Benefits of Reducing Alcohol Consumption in Alcohol Dependence: A New Treatment Option

Wim van den Brink
Academic Medical Centre, University of Amsterdam, The Netherlands

Lundbecksymposiet 2014
Oslo, 3 April 2014
Content

- Alcohol use and AUDs in Norway
- Addiction a treatable and preventable brain disease
- The treatment gap
- Need for reduced risk drinking interventions
- Effectiveness of reduced risk drinking interventions
- Conclusions
Total adult per capita alcohol consumption (recorded and unrecorded) in 2005

* Norway: moderate level of per capita alcohol consumption (7.8 litres)

WHO, 2011
Alternative slide suggestion with nicer looking map.
The map here has been taken from the 'Map gallery' on the WHO website.

Jenny, 17.02.2012
Patterns of consumption 2005

Least risky = regular drinking, often with meals and without infrequent heavy drinking bouts

Most risky = infrequent but heavy drinking outside of meals

* Norway: medium risky drinking pattern

WHO, 2011
Alternative slide for the map has been included. The map has been taken from the 'Map gallery' on the WHO website.

jenny, 17.02.2012
Change in adult alcohol consumption 2001-2005

* Norway: increasing consumption

WHO, 2011
Alternative slide for the map has been included. The map has been taken from the 'Map gallery' on the WHO website.

jenny; 17.02.2012
WHO Country Report Norway

**Health Consequences**

**Morbidity**

- Prevalence estimates (12-month prevalence for 2004):
  - Alcohol use disorders (15+ years): 9.05% Males, 2.55% Females

- Total: 5.80%
Model for Alcohol Comparative Risk Analysis

**Societal factors**
- Drinking culture
- Alcohol policy
- Drinking environment
- Health care system

**Individual**
- Alcohol consumption
  - Volume
  - Patterns
  - Quality
  - Incidence & disability chronic
  - Incidence & disability acute

**Population group**
- Gender
- Age
- Poverty marginalisation

**Health outcomes**
- Mortality by cause
Burden of disease attributable to 20 leading risk factors in 2010 – worldwide

1.5 million deaths per year

- Tobacco smoking, including second-hand smoke
- High blood pressure
- Alcohol use
- Diet low in fruits
- Household air pollution from solid fuels
- High fasting plasma glucose
- High body-mass index
- Ambient particulate matter pollution
- Childhood underweight
- Diet high in sodium
- Physical inactivity and low physical activity
- Diet low in nuts and seeds
- Suboptimal breastfeeding
- Diet low in whole grains
- Diet low in vegetables
- High total cholesterol
- Occupational risk factors for injuries
- Iron deficiency
- Diet low in seafood omega-3 fatty acids
- Drug use

Disability-adjusted life-years (%)

- Cancer
- Cardiovascular and circulatory diseases
- Chronic respiratory diseases
- Cirrhosis
- Digestive diseases
- Neurological disorders
- Mental and behavioural disorders
- Diabetes, urogenital, blood, and endocrine
- Musculoskeletal disorders
- Other non-communicable diseases
- HIV/AIDS and tuberculosis
- Diarrhoea, lower respiratory infections, and other common infectious diseases
- Neglected tropical diseases and malaria
- Maternal disorders
- Neonatal disorders
- Nutritional deficiencies
- Other communicable diseases
- Transport injuries
- Unintentional injuries
- Intentional injuries
- War and disaster

Lim et al. Lancet 2012;380(9859):2224–2260
## Alcohol-attributable deaths in Europe: Netto 120,000 premature deaths each year

<table>
<thead>
<tr>
<th>Detrimental effects</th>
<th>Men (n)</th>
<th>Men (%)</th>
<th>Women (n)</th>
<th>Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>17,358</td>
<td>15.9</td>
<td>8,668</td>
<td>30.7</td>
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<tr>
<td>CVD other than IHD</td>
<td>7,914</td>
<td>7.2</td>
<td>3,127</td>
<td>11.1</td>
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<tr>
<td>Mental and neurological disorders</td>
<td>10,868</td>
<td>9.9</td>
<td>2,330</td>
<td>8.3</td>
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<tr>
<td>Liver cirrhosis</td>
<td>28,449</td>
<td>26.0</td>
<td>10,508</td>
<td>37.2</td>
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<tr>
<td>Unintentional injury</td>
<td>24,912</td>
<td>22.8</td>
<td>1,795</td>
<td>6.4</td>
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<tr>
<td>Intentional injury</td>
<td>16,562</td>
<td>15.1</td>
<td>1,167</td>
<td>4.1</td>
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<tr>
<td>Other detrimental</td>
<td>3,455</td>
<td>3.2</td>
<td>637</td>
<td>2.3</td>
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<tr>
<td>Total detrimental</td>
<td>109,517</td>
<td>100.0</td>
<td>28,232</td>
<td>100.0</td>
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</table>

<table>
<thead>
<tr>
<th>Beneficial effects</th>
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<tr>
<td>IHD</td>
<td>14,736</td>
<td>97.8</td>
<td>1,800</td>
<td>61.1</td>
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<tr>
<td>Other beneficial</td>
<td>330</td>
<td>2.2</td>
<td>1,147</td>
<td>38.9</td>
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<td>Total beneficial</td>
<td>15,065</td>
<td>100.0</td>
<td>2,947</td>
<td>100.0</td>
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CVD = cardiovascular disease; IHD = ischaemic heart disease

WHO, 2012; Rehm et al., 2012
How many deaths are attributable to alcohol dependence?

Rehm et al  Eur Neuropsychopharm 2012

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<tr>
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<th>Men</th>
<th>Women</th>
<th>Total</th>
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<tr>
<td>Alcohol-attributable</td>
<td>16.1%</td>
<td>8.5%</td>
<td>13.6%</td>
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<tr>
<td>Alcohol-attributable (net)</td>
<td>13.9%</td>
<td>7.7%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Heavy drinking</td>
<td>11.1%</td>
<td>5.3%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>10.7%</td>
<td>3.7%</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

Men:  heavy drinking 11.1/13.9 = 79.9%; alcohol dependence 10.7/13.9 = 77.0%
Women: heavy drinking 5.3/7.7 = 68.8%; alcohol dependence 3.7/7.7 = 48.1%
Total: heavy drinking 9.2/11.8 = 78.0%; alcohol dependence 8.4/11.8 = 71.2%
Addiction a treatable and preventable brain disease
History of the concept of alcoholism

1. Moral model
2. Pharmacological model
3. Symptomatic model
4. Disease model
5. Learning model
6. Social model
7. Brain disease model

1976: Edwards & Gross
Biopsychosocial model
Alcohol dependence syndrome
Addiction: a treatable brain disease

Scientific advances over the past 20 years have shown that drug addiction is a chronic, relapsing disease that results from the prolonged effects of drugs on the brain. As with many other brain diseases, addiction has embedded behavioral and social-context aspects that are important parts of the disorder itself. Therefore, the most effective treatment approaches will include biological, behavioral, and social-context components. Recognizing addiction as a chronic, relapsing brain disorder characterized by compulsive drug seeking and use can impact society’s overall health and social policy strategies and help diminish the health and social costs associated with drug abuse and addiction.
Addiction – a brain disease

- Genetic vulnerability 50–70%
- Biological risk factors low alcohol response
- Brain abnormalities cue-reactivity, impulsivity (ACC)
- Effective neurobiological interventions
- Effective neurobiological preventions
Addiction – a brain disease

• **Genetic vulnerability** heritability 50–70%

• Biological risk factors anhedonia

• Brain abnormalities DA receptors NAc

• Effective neurobiological interventions

• Effective neurobiological preventions

DA=dopamine; NAc=nucleus accumbens
Heritability estimates for alcohol dependence, nicotine dependence, cannabis and other illicit drug use disorders across samples of twins

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<th>Heritability</th>
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<tr>
<td>Alcohol</td>
<td>50–70%</td>
</tr>
<tr>
<td>Nicotine</td>
<td>50–75%</td>
</tr>
<tr>
<td>Cannabis</td>
<td>35–75%</td>
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<tr>
<td>Cocaine</td>
<td>35–80%</td>
</tr>
<tr>
<td>Heroin</td>
<td>40–60%</td>
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Agrawal & Lynskey. Addiction 2008;103(7):1069–1081
Addiction – a brain disease

• Genetic vulnerability heritability 50–70%

• **Biological risk factors** low alcohol response

• Brain abnormalities DA receptors NAc

• Effective neurobiological interventions

• Effective neurobiological preventions

DA=dopamine; NAc=nucleus accumbens
Phenotype

Endophenotype

Genotype

Please provide full reference details for Ooteman et al 2006?
Jenny Muiry, 24.10.2012
Addiction – a brain disease

• Genetic vulnerability  heritability 50–70%

• Biological risk factors  low alcohol response

• **Brain abnormalities**  DA receptors NAc

• Effective neurobiological interventions

• Effective neurobiological preventions

DA=dopamine; NAc=nucleus accumbens
## Development of addiction

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<tr>
<th>Stages</th>
<th>Brain functions/structures</th>
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<tbody>
<tr>
<td>No use</td>
<td></td>
</tr>
<tr>
<td>Experimental use</td>
<td>Reward: VTA, NAc (V striatum)</td>
</tr>
<tr>
<td>Recreational use</td>
<td>Reward: VTA, NAc (V striatum)</td>
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<tr>
<td>Abuse</td>
<td>Impulsivity: DLPFC, ACC</td>
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<tr>
<td>Dependence</td>
<td>Craving/salience: OFC, V striatum</td>
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<tr>
<td>Addiction</td>
<td>Habit formation: D striatum</td>
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</tbody>
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VTA=ventral tegmental area; NAc=nucleus accumbens; V=ventral; D=dorsal; DLPFC=dorsolateral prefrontal cortex; ACC=anterior cingulate cortex; OFC=orbitofrontal cortex
## Neurobiology of addiction

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Nc=nucleus; CRH=corticotropin-releasing hormone

# Neurobiology of addiction

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Naive  
Experimenting moderate use  
Binging  
Abuse  
Dependence (craving)  
Addiction (compulsive use)  

Nc=nucleus; CRH=corticotropin-releasing hormone

Reward Deficiency - Anhedonia

Lower DA binding in striatum in alcohol and drug dependent patients after sustained abstinence

→

Anhedonia?
Reward Deficiency?
## Neurobiology of addiction

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Conflict Monitoring and Inhibition

A1: ACC activation during conflict trials; A2: ACC activation during error trials
D: Correlation ACC activation previous trial en activation PFC current trial
Conflict Monitoring

Opiate Addicts Lack Error-Dependent Activation of Rostral Anterior Cingulate

Steven D. Forman, George G. Dougherty, B.J. Casey, Greg J. Siegle, Todd S. Braver, Deanna M. Ranch, V. Andrew Stenger, Charleen Wick-Hull, Liubomir A. Pisanov, and Emily Lorensen

Figure 2. Attenuated FA event-related ACC activation in opiate addicts. (A) Region of interest associated with FA error activity. The white lines define the anterior-posterior extent of the region examined. (B) Matched control group shows elevated mean levels (+ SEM) of event-related ACC activation with FA (gray bars) over that of the OD group—activation averaged across all the voxels in the region of interest for each group (and presented in units of standardized regression coefficient for the respective predictor of the fMRI time course, e.g., FA events or CR events). Neither group showed any event-related ACC activation with CR (open bars). (C) Increased FA-related ACC activation is associated with improved discriminative sensitivity in matched controls but not opiate addicts. The line is a plot of linear regression fit to the matched control data ($F^2 = .41$, $p < .03$). Solid circles (Opiate-Addicted), open circles (Matched Control). FA, false alarm: ACC, anterior cingulate cortex; OD, opiate dependence; fMRI, functional magnetic resonance imaging; CR, correct rejection. SAG, sagittal; COR, coronal; TRA, transverse.
Disinhibition – Lower PFC activity in cocaine abusers

FIGURE 3. Lower Relative Glucose Metabolism in the Prefrontal Cortex and Anterior Cingulate Gyrus of a Cocaine Abuser Than in a Normal Comparison Subject
Connection Striatal–Orbitofrontal Activity
(Goldstein and Volkow, 2001)
### Neurobiology of addiction

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Naive
Experimenting
moderate use
Binging
Abuse
Dependence
(craving)
Addiction
(compulsive use)

Van Ree. 2002; de Vries & Schippenberg. 2002; Kreek et al. 2002;
Van den Brink. 2006; Volkow. 2004; Koob & Volkow. 2010
Attentional bias – craving – relapse
Attentional bias – craving – relapse
Attentional bias – craving – relapse
Cue reactivity: alcohol-associated stimuli activate the ventral striatum in abstinent alcoholics

- During early abstinence, alcohol-related visual stimuli results in strong activation of the ventral striatum
- Activation of the ventral striatum is strongly associated with probability of relapse (Grüsser et al., 2004)

Attentional bias – cue-reactivity – craving and relapse

Repeated reward

Attentional bias → Cue-reactivity

Detection threshold

Drug-related stimulus

Stress

Cue-reactivity

Craving

Inhibition

Conflict registration

Relapse
# Neurobiology of addiction

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From reward to relief and from impulsive to compulsive

Adapted from Heilig et al., 2010
Addiction – a brain disease

- Genetic vulnerability: heritability 50–70%
- Biological risk factors: reward deficiency
- Brain abnormalities: DA receptors NAc
- **Effective neurobiological interventions**
- Effective neurobiological preventions

DA=dopamine; NAc=nucleus accumbens
Mesa Grande: a review of clinical trials of alcohol treatments

**Mesa Grande Study**
- 361 controlled trials; 72,052 patients
- 62 trials with excellent methodology
- 46 treatment modalities with 3 or more controlled trials

**Most effective interventions:**
- Brief intervention, MET, CBT, CRA
- Acamprosate, Naltrexone, Disulfiram

**Ineffective interventions:**
- Minnesota, Insight Oriented Psychotherapy, SSRIs, Lithium
New (potentially) effective treatments since 2002

**Pharmacotherapy**
- Nalmefene
- Topiramate?
- Baclofen?
- Modafinil?
- GHB??

**Psychotherapy**
- CE
- TSF

Pharmacotherapy Alcohol Dependence

- **Antagonist**
  - Disulfiram
  - Naltrexone
  - Nalmefene

- **Detection threshold**
  - Cue-reactivity
  - Stress

- **Drug-related stimulus**
  - Attentional bias

- **Craving**
  - Anti-craving drug
  - Acamprosate
  - Topiramate?
  - NAC?

- **Relapse**
  - Inhibition
  - Baclofen?
  - Memantine?
  - Cognitive enhancer
  - Modafinil?

- **Conflict registration**

- **Repeated reward**
Addiction – a brain disease

- Genetic vulnerability heritability 50–70%
- Biological risk factors anhedonia
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DA=dopamine; NAc=nucleus accumbens
Does ADHD treatment prevent addiction?

ADHD = attention deficit/hyperactivity disorder; SUD = substance use disorder
Alcohol dependence is treatable and preventable brain disease
Large Treatment Gap
The Problem
### Proportion of individuals consulting any type of formal health services in the previous 12 months, according to 12-month mental disorder status

<table>
<thead>
<tr>
<th>Mental health state</th>
<th>Unweighted, n</th>
<th>Weighted, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall sample</td>
<td>21,425</td>
<td>6.4</td>
<td>5.9–6.8</td>
</tr>
<tr>
<td>No 12 month mental disorders</td>
<td>19,349</td>
<td>4.3</td>
<td>3.9–4.7</td>
</tr>
<tr>
<td>Any disorder</td>
<td>2,076</td>
<td>25.7</td>
<td>23.3–28.1</td>
</tr>
<tr>
<td>Any mood</td>
<td>972</td>
<td>36.5</td>
<td>32.5–40.5</td>
</tr>
<tr>
<td>Any anxiety</td>
<td>1,325</td>
<td>26.1</td>
<td>23.1–29.1</td>
</tr>
<tr>
<td>Any alcohol disorder</td>
<td>209</td>
<td>8.3</td>
<td>3.8–12.8</td>
</tr>
<tr>
<td>Only one 12 month mental disorder</td>
<td>1,435</td>
<td>19.6</td>
<td>17.1–22.2</td>
</tr>
<tr>
<td>More than one</td>
<td>641</td>
<td>40.0</td>
<td>35.0–45.0</td>
</tr>
</tbody>
</table>

In 2004 in Europe, 37% of persons with a mood disorder and 26% of persons with an anxiety disorder were consulting formal health services in the previous 12 months, whereas this was only 8% for persons with an alcohol use disorder!!

CI=confidence interval
Treatment gap in alcohol dependence

Alcohol abuse and dependence have the widest treatment gap among all mental disorders – less than 10% of patients with alcohol abuse and dependence are treated

* Treatment gap = difference between number needing MH Tx and number receiving MH Tx

Number of deaths avoided over one year in men by treatment for AD in the EU in 2004 by five different treatment modalities

AD=alcohol dependence; MI=motivational interviewing; CBT=cognitive-behavioural therapy; BI=brief interventions

Rehm et al  Eur Neuropsychopharm 2012
Large Treatment Gap
Reasons
Self-reported reasons not receiving alcohol treatment in the past year (persons ≥12 years who needed treatment and perceived a need for it)

- Not ready to stop using
- Cost/insurance barriers
- Social stigma
- Access
  - Did not think needed treatment/thought could handle without treatment
  - Did not know where to go for treatment
- Did not have time
- Treatment would not help
- Other barriers

SAMHSA 2007, National Survey on Drug Use and Health (NSDUH)
Reasons for treatment gap

• Perceived stigmatisation

• Neglect patient preference: non-abstinence treatments

• Perceived low treatment effectiveness
Reasons for treatment gap
Stigmatisation
Stigma of alcohol dependence vs. other mental disorders: a review

**Results:** “Compared with people suffering from other, substance-unrelated mental disorders, alcohol-dependent persons are less frequently regarded as mentally ill, and held much more responsible for their condition, provoke more social rejection and more negative emotions, and they are at particular risk for structural discrimination. Only with regard to being a danger, they are perceived to be at a similar negative level to that of people suffering from schizophrenia.”

Schomerus et al. Alcohol Alcohol 2011;46(2):105–112
### Perceived stigmatisation and treatment seeking

Association between alcohol stigma and any lifetime utilisation among individuals with a lifetime alcohol disorder, US, 2004–2005 (n=6,309)

<table>
<thead>
<tr>
<th>Utilised alcohol services, lifetime (n=1,401)</th>
<th>% (SE)</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>Adjusted OR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>High stigma (n=1,911)</td>
<td>21.25 (1.32)</td>
<td>0.88</td>
<td>0.71, 1.08</td>
<td>0.37</td>
<td>0.18, 0.76</td>
</tr>
<tr>
<td>Middle high (n=1,692)</td>
<td>17.69 (1.06)</td>
<td>0.70</td>
<td>0.58, 0.84</td>
<td>0.47</td>
<td>0.23, 0.95</td>
</tr>
<tr>
<td>Middle low (n=1,533)</td>
<td>17.17 (1.05)</td>
<td>0.67</td>
<td>0.57, 0.81</td>
<td>0.61</td>
<td>0.32, 1.16</td>
</tr>
<tr>
<td>Low stigma (n=1,172)</td>
<td>23.51 (1.06)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Perceived stigmatisation of alcoholism reduces the probability that persons with an alcohol use disorder will seek treatment

<sup>a</sup>Adjusted for sex, age, race/ethnicity, income, education, marital status, and number of lifetime alcohol dependence criteria met

Keyes et al. 2010
Reasons for treatment gap
Neglect of patient preference
The reduction concept provides patients with a choice of treatment goals

UK survey of patients with alcohol problems (n=742)

Canadian study of patients with chronic alcoholism (n=106)

Heather et al. Alcohol Alcohol 2010;45(2):128–135;
Hodgins et al. Addict Behav 1997;22(2):247–255
An example of goal shifts

Initial goal preferences and changes at 4 weeks

<table>
<thead>
<tr>
<th>Initial goal preference</th>
<th>At Week 4 (after 4 sessions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinence: n=49 (46.2%)</td>
<td>n=69 (65%)</td>
</tr>
<tr>
<td>Reduction: n=47 (44.3%)</td>
<td>n=34 (32%)</td>
</tr>
<tr>
<td>Uncertain: n=10 (9.4%)</td>
<td>n=3 (2%)</td>
</tr>
</tbody>
</table>

Hodgins et al. Addict Behav 1997;22(2):247–255
Alcohol is the main cause of liver cirrhosis – a major public health problem in Europe


Relative risk of liver cirrhosis

Men

Women

Relative risk

0 10 20 30 40

0 12 24 36 48 60 72 84 96 108 120

Alcohol consumption (g/day)

Mortality

Morbidity

Benefits of reduction

- Reduction of 36 g/day (3 drinks) from a baseline of 60 g/day corresponds to reduced mortality risk of 38 per 10,000
- Reduction of 36 g/day from a baseline of 96 g/day (8 drinks) corresponds to reduced mortality risk of 119 per 10,000
- cf: brief lag between changes in per capita consumption and liver deaths?

It’s the heavy drinking day that leads to harm

Rehm et al. Addiction 2011;106(Suppl 1):11–19;
Rehm & Roerke. Alcohol Alcohol 2013;48:509–513
We have animated this slide, as requested.

Michelle Pelling-West; 05.09.2013
Acceptance reduced-risk drinking by professionals

Reduced-risk drinking is accepted as a treatment goal in France (50%), Britain (76%), Australia (72%), Switzerland (22–70%), Canada (27–62%), but not (yet) in the USA (17%).
I think that the US percentage is actually approx 38% - see abstract in notes page.
Jenny Muiry; 24.10.2012
Reduction is accepted in guidelines

Alcohol reduction concept supported by guidelines from:

• European Medicines Agency (EMA), 2010

• US National Institute on Alcohol Abuse and Alcoholism (NIAAA), 2007

• National Institute for Health and Clinical Excellence (NICE), 2011
Reduced drinking as a viable treatment goal

Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence

Jan van Amsterdam* and Wim van den Brink1

Abstract
This review describes and discusses studies related to reduced-risk drinking as an additional treatment option for patients with problematic alcohol use and alcohol dependence. The review provides some empirical support for the following statements: (a) reduced-risk drinking is a viable option for at least some problem and dependent drinkers; (b) abstinence and non-abstinence-based treatments appear to be equally effective; (c) allowing patients to choose their treatment goal increases the success rate. The relatively short follow-up period (1–2 years) of the studies hampers a proper evaluation of the added value of the reduced-risk drinking approach.
Reasons for treatment gap
Neglect of patient preference
Pharmacologically supported reduced risk drinking
Nalmefene: the molecule

- Nalmefene is an opioid system modulator with a distinct μ, δ and κ opioid receptor profile
  - μ- and δ-opioid receptor antagonist and κ-opioid receptor partial agonist
  - equal high potency on μ and κ opioid receptors, but lower potency on δ opioid receptors
- Nalmefene diminishes the reinforcing effects of alcohol, helping the patient to reduce drinking, and …….
Nalmefene as-needed: Pharmacokinetics

- Rapidly absorbed with peak plasma level at 1 hour\(^1\)
- Half life (\(t_{1/2}\)) approximately 12.5 hours\(^2\)
- High receptor occupancy (87–100%) within 3 hours and also after 26 hours (83–100%)\(^1\)

1. Ingman et al. 2005
Feasibility and efficacy of pharmacologically supported reduced risk drinking: the case of nalmefene

Three randomised, double-blind, placebo-controlled, parallel-group studies in patients with alcohol dependence
Active compound: 20 mg nalmefene hydrochloride (~18 mg base)

Dose regimen: as-needed

<table>
<thead>
<tr>
<th>Study name</th>
<th>Study duration</th>
<th>Patients enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESENSE 1</td>
<td>24-week plus 4-week run-out</td>
<td>604 (306 NMF + 298 PBO)</td>
</tr>
<tr>
<td>(12014A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESENSE 2</td>
<td>24-week plus 4-week run-out</td>
<td>718 (358 NMF + 360 PBO)</td>
</tr>
<tr>
<td>(12023A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SENSE</td>
<td>52-week</td>
<td>675 (509 NMF + 166 PBO)</td>
</tr>
<tr>
<td>(12013A)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NMF=nalmefene; PBO=placebo

Geographical overview

- ESENSE 1 (604 patients)
- ESENSE 2 (718 patients)
- SENSE (675 patients)
Study design 6-months studies: ESENSE 1 & 2

Main exclusion criteria:
- Patients with below medium EMA/WHO drinking risk level (DRL) at baseline
- Patients with <6 HDDs in previous 4 weeks
- S-ASAT and/or S-ALAT levels >3 times upper normal limit
- Psychiatric comorbidities
- CIWA-Ar score ≥10

NMF=nalmefene; V=visit; S-ASAT=aspartate aminotransferase; S-ALAT=alanine transaminase; CIWA-Ar=Revised Clinical Institute Withdrawal Assessment for Alcohol

Pharmacologically supported reduced-risk drink works: the case of nalmefene

Extending the Treatment Options in Alcohol Dependence: A Randomized Controlled Study of As-Needed Nalmefene

Karl Mann, Anna Baditión, Lars Torup, Antoni Gual, and Wim van den Brink

Background: There is a large treatment gap in alcohol dependence, and current treatments are only moderately effective in preventing relapse. New treatment modalities, allowing for reduction of alcohol consumption as a treatment goal are needed. This study evaluated the efficacy of as-needed use of the opioid system modulator nalmefene in reducing alcohol consumption in patients with alcohol dependence.

Methods: Six hundred and four patients (placebo = 298; nalmefene = 306) 218 years of age, with a diagnosis of alcohol dependence, 26 heavy drinking days, and average alcohol consumption (World Health Organization medium drinking risk level) in the 4 weeks preceding screening were randomized (1:1) to 24 weeks of as-needed placebo or nalmefene 18 mg.

Results: Patients taking placebo in 20% and patients taking nalmefene in 29% were included in the efficacy analysis. At Month 6, a significant effect of nalmefene compared to placebo in reducing the number of heavy drinking days (2.12 days; 95% confidence interval: 1.39 to 2.85; p = 0.052) and total alcohol consumption (<1.9 g/day; 95% confidence interval: -16.3 to -5.1; p = 0.003). Improvements in Clinical Global Impression and four measures were larger in the nalmefene group compared to placebo in Week 24. Adverse events (most mild or moderate) and dropouts due to adverse events were more common with nalmefene than placebo. The number of patients with serious adverse events was similar in the two groups.

Conclusions: Nalmefene provides clinical benefit, constitutes a potential new pharmacological treatment paradigm in the treatment goal and dosing regimes, and provides a method to address the unmet medical need in patients with alcohol dependence that need to reduce their alcohol consumption.
Reduction prior to randomisation

- A reduction in alcohol consumption during the assessment period prior to randomisation is a known phenomenon\(^1,2\)
- In the nalmefene studies:

Post hoc analysis;  
TLFB=time-line follow back


---

**Consumption requirements at screening (baseline measure)**

- At least 6 heavy drinking days (HDD) in the preceding 4 weeks
- At least medium risk levels in the preceding 4 weeks
But … many reduced their drinking before randomisation

Percentage of patients who reduced their alcohol consumption in the period between screening and randomisation

- **ESENSE 1** (n=579)
  - Reduced prior to randomisation: 18%
  - Did not reduce prior to randomisation: 82%

- **ESENSE 2** (n=665)
  - Reduced prior to randomisation: 33%
  - Did not reduce prior to randomisation: 67%

- **SENSE** (n=552)
  - Reduced prior to randomisation: 39%
  - Did not reduce prior to randomisation: 61%

FAS=full analysis set

Gual et al. Eur Neuropsychopharmacol 2013, Epub ahead of print;
van den Brink et al. J Psychopharmacoloy (in press)
Early reducers prior to randomisation

Same pattern was seen for both HDD and TAC, across all three studies

S=screening;
R=randomisation

van den Brink et al. Alcohol and Alcoholism, 2013, 48: 570-578
Patients with high or very high DRL at screening and randomisation

No reduction prior to randomisation

EMA focus on high and very high DRL

Most pronounced clinical benefits of treatment?

EMA=European Medicines Agency; DRL=Drinking Risk Level
Demographics of the target (total) population

No significant differences between placebo and nalmefene arms at baseline

Number of patients: 854 (1,997)

Gender: 63–78% (67–77%) men

Age: 45–52 yrs (44–52 yrs)

Family history: 47–65% (49–61%)

Years since onset: 11–14 yrs (11–14)

Employed: 54–63% (61–64%)

Higher education: 26–37% (23–32%)

With someone: 67–84% (65–84%)

Previously treated: 60–76% (60–76%)

Not previously treated: 60–76% (60–76%)

Numbers in (...) = total sample

Data show range of the means from individual studies
Results nalmefene vs. placebo target population

ESENSE 1 and ESENSE 2
Results nalmefene vs. placebo target population
ENSENSE 1 and ESENSE 2

ENSENSE - change in HDDs

22.6 HDDs

ENSENSE - change in TAC

105 g/d

Δ = 3.2 HDDs

10 HDDs

Δ = 14 g/d

105 g/d

40 g/d

MMRM (OC) FAS estimates and SE; *p<0.05;
MMRM=mixed-effect model repeated measure;
OC=observed cases; FAS=full analysis set; SE=standard error

van den Brink et al. Alcohol & Alcoholism, 2013
Results 12 month safety and efficacy study (SENSE)

Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study

Wim van den Brink1, Per Sorensen2, Lars Torup2, Karl Mann3, Antoni Gual4 for the SENSE Study Group

Abstract
This study evaluated the long-term efficacy and safety of nalmefene treatment in reducing alcohol consumption. We randomised (1:1) 675 alcohol-dependent patients ≥18 years of age to 52 weeks of as-needed treatment with placebo or nalmefene 18 mg/day. A total of 112 patients (68%) in the placebo group and 313 (52%) in the nalmefene group completed the study. At month 6, the co-primary outcome variables showed no statistically significant differences between the treatment groups: but at month 13, nalmefene was more effective than placebo, both in the reduction of the number of heavy drinking days (HDD) (−1.4 days/month; 95% CI: −2.9: −0.3; p = 0.017) and the reduction of total alcohol consumption (TAC) (−6.5 g/day last month; 95% CI: −12.5: −0.5; p = 0.016). In a subgroup analysis of patients with high/very high drinking risk levels at screening and at randomisation (the target population), there was a significant effect in favor of nalmefene on TAC at month 6. and on both HDD and TAC at month 13. Improvements in Clinical Global Impression and liver enzymes were greater with nalmefene, compared to placebo. Most adverse events were mild or moderate, and transient; adverse events, including those leading to dropout, were more common with nalmefene. This study provides evidence for the long-term safety and efficacy of nalmefene as-needed in alcohol-dependent patients who continue to drink heavily, following a brief intervention.

Keywords
Addiction, adverse effects, alcohol dependence, alcoholism, as-needed therapy, Clinical Global Impression, harm reduction, liver enzymes, nalmefene
Results nalmefene vs. placebo target population (HDDs) SENSE

Responder analysis (2) target population
ESENSE 1 & ESENSE 2

<table>
<thead>
<tr>
<th>Responder analysis</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30% reduction</td>
<td>2.44</td>
<td>1.64–3.66</td>
<td>7</td>
</tr>
<tr>
<td>&gt;50% reduction</td>
<td>2.15</td>
<td>1.54–3.00</td>
<td>6</td>
</tr>
<tr>
<td>&gt;70% reduction</td>
<td>1.88</td>
<td>1.32–2.70</td>
<td>9</td>
</tr>
</tbody>
</table>

*p<0.05; based on MMRM imputed TAC values

Data on file
Serum GGT and ALAT in target population ESENSE 1 and ESENSE 2

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Placebo</th>
<th>Nalmefene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Geometric Mean</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>320</td>
<td>57.6</td>
</tr>
<tr>
<td>Adjusted geometric mean at</td>
<td>220</td>
<td>53.0</td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALAT (IU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>319</td>
<td>29.2</td>
</tr>
<tr>
<td>Adjusted geometric mean at</td>
<td>218</td>
<td>30.7</td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GGT=γ-glutamyltransferase; ALAT=alanine aminotransferase; Gual et al. Poster at WONCA 2013; van den Brink et al. Alcohol Alcohol 2013;48(5):570–578
### Adverse Events in All Patient Treated Set Total Population

Side effects were generally transient, mild and only after the first dosis.

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Placebo (n=797)</th>
<th></th>
<th>Nalmefene (n=1,144)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Patients with AEs</td>
<td>500</td>
<td>62.7%</td>
<td>855</td>
<td>74.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>47</td>
<td>5.9%</td>
<td>253</td>
<td>22.1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>44</td>
<td>5.5%</td>
<td>208</td>
<td>18.2%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>43</td>
<td>5.4%</td>
<td>153</td>
<td>13.4%</td>
</tr>
<tr>
<td>Headache</td>
<td>66</td>
<td>8.3%</td>
<td>141</td>
<td>12.3%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>73</td>
<td>9.2%</td>
<td>107</td>
<td>9.4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>2.3%</td>
<td>100</td>
<td>8.7%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>4.6%</td>
<td>95</td>
<td>8.3%</td>
</tr>
</tbody>
</table>
Nalmefene indication

- Nalmefene is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (DRL), without physical withdrawal symptoms and who do not require immediate detoxification.
- Nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.
- Nalmefene should be initiated only in patients who continue to have a high DRL two weeks after initial assessment.
Adverse Events leading to Withdrawal in the All Patient Treated Set (APTS) – Total Population (incidence ≥0.5%)\(^1,2\)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Placebo (n=797)</th>
<th>Nalmefene (n=1,144)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Patients with TEAEs leading to withdrawal</td>
<td>47</td>
<td>5.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Alcohol withdrawal syndrome</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Reasons for treatment gap
Assumed limited effectiveness interventions
### Standardised Effect Sizes for Nalmefene Comparable to other mental disorders

<table>
<thead>
<tr>
<th>Effect Size (Cohen’s d)</th>
<th>Nalmefene</th>
<th>HDDs</th>
<th>TAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESENSE 1</td>
<td>0.37</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>ESENSE 2</td>
<td>0.27</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect Size (Cohen’s d)</th>
<th>Alcoholtreatment&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>0.12 to 0.33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect Size (Cohen’s d)</td>
<td>Antidepressants&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.24 to 0.35</td>
</tr>
<tr>
<td>Effect Size (Cohen’s d)</td>
<td>Antipsychotics&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.30 to 0.53</td>
</tr>
</tbody>
</table>

2. NICE. Alcohol dependence and harmful alcohol use: appendix 17d – pharmacological interventions forest plot. 2011.
Putting the Efficacy of Psychiatric and General Medicine Medication into Perspective: Review of Meta-analyses

Conclusions
Conclusions

- Alcohol dependence is a (stigmatised) treatable brain disease
- Current treatment is predominantly abstinence orientated
- About 50% of the patients do not want abstinence treatment
- Large treatment gap
- Effective reduced-risk drinking interventions may narrow treatment gap
- Nalmefene as-needed is an effective and safe treatment directed at reduced drinking
- Personalized treatment needed to increase treatment effectiveness and efficiency
Thank You

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