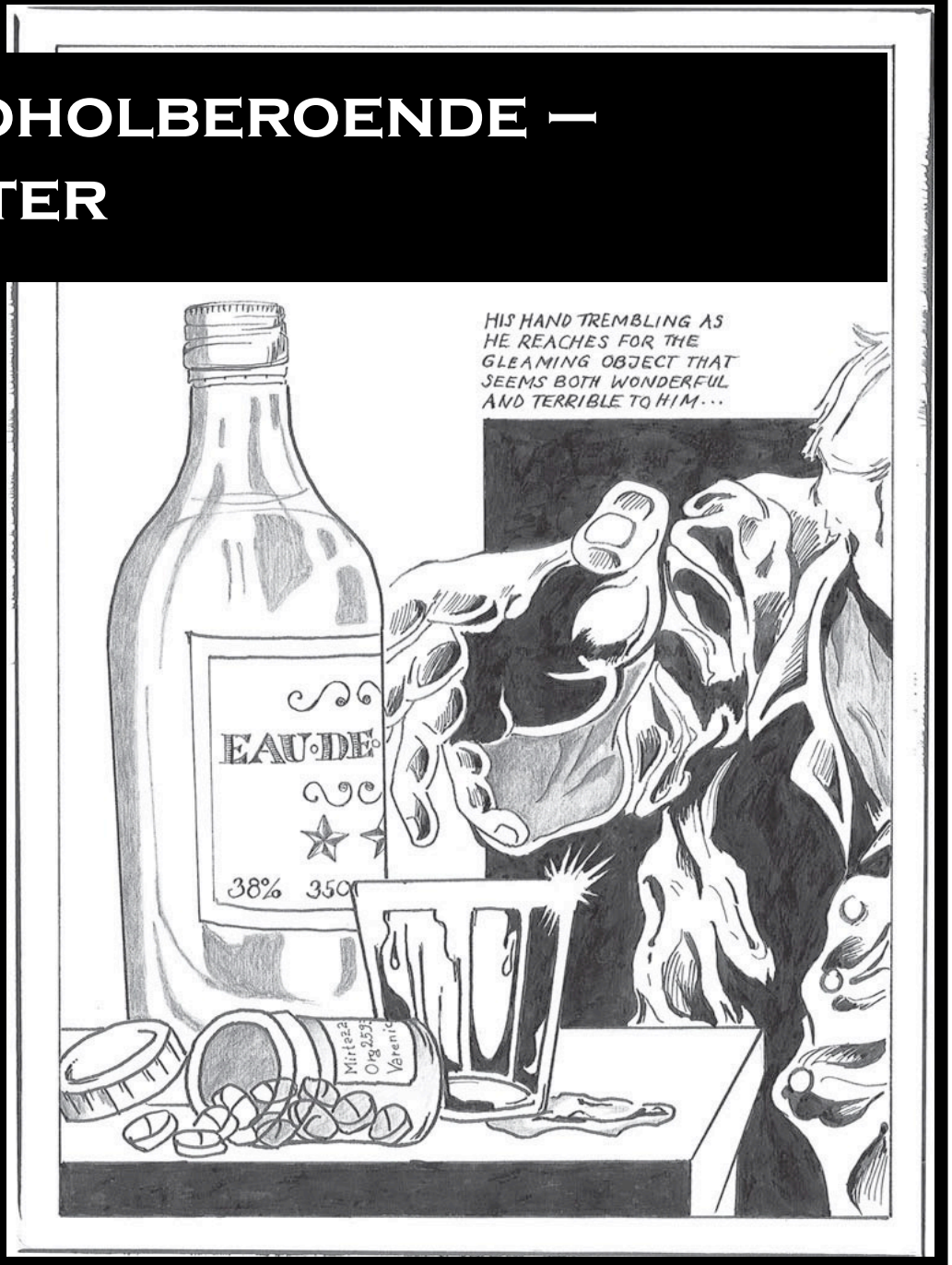
Läkemedel vid alkoholberoende – framtida möjligheter



Regional Läkemedelsdag 26 oktober 2017

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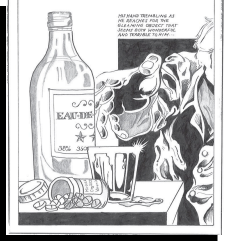
Addiction Biology Unit – Clinical Trials
Inst Neuroscience & Physiology
Sect Psychiatry & Neurochemistry
Sahlgrenska Academy

The history of the diagnose



Ancient Mesopotamians
birth defects

11th cent.
inflammation of the liver

Hippocrates
abstinence

1774 The Mighty Destroyer
1784 disease treated by physicians

1849 Huss
Alcoholismus Chronicus

Early 1900 S
institutions and detox

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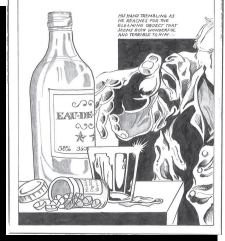
The History of alcohol treatments



Late 1800s

The Keely cure

coca, morphine, arsenic, strychnine

side effects: death and insanity

Late 1800s

Laudanum

morphine

side effects:

morphine dependence

1930s

Adverse therapy

1950s US

Serum therapy

prisons and asylums

1920s US

sterilization

1948-52

9 cases of lobotomy

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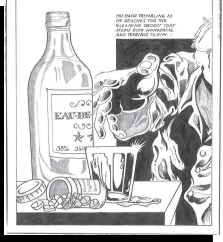

Treatments of today

Acamprosate (Campral) approved 2004

Meta analyses show NNT 7.5 (abstinence)
Maisel et al., 2013

Health economic studies show life-time savings
Palmer et al.,2000, Foster et al., 1999, Schadlich et al.,1998

No difference in effect with different psychosocial support
deWildt et al., 2002, Hammarberg et al., 2004

Disulfiram (Antabus)

Serendipity 1940s
Heughes et al., 1997

Meta analyses show superiority to placebo
Jorgensen et al., 2011

Long term supervised superior to acamprosate
Diehl et al., 2010

Naltrexone approved 1994

Meta analyses show effects from NNT 8.6 (prevention of return to heavy drinking)
Maisel et al.,

to NNT 13 (short term treatment effects) and a relapse risk reduction of 36% Rosner et al., 2010

Treatment gap in Europa 92%

depression 45 %
bipolar 40 %

Kohn et al.,2004

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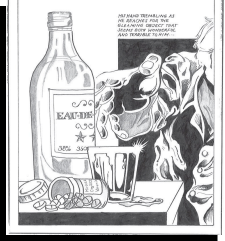
New potential treatments



topiramate	Anticonvulsant GABA$_A$	7 RCTs meta analysis show good effect size Blodgett et al., 2014
baclofen	Spacticity GABA $_B$	Few and small studies Brennan et al., 2013 Effect on alc+liver disease w no liver side effects Adolorato et al., 2007
ondansetron	Antiemetic 5-HT3 antagonist	Effect in early onset alcoholics Johnson et al., 2000, Kranzler et al., 2003
sodium oxybate	Illegal drug GHB	Approved in Italy and Austria for both withdrawal and abstinance mainatnance Keating et al., 2014

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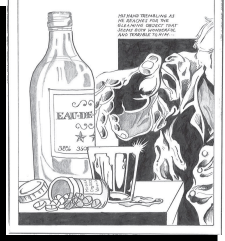
New potential treatments - mirtazapine



Antidepressant
with serotonergic & noradrenergic action

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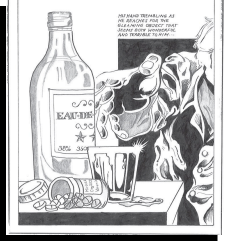
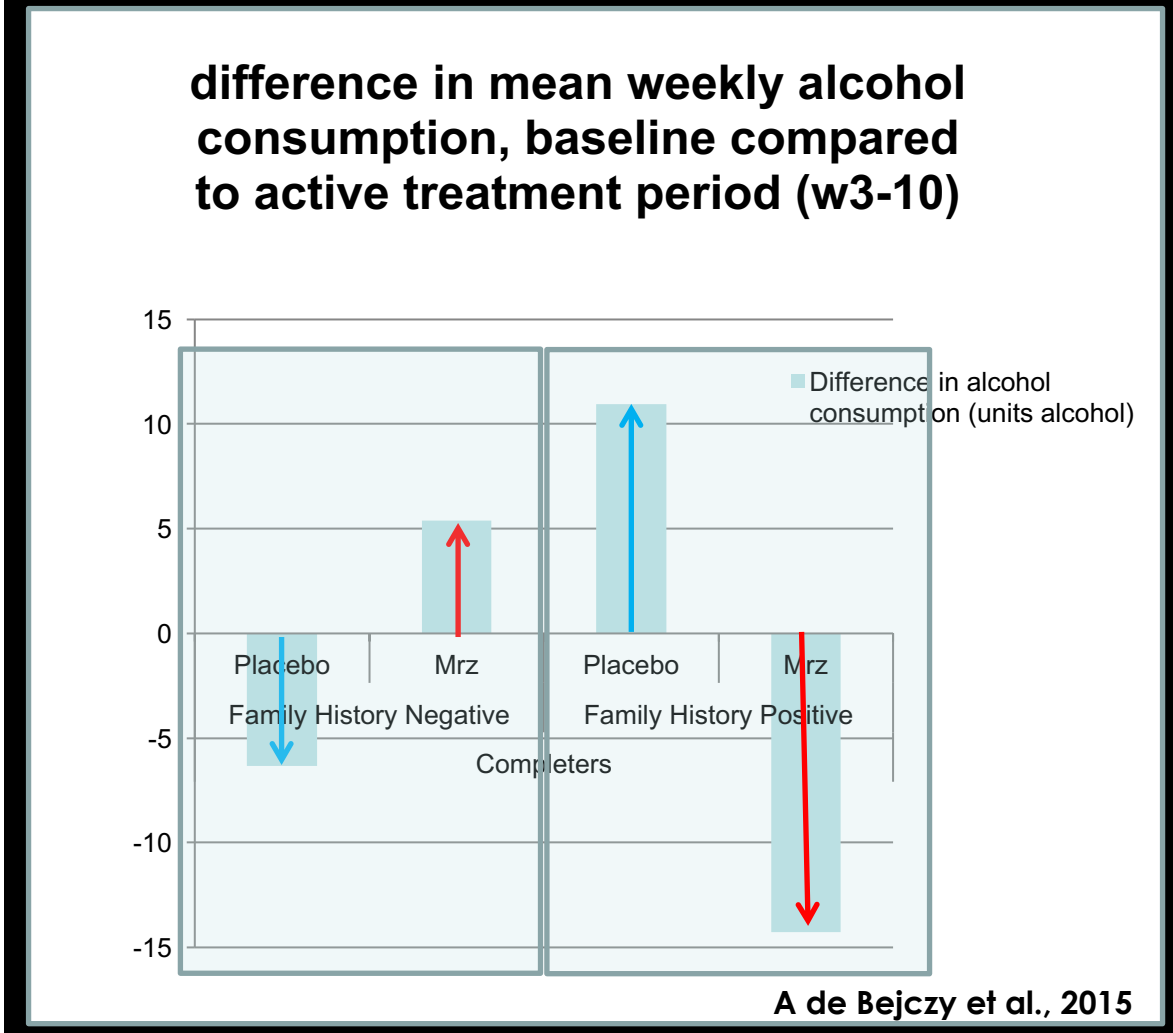
New potential treatments - mirtazapine





mirtazapine lowered alcohol intake in males with high alcohol consumption and heredity for alcohol use disorder

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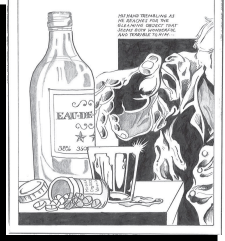
New potential treatments - varenicline



smoking cessation drug (Champix)
acts on nicotinic acetylcholine receptors (nAChRs)

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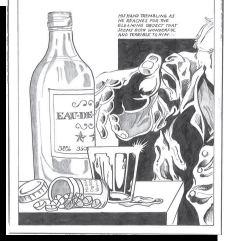
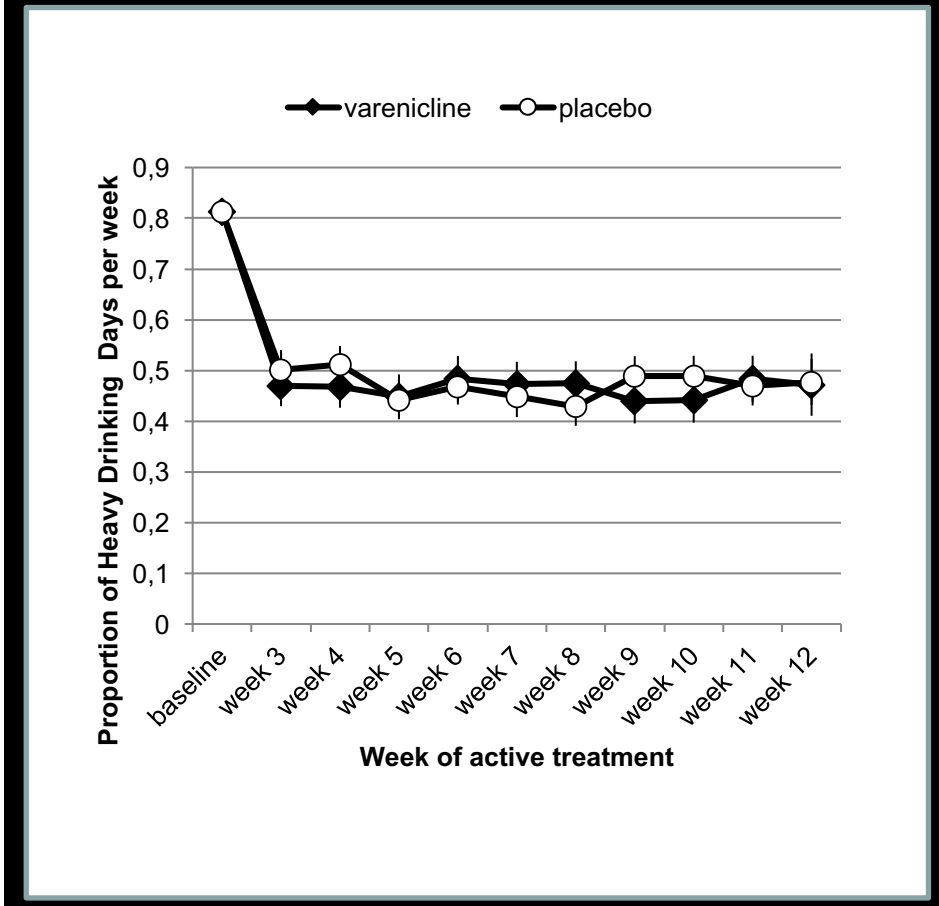
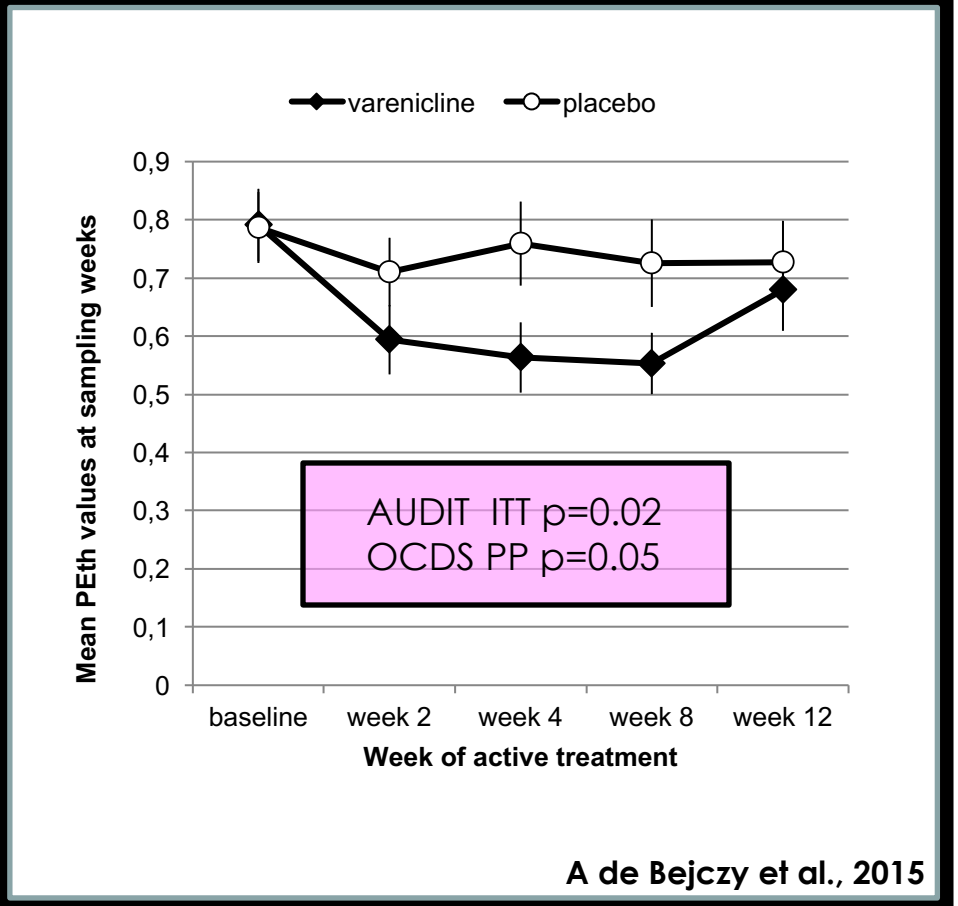
New potential treatments - varenicline







A de Bejczy et al., 2015

self-reported consumption showed no difference between treatment groups (p=0.73)

PEth as outcome showed treatment effect (p= 0.02)

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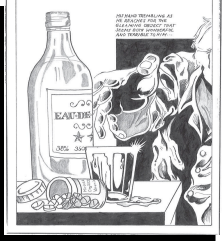
BIOMARKERS



PEth was the alcohol marker that correlated best with self-reported alcohol consumption

Table 5 Spearman's correlations between blood levels of PEth/ CDT/GGT as the mean for week 2, 4 and 8 of active treatment period and reported alcohol consumption as the mean number of drinks over the active treatment period

Alkohol marker	All (95% CI)	Varenicline (95% CI)	Placebo (95% CI)
PEth	0.51 (0.35 ;0.65)	0.61 (0.40; 0.76)	0.42 (0.16; 0.63)
CDT	0.36 (0.19; 0.52)	0.54 (0.29; 0.72)	0.15 (-0.11; 0.39)
GGT	0.26 (0.06; 0.45)	0.42 (0.12; 0.66)	0.10 (-0.16; 0.35)

PEth: phosphatidylethanol, CDT: carbohydrate-deficient transferrin, GGT: γ -glutamyltransferase, CI: confidence interval

A de Bejczy et al., 2015

the varenicline group showed better correlation than the placebo group

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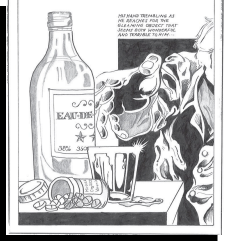
A HETEROGENOUS DISEASE



State marker
Related to recent drinking - biomarkers

Trait markers
Factors associated with increased risk, present before and related to disease

- Heritability
- Personality traits
- Response to alcohol
- Genetics

Phenotypes

delta gamma (severity)
Jellinek, 1960

Type I Type II (enviromental vs inherited)
Cloninger, 1987

Lesch typology I-IV (drinking pattern and craving)
Lesch et al., 1988

Type A Type B (severity, age of onset and prognosis)
Babor et al., 1992, schuckit et al., 1995

Early onset (EOA) vs Late onset (LOA)
Proxy for inherited and biological vulnerability
Johnson et al., 2000

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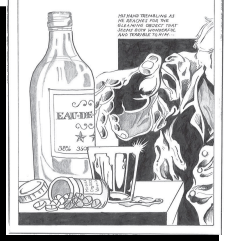
Precision medicine



Polymorphisms and treatment response

Sodium oxybate
Lesh typology more severe better effect
Caputo et al., 1988

Acamprosate
Kiefer 2011

Naltrexone
Oslin 2003

Topiramate
Kranzler 2014

Ondansetron
Kenna 2014

Combinations?

Ondansetron
Early Onset Alcoholics, gene variation?
Johnson 2011

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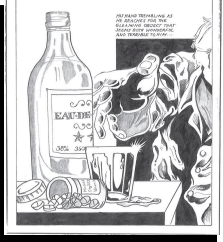
Abstinence vs harm reduction



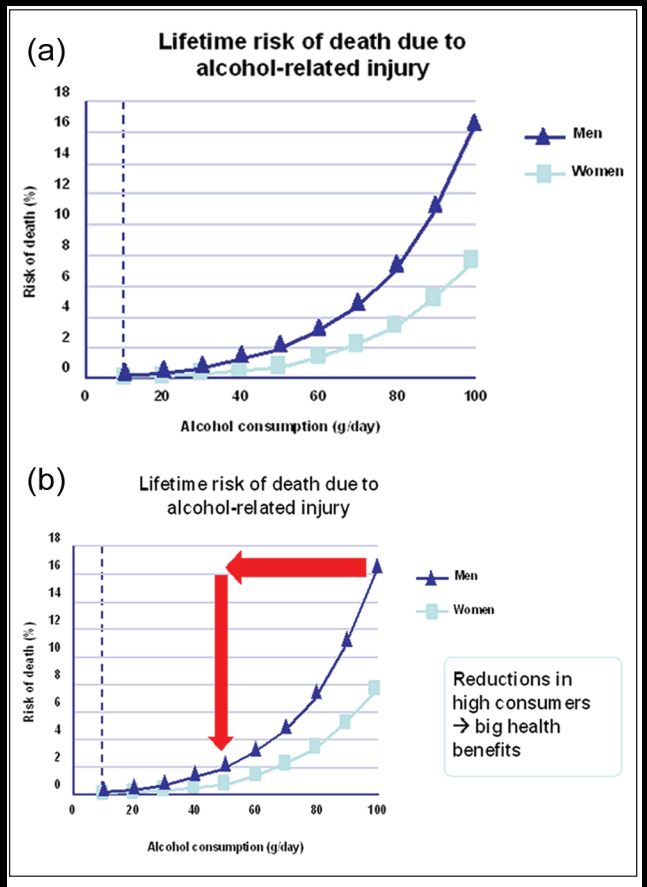


Figure 2. Lifetime risk of death due to alcohol-related injury, and the effect of reduction of consumption (adapted from Rehm J, Zatonski W, Taylor B, et al. (2011) Epidemiology and alcohol policy in Europe. Addiction 106: S11–S19 with permission from John Wiley & Sons, Inc). (a) shows the exponential rise in alcohol-related injury deaths with increase in intake; (b) shows how a 50% reduction in consumption from 100 g/day gives an eight-fold benefit in terms of harm. Note that these calculations are based on sustained changes. **Nutt et al., 2014**

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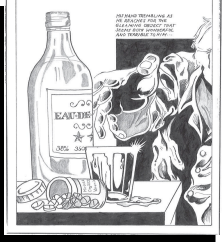
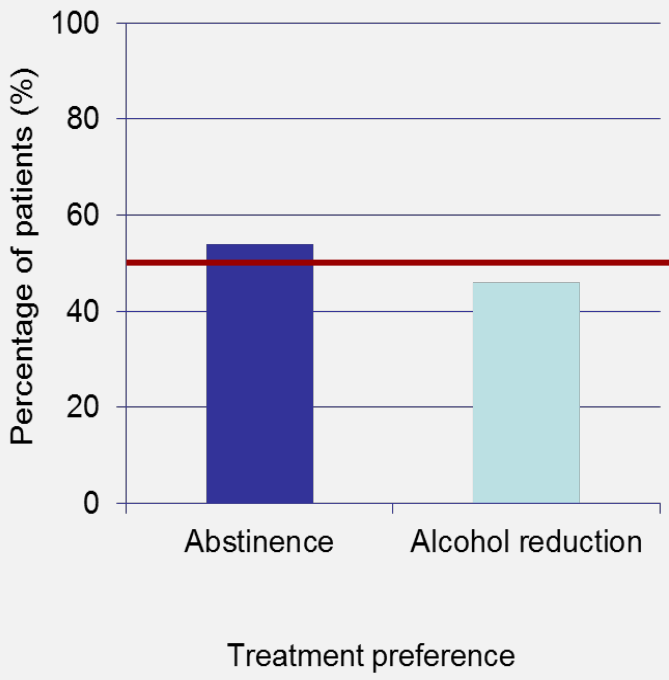
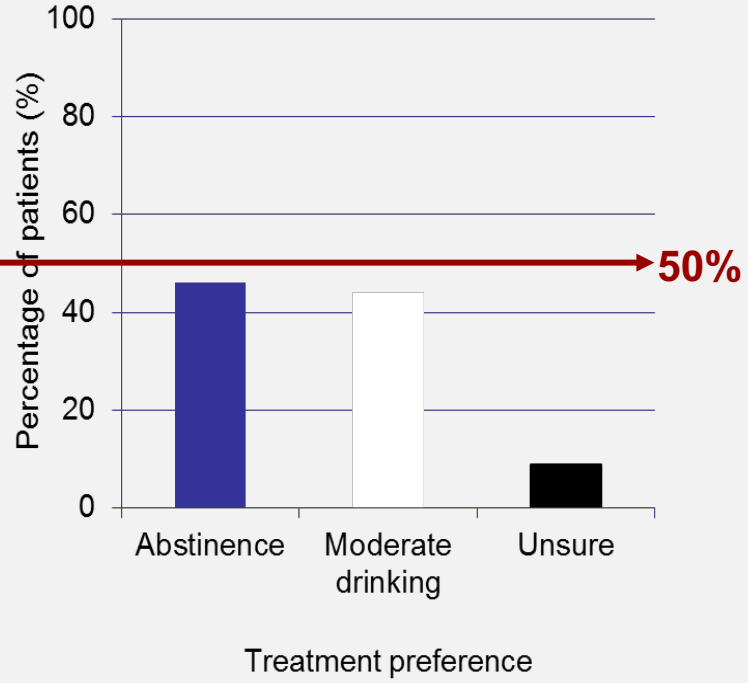
Treatment goals



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

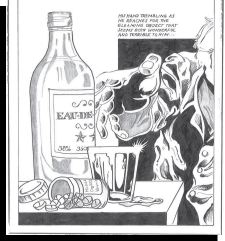


Canadian study of patients with chronic alcoholism (n=106)



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

Study design



outcome measures objective vs subjective

abstinence or harm-reduction detoxification or not

participation effect brief intervention, support, placebo,

selection demographics and motivation

the subject individual effect of the drug and dose

analysis Intention-To-Treat vs Per Protocol (compliance)

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collegues and collaborators in performing the RCTs

The Addiction Biology Unit

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Barbro Askerup
Cecilia Nilsson-Wallmark
Helga Lidö
Gunilla Barr
Anna Gordh

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Louise Adermark
Rosita Stomberg
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