those beneficial effects of alcohol? The example of coronary heart disease (CHD)
A six item tool-kit of evidence-based policies to reduce alcohol-related harm

• What works:
  • High taxation
  • Effective drunk-driving legislation
  • Banning advertising
  • Limiting availability (while preventing illegal production)
  • Providing help for hazardous drinking

• Effectiveness of brief interventions is encouraging for doctors

• What does not work:
  • Education in isolation (such as industry-favoured school-based programmes) - ineffective window dressing

Andersson et al., The Lancet 2009

If total alcohol consumption is what determines the public health impact of alcohol...

Why focus on "alcoholism"?

The majority of alcohol is consumed by a minority of people:

Ledermann 1965, Burgh 1983
People with Alcohol Use Disorders account for a disproportionate fraction of consumption

- Alcohol Abuse:
  - a less well defined diagnostic entity - has been dropped in DSM-5
  - a pattern of maladaptive behaviors
  - largely related to risky behavior (mostly drunk driving)

- Alcohol Use Disorder (mild – moderate – severe) – current DSM-5 term

  - Alcoholism = “alcohol dependence syndrome”, “alcohol addiction”
  - a reasonably defined clinical condition (Edwards and Gross Brit Med J 1975)
  - a chronic, relapsing disorder
  - not unlike diabetes, or hypertension
  - can presently not be cured, but can be successfully managed

Like all addictions, alcoholism is a chronic relapsing illness

Relapse rate over time

<table>
<thead>
<tr>
<th>Months</th>
<th>% Abstainers</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>80</td>
</tr>
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<td></td>
<td>100</td>
</tr>
</tbody>
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Hunt et al, J Clin Psychol 1971

What can treatment offer?

Hunt et al, J Clin Psychol 1971
Inexpensive behavioral treatments can do some good (but few patients receive them)

<table>
<thead>
<tr>
<th></th>
<th>Evidence strength</th>
<th>Study quality</th>
<th>Patient severity</th>
<th>Treatment cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief intervention</td>
<td>390</td>
<td>13.3</td>
<td>2.6</td>
<td>46</td>
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<tr>
<td>Motivational enhancement</td>
<td>189</td>
<td>12.8</td>
<td>2.7</td>
<td>46</td>
</tr>
<tr>
<td>Community reinforcement</td>
<td>110</td>
<td>14.0</td>
<td>3.4</td>
<td>492</td>
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<tr>
<td>Cognitive behavioral</td>
<td>21</td>
<td>13.3</td>
<td>3.0</td>
<td>433</td>
</tr>
<tr>
<td>therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For comparison:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acamprosate</td>
<td>116</td>
<td>11.6</td>
<td>3.8</td>
<td>*</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>100</td>
<td>11.3</td>
<td>3.2</td>
<td>*</td>
</tr>
</tbody>
</table>

... while most patients receive (expensive) treatments without evidence for efficacy

<table>
<thead>
<tr>
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<th>Evidence strength</th>
<th>Study quality</th>
<th>Patient severity</th>
<th>Treatment cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient education</td>
<td>-443</td>
<td>9.8</td>
<td>2.4</td>
<td>135</td>
</tr>
<tr>
<td>General alcoholism</td>
<td>-284</td>
<td>11.3</td>
<td>3.2</td>
<td>768</td>
</tr>
<tr>
<td>counseling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>-207</td>
<td>10.9</td>
<td>3.3</td>
<td>4050</td>
</tr>
<tr>
<td>Confrontational counseling</td>
<td>-183</td>
<td>10.2</td>
<td>3.0</td>
<td>375</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>-6</td>
<td>11.1</td>
<td>3.7</td>
<td>637</td>
</tr>
<tr>
<td>Serotonin-reuptake</td>
<td>-16</td>
<td>8.6</td>
<td>2.7</td>
<td>*</td>
</tr>
<tr>
<td>inhibitors</td>
<td></td>
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</tbody>
</table>

What can pharmacotherapy offer?
The pharmacology of alcohol is complicated:
Ligand-gated ion-channels are primary targets

- Glutamate receptors (control CNS excitability; targets for some anti-epileptics)
- GABA-A receptors (control CNS inhibition; targets e.g. for benzodiazepines)
- Other ion-channels? (e.g. voltage gated potassium channels)

Dysregulation of glutamatergic transmission in alcoholism: Target for acamprosate (Campral)


Dysregulation of glutamatergic transmission in alcoholism: Target for acamprosate (Campral)

Umhau et al, Arch Gen Psychiat 2010

We can measure it using the MR camera
Dysregulation of glutamatergic transmission in alcoholism: Target for acamprosate (Campral)

![Graph](Image)

The pharmacology of alcohol is complicated: multiple reward- and stress-related secondary targets

- Endogenous opioids
  - Via µ-opioid (morphin) receptors

- Dopamine
  - Via D2 receptors?
  - Indirect effects?

- Endocannabinoids
  - Via CB1 receptors

Where to look for pharmacotherapy targets: A Schematic of the Addicted Brain

![Diagram](Image)
Where to look for pharmacotherapy targets: A Slightly Simplified Schematic of the Addicted Brain

Think about it
"decision making"
"impulse control"
"temporal discounting"

Approach
"reward"

Avoid
"aversion"
"negative affect"
"stress"

The canonical view of dopamine-mediated drug-reward as a central phenomenon in drug addiction

Cocaine

Alcohol

Heroin

Nicotine

Alcohol reward as a therapeutic target?
"Why we like to drink"

Gilmour et al., J Neurosci 2008
Note: Alcohol-induced psychomotor stimulation and dopamine release seem to mostly happen in males

Urban et al., Biol Psychiat 2010

Alcohol drives activity of brain reward circuitry in part through release of endogenous opioids

Mitchell et al., Sci Transl Med 2012

How we think the cascade works:

Alcohol intake → Endogenous opioid release → Dopamine release → "Reward"

Spanagel and Shippenberg, PNAS 1992; Tanda and Di Chiara 1998
The opioid antagonist naltrexone presumably blocks this cascade; that is why it works… sort of

Maisel et al., Addiction 2013

Opioid antagonism is a pharmacotherapy for alcoholism

- Important proof of concept for pharmacotherapy of alcoholism
  - µ-opioid receptor antagonism – naltrexone
  - 30+ randomized controlled trials
  - efficacy supported by meta-analysis
    (e.g. Bouza et al., Addiction 2004; Srisurapanont et al., Cochrane 2005)
- but:
  - while some patients respond well, others don’t
  - overall, effect size of naltrexone is small (Cohen’s D≈0.20)
  - market penetration is marginal
- So far, we have not transformed clinical practice

Patients with alcoholism may look the same, but they get there through very different trajectories

Environment:
- no alcoholism without alcohol
- kindling – like process
- stress interacts with drug

Genes
- heritability ≈ 50 – 60% (Goldman et al. 2005)
- numerous susceptibility loci
- each of small effect (e.g. Teubl et al. 2009)

Heilig et al., Nat Rev Neurosci 2011
The promise of personalized medicine

If patients respond differently, maybe they are different? The gene encoding the µ-opioid receptor varies

Bond et al., PNAS 1998

Association of a Functional Polymorphism in the µ-Opioid Receptor Gene With Alcohol Response and Consumption in Male Rhesus Macaques

Christina S. Hart, MD, PhD; Melanie Schneider, MD; Stephen G. Lindell, MD; Scott J. Chen, PhD; David Goldman, MD; Stephen J. Suomi, MD; J. Dee Bigelow, PhD; Markus Heilig, MD, PhD

Arch Gen Psychiatry. 2007;64:369-376
Do the findings in rhesus monkeys translate to humans?

- **Premise:**
  - Alcohol reward in part due to dopamine response

- **Hypothesis:**
  - Alcohol (most) rewarding in \textit{OPRM1-118G} carriers

- **Strategy:**
  - \([^{11}C]\)-raclopride displacement by PET (\(\Delta BP\))

- **Prediction:** \(\Delta BP\) in 118GX subjects > 118AA subjects

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Dopamine release in ventral striatum of men is restricted to \textit{OPRM1} - 118G carriers

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But gene variants travel in packs – if you select people for one of them, they will be different elsewhere, too

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Ramchandani et al., Mol Psychiat 2011

But gene variants travel in packs – if you select people for one of them, they will be different elsewhere, too

---

Zhang et al., Hum Mol Genet 2006

---
A reverse - translational tool: mice "humanized" for the µ-opioid receptor gene

Ramchandani et al., Mol Psychiat 2011

Alcohol produces greatly increased dopamine release in mice with the less common variant of the µ-receptor

Does the altered dopamine release translate into altered alcohol reward?
A classical measure of drug reward: Intracranial Self-Stimulation (ICSS)

Enhanced alcohol reward in OPRM1 118GG mice mediated by endogenous opioids: reversal by ntx

Increased consumption of alcohol, and sensitivity to naltrexone in 118GG mice
Association of µ-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis

Chamorro et al, Addiction Biol 2012

Interim conclusion:
Alcohol reward as a target for pharmacotherapy

- Alcohol leads to release of endogenous opioids
- Activation of mesolimbic dopamine downstream of opioid activation
- Alcohol-reward cascade can be blocked with naltrexone
- Important in early stages of the addictive process
- Important in people with the right (or, rather, wrong) OPRM1 genetics

Anti-stress mechanisms as a therapeutic target?

- High co-morbidity of alcoholism with mood and anxiety disorders (Grant et al 2004)
- Sensitization of stress responses with progression of dependence (Vahle et al., 2003; O'Donnell et al., 2002; Breese et al., 2004a,b; Sommer et al., 2008)
- Stress promotes relapse and escalation of voluntary alcohol intake (for review, see Spanagel, Noori, Heilig 2014)
A system involved both in "rewarding" and "relieving" properties of alcohol: The endocannabinoid machinery

Cannabinoids and alcohol

- CB₁ receptor stimulation promotes alcohol reward and intake
- CB₁ receptor blockade inhibits alcohol reward and intake
- Chronic alcohol administration: decreased CB₁ receptors

Endocannabinoid signaling via cannabinoid receptor 1 is involved in ethanol preference and its age-dependent decline in mice

Genetic Impairment of Frontocortical Endocannabinoid Degradation and High Alcohol Preference
BUT...

Cannabinoid Receptor 1 Blocker Rimonabant (SR 141716) for Treatment of Alcohol Dependence
Results from a Placebo-Controlled, Double-Blind Trial
Michael Schlae, MD, PhD, Gabrielle Kiefer, MD, Peggy Schmidt, PhD, Otho Michael Luehr, MD
Martin Czermak, MD, Christoph Tiele, MD, J. H. Graf, MD, Karl F. Mann, MD
and the investigators involved in the ACER SCIR
Journal of Clinical Psychopharmacology Volume 28, Number 3, June 2008

Rimonabant (SR141716) has no effect on alcohol self-administration or endocrine measures in non-treatment-seeking heavy alcohol drinkers

Bartel Beck, Jean-Marie; Konnese, M.; Kooistra, M.; van der Stelt, M.; Klaassen, D. J.; Kooistra, M.

Trends in Pharmacological Sciences
Accumulating recent evidence that impaired endocannabinoid signaling is associated with sensitized stress responses - e.g.

FAAH in protection and recovery from stress

[18F]FMPEP-d2: An PET ligand to study the CB₂ receptor

Terry, Hirvonen... and Innis. Eur J Neurosci 2010

CB₂ receptors are down-regulated in alcohol dependence in a wide-spread manner

Hirvonen et al. Molecular Psychiatry, 2012

Widespread down-regulation of CB₂ receptors in alcohol dependence: Anterior Cingulate Cortex

Anterior Cingulate Cortex

Hirvonen et al. Molecular Psychiatry, 2012
Reduction in CB₁ receptor binding capacity correlates with years of alcohol abuse, independent of age

\[ R = 0.61, p = 0.008 \]

\[ R = 0.07, p = 0.682 \]

Hirvonen et al. Molecular Psychiatry, 2012

CB₁ down-regulation in alcoholism persists into abstinence

Hirvonen et al. Molecular Psychiatry, 2012

CNRI variation previously associated with alcohol dependence and higher CB₁ receptor binding in vitro (rs2023239)

Previously published, in vitro

Replication in vivo

Hatchios et al. Arch Gen Psychiatry 2008

Hirvonen et al. Molecular Psychiatry, 2012

F = 4.44, p = 0.043
Interim conclusion: Time for a fresh look at the endocannabinoid system as a target?

- EC activity important both for alcohol reward and stress coping
- Genetically driven increase in CB1 expression a risk factor for initiation
- But what gets you in trouble isn't necessarily what keeps you in trouble
- Decreased CB1 expression following dependence is a double-whammy
  - Decreased alcohol reward
  - Impaired stress coping and extinction of fear memories
  - Dual incentives for maintenance of alcohol use
- Better to restore impaired EC function than to block it?
- FAAH inhibition as a novel therapeutic mechanism?

Other targets in various stages of development – most have potentially functional genetic variation!

- Corticotropin Releasing Hormone (CRH) 1 receptor
- Neuropeptide Y (NPY) 1 receptor (agonists)
- NPY 2 receptor (antagonists)
- Nociceptin (NOP) receptor
- Neuropeptide S (NPS) receptor
- Melanin Concentrating Hormone (MCH) 1 receptor

- There will not be a magic bullet
- For each treatment: Who is the right patient?
- A range of personalized treatments will combine to improve outcomes in alcohol addiction

Laboratory of Clinical and Translational Studies

Faculty
Lorenzo Leggio
Vijay Ramchandani
Ted George
Markus Heilig

Staff Scientists
Janice Tapocik
Marie Daniels
Robert Eskin
Anna Thorsell
Wolfgang Sommer

Clinical Support
Rosa Clark
and all wonderful Nursing Staff

Collaborators
Peter Herscovitch, NIH PET Center
CJ Malanga, UNC
Loren Parsons, Scripps
Michael Schoor, Taconic

Research Support
Ruslan Damadric
Eui Sun
Eric Singley
Debby Hill
Cheryl Jones
Monie Phillips
Beth Israel
Mike Kerich
Betsy Davis

Other Support
Macy McRae
Dena Stringer
Karen Smith
Juan Rivas

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