De Behandeling van Alcoholproblemen

Wat is Nieuw?

Wim van den Brink
Academisch Medisch Centrum,
Universiteit van Amsterdam

VAD studiedag: Over alcohol, geen klein bier!
Brussel, 25 november 2016

Potentiele Belangenverstrengeling

Belang	Naam van de organisatie
Subsidies	Neurosearch, Alkermes
Honoraria	Lundbeck, Merck Serono, Eli Lilly, Indivior, Pfizer,
Adviesraad/consulent	Lundbeck, Merck Serono, Indivior, Mundipharma, D&A Pharma, Bioproject, Novartis, Kinnov Therapeutics

Inhoudsopgave

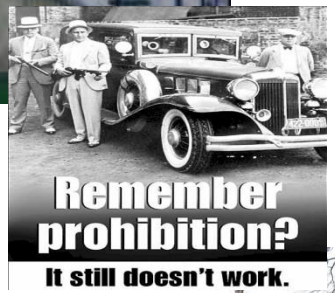
Inhoudsopgave

- Nieuwe theorie - psychopathologie van verslaving
- Nieuwe behandeldoelen
- Nieuwe farmacotherapie
- Nieuwe psychotherapie
- Neuromodulatie
- Conclusies

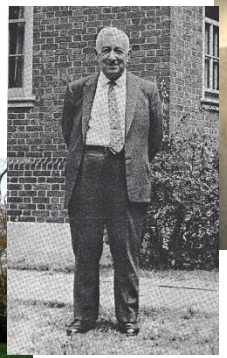
Nieuwe theorie - psychopathologie

Geschiedenis van het begrip verslaving

1. Morele model

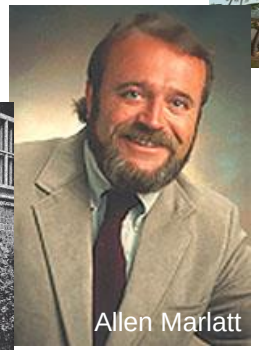


2. Farmacologische model



3. Symptomatische model

4. Ziektemodel



5. Leertheoretisch model

6. Sociale model

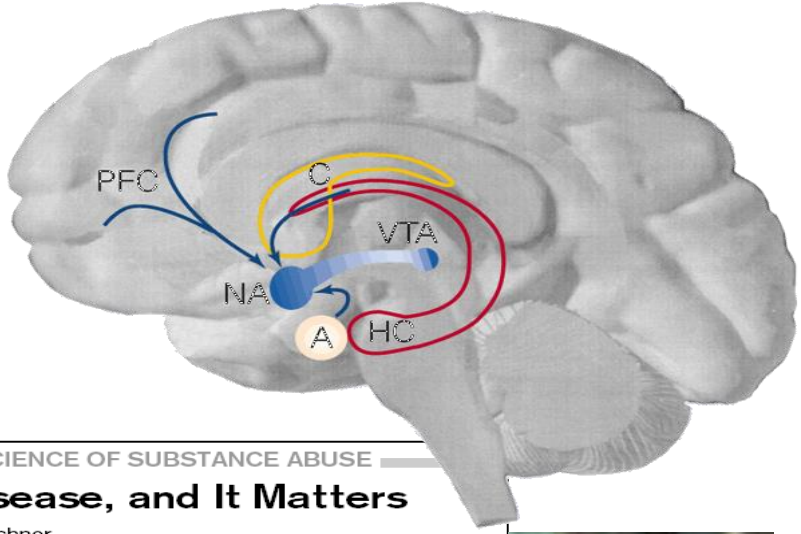
7. Hersenziekte model

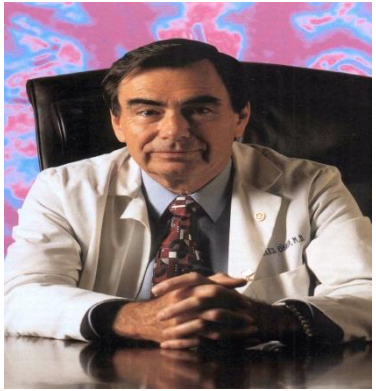
Ideologisch → Empirisch

1976: Edwards & Gross
Biopsychosociale model
(Herstelmodel)
Alcoholafhankelijkheidssyndroom

Addiction: a treatable brain disease

Nora Volkow





Charles O'Brien

FRONTIERS IN NEUROSCIENCE: THE SCIENCE OF SUBSTANCE ABUSE

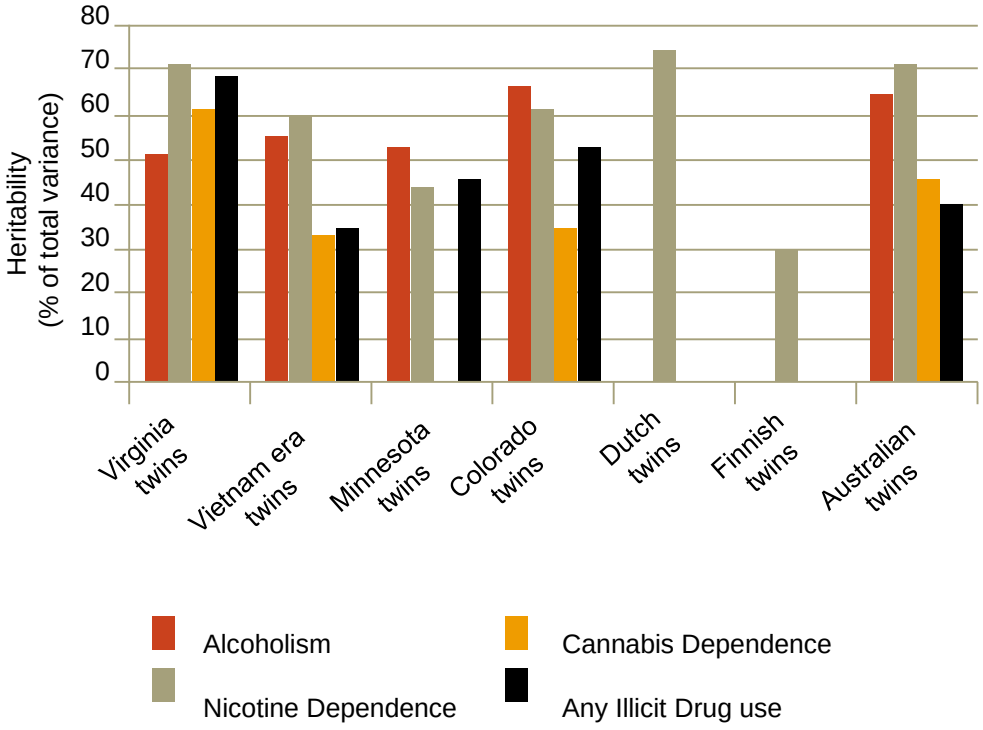
Addiction Is a Brain Disease, and It Matters

Alan I. Leshner

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.

affects both the health of the individual and the health of the public. The use of drugs has well-known and severe negative consequences for health, both mental and physical. But drug abuse and addiction also have tremendous implications for the health of the public, because drug use, directly or indirectly, is now a major vector for the transmission of many serious infectious diseases—particularly acquired immunodeficiency syndrome (AIDS), hepatitis, and tu-

Erfelijkheidsschattingen volgens tweelingstudies



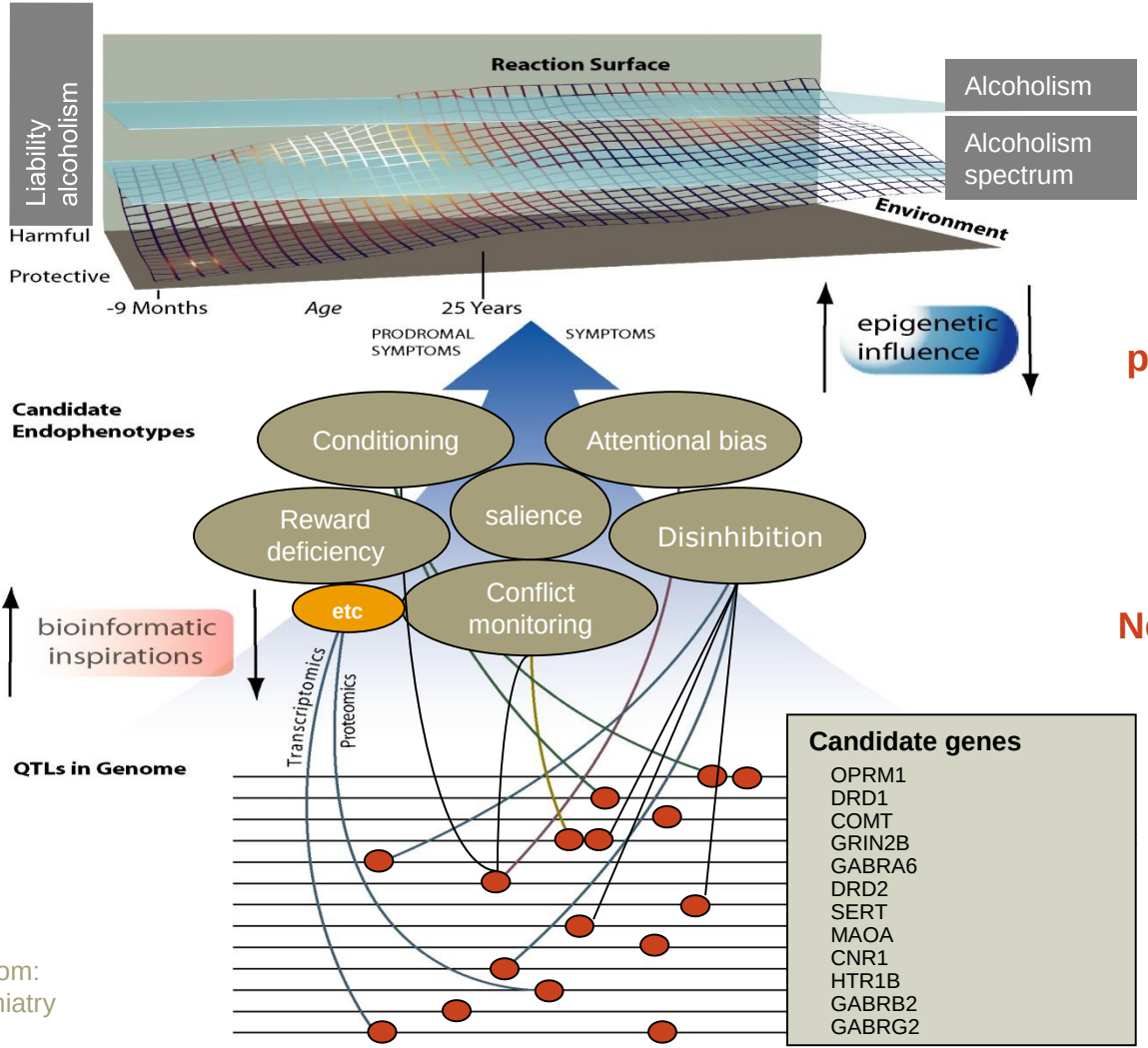
Type of dependence	Heritability
Alcohol	50–70%
Nicotine	50–75%
Cannabis	35–75%
Cocaine	35–80%
Heroin	40–60%

Agrawal & Lynskey. Addiction 2008;103(7):1069–1081

Fenotype

Endofenotype

Genotype



Sociale steun

Inzicht-gevende psychotherapie

CGT

Medicatie Neuromodulatie

Farmaco-genetica

Gen therapie

Ooteman et al (2006) adapted from: Gottesman & Gould. Am J Psychiatry 2003;160:636–645

Neurobiologie van Verslaving

Function	Brain structures	Neurotransmitters
Reward deficiency	Ventral tegmental area (VTA) Nucleus accumbens (NAc)	Endorphins (μ-receptors) Dopamine
Disinhibition Impulsivity	DLPFC ACC	Noradrenalin, 5-HT GABA, glutamate
Conditioning Craving	NAc (ventral striatum) Amygdala Thalamus Prefrontal cortex (OFC, ACC)	Dynorphins (κ-receptors) Dopamine CRH Glutamate
Attentional bias/ salience	OFC VMPFC	Dopamine
Withdrawal	Locus coeruleus	Noradrenalin, CRH Glutamate
Habit formation	Putamen, Nc caudatus (dorsal striatum)	Dopamine

Naief
Experimenteren
Gematigd gebruik

Binging

Misbruik

Afhankelijkheid
(craving)

Verslaving
(compulsief gebruik)

Neurobiologie van Verslaving

Function	Brain structures	Neurotransmitters
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Naief

Experimenteren

Gematigd gebruik

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Misbruik

Afhankelijkheid

(craving)

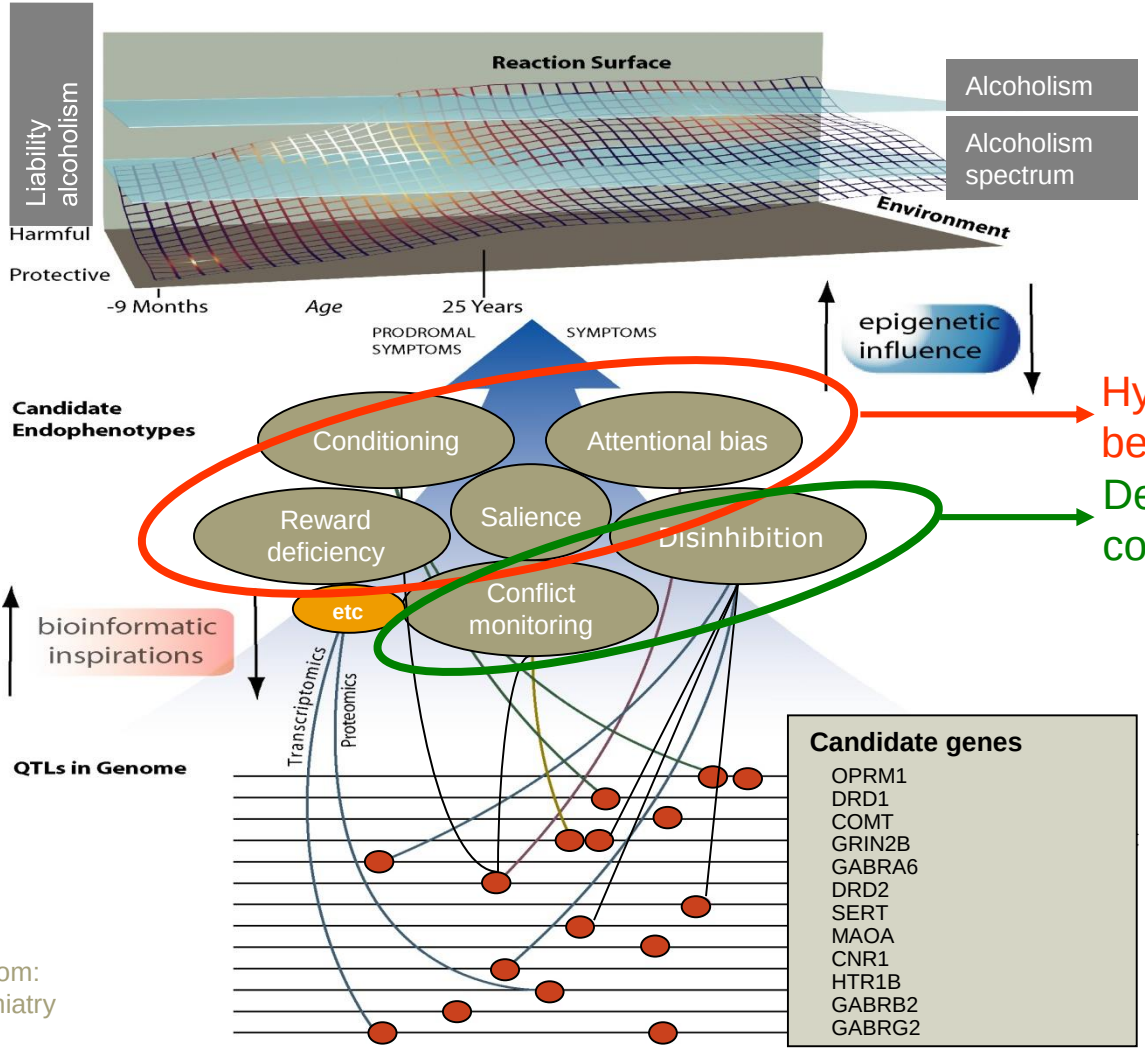
Verslaving

(compulsief gebruik)

Fenotype

Endofenotype

Genotype



Hyperactief beloningssysteem

Deficiënt controlesystem

Ooteman et al (2006) adapted from: Gottesman & Gould. Am J Psychiatry 2003;160:636–645

Reward → attentional bias → cue-reactivity → craving - deficient cognitive control - → relapse

Repeated reward

Attentional bias → Cue-reactivity → Craving → **Relapse**

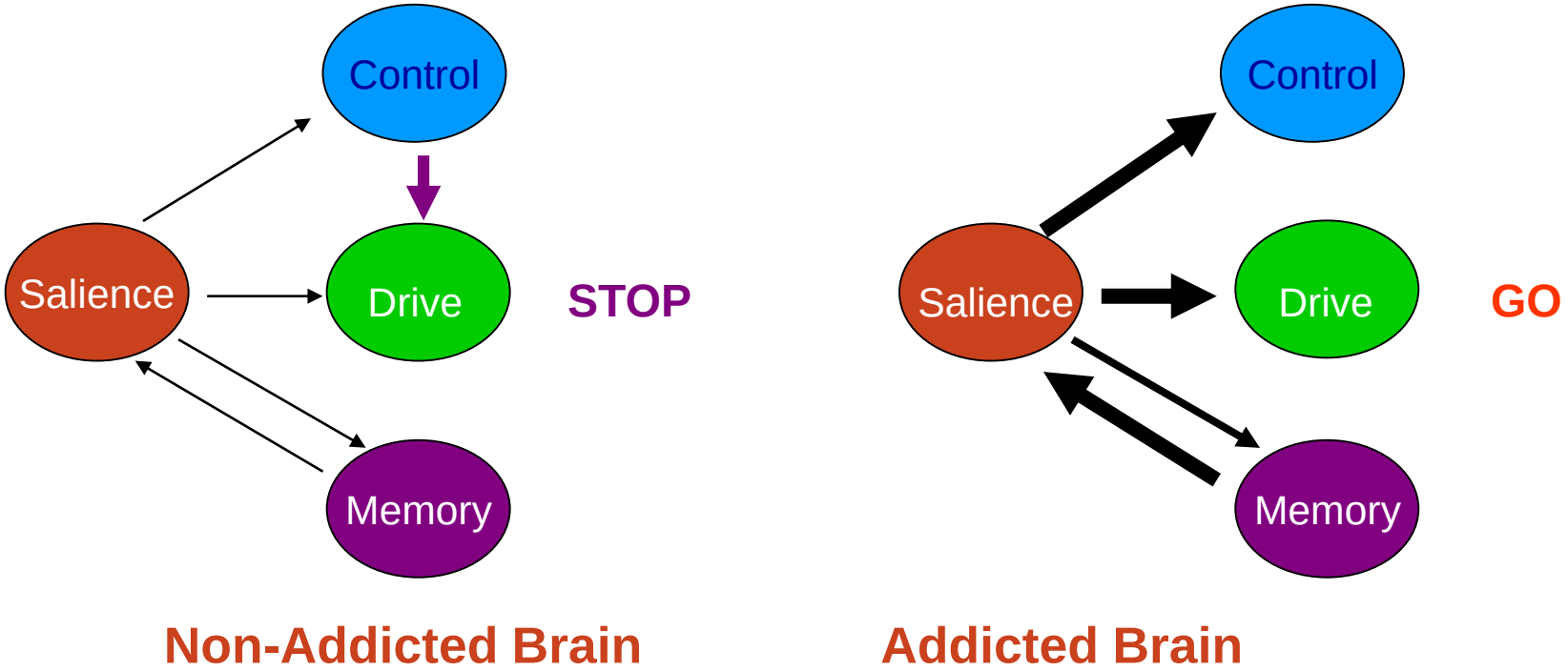
Detection threshold

Inhibition

Conflict registration

Drug-related stimulus

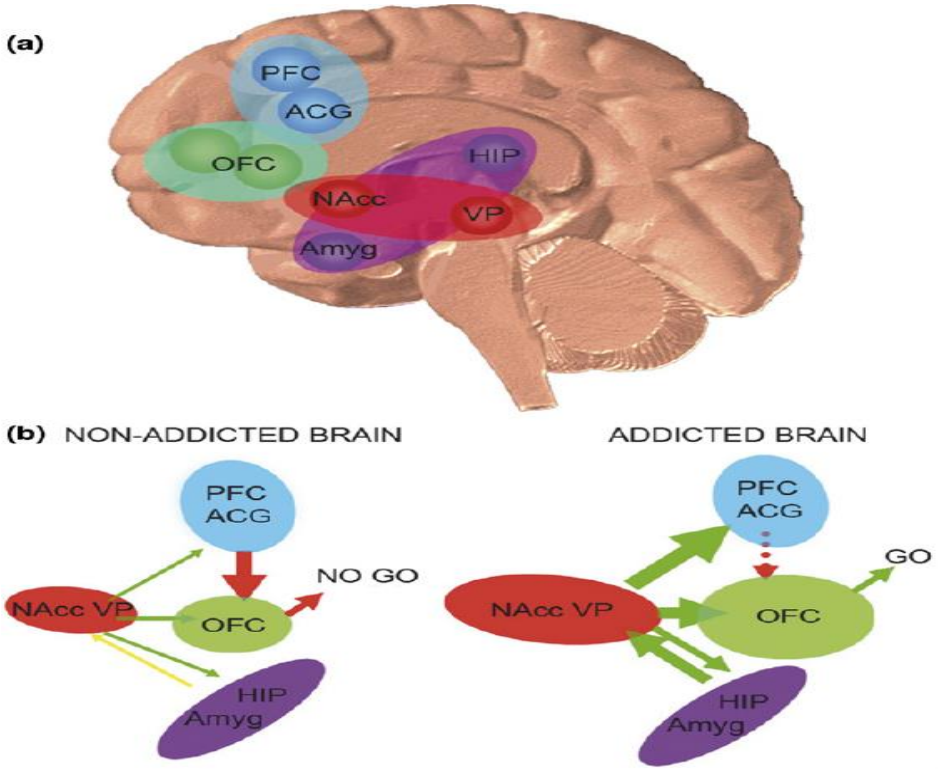
The Addicted Brain



Non-Addicted Brain

Addicted Brain

Brain Structures and Functions in Addiction



Baler and Volkow, 2006

Neurobiologie van Verslaving

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Naief

Experimenteren

Gematigd gebruik

Binging

Misbruik

Afhankelijkheid

(craving)

Verslaving

(compulsief gebruik)

Hyperresponsiveness of the Neural Fear Network During Fear Conditioning and Extinction Learning in Male Cocaine Users

Anne Marije Kaag, M.Sc., Nina Levar, M.Sc., Karlijn Woutersen, M.Sc., Judith Homberg, Ph.D., Wim van den Brink, Ph.D., M.D., Liesbeth Reneman, Ph.D., M.D., Guido van Wingen, Ph.D.

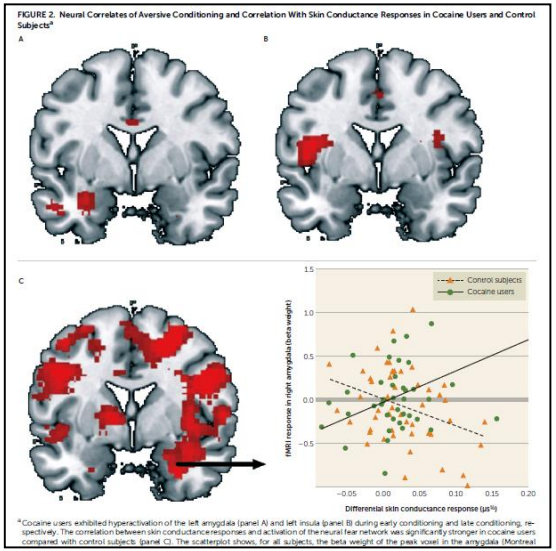
AJP in Advance (doi: 10.1176/appi.ajp.2016.15040433)

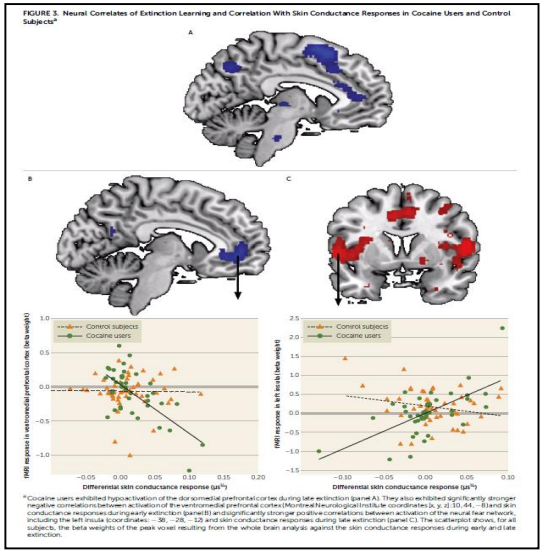
Positieve bekrachtiging en (geconditioneerde) beloningscraving staan centraal in de theorieën over verslaving en terugval

Recent meer aandacht voor negatieve bekrachtiging en verzachtingscraving. Maar nog maar heel weinig neurobiologische humane data.

Mannelijke cocainegebruikers/verslaafden (N=50) and gezonde, niet-gebruikende controles (N=51) die onderworpen werden aan fear conditioning en fear extinction (shocks) terwijl ook hersenactivatie (fMRI) en huidweerstand werden gemeten.

Fear conditioning and extinction in regelmatige cocaine gebruikers (RCU) en gezonde controles (HC)





CRU gevoeliger voor angst
Meer activatie li amygdala and li insula tijdens conditionering en sterkere correlatie tussen angstnetwerk (amydala) en huidweerstand in RCU vs HC

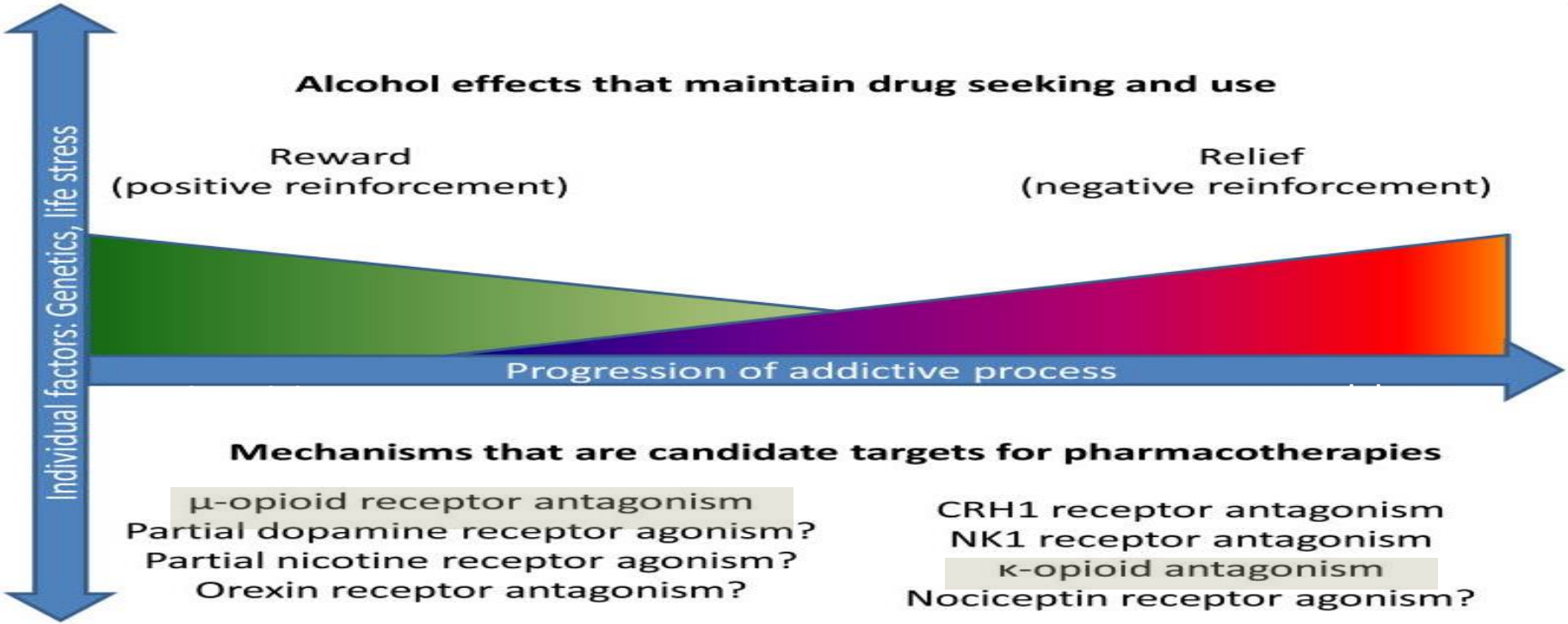
CRU minder goed in uitdoving angst
Minder activatie in dmPFC en sterkere sterkere pos correlaties tussen angstnetwerk (li insula) en huidweerstand tijdens extinctie

Conclusies en behandelingmogelijkheden

Conclusions: Increased sensitivity to aversive conditioned cues in cocaine users might be a risk factor for stress-relief craving in cocaine use disorder. These results support the postulated role of altered aversive conditioning in cocaine use disorder and may be an important step in understanding the role of aversive learning in the pathology of cocaine use disorder.

These findings emphasize that in addition to reducing drug-conditioned responses (reward craving), treatment should also try to reduce the (neural) sensitivity to stressors (relief craving). This could be achieved by means of cognitive-behavioral treatment (e.g., mindfulness-based relapse prevention [38]) or pharmaceutical treatments that target the noradrenergic stress system (e.g., propranolol [39]).

Van geluk naar troost en van impulsiviteit naar compulsiviteit



Adapted from Heilig et al., 2010

Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum

Sabine Vollstädt-Klein[1], Svenja Wichert[1], Juri Rabinstein[1], Mira Bühler[1], Oliver Klein[1], Gabriele Ende[2], Derik Hermann[1] & Karl Mann[1]

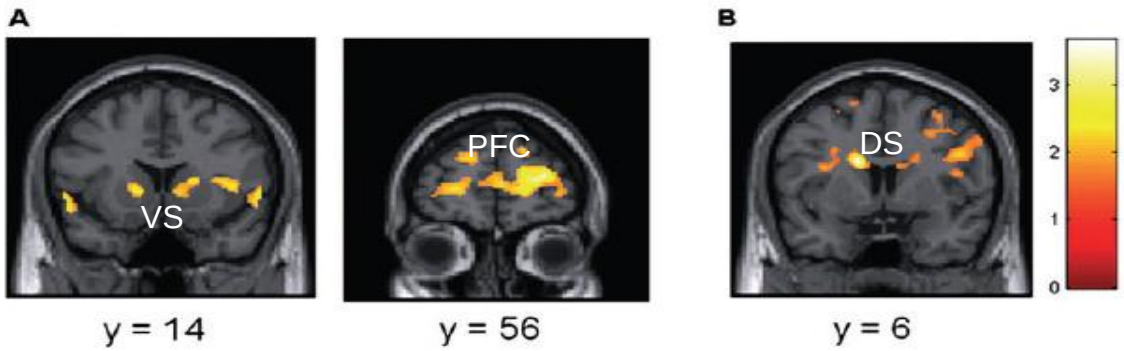


Figure 3 Alcohol cue-induced brain activation (contrast 'favourite drinks versus neutral cues') in light social drinkers ($n = 10$) compared to heavy social drinkers ($n = 21$), $P < 0.05$ small volume corrected [false discovery rate (FDR)]; for illustration purposes $P < 0.05$ uncorrected; (a) increased activation in light social drinkers in the ventral striatum and the prefrontal cortex; (b) heavy drinkers showed enhanced activation in the dorsal striatum

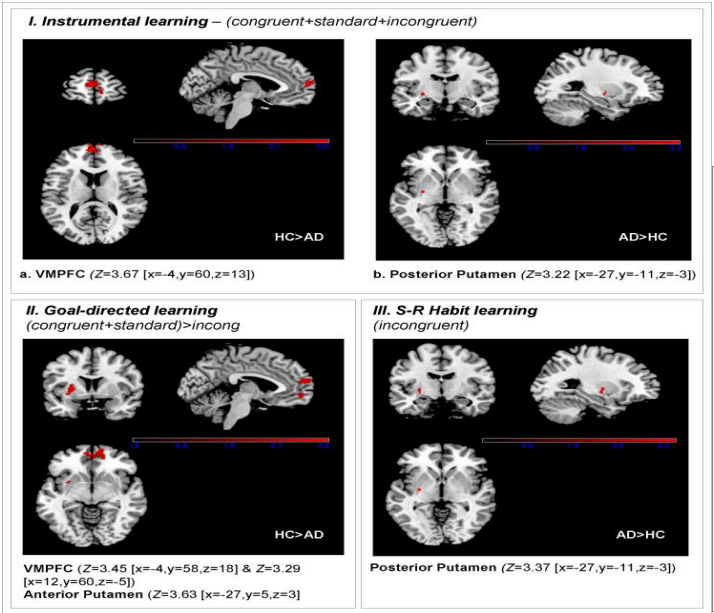
Social Drinkers
OCDS = 1.8

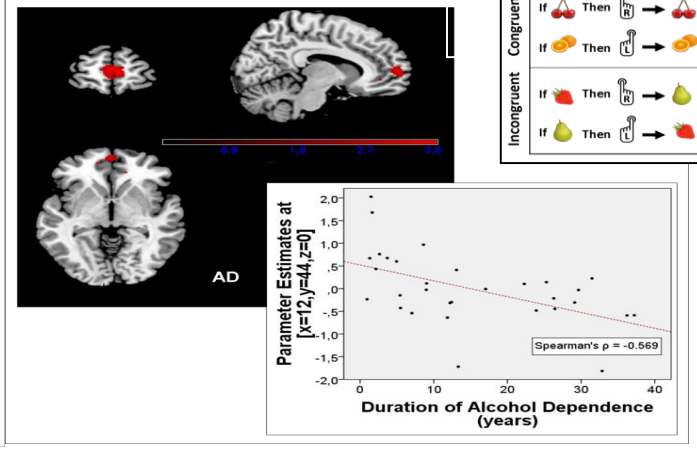
Heavy Drinkers
OCDS = 11.5

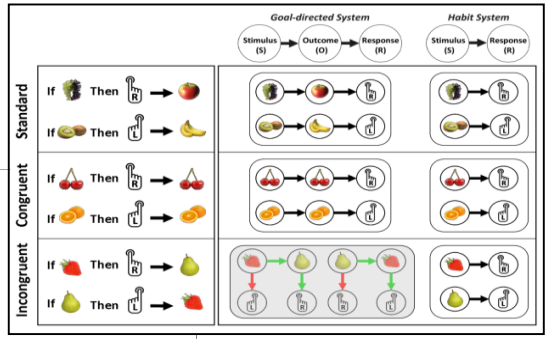
Behavioral and neuroimaging evidence for overreliance on habit learning in alcohol-dependent patients

Z Sjoerds[1,2], S de Wit[3,4], W van den Brink[2], TW Robbins[5], ATF Beekman[1], BWJH Penninx[1,6,7] and DJ Veltman[1,2]

2013







* HC meer goal-directed learning (vmPFC); AD meer habit-learning (post. putamen)

*** Binnen groep AD: nog minder goal-directed learning (vmPFC) bij langere duur AD**

Reward → attentional bias → cue-reactivity → craving - deficient cognitive control - → relapse

Repeated reward

Attentional bias → Cue-reactivity → Craving → **Relapse**

Detection threshold

Inhibition

Conflict registration

Drug-related stimulus

Reward → attentional bias → cue-reactivity → craving - deficient cognitive control - → relapse

Repeated reward

Attentional bias → Cue-reactivity → Craving → **Relapse**

Detection threshold

Inhibition

Conflict registration

Drug-related stimulus

STRESS

WITHDRAWAL

Model voor Farmacotherpie Verslaving

Repeated reward

Antagonist

Attentional bias → Cue-reactivity

Drug-related stimulus

Stress

Anti-stress medicatie

Detection threshold

Anti-craving drug

Craving

Inhibition

Cognitive enhancer

Agonist

Relapse

Conflict registration

Model voor Psychotherapie Verslaving

Repeated reward

Counterconditionering

Attentional bias → Cue-reactivity

Drug-related stimulus

Stress

CGT
Mindfulness

Detection threshold

CET
ACT
EMDR?

Craving

Inhibition

MGV
Werkgeheugen

Conflict registration

CM
CRA

Relapse

Proposed Model of the Neurobiological Mechanisms Underlying Psychosocial Alcohol Interventions: The Example of Motivational Interviewing*

SARAH W. FELDSTEIN EWING, PH.D.,† FRANCESCA M. FILBEY, PH.D.,† CHRISTIAN S. HENDERSHOT, PH.D.,† AMBER D. MCEACHERN, PH.D., AND KENT E. HUTCHISON, PH.D.†

Mind Research Network, Pete & Nancy Domenici Hall, 1101 Yale Boulevard NE, Albuquerque, New Mexico 87106

JSAD, 2011

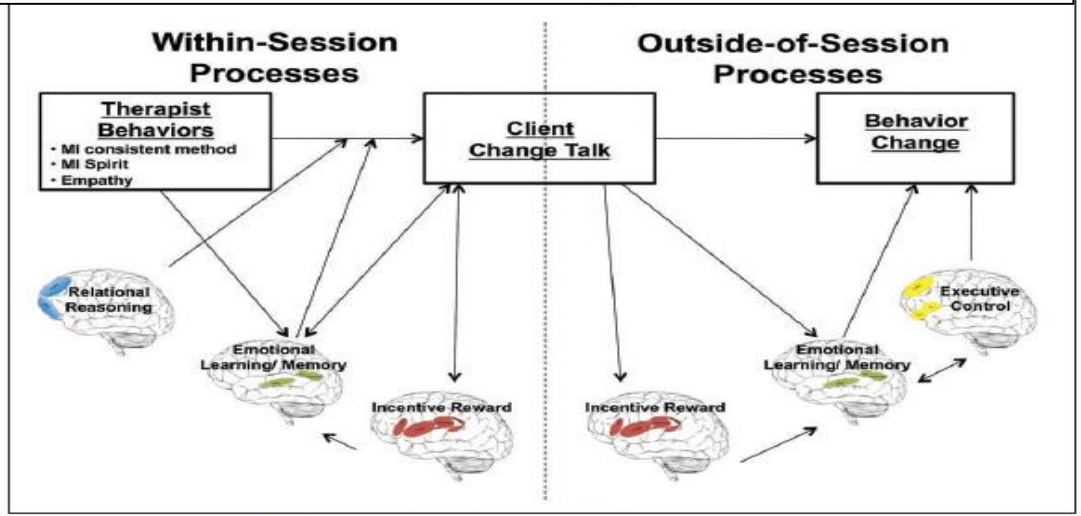
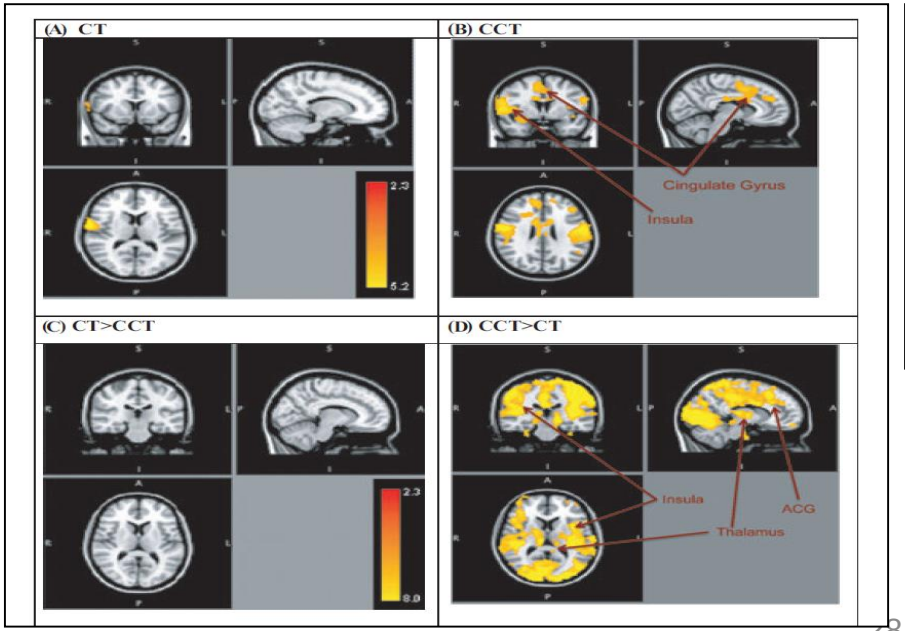


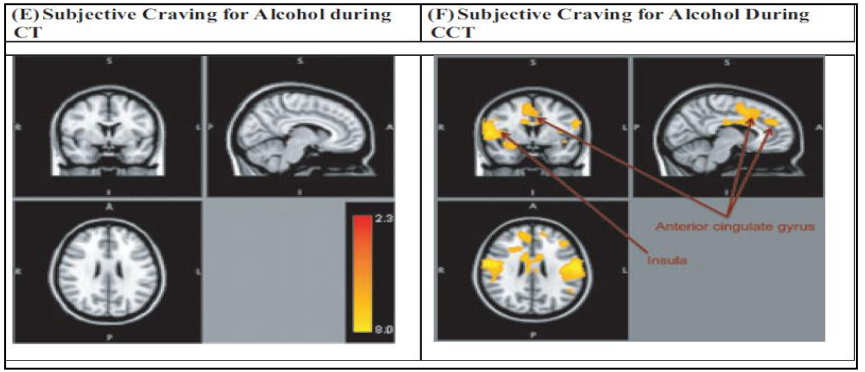
FIGURE 2. Neural circuitry associated with the proposed model; MI = motivational interviewing

How Psychosocial Alcohol Interventions Work: A Preliminary Look at What fMRI Can Tell Us

Sarah W. Feldstein Ewing, Francesca M. Filbey, Amithrupa Sabbineni, Lindsay D. Chandler, and Kent E. Hutchison

ACER, 2011





"Change talk" vermindert activatie tijdens cue-reactivity regio's tijdens kleine dosis voorkeursdrank en leidt tot minder craving

Farmacotherapie voor alcoholafhankelijkheid

Farmacotherapie bij Alcoholafhankelijkheid

Repeated reward

Antagonist

- **Disulfiram**
- **Naltrexon p.o./i.m.**
- **Nalmefeen**

Attentional bias → Cue-reactivity

Drug-related stimulus

Stress

Anti-stress drug

doxazosine

Detection threshold

Anti-craving drug

- **Acamprosaat**
- Topiramate?
- Varenicline??

Craving

Inhibition

Cognitive enhancer

- Modafinil?

Conflict registration

Agonist

- Baclofen?
- Gabapentin?
- GHB??

Relapse

Farmacotherapie voor alcoholafhankelijkheid
Nieuw: Nalmefeen

Farmacotherapie bij Alcoholafhankelijkheid

Repeated reward

Antagonist

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Conflict registration

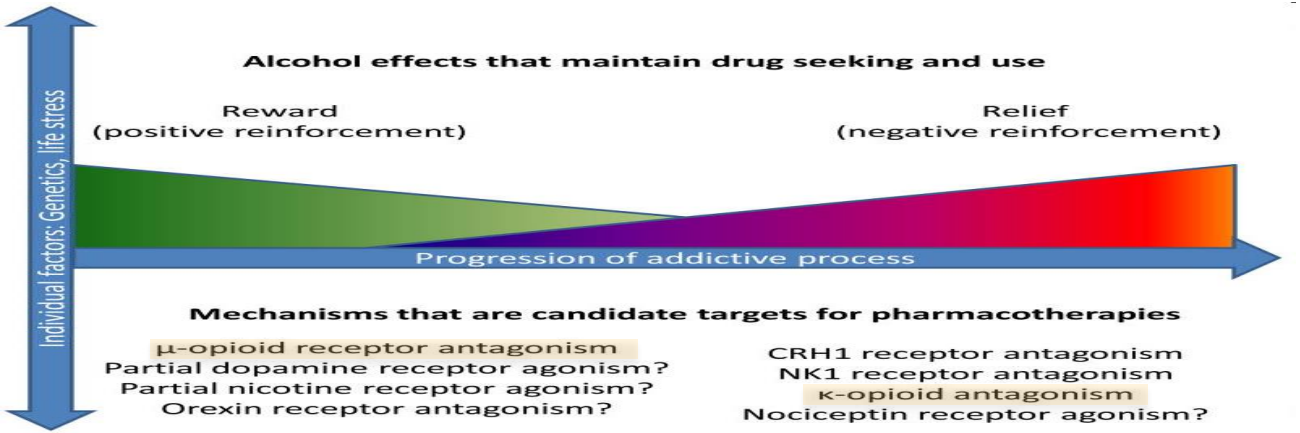
- Baclofen?
- Gabapentin?
- GHB??

Agonist

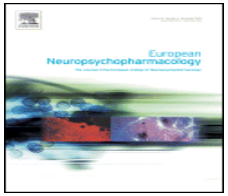
Relapse

Nalmefeen

- Niet elke dag, maar zo nodig → eigen verantwoordelijkheid/empowerment
- Gericht op minder/gecontroleerd drinken ipv abstinentie
- Naast mu en delta antagonisme, ook partieel kappa agonisme



Gecontroleerd drinken met nalmefeen zo-nodig



PRIORITY COMMUNICATION

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

Karl Mann, Anna Bladström, 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), ≥18 years of age, with a diagnosis of alcohol dependence, ≥6 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 ($n = 289$) and patients taking nalmefene ($n = 290$) were included in the efficacy analyses. At Month 6, there was a significant effect of nalmefene compared with placebo in reducing the number of heavy drinking days (−2.3 days [95% confidence interval: −3.8 to −.8]; $p = .0021$) and total alcohol consumption (−11.0 g/day [95% confidence interval: −16.8 to −5.1]; $p = .0003$). Improvements in Clinical Global Impression and liver enzymes were larger in the nalmefene group compared with placebo at 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 terms of the treatment goal and dosing regimen, and provides a method to address the unmet medical need in patients with alcohol dependence that need to reduce their alcohol consumption.

A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence

Antoni Gual[a,*], Yuan He[b], Lars Torup[b], Wim van den Brink[c,1], Karl Mann[d,1], for the ESENSE 2 Study Group

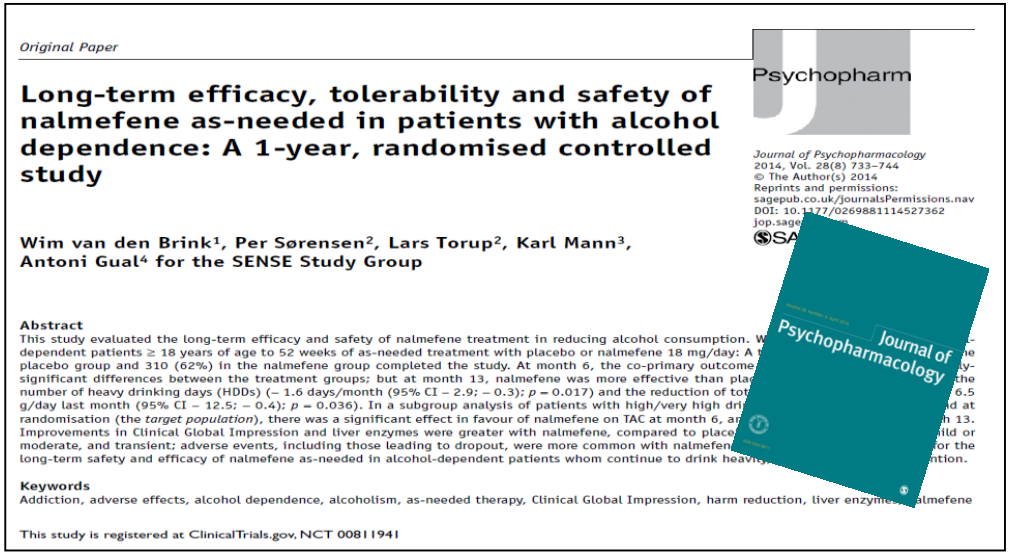
[a]*Neurosciences Institute, Hospital Clinic, Barcelona, Spain*
[b]*H. Lundbeck A/S, Copenhagen, Denmark*
[c]*Academic Medical Center, Department of Psychiatry, University of Amsterdam, Amsterdam, The Netherlands*
[d]*Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany*

Received 16 October 2012; received in revised form 17 January 2013; accepted 28 February 2013

KEYWORDS
Alcohol dependence;
Harm-reduction;
Nalmefene;
Opioid antagonist;
As-needed;
Treatment

Abstract
This study evaluated the efficacy of as-needed use of the opioid system modulator nalmefene in reducing alcohol consumption in patients with alcohol dependence. Seven hundred and eighteen patients (placebo=360; nalmefene=358), ≥18 years of age, with a diagnosis of alcohol dependence, ≥6 heavy drinking days and an average alcohol consumption ≥WHO medium drinking risk level in the 4 weeks preceding screening, were randomised (1:1) to 24 weeks of as-needed placebo or nalmefene 18 mg/day.
The co-primary efficacy analyses showed a significantly superior effect of nalmefene compared to placebo in the change from baseline to month 6 in heavy drinking days (group difference: −1.7 days/month [95% CI −3.1; −0.4]; $p=0.012$) and a better but not significant effect in reducing total alcohol consumption (group difference: −5.0 g/day last month [95% CI −10.6; 0.7]; $p=0.088$). A subgroup analysis showed that patients who did not reduce their drinking prior to randomisation benefitted more from nalmefene. Improvements in Clinical Global Impression and reductions in liver enzymes were greater in the nalmefene group than in the placebo group. Adverse events were more common with nalmefene; the incidence of adverse events leading to dropout was similar in both groups.
This study provides evidence for the efficacy of nalmefene, which constitutes a new pharmacological treatment paradigm in terms of treatment goal (reduced drinking) and dosing regimen (as-needed), in alcohol dependent patients unable to reduce alcohol consumption on their own.

Gecontroleerd drinken met nalmefeen zo-nodig



Original Paper

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

Wim van den Brink[1], Per Sørensen[2], Lars Torup[2], Karl Mann[3], Antoni Gual[4] for the SENSE Study Group

Psychopharm

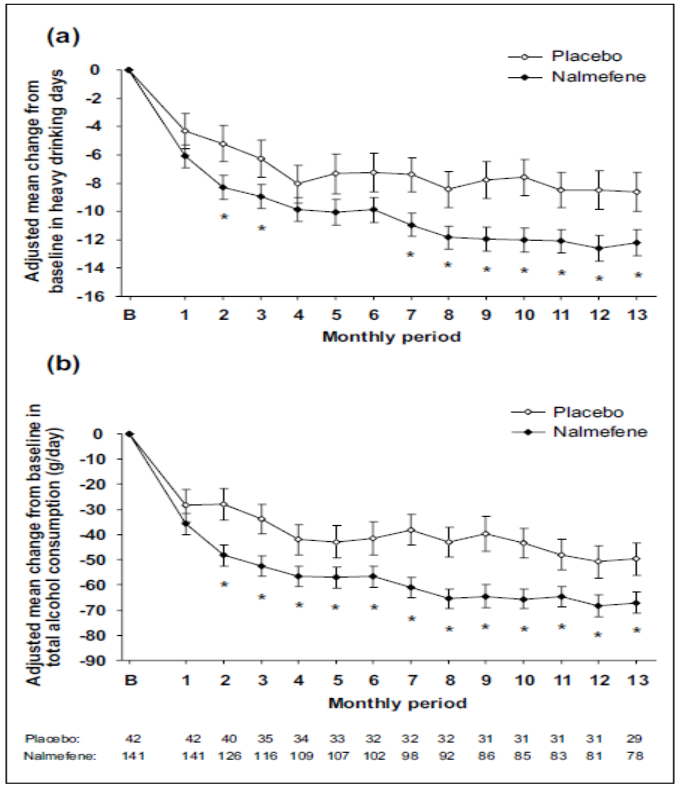
Journal of Psychopharmacology
2014, Vol. 28(8) 733–744

DOI: 10.1177/0269881114527362
jop.sage

Abstract
This study evaluated the long-term efficacy and safety of nalmefene treatment in reducing alcohol consumption. W
dependent patients ≥ 18 years of age to 52 weeks of as-needed treatment with placebo or nalmefene 18 mg/day: A t
placebo group and 310 (62%) in the nalmefene group completed the study. At month 6, the co-primary outcome
significant differences between the treatment groups; but at month 13, nalmefene was more effective than pla
number of heavy drinking days (HDDs) (– 1.6 days/month (95% CI – 2.9; – 0.3); $p = 0.017$) and the reduction of tot
g/day last month (95% CI – 12.5; – 0.4); $p = 0.036$). In a subgroup analysis of patients with high/very high dri
randomisation (the *target population*), there was a significant effect in favour of nalmefene on TAC at month 6, a
Improvements in Clinical Global Impression and liver enzymes were greater with nalmefene, compared to place
moderate, and transient; adverse events, including those leading to dropout, were more common with nalmefen
long-term safety and efficacy of nalmefene as-needed in alcohol-dependent patients whom continue to drink heavi

Keywords
Addiction, adverse effects, alcohol dependence, alcoholism, as-needed therapy, Clinical Global Impression, harm reduction, liver enzym
almefene

This study is registered at ClinicalTrials.gov, NCT 00811941



Nalmefeen zo-nodig wordt goed verdragen, heeft goede behandelretentie (55%) en leidt tot minder drinken ook nog na 1 jaar.

Review en Meta-analyse

European Neuropsychopharmacology (▪▪▪▪) ▪, ▪▪▪–▪▪▪

ELSEVIER

www.elsevier.com/locate/euroneuro

Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis on its clinical efficacy

Karl Mann[a,*], Lars Torup[b], Per Sørensen[c], Antoni Gual[d], Robert Swift[e], Brendan Walker[f], Wim van den Brink[g]

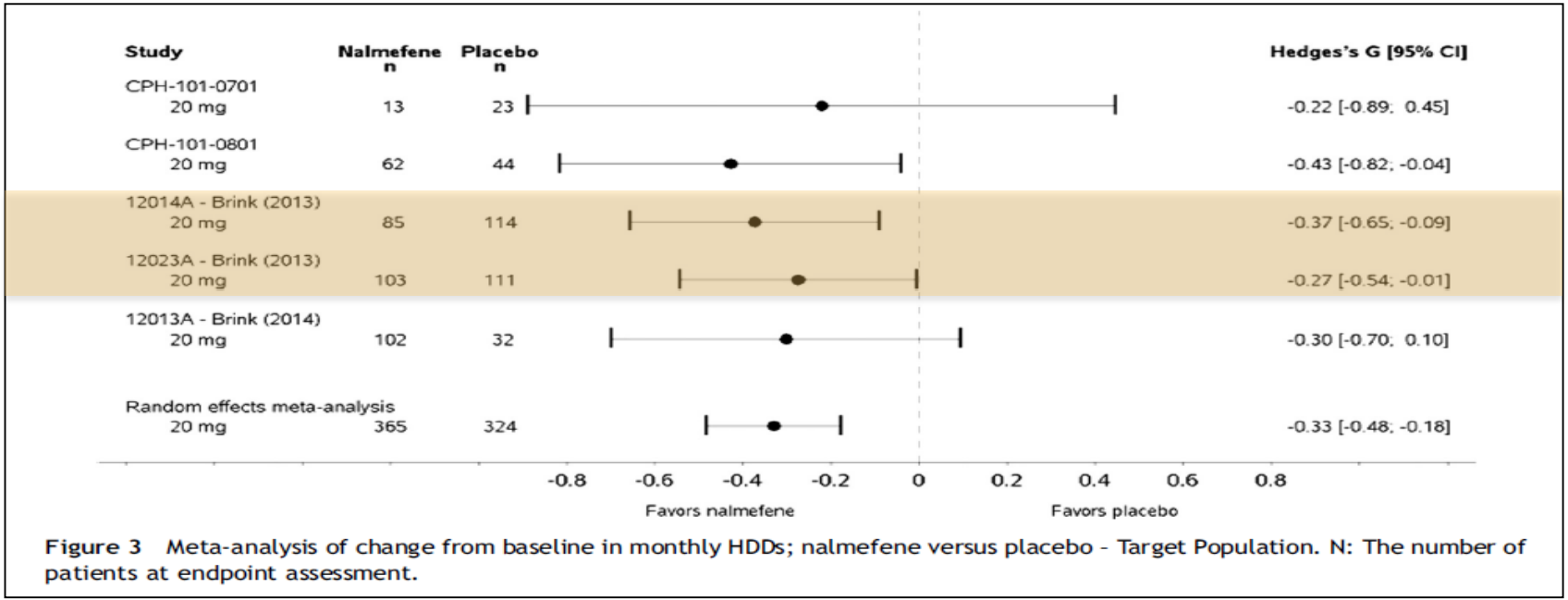


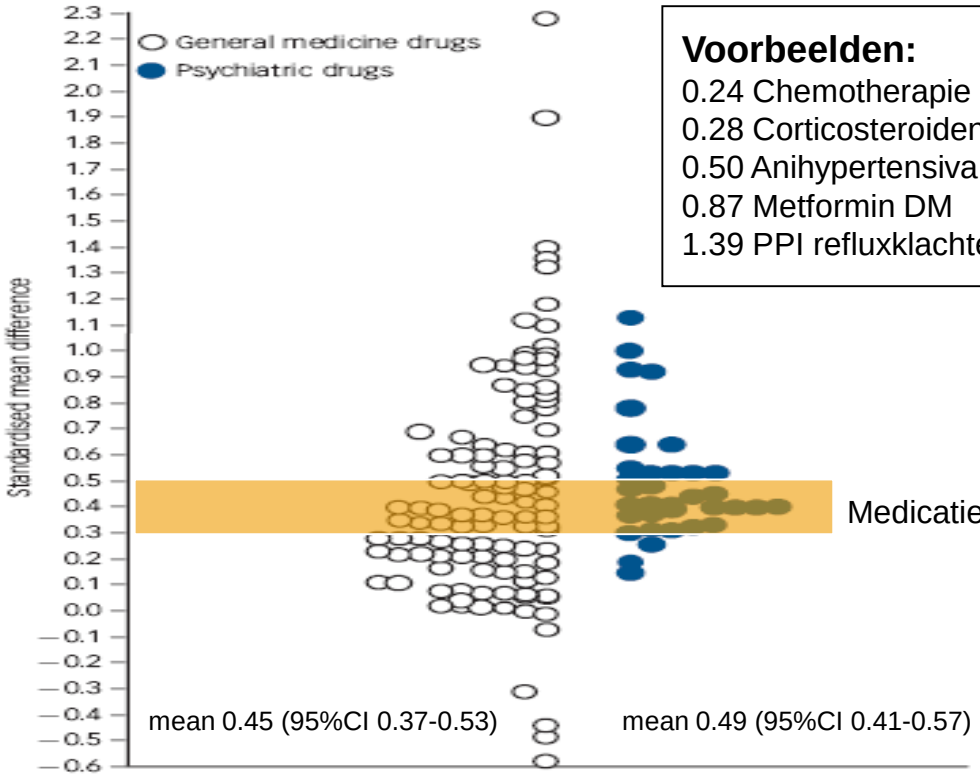
Figure 3 Meta-analysis of change from baseline in monthly HDDs; nalmefene versus placebo - Target Population. N: The number of patients at endpoint assessment.

Vergelijkende effectgrootte van alcoholmedicijnen

	Effect Size (Cohen's d)	
Nalmefene	**HDDs**	**TAC**
ESENSE 1	0.37	0.46
ESENSE 2	0.27	0.25
Alcohol treatment[1,2]	0.12 to 0.33	
Antidepressants[3]	0.24 to 0.35	
Antipsychotics[3]	0.30 to 0.53	

1. Kranzler HR, Van Kirk J. Alcohol Clin Exp Res 2001; 25: 1335-1341.
2. NICE. Alcohol dependence and harmful alcohol use: appendix 17d – pharmacological interventions forest plot. 2011.
3. Leucht. BJP. 2012; 200: 97-106.

Relatieve effectiviteit medicatie tegen terugval



Voorbeelden:

0.24 Chemotherapie borstkanker
0.28 Corticosteroiden COPD
0.50 Anihypertensiva hypertensie
0.87 Metformin DM
1.39 PPI refluxklachten

Voorbeelden:

0.35 Antidepressiva depressi
0.40 Lithium bipolaire stoornis
0.50 Antipsychotica psychose
0.78 Methylfenidaa ADHD
0.40 Terugvalmedicatie alcohol

Medicatie tegen terugval In (overmatig) alcoholgebruik

Leucht et al., British Journal of Psychiatry (2012) 200, 97–106.

Farmacotherapie voor alcoholafhankelijkheid Nieuw: Anti-Stress Medicatie

Model voor Farmacotherpie Verslaving

Repeated reward

Antagonist

Attentional bias → Cue-reactivity

Drug-related stimulus

Stress

Anti-stress medicatie

Detection threshold

Anti-craving drug

Craving

Inhibition

Cognitive enhancer

Agonist

Relapse

Conflict registration

Hyperresponsiveness of the Neural Fear Network During Fear Conditioning and Extinction Learning in Male Cocaine Users

Anne Marije Kaag, M.Sc., Nina Levar, M.Sc., Karlijn Woutersen, M.Sc., Judith Homberg, Ph.D., Wim van den Brink, Ph.D., M.D., Liesbeth Reneman, Ph.D., M.D., Guido van Wingen, Ph.D.

AJP in Advance (doi: 10.1176/appi.ajp.2016.15040433)

These findings emphasize that in addition to reducing drug-conditioned responses (reward craving), treatment should also try to reduce the (neural) sensitivity to stressors (relief craving). This could be achieved by means of cognitive-behavioral treatment (e.g., mindfulness-based relapse prevention [38]) or pharmaceutical treatments that target the noradrenergic stress system (e.g., propranolol [39]).

Addiction Biology

SSA SOCIETY FOR THE STUDY OF ADDICTION

CLINICAL STUDY

doi:10.1111/adb.12275

Role of the α_1 blocker doxazosin in alcoholism: a proof-of-concept randomized controlled trial

George A. Kenna[1], Carolina L. Haass-Koffler[2,3], William H. Zywiak[1,4], Steven M. Edwards[5], Michael B. Brickley[2], Robert M. Swift[1,6] & Lorenzo Leggio[2,3]

2016

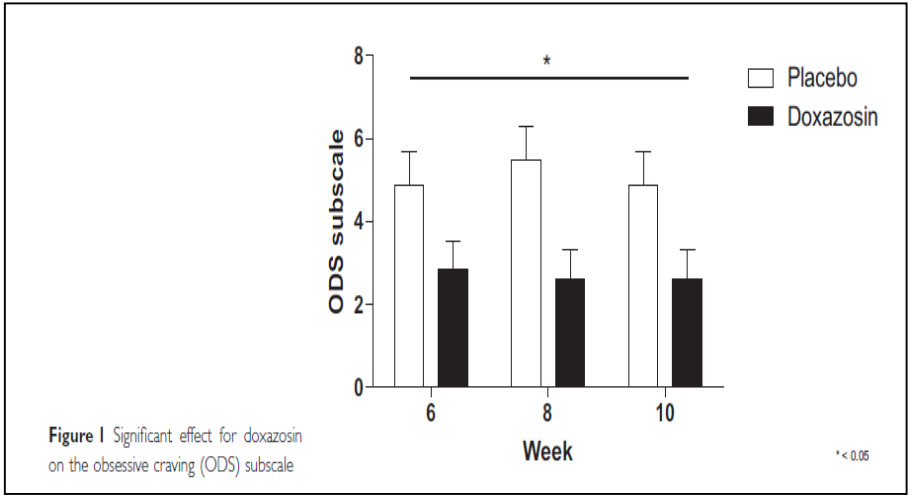


Figure 1 Significant effect for doxazosin on the obsessive craving (ODS) subscale

* < 0.05

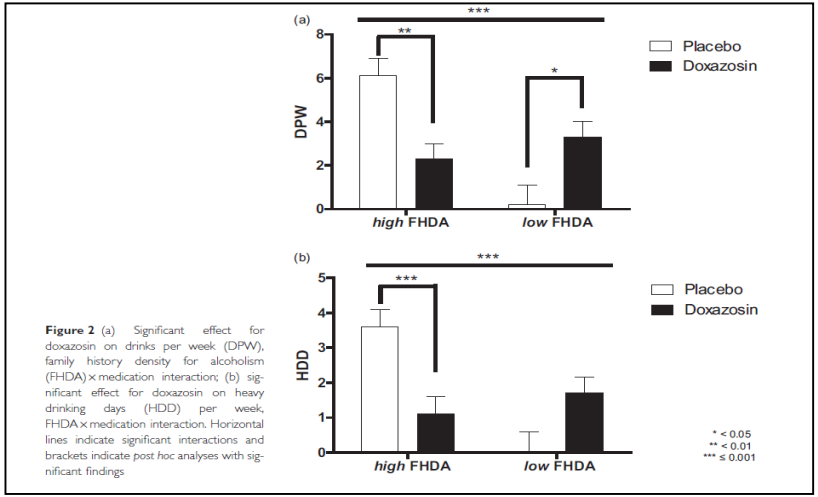


Figure 2 (a) Significant effect for doxazosin on drinks per week (DPW), family history density for alcoholism (FHDA) × medication interaction; (b) significant effect for doxazosin on heavy drinking days (HDD) per week, FHDA × medication interaction. Horizontal lines indicate significant interactions and brackets indicate *post hoc* analyses with significant findings

De α1 adrenergic antagonist doxazosin (vgl ook prazosine*) leidt tot minder craving en minder drinkdagen en minder HDDs in patiënten met $FH_{alcohol}$+.

* Prazosin: Simpson et al., 2009, 2015, but Petrakis et al., 2016 (PTSD + AD in VA patients)

A Phase 2, Double-Blind, Placebo-Controlled Randomized Trial Assessing the Efficacy of ABT-436, a Novel V1b Receptor Antagonist, for Alcohol Dependence

Vasopressin

Neuropsychopharmacology (2016), 1–12

Megan L Ryan*,[1], Daniel E Falk[1], Joanne B Fertig[1], Beatrice Rendenbach-Mueller[2], David A Katz[2], Katherine A Tracy[2], Eric C Strain[3], Kelly E Dunn[3], Kyle Kampman[4], Elizabeth Mahoney[4], Domenic A Ciraulo[5], Laurie Sickles-Colaneri[5], Nassima Ait-Daoud[6], Bankole A Johnson[6], Janet Ransom[7], Charles Scott[7], George F Koob[1] and Raye Z Litten[1] for the National Institute on Alcohol Abuse and Alcoholism Clinical Investigations Group (NCIG) Study Group

Table 2 Treatment Outcomes: Differences Between Placebo and ABT-436 during Study Maintenance Phase (Weeks 2–12)

Drinking outcomes[b]	Placebo ($n=70$)			ABT-436 ($n=73$)[a]			LSMEAN difference	SE	|d|	*P*-value
	LSMEAN[b]	SE	95% CI	LSMEAN	SE	95% CI				
Percent heavy drinking days (primary outcome)										
No imputation	37.6	4.21	29.2–45.9	31.3	3.99	23.4–39.2	6.3	4.59	0.20	0.172
Missing drinking days imputed as heavy drinking days	43.8	4.49	34.9–52.6	34.5	4.31	26.0–43.0	9.3	4.92	0.26	0.061
Multiple imputation	37.8	4.08	29.8–45.8	31.8	3.88	24.1–39.4	6.0	4.44	0.19	0.175
Percent days abstinent	41.6	4.24	33.2–49.9	51.2	4.03	43.2–59.2	-9.7	4.58	0.31	0.037
Drinks per day	3.6	0.46	2.7–4.5	3.1	0.43	2.3–4.0	0.5	0.50	0.17	0.246
Drinks per drinking day	4.9	0.49	3.9–5.8	4.8	0.46	3.9–5.7	0.1	0.54	0.08	0.530
Percent very heavy drinking days (8+/10+)	11.2	2.90	5.5–17.0	12.1	2.73	6.7–17.5	-0.9	3.16	0.02	0.860
	%	*n*	denom	%	*n*	denom			OR (95% CI)[c]	*p*-value
Percent subjects abstinent	5.7	4	70	5.5	4	73			1.0 (0.2–4.0)	0.951
Percent subjects with no heavy drinking days	10.0	7	70	12.3	9	73			1.3 (0.4–3.6)	0.659
Non-drinking outcomes[d]	**LSMEAN**	**SE**	**95% CI**	**LSMEAN**	**SE**	**95% CI**	**LSMEAN difference**		**|d|**	***p*-value**
Cigarettes per week[e]	98.3	4.26	89.7–106.9	89.1	4.55	79.9–98.3	9.2	6.25	0.39	0.046
Penn Alcohol Craving Scale (PACS) score[f]	10.3	0.65	9.0–11.6	9.9	0.62	8.7–11.1	0.4	0.72	0.08	0.571
Alcohol-related consequences (ImBIBe) score[g]	11.6	1.00	9.7–13.6	12.9	0.96	10.9–14.8	-1.2	1.37	0.05	0.768

Effect ABT-436 seems dependent on anxiety level

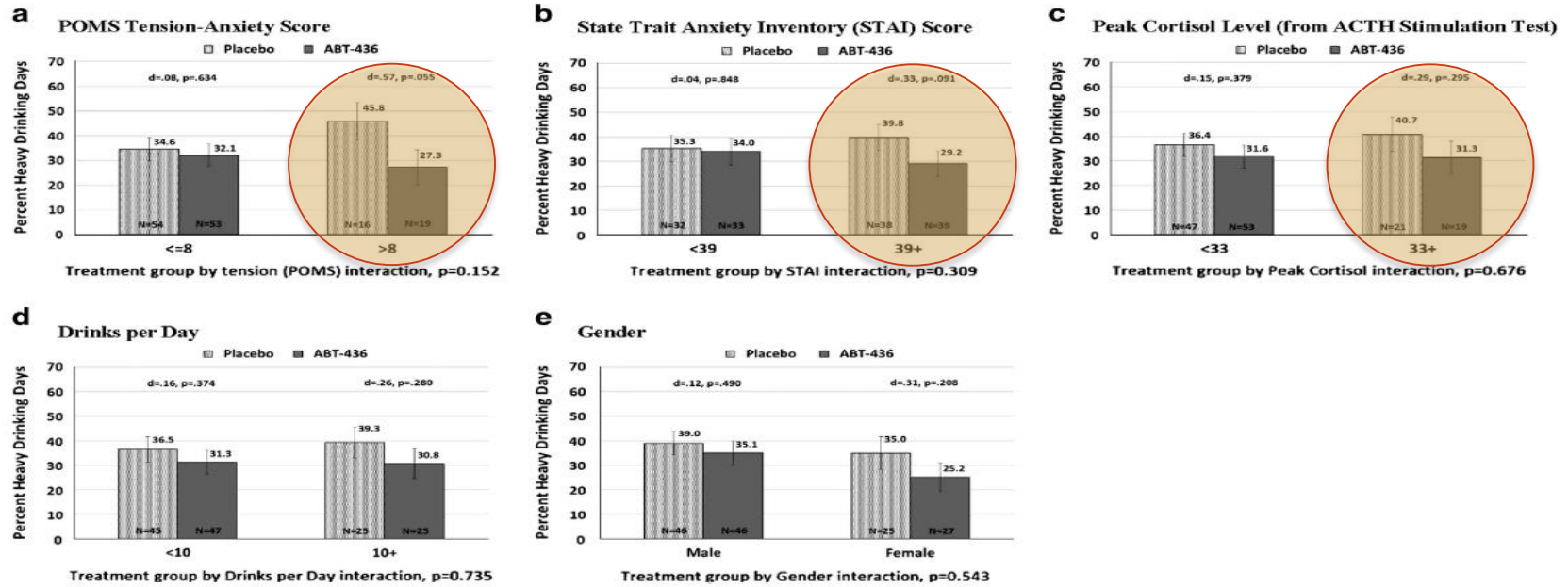


Figure 2 (a) POMS tension-anxiety score. Treatment group by tension (POMS) interaction, $p = 0.152$. (b) State trait anxiety inventory (STAI) score. Treatment group by STAI interaction, $p = 0.309$. (c) Peak cortisol level (from ACTH stimulation test). Treatment group by peak cortisol interaction, $p = 0.676$. (d) Drinks per day. Treatment group by drinks per day interaction, $p = 0.735$. (e) Gender. Treatment group by gender interaction, $p = 0.543$.

Farmacotherapie voor alcoholafhankelijkheid Nieuw: Baclofen

Farmacotherapie bij Alcoholafhankelijkheid

Repeated reward

Antagonist

- **Disulfiram**
- **Naltrexon p.o./i.m.**
- **Nalmefeen**

Attentional bias → Cue-reactivity

Drug-related stimulus

Stress

Anti-stress drug

doxazosine

Detection threshold

Anti-craving drug

- **Acamprosaat**
- Topiramate?
- Varenicline??

Craving

Inhibition

Cognitive enhancer

- Modafinil?

Conflict registration

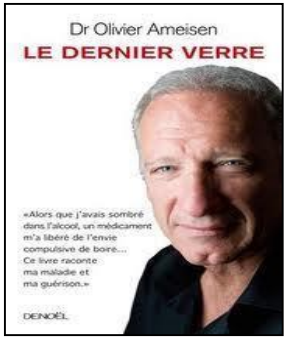
Agonist

- **Baclofen?**
- Gabapentin?
- GHB??

Relapse

HD Baclofen for Tx of Alcohol Dependence

- 5 RCTs low dose (30-60 mg) baclofen → 2x pos and 3x neg*
- Secondary dose-response analysis: 60 mg better than 30 mg#
- Large case studies France with HD baclofen (up to 300 mg)
- Special exception in France for prescription of HD baclofen
- 2015 First RCT with HD baclofen in Germany



* Addolerato et al., 2002 (+), Addolerato et al., 2007 (+), Garbutt et al. 2010 (-); Ponizovsky et al., 2015 (-); Krupitsky et al., 2015 (-)
\# Addolerato et al., 2011

Baclofen HD: Duitse Studie

High-dose baclofen for the treatment of alcohol dependence (BACLAD study): A randomized, placebo-controlled trial

Christian A. Müller[a,*], Olga Geisel[a], Patricia Pelz[a], Verena Higl[a], Josephine Krüger[a], Anna Stickel[a], Anne Beck[a], Klaus-Dieter Wernecke[b], Rainer Hellweg[a], Andreas Heinz[a]

[a]*Department of Psychiatry, Campus Charité Mitte, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany*
[b]*Charité - Universitätsmedizin Berlin and Sostana GmbH Berlin, Germany*

Received 24 January 2015; received in revised form 13 March 2015; accepted 1 April 2015

Abstract
Previous randomized, placebo-controlled trials (RCTs) assessing the efficacy of the selective γ-aminobutyric acid (GABA)-B receptor agonist baclofen in the treatment of alcohol dependence have reported divergent results, possibly related to the low to medium dosages of baclofen used in these studies (30-80 mg/d). Based on preclinical observations of a dose-dependent effect and positive case reports in alcohol-dependent patients, the present RCT aimed to assess the efficacy and safety of individually titrated high-dose baclofen for the treatment of alcohol dependence. Out of 93 alcohol-dependent patients initially screened, 56 were randomly assigned to a double-blind treatment with individually titrated baclofen or placebo using dosages of 30-270 mg/d. The multiple primary outcome measures were (1) total abstinence and (2) cumulative abstinence duration during a 12-week high-dose phase. More patients of the baclofen group maintained total abstinence during the high-dose phase than those receiving placebo (15/22, 68.2% vs. 5/21, 23.8%, $p=0.014$). Cumulative abstinence duration was significantly higher in patients given baclofen compared to patients of the placebo group (mean 67.8 (SD 30) vs. 51.8 (SD 29.6) days, $p=0.047$). No drug-related serious adverse events were observed during the trial. Individually titrated high-dose baclofen effectively supported alcohol-dependent patients in maintaining alcohol abstinence and showed a high tolerability, even in the event of relapse. These results provide further evidence for the potential of baclofen, thereby possibly extending the current pharmacological treatment options in alcohol dependence.

RCT
Patienten
* N=28 baclofen (30-270; x=180 mg)
* N=28 placebo (x=260 mg)
Kenmerken baseline:
* leeftijd x=46
* 200 gr alcohol/dag
* abstinentie: 12 dagen
Individuele titratie op bijwerkingen
Baclofen HD/placebo 12 weken

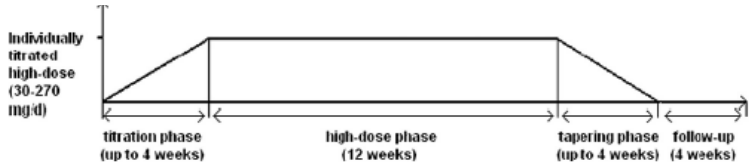
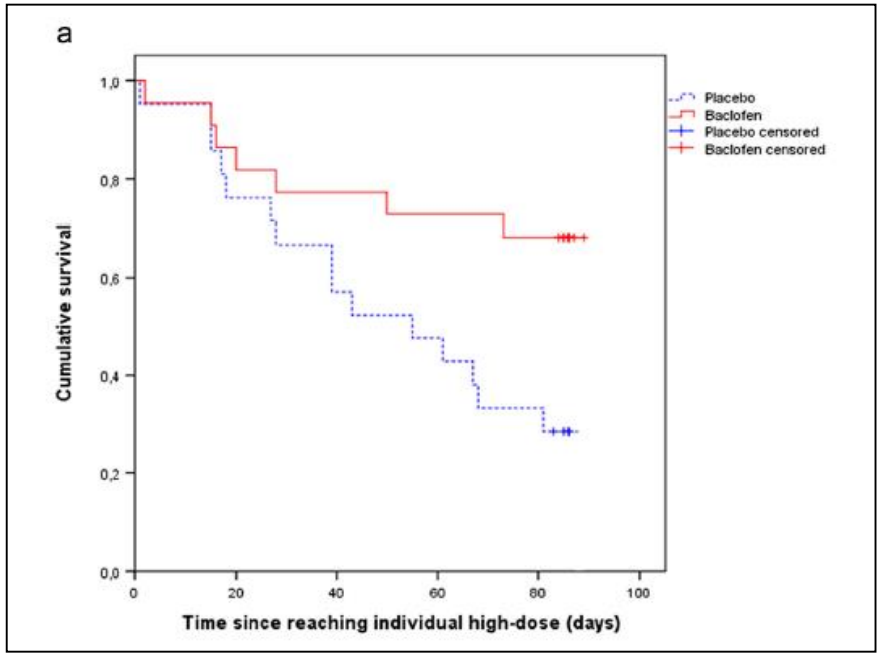
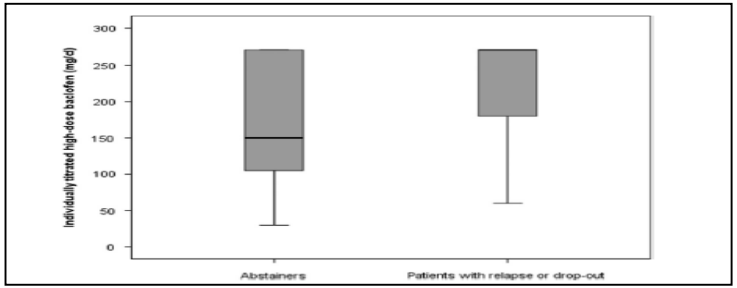


Figure 1 BACLAD trial profile.

High-dose baclofen for the treatment of alcohol dependence (BACLAD study): A randomized, placebo-controlled trial





Resultaten:

* Sterk pos effect op abstinentie **(68% vs. 24% → NNT=2.3)**
* Geen effect of craving
* Geen effect op angst, depressie
* Geen duidelijk effect van dosis

Hoe zit het met de Nederlandse RCT ……

…. en wat is er door de Fransen gevonden?

Nederlandse Baclofen RCT

Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence: A multicentre, randomised, double-blind controlled trial

Esther Beraha, Elske Salemink, Anneke Goudriaan,, Abraham Bakker, David de Jong, Natasha Smits, Jan Willem Zwart, Dick van Geest, Pieter Bodewits, Tom Schiphof, Harma Defourny, Mirjam van Tricht, Wim van den Brink*, Reinout Wiers*

submitted

RCT: dubbelblind

N=481 patiënten gescreend: N=157 patiënten gerandomiseerd

* N=58 HD baclofen max 150 mg; gem. 93.6 mg; N=9 (15.5%) met 150 mg

* N=31 LD baclofen max 30 mg

* N=62 Placebo

Alle patiënten krijgen ook TAU, inclusief detox + CBT

Alcoholconsumptie op baseline: gemiddeld 140 gr/dag

Results Dutch LD/HD Baclofen RCT

	Drop-out (%)	Time to relapse (days)	Relapse (%)	Abstinence (%)
High Dose Phase (70 days)				
HD baclofen	25	62.5	27.5	62,5
LD baclofen	10	65.3	20.0	65.0
Placebo	2	59.9	25.0	65.9
Significance	P=0.0281	**P=0.813**	**P=0.819**	**P=0.947**
Complete Medication Period (112 days)				
HD baclofen	14	79.3	50.0	43.1
LD baclofen	26	76,4	48.4	41.9
Placebo	15	77.7	46.8	46.8
Significance	P=0.297	**P=0.982**	**P=0.939**	**P=0.879**

In HD group, survival was associated with baclofen dose (HR=0.99; p=0.022) and mean dose in relapsed group was lower (84.8 mg) than in abstinent group (102.4 mg) →

Preliminary findings French studies + Conclusion

ALPADIR Study

- Placebo-controlled RCT: N=320 (N=158 baclofen; N=162 placebo)
- 7 weeks titration (max 180 mg/day: mean 96 mg/day) + 17 weeks high dose
- Result: continuously abstinent: baclofen 11.9% vs. placebo 10.5% (ns)

BACLOVILLE

- Multicenter (N=60) primary care placebo-controlled RCT (N=320)
- Flexible titration (max 300 mg/day; mean 165 mg/day) + 10 months HD
- Result: responders (≤ low DRL): baclofen 56.8% vs. placebo 36.5% (p=0.004)

Conclusion

Inconsistent findings for both LD and HD baclofen, baclofen probably best in patients with high alcohol consumption and no psychotherapy

Farmacotherapie voor alcoholafhankelijkheid Nieuw: Gabapentin

Farmacotherapie bij Alcoholafhankelijkheid

Repeated reward

Antagonist

- **Disulfiram**
- **Naltrexon p.o./i.m.**
- **Nalmefeen**

Attentional bias → Cue-reactivity

Drug-related stimulus

Stress

Anti-stress drug

- Doxazosine
- **Gabapentin**

Detection threshold

Anti-craving drug

Craving

- **Acamprosaat**
- Topiramate?
- Varenicline??

Inhibition

Cognitive enhancer

- Modafinil?

Conflict registration

Agonist

- Baclofen?
- **Gabapentin?**
- GHB??

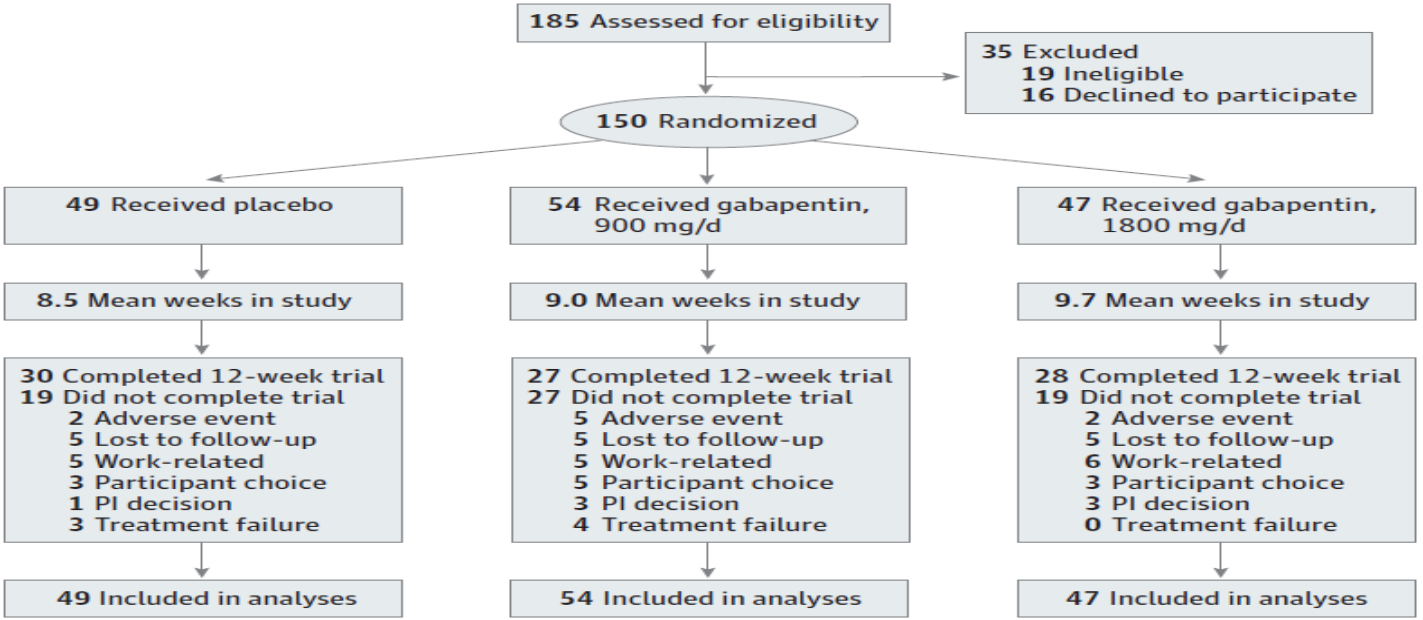
Relapse

Gabapentin Treatment for Alcohol Dependence
A Randomized Clinical Trial

Barbara J. Mason, PhD; Susan Quello, BA, BS; Vivian Goodell, MPH; Farhad Shadan, MD; Mark Kyle, MD; Adnan Begovic, MD

JAMA Psychiatry, 2014

Figure 1. Flow of Participants Through the Trial

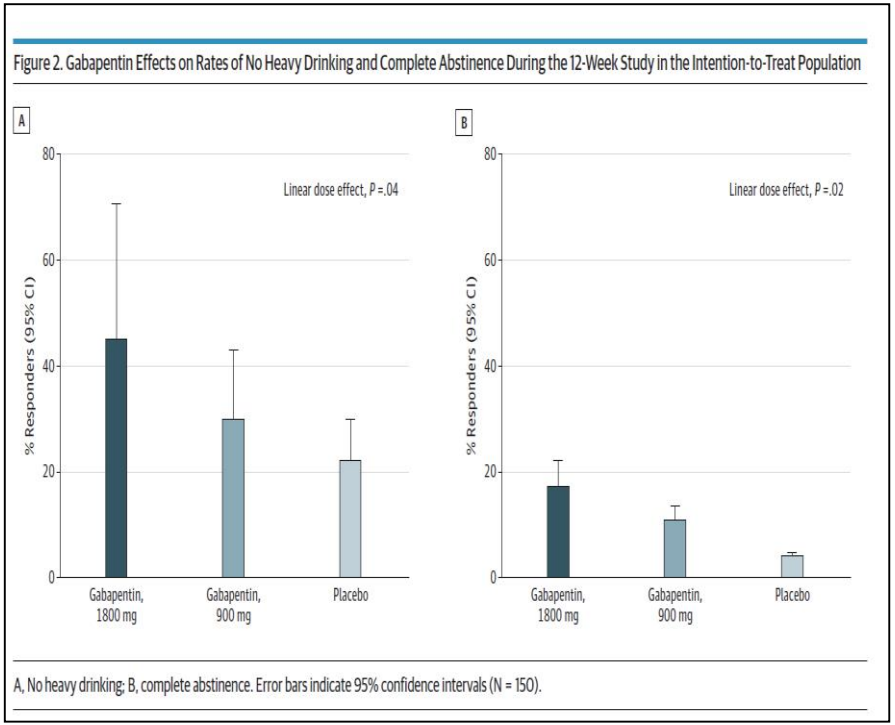


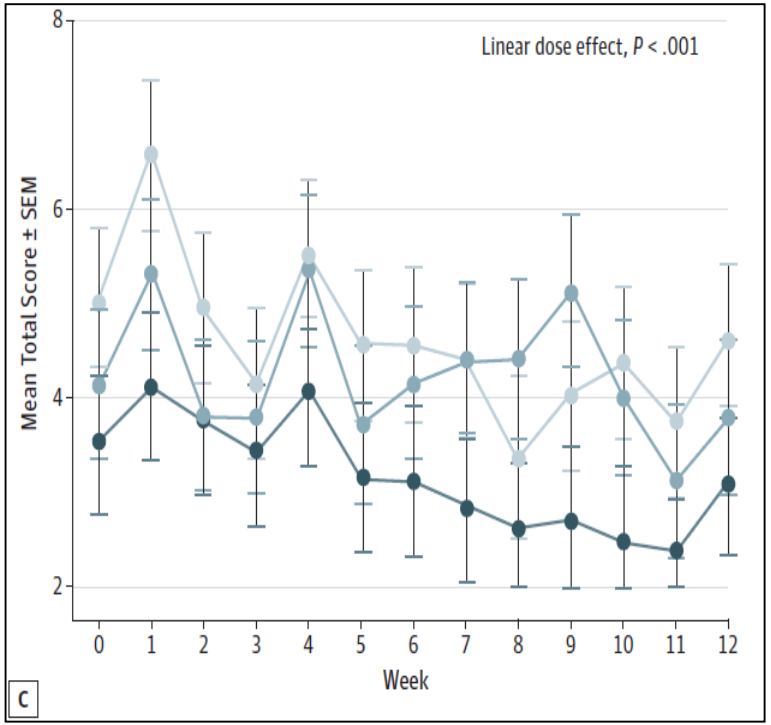
Effect Gabapentin op HDDs, Abstinentie en Slaap

Geen HDDs

Abstinentie

Slaapproblemen





Also: Karam-Hage et al., 2000; Furieri et al., 2007; Brower et al., 2008; Anton et al., 20011

Farmacotherapie voor alcoholafhankelijkheid Oud plus Nieuw

Effectieve geneesmiddelen tegen alcohol

Behandeldoel	1e Keus	2e Keus	3e Keus
Abstinentie ↕ Minder drinken	**Acamprosate** (NNT=11**)** **Naltrexon??** (NNT=20)	**Disulfiram** (NNT=25; NS)*	LD Baclofen?? Gabapentin (GHB??)
	Naltrexon# (NNT=11)	Topiramaat?	Modafinil?? Varenicline?? HD Baclofen?? Doxazepine??

* no supervision
# off-label

Farmacotherapie voor alcoholafhankelijkheid

Kan het beter?

Hoe kan het beter?

Mogelijke oplossingen

- Verbeter therapietrouw; psychotherapie, langwerkende preparaten
- Combineer farmacotherapie mey psychotherapie
- Combineeer verschillende medicijnen: polyfarmacie
- Nieuwe medicijnen: op basis van nieuwe modellen, “repurposing”
- Betere patient-treatment matching: personalized medicine

  * fenotype, endofenotype, genotype: farmacogenetica
- Neuromodulatie

Hoe kan het beter?

Mogelijke oplossingen

- Verbeter therapietrouw; psychotherapie, langwerkende preparaten
- Combineer farmacotherapie mey psychotherapie
- Combineeer verschillende medicijnen: **polyfarmacie**
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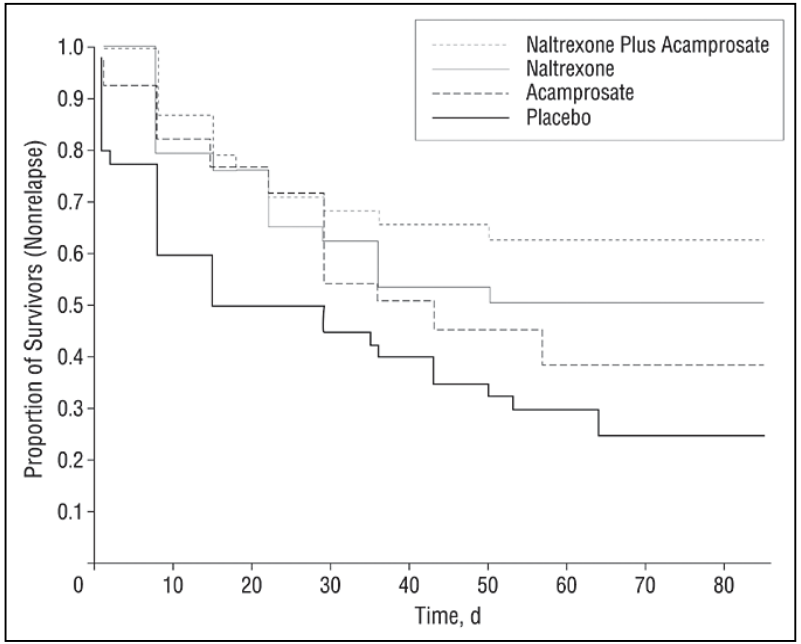
- Betere patient-treatment matching: **personalized medicine**

  * fenotype, endofenotype, genotype: farmacogenetica
- Neuromodulatie

Farmacotherapie voor alcoholafhankelijkheid

Polyfarmacie?

Kan het beter? Polyfarmacie?



Kiefer et al. 2003

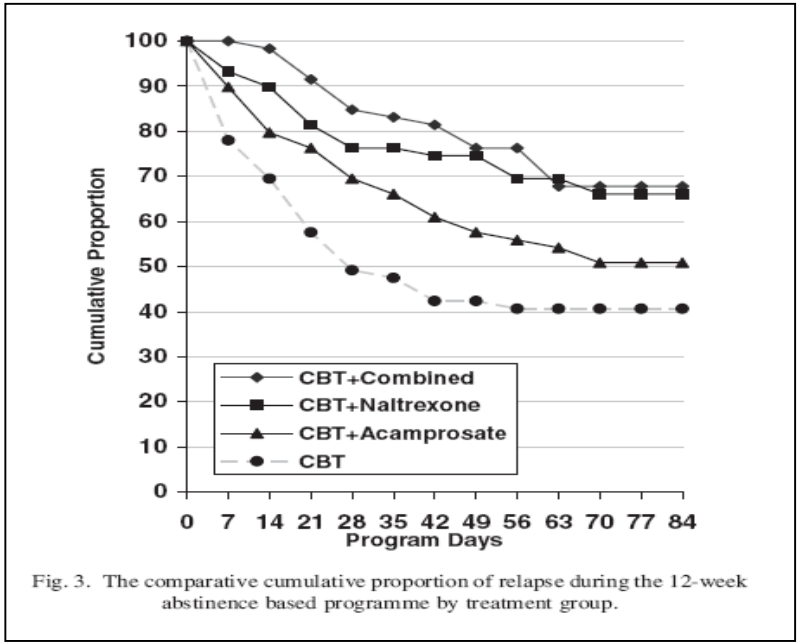


Fig. 3. The comparative cumulative proportion of relapse during the 12-week abstinence based programme by treatment group.

Feeney et al., 2006

Farmacotherapie voor alcoholafhankelijkheid

Personalized Medicine?

Psychopharmacology (2005) 178: 167–173
DOI 10.1007/s00213-004-1991-7

ORIGINAL INVESTIGATION

Roel Verheul · Philippe Lehert · Peter J. Geerlings ·
Maarten W. J. Koeter · Wim van den Brink

Predictors of acamprosate efficacy: results from a pooled analysis of seven European trials including 1485 alcohol-dependent patients

	Predictor (P)	Interaction P x Tx
Severity Physical Dependence	P=0.155	P=0.975
Severity Craving	**P<0.000**	P=0.626
Positive Family History of Alcoholism	P=0.301	P=0.294
Age of Onset Alcohol Problems	P=0.519	P=0.599
Anxiety at Baseline	**P<0.000**	P=0.705

Phenotypical characteristics (craving, anxiety) do predict course, but they do NOT predict treatment effect

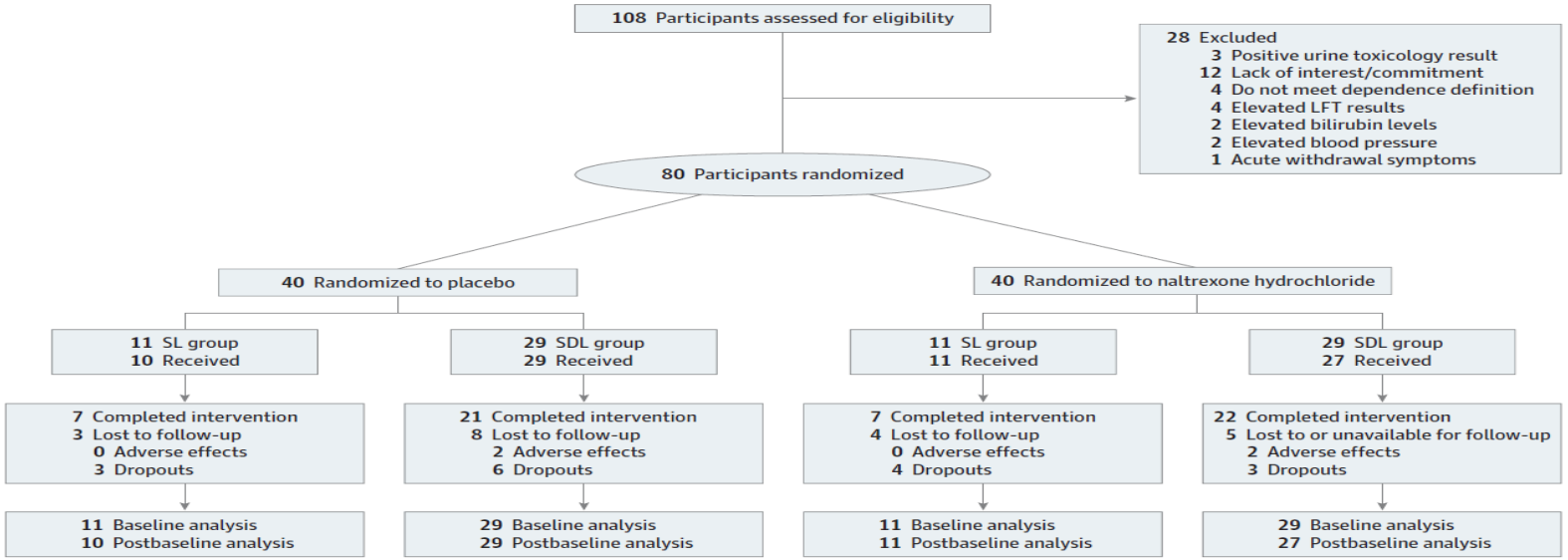
JAMA Psychiatry | Original Investigation

Association of the Sweet-Liking Phenotype and Craving for Alcohol With the Response to Naltrexone Treatment in Alcohol Dependence
A Randomized Clinical Trial

James C. Garbutt, MD; Alexey B. Kampov-Polevoy, MD, PhD; Linda S. Kalka-Juhl, MEd; Robert J. Gallop, PhD

JAMA Psychiatry, 2016

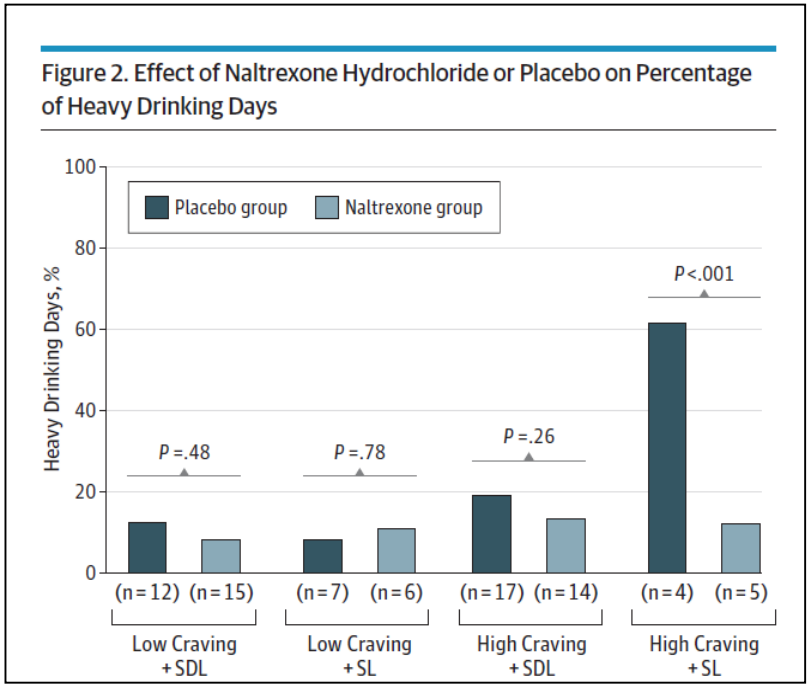
Figure 1. CONSORT Diagram



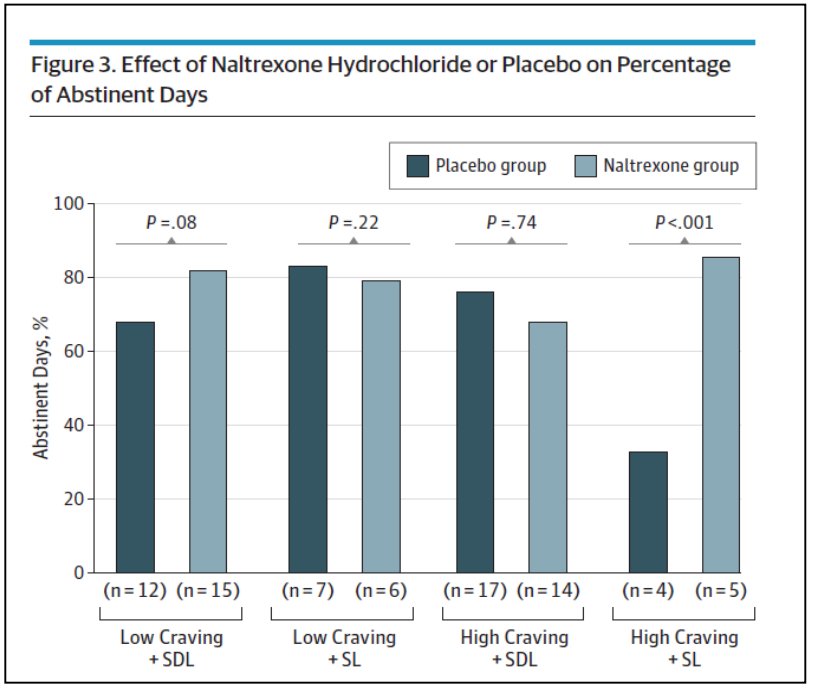
Active treatment consisted of naltrexone hydrochloride, 50 mg/d. LFT indicates liver function tests; SDL, sweet-disliking phenotype; and SL, sweet-liking phenotype.

Sweet (dis)liking en NTX-effect op HDDs en abstinentie

HDDs



Abstinentie



Also: Garbutt et al., 2009; Laaksonen et al., 2011

Effect of modafinil on impulsivity and relapse in alcohol dependent patients: A randomized, placebo-controlled trial

2012

Leen Joos[a,*], Anna E. Goudriaan[b,c], Lianne Schmaal[b], Erik Fransen[d], Wim van den Brink[b], Bernard G.C. Sabbe[a], Geert Dom[a,e]

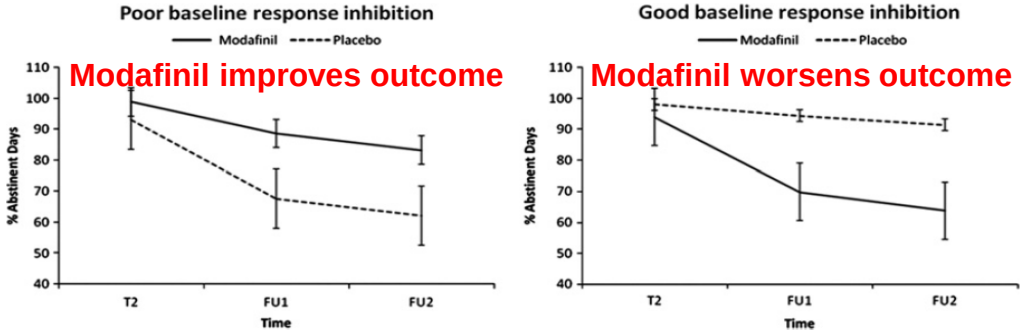


Figure 4 Time × treatment (modafinil vs. placebo) interaction based on MMRM for percentage abstinent days in subgroups of alcohol dependent patients with poor baseline response inhibition (n=30 (sample at T2); SSRT > 233.22) versus alcohol dependent patients with good baseline response inhibition (n=22 (sample at T2); SSRT < 233.22), adjusted for baseline percentage abstinent days and with error bars representing standard errors.

T2: testing after treatment; FU1: follow-up interview after 3 months counted from the end of treatment; FU2: follow-up interview after 6 months counted from the end of treatment; MMRM: Mixed-model Repeated Measures analysis; SSRT: Stop Signal Reaction Time.

Experimental and Clinical Psychopharmacology
2007, Vol. 15, No. 3, 272–281

DOI: 10.1037/1064-1297.15.3.272

Family History and Antisocial Traits Moderate Naltrexone's Effects on Heavy Drinking in Alcoholics

Damaris J. Rohsenow
Providence Veterans Affairs Medical Center and Brown University School of Medicine

Robert Miranda Jr.
Brown University School of Medicine

John E. McGeary and Peter M. Monti
Providence Veterans Affairs Medical Center and Brown University School of Medicine

NS

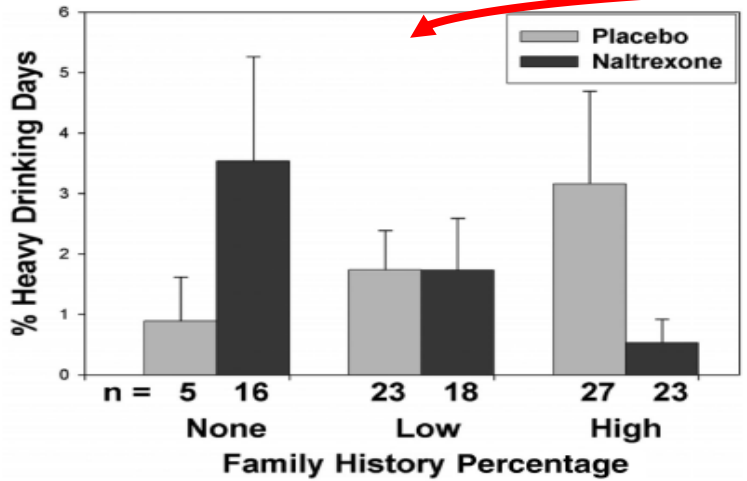


Figure 1. Percentage of heavy drinking days during 6-month follow-up by medication (naltrexone vs. placebo) and percentage of family members with a history of problem drinking (0%, <20%, or ≥20% relatives with problems). The interaction of family history percentage and medication was significant using family history as a continuous variable in the regression; this figure illustrates the nature of the interaction. Error bars represent standard errors.

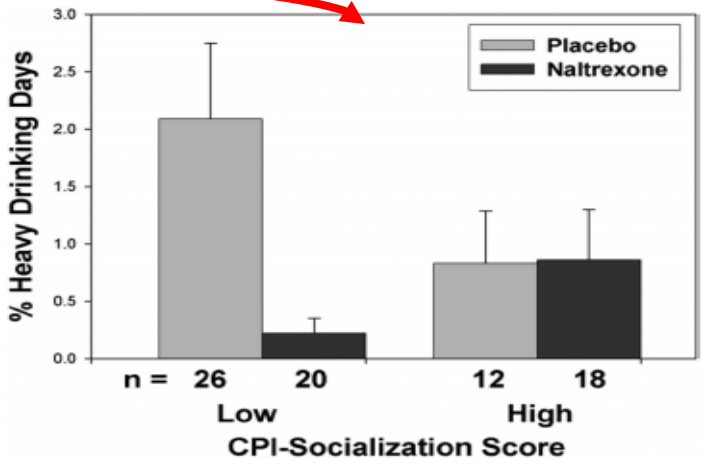
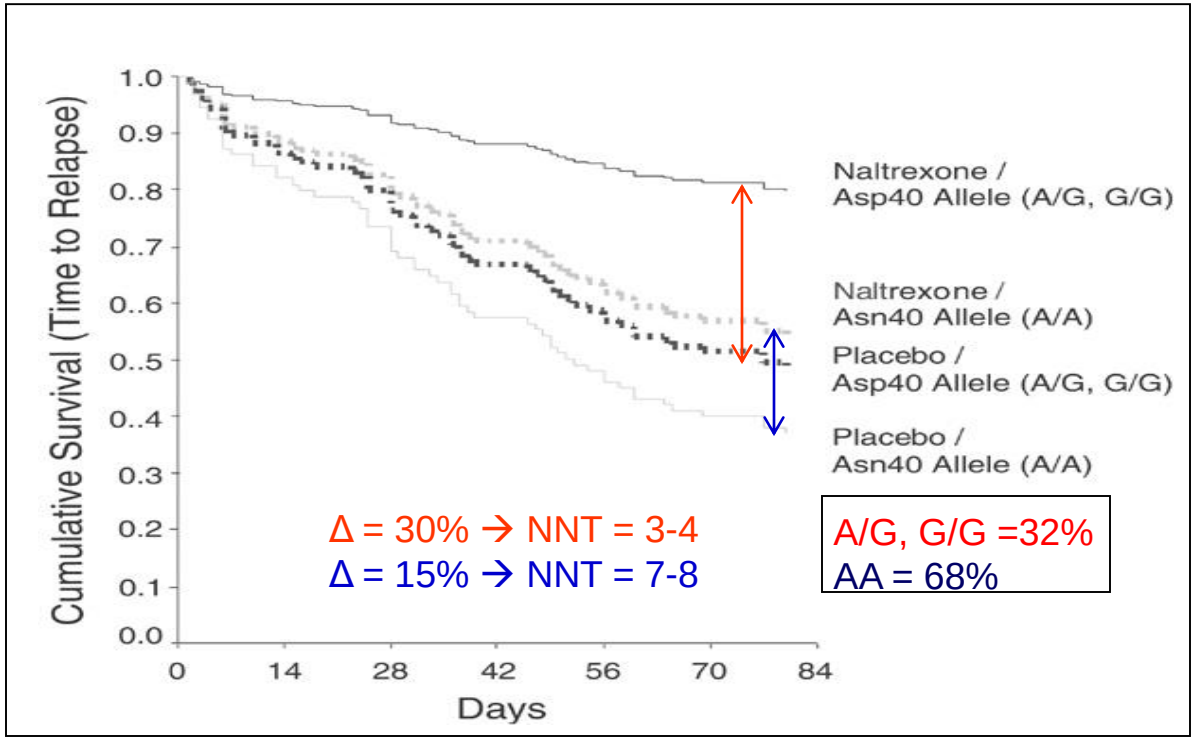


Figure 2. Among patients compliant with ≥70% of medication doses, percentage of heavy drinking days during 6-month follow-up by medication (naltrexone vs. placebo) and socialization (California Personality Inventory-Socialization scale [CPI-So] score ≤24 or >24). The interaction of CPI-Socialization with medication was significant using CPI-Socialization as a continuous variable in the regression; this figure illustrates the nature of the interaction. Error bars represent standard errors.

Candidate Genes: Naltrexone and OPRM1



Oslin et al. 2003	+
McGeary et al. 2006	+
Anton et al. 2008	+
Kim et al. 2008	+
Ooteman et al. 2009	+
Gerlernter et al. 2007	-
Tidey et al. 2008	-
Oroszi et al., 2009	+
Coller et al., 2011	-

Association of μ-opioid receptor (*OPRM1*) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis

Antonio-Javier Chamorro[1]*, Miguel Marcos[2,3]*, José-Antonio Mirón-Canelo[4], Isabel Pastor[2,3], Rogelio González-Sarmiento[3] & Francisco-Javier Laso[2]

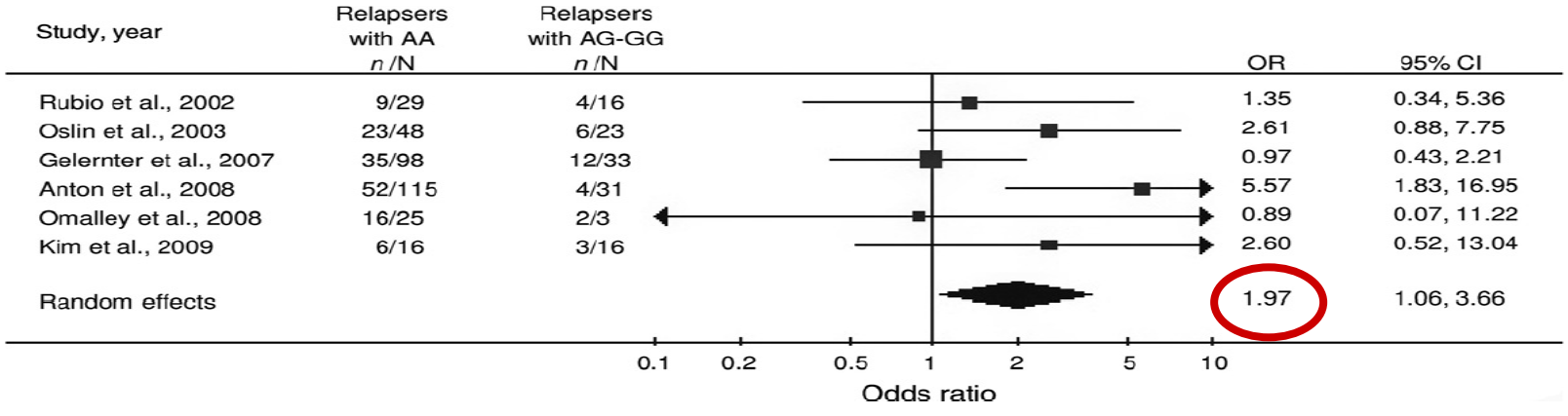


Figure 2 Meta-analysis of the association of A118G opioid μ-receptor polymorphism with relapse rates after naltrexone treatment in patients with alcohol dependence. Naltrexone-treated patients with AA genotype (cases) are compared with those with G allele (controls) under a random-effects model ($Z = 2.14$, $P = 0.03$). Test for heterogeneity: $\chi^2 = 7.28$ ($P = 0.20$), $I^2 = 31.3\%$. Each study is shown by an OR estimate with the corresponding 95% CI

Meta-analysis 6 studies: NTX is twice as effective in the prevention of relapse in patients with the AG/GG allel compared to patients with the AA allel in OPRM1.

Molecular Psychiatry (2010), 1–9

www.nature.com/mp

ORIGINAL ARTICLE

A genetic determinant of the striatal dopamine response to alcohol in men

VA Ramchandani[1], J Umhau[1], FJ Pavon[2], V Ruiz-Velasco[3], W Margas[3], H Sun[1], R Damadzic[1], R Eskay[1], M Schoor[4], A Thorsell[1], ML Schwandt[1], WH Sommer[1,5], DT George[1], LH Parsons[2], P Herscovitch[6], D Hommer[1] and M Heilig[1]

2010

[^{11}C]-raclopride PET

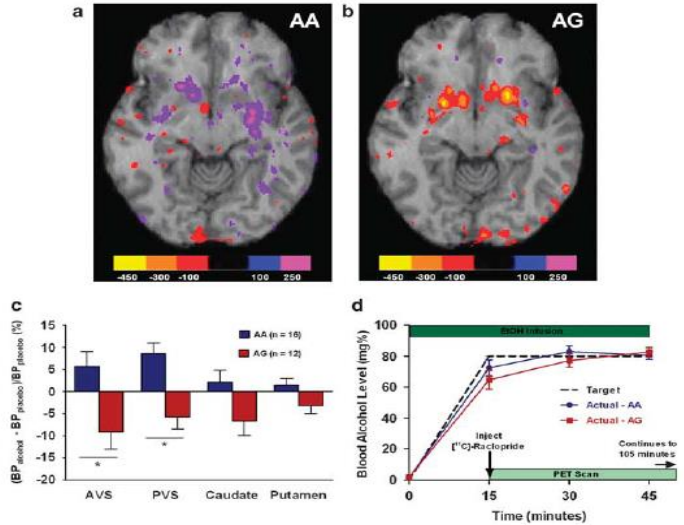
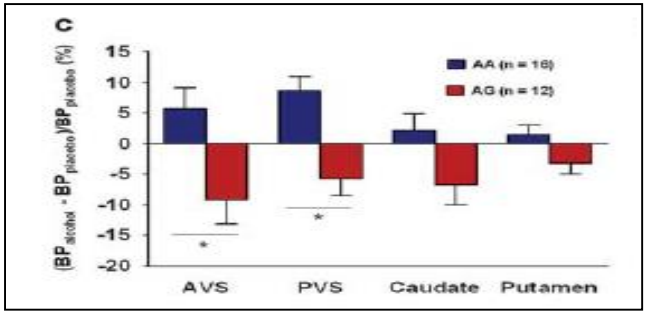


Figure 1 Human PET study. Axial view of group maps showing change of [^{11}C]-raclopride binding potential (ΔBP; nCi ml^{-1}) between placebo and alcohol sessions in (**a**) AA individuals and (**b**) AG individuals. Color bars indicate corresponding ΔBP values. Reduction in raclopride binding is attributed to competition with dopamine released by the alcohol challenge; thus, a negative ΔBP indicates an increase in endogenous dopamine release. (**c**) Relative change in binding potential (%ΔBP) for [^{11}C]-raclopride between alcohol and placebo sessions in four striatal regions of interest. Data are least square means (± s.e.m.). Main genotype effect: $P = 0.006$; $^*P < 0.05$ on *post hoc* tests within individual regions. AVS, anterior ventral striatum; PVS, posterior ventral striatum. (**d**) Schematic of PET sessions, and blood alcohol concentration profiles over time during the alcohol session (mean ± s.e.m.). There was no significant difference between genotypes ($F[1,24] = 0.51$, $P = 0.48$).

Subjects with OPRM1-AA release less dopamine in het ventral striatum in response to alcohol than subjects with OPRM1-AG



Clinical and biological moderators of response to naltrexone in alcohol dependence: a systematic review of the evidence

James C. Garbutt[1], Amy M. Greenblatt[2], Suzanne L. West[2], Laura C. Morgan[2], Alexei Kampov-Polevoy[1], Harmon S. Jordan[2] & Georgiy V. Bobashev[2]

Department of Psychiatry and Bowles Center for Alcohol Studies, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA[1] and RTI International, Research Triangle Park, NC, USA[2]

2014

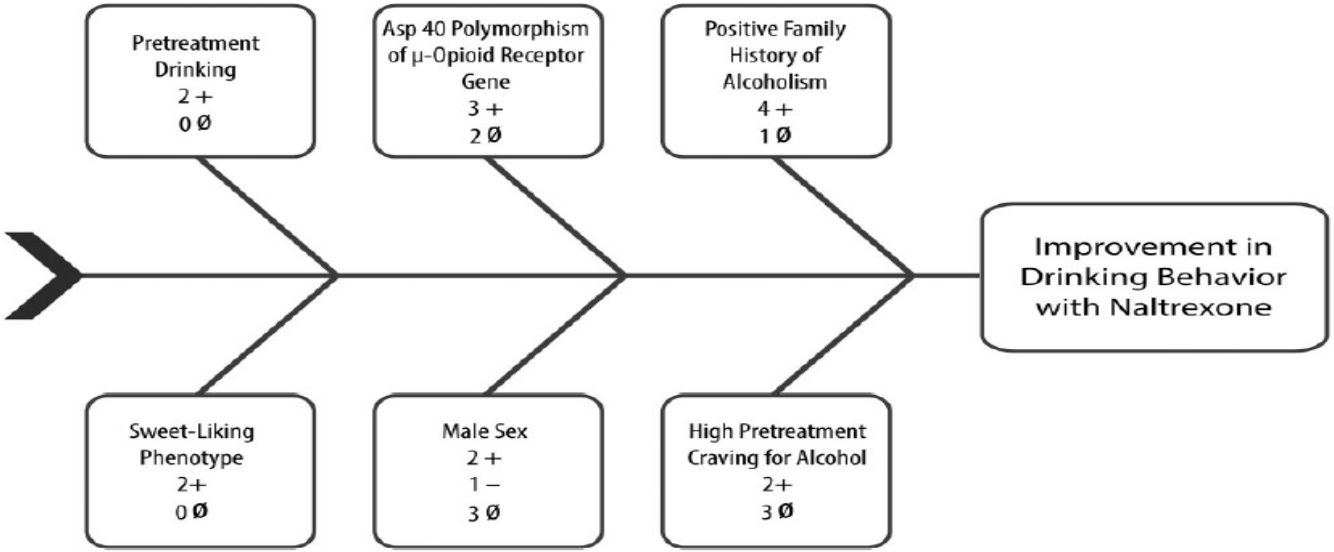


Figure 2 Fishbone diagram of possible moderators of response to naltrexone in alcohol dependence. For each bone, we provide the number of studies that indicate a positive (+) or negative (–) association or mixed/neutral evidence (ø) between the moderator and naltrexone response

BUT .....

Original Investigation

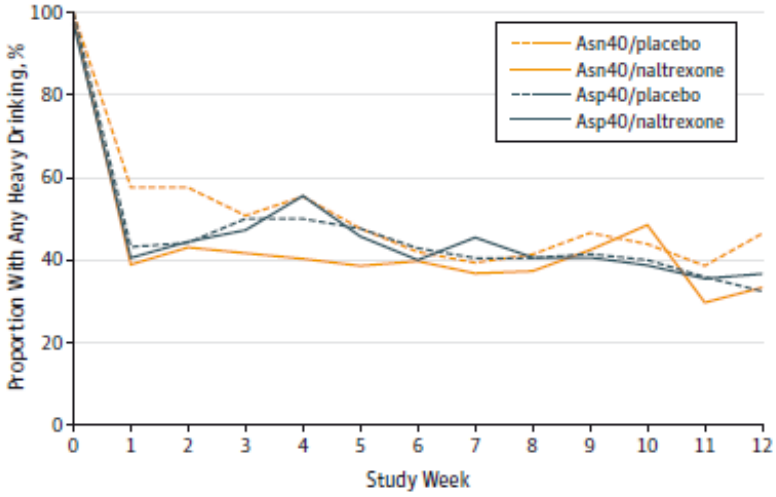
Naltrexone vs Placebo for the Treatment of Alcohol Dependence
A Randomized Clinical Trial

David W. Oslin, MD; Shirley H. Leong, PhD; Kevin G. Lynch, PhD; Wade Berrettini, MD, PhD; Charles P. O'Brien, MD, PhD; Adam J. Gordon, MD, MPH; Margaret Rukstalis, MD

2015

Prospective RCT did NOT confirm the moderating effect of the OPRM1 gen variation!!

Figure 2. The Proportion of Participants With Any Heavy Drinking Within a Given Treatment Week Separated by Genotype and Treatment Group



There were no significant differences in outcomes among the 4 groups when adjusting for site and baseline rates of heavy drinking.

Article

Topiramate Treatment for Heavy Drinkers: Moderation by a *GRIK1* Polymorphism

Henry R. Kranzler, M.D.

Jonathan Covault, M.D., Ph.D.

Richard Feinn, Ph.D.

Stephen Armeli, Ph.D.

Howard Tennen, Ph.D.

Albert J. Arias, M.D.

Joel Gelernter, M.D.

Timothy Pond, M.P.H.

Cheryl Oncken, M.D., M.P.H.

Kyle M. Kampman, M.D.

Objective: Topiramate has been shown to reduce drinking and heavy drinking in individuals with alcohol dependence whose goal was to stop drinking. The authors evaluated the efficacy and tolerability of topiramate in heavy drinkers whose treatment goal was to reduce drinking to safe levels.

Method: A total of 138 individuals (62.3% men) were randomly assigned to receive 12 weeks of treatment with topiramate (N=67), at a maximal daily dose of 200 mg, or matching placebo (N=71). Both groups received brief counseling to reduce drinking and increase abstinent days. It was hypothesized that topiramate-treated patients would be better able to achieve these goals, and it was predicted that based on prior research, the effects would be moderated by a single nucleotide polymorphism (rs2832407) in *GRIK1*, encoding the kainate GluK1 receptor subunit.

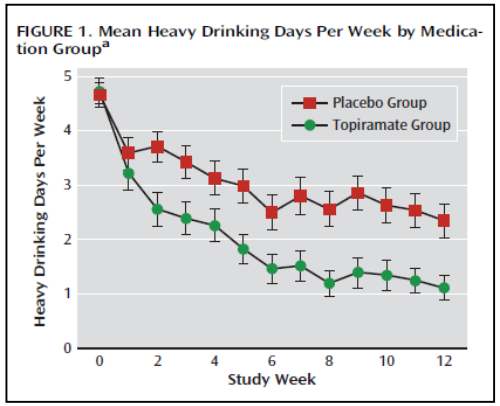
Results: The rate of treatment completion was 84.9% and equal by treatment group. Topiramate treatment significantly reduced heavy drinking days and increased abstinent days relative to placebo. Patients receiving topiramate also had lower concentrations of the liver enzyme γ-glutamyl transpeptidase and lower scores on a measure of alcohol-related problems than the placebo group. In a European American subsample (N=122), topiramate's effect on heavy drinking days was significantly greater than that for placebo only in rs2832407 C-allele homozygotes.

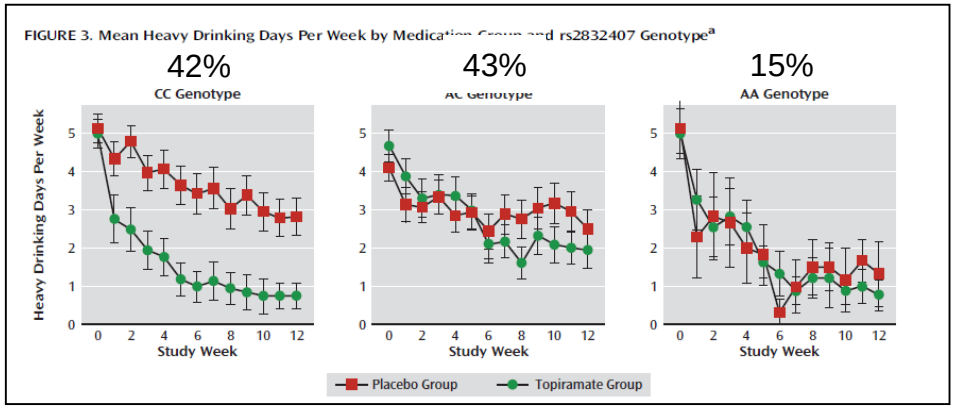
Conclusions: These findings support the use of topiramate at a daily dose of 200 mg to reduce heavy drinking in problem drinkers. The moderator effect of rs2832407, if validated, would facilitate the identification of heavy drinkers who are likely to respond well to topiramate treatment and provide an important personalized treatment option. The pharmacogenetic findings also implicate the kainate receptor in the mechanism of topiramate's effects on heavy drinking.

(Am J Psychiatry 2014; 171:445–452)

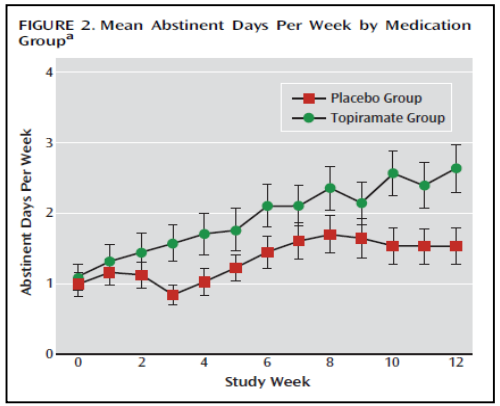
Candidate Genes: Topiramate (200mg) and GRK1

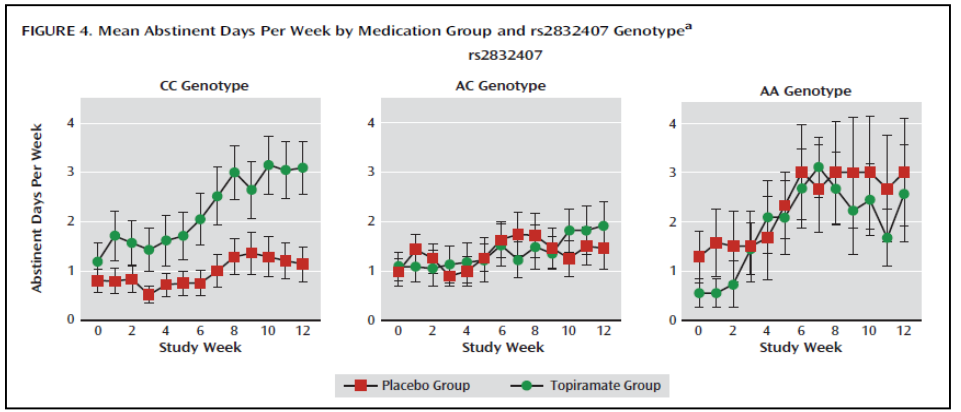
HDDs per week





Abstinence days/week





GWAS

Genome-wide Association Study of Alcohol Dependence

Jens Treutlein, PhD; Sven Cichon, PhD*; Monika Ridinger, MD*; Norbert Wodarz, MD; Michael Soyka, MD; Peter Zill, PhD; Wolfgang Maier, MD; Rainald Moessner, MD; Wolfgang Gaebel, MD; Norbert Dahmen, MD; Christoph Fehr, MD; Norbert Scherbaum, MD; Michael Steffens, MD; Kerstin U. Ludwig, MSc; Josef Frank, MA; H. Erich Wichmann, MD, PhD; Stefan Schreiber, MD; Nico Dragano, PhD; Wolfgang H. Sommer, MD, PhD; Fernando Leonardi-Essmann, MA; Anbarasu Lourdusamy, PhD; Peter Gebicke-Haerter, PhD; Thomas F. Wienker, MD; Patrick F. Sullivan, MD; Markus M. Nöthen, MD; Falk Kiefer, MD; Rainer Spanagel, PhD*; Karl Mann, MD*; Marcella Rietschel, MD**

2009

Table 1. SNPs Confirmed in the Follow-up Study: Location According to Chromosomal Bands and Gene Annotation

SNP	Chromosomal Band	Genes[a]
rs1344694	2q35	NA
rs7590720	2q35	NA
rs705648	2q35	Peroxisomal trans-2-enoyl-CoA reductase *(PECR)*
rs1614972[b]	4q23	Alcohol dehydrogenase 1C (class I), gamma polypeptide *(ADH1C)*
rs13362120	5q15	Calpastatin *(CAST)*
rs13160562	5q15	Endoplasmic reticulum aminopeptidase 1 *(ERAP1)*; calpastatin *(CAST)*
rs1864982	5q32	Protein phosphatase 2 (formerly 2A), regulatory subunit B, beta isoform *(PPP2R2B)*
rs6902771	6q25.1	Estrogen receptor 1 *(ESR1)*
rs729302	7q32.1	NA
rs13273672[b]	8p23.1	GATA binding protein 4 *(GATA4)*
rs1487814	11p14.3	NA
rs7138291	12q22	Coiled-coil domain containing 41 *(CCDC41)*
rs36563	14q24.2	NA
rs11640875[b]	16q23.3	Cadherin 13, H-cadherin (heart) *(CDH13)*
rs12388359	Xp22.2	NA

Abbreviations: CoA, coenzyme A; NA, not applicable; SNP, single-nucleotide polymorphism.
[a] Annotation according to SNP database build 129.
[b] Selected following the strategy of "rodent candidate gene."

GATA binding Protein 4 = transcription factor regulating the transciption of Atrial Natriuretic Peptide (ANP) and involved in neuroendocrine stress response

Involvement of the atrial natriuretic peptide transcription factor *GATA4* in alcohol dependence, relapse risk and treatment response to acamprosate

F Kiefer[1,12], SH Witt[2,12], J Frank[2], A Richter[1], J Treutlein[2], T Lemenager[1], MM Nöthen[3,4], S Cichon[3,4], A Batra[5], M Berner[6], N Wodarz[7], US Zimmermann[1,8], R Spanagel[9], K Wiedemann[10], MN Smolka[8], A Heinz[11], M Rietschel[2,12] and K Mann[1,12]

2010

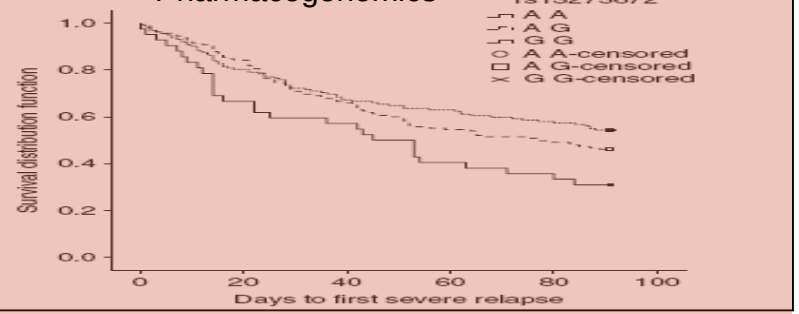
PREDICT Study

Table 2 Association tests between *GATA4* SNP rs13273672 and abstinence proportion after 90 days of pharmacological treatment

	Group size[a]	*P-value*[b]	*Allele A*	*Allele B*	*Frequency A Abstinent*	*Frequency A Relapsed*	*Odds ratio*	*CI (OR)*
Acamprosate	147	0.0013	A	G	0.725	0.539	2.255	1.385–3.670
Naltrexone	148	0.3006	A	G	0.717	0.665	1.281	0.780–2.105
Placebo	74	1.0000	A	G	0.676	0.676	1.000	0.502–1.990

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.
[a]Effective sample size after excluding missing values.
[b]Cochran–Armitage test for trend.

Pharmacogenomics



Gene expression

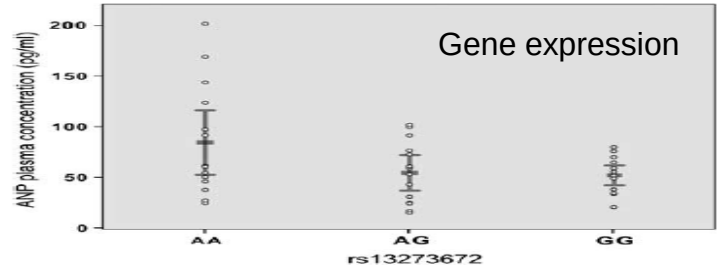


Figure 2 Atrial natriuretic peptide (ANP) plasma concentration as a function of *GATA4* (gene for GATA-binding protein 4) single nucleotide polymorphism (SNP) rs13273672 (modified Levene test of variance differences: $P = 0.003$; $n = 42$).

Personalized pharmacotherapy

Behandeldoel	1e Keus	2e Keus	3e Keus
Abstinentie ↕ **Minder drinken**	**Acamprosaat** (anxiety, withdrawal, GATA4) **Naltrexon??** (ASPD, SL+, FH+, OPRM1)	**Disulfiram** (partner)	Baclofen (anxiety, withdrawal) Gabapentin (sleep problems) (GHB??)
	Naltrexon# (ASPD, SL+, FH+, OPRM1) **Nalmefeen** (dysphoria??)	Topiramaat (GRIK1, PTSD?)	Modafinil (impulsivity) Varenicline (smoking?) Doxazepine (FH+)

off-label

Psychotherapie voor alcohol afhankelijkheid

Model voor Psychotherapie Verslaving

Repeated reward

Aversive Conterconditionering

Attentional bias → Cue-reactivity

Drug-related stimulus

Stress

CGT
Mindfulness
ACT

Detection threshold

CET (+DCS)
ACT
EMDR?

Craving

Inhibition

MGV
Werkgeheugen

Conflict registration

CM
CRA

Relapse

Psychotherapie voor alcohol afhankelijkheid Counterconditionering

Model voor Psychotherapie Verslaving

Repeated reward

Aversive Conterconditionering

Attentional bias → Cue-reactivity

Stress

Drug-related stimulus

Detection threshold → Craving → **Relapse**

Inhibition

Conflict registration

Aversive Counterconditioning Attenuates Reward Signaling in the Ventral Striatum

Anne Marije Kaag[1,2,3†], Renée S. Schluter[2†], Peter Karel[4], Judith Homberg[4], Wim van den Brink[2], Liesbeth Reneman[1] and Guido A. van Wingen[2,3,5]*

frontiers in Human Neuroscience

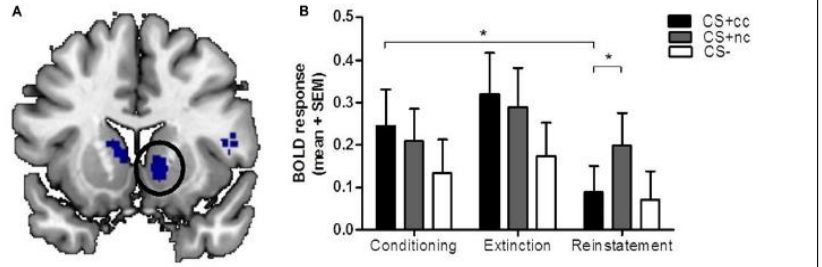


FIGURE 2 | The neural response to counterconditioned versus non-counterconditioned CS+. The figures on the left **(A)** show the neural responses after reinstatement to the counterconditioned versus the non-counterconditioned CS+stimuli in the ventral striatum. The bar graphs on the right **(B)** are a visual presentation of the response to the counterconditioned CS+ ($CS+_{cc}$; black), non-counterconditioned CS+ ($CS+_{nc}$; gray) and CS− (white) at the peak voxel (MNI: 12 10 −6, $z = 2.91$). Compared to the conditioning phase, ventral striatal BOLD response during reinstatement is significantly decreased for the counterconditioned CS+, but not for the other stimuli. During reinstatement, the ventral striatal BOLD response for the non-counter CS is significantly higher compared to the BOLD response for the counterconditioned stimulus. The figures are displayed at $p < 0.001$ uncorrected for visualization purpose. * = whole brain significant stimulus type ($CS+_{cc}$ versus $CS+_{nc}$) by phase (conditioning versus reinstatement) interaction effect.

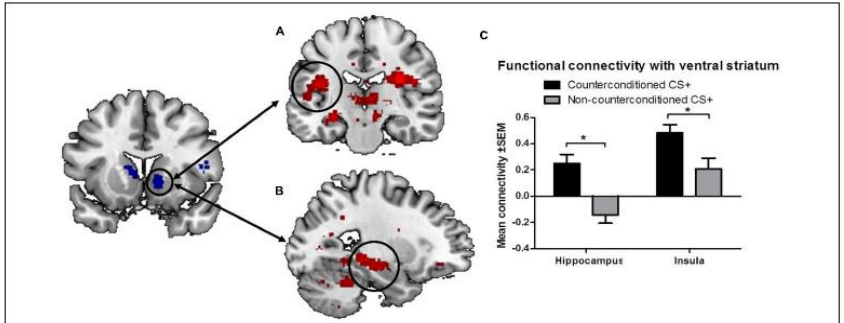


FIGURE 3 | Functional connectivity of the ventral striatum. The figure shows significant differences in functional connectivity for the counterconditioned versus non-counterconditioned CS+ following reinstatement. Counterconditioning strengthened the functional connectivity of the ventral striatum seed region (left) with the left insula **(A)** and left hippocampus **(B)**. The figures are displayed at $p < 0.001$ uncorrected for visualization purpose. The graph **(C)** is a visual representation of the functional connectivity changes with the ventral striatum in response to counterconditioned and non-counterconditioned CS+, in the insula and hippocampus. * = whole brain significant main effect of stimulus type ($CS+_{cc}$ versus $CS+_{nc}$) on ventral striatal connectivity following reward reinstatement.

In gezonde controles leidt aversieve counterconditionering tot verminderde activiteit van VS tijdens reinstatement

Dit effect komt waarschijnlijk tot stand door verhoogde connectiviteit tussen VS met hippocampus en insula

Rewriting the valuation and salience of alcohol-related stimuli via memory reconsolidation

RK Das, W Lawn and SK Kamboj

Transl Psychiatry (2015)

Ook bij overmatige drinkers lijkt counterconditionering te werken

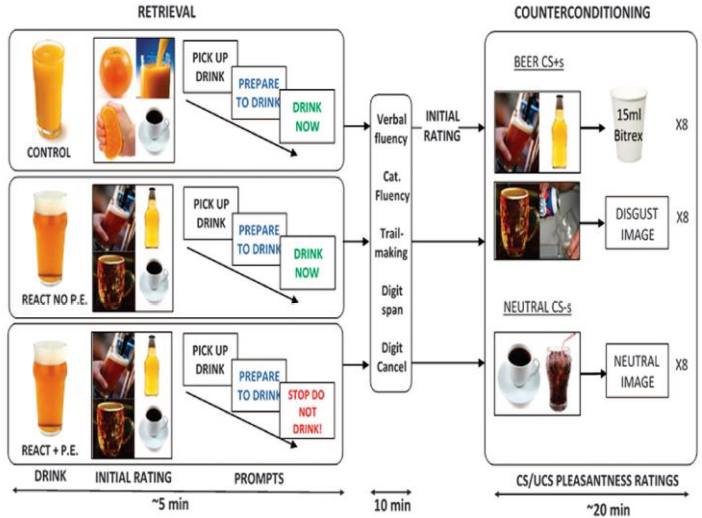


Figure 1. Schematic diagram of retrieval/counterconditioning procedure. Counterconditioning is identical for all groups. All groups initially are given a drink and told they will consume it after rating some pictures. In the REACT no PE and REACT+PE groups this is 150 ml beer, in the Control group 150 ml orange juice. Control and REACT no PE consume the drink as expected. In REACT+PE, it is withheld at the last moment. Note the Control group rate the beer images at the beginning of counterconditioning (with no time delay). CS, conditioned stimuli; PE, prediction error; REACT, reactivation.

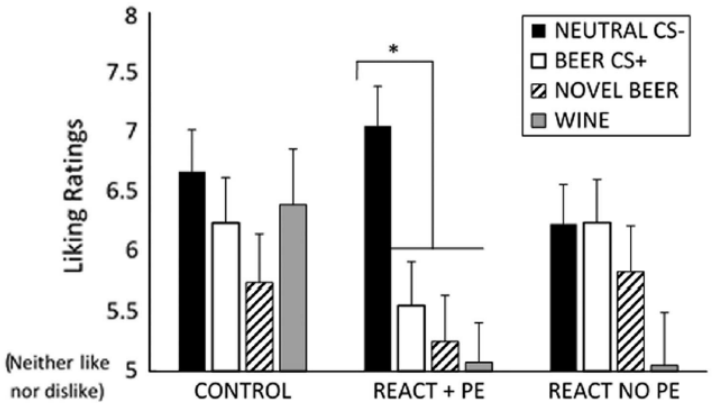


Figure 2. Reduced liking of alcohol stimuli produced by counter-conditioning following MMM reactivation with prediction error. Bars represent mean ± s.e.m. A score of five denotes neither liking nor disliking of the stimuli. CS, conditioned stimuli; MMM, maladaptive motivational memory; PE, prediction error.

Psychotherapie voor alcohol afhankelijkheid Mindfulness Training

Model voor Psychotherapie Verslaving

Repeated reward

Attentional bias → Cue-reactivity

Detection threshold → Craving

Inhibition → Craving

Craving → **Relapse**

Conflict registration

Drug-related stimulus

Stress

Mindfulness

Substance Abuse, 30:295–305, 2009

ISSN: 0889-7077 print / 1547-0164 online
DOI: 10.1080/08897070903250084

Routledge
Taylor & Francis Group

Mindfulness-Based Relapse Prevention for Substance Use Disorders: A Pilot Efficacy Trial

Sarah Bowen, PhD
Neharika Chawla, MS
Susan E. Collins, PhD
Katie Witkiewitz, PhD
Sharon Hsu, BA
Joel Grow, BA
Seema Clifasefi, PhD
Michelle Garner, PhD
Anne Douglass, BA
Mary E. Larimer, PhD
Alan Marlatt, PhD

* 45% primair alcohol afhankelijkheid

* RCT: N=168; TAU vs TAU + 8 wekelijkse MBRP groepssessies

* FU 4 maanden

TABLE 2. Generalized Estimating Equations Models Evaluating Treatment Effects on Main and Process Outcomes

	AOD use ($N = 163$)			
Predictors	IRR	CI (95%)	*z*	*P*
t	.10	.05–.24	−5.31	<.001
t^2	1.80	1.42–2.27	4.86	<.001
Total treatment hrs	1.00	.97–1.03	−.04	.97
Race	1.02	.76–1.36	.10	.92
Treatment	.92	.67–1.25	−.54	.59
t × treatment	.14	.03–.70	−2.40	.02
t^2 × treatment	1.91	1.16–3.15	2.55	.01
	Craving ($N = 166$)			
Predictors	Exp(B)	CI (95%)	*z*	*P*
t	1.06	.76–1.47	.35	.73
t^2	.95	.86–1.07	−.83	.41
Total treatment hours	.99	.97–1.01	−1.34	.18
Race	1.55	1.24–1.94	3.84	<.001
Treatment	.84	.66–1.06	−1.46	.14
t × treatment	.68	.49–.95	−2.27	.02
t^2 × treatment	1.13	1.01–1.26	2.21	.03
	Acceptance ($N = 163$)			
Predictors	*β*	CI (95%)	*z*	*P*
t	.03	−.26, .32	0.21	.84
t^2	.06	−.25, .36	0.36	.72
Total treatment hours	−.05	−.18, .08	−.71	.48
Race	−.05	−.21, .10	−0.68	.50
Treatment	.03	−.14, .20	0.35	.73
t × treatment	.44	.01, .87	2.00	.045
t^2 × treatment	−.40	−.83, .01	−1.88	.047
	Acting with awareness ($N = 165$)			
Predictors	*β*	CI (95%)	*z*	*P*
t	−.48	−.85, −.11	−2.53	.01
t^2	.52	.10, .93	2.44	.02
Total treatment hours	−.03	−.20, .13	−0.40	.69
Race	−.09	−.23, .06	−1.18	.24
Treatment	−.09	−.27, .09	−1.03	.30
t × treatment	.67	.15, 1.18	2.54	.01
t^2 × treatment	−.61	−1.11, −.11	−2.43	.02

Mindfulness Nazorg

Original Investigation

Relative Efficacy of Mindfulness-Based Relapse Prevention, Standard Relapse Prevention, and Treatment as Usual for Substance Use Disorders
A Randomized Clinical Trial

Sarah Bowen, PhD; Katie Witkiewitz, PhD; Seema L. Clifasefi, PhD; Joel Grow, PhD; Neharika Chawla, PhD; Sharon H. Hsu, MS; Haley A. Carroll, BS; Erin Harrop, BS; Susan E. Collins, PhD; M. Kathleen Lustyk, PhD; Mary E. Larimer, PhD

JAMA Psychiatry. 2014;71(5):547-556. doi:10.1001/jamapsychiatry.2013.4546
Published online March 19, 2014.

N=286 SUD patiënten (**15% alleen alcohol**; 85% polydruggebruik) voor nazorg na 1 maand klinische of 3 maanden intensieve ambulante behandeling

* randomisatie nazorg: 8 weken TAU (12 stappen), RP of MBRP
* follow-up 12 maanden

Mindfulness Nazorg

Table 3. Results From Cox Proportional Hazards Regression Models for Time to First Lapse

Covariate[a]	B (SE)	HR (95% CI for Hazard Odds)
Time to first drug use day		
Contrast 1: TAU (−) vs RP/MBRP (+)	−0.77 (0.05)[b]	0.46 (0.42-0.51)
Contrast 2: RP (−) vs MBRP (+)	0.19 (0.05)[b]	1.21 (1.10-1.33)
Age	−0.05 (0.002)[b]	0.95 (0.95-0.96)
Treatment history	−0.04 (0.01)[b]	0.96 (0.94-0.98)
SDS baseline	0.17 (0.005)[b]	1.18 (1.17-1.19)
Treatment hours	−0.05 (0.003)[b]	0.95 (0.95-0.96)
Treatment site, coded 0, 1	0.48 (0.04)[b]	1.61 (1.50-1.73)
Time to first heavy drinking day		
Contrast 1: TAU (−) vs RP/MBRP (+)	−0.89 (0.05)[b]	0.41 (0.37-0.46)
Contrast 2: RP (−) vs MBRP (+)	0.02 (0.06)	0.72 (0.91-1.15)
Age	0.01 (0.002)[b]	1.01 (1.01-1.02)
Treatment history	0.07 (0.01)[b]	1.08 (1.05-1.10)
SDS baseline	0.08 (0.006)[b]	1.08 (1.07-1.09)
Treatment hours	0.001 (0.003)	1.001 (0.99-1.01)
Treatment site, coded 0, 1	−0.71 (0.05)[b]	0.49 (0.45-0.54)

Table 2. Outcome Variable Findings at Follow-up

Characteristic	TAU (n = 95)	RP (n = 88)	MBRP (n = 103)
Sample size % completed, No. (%)			
3 mo	82 (86.3)	80 (90.9)	95 (92.2)
6 mo	77 (81.1)	75 (85.2)	89 (86.4)
12 mo	76 (80.0)	72 (81.8)	83 (80.6)
Drug use days, TLFB, mean (SD)			
3 mo	5.23 (15.43)	2.09 (10.65)	3.92 (16.24)
6 mo	5.81 (19.11)	1.71 (10.77)	2.73 (12.00)
12 mo	4.63 (16.03)	6.09 (19.05)	3.06 (15.08)
Any drug use, TLFB, No. (%)			
3 mo	20 (21.0)	11 (12.5)	14 (13.6)
6 mo	20 (21.0)	7 (8.0)	10 (9.7)
12 mo	13 (13.7)	15 (17.0)	9 (8.7)
Heavy drinking days, TLFB, mean (SD)			
3 mo	2.64 (10.64)	2.13 (7.75)	1.99 (8.06)
6 mo	2.61 (9.93)	1.13 (5.96)	1.63 (8.53)
12 mo	4.65 (14.93)	3.89 (12.17)	1.44 (7.66)
Any heavy drinking, TLFB, No. (%)			
3 mo	19 (20.0)	18 (20.5)	12 (11.7)
6 mo	15 (15.8)	8 (9.1)	8 (7.8)
12 mo	19 (20.0)	17 (19.3)	8 (7.8)

- RP en MBRP leiden tot minder snelle terugval dan TAU
- MBRP leidt tot betere lange termijn uitkomsten dan TAU en RP!!
- Geen goede RCT met alleen alcoholafhankelijkheid

Psychotherapie voor alcohol afhankelijkheid Acceptance and Commitment Therapy

Model voor Psychotherapie Verslaving

Repeated reward

Attentional bias → Cue-reactivity

Detection threshold

Inhibition

Craving → **Relapse**

ACT

Conflict registration

Stress

Drug-related stimulus

ACT

An initial meta-analysis of Acceptance and Commitment Therapy for treating substance use disorders

Eric B. Lee *, Woolee An, Michael E. Levin, Michael P. Twohig

DAD, 2015

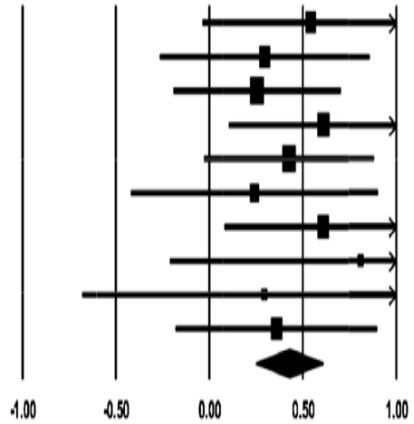
Table 1
Characteristics of studies.

Study	Problem area	Treatment format/setting	Control condition(s)	Follow-up	Sample size	Mean age (SD)	% Female	Ethnicity % White	Attrition %
Bricker et al. (2014a)	Smoking	Mobile app and email	QuitGuide app	2 month	196	41.55 (12.95)	52	89.5	ACT: 18.4 TAU: 14.3
Bricker et al. (2014b)	Smoking	Telephone	CBT	3 and 6 month	121	39.08 (9.80)	69	73	ACT: 32.2 TAU: 35.5
Bricker et al. (2013)	Smoking	Web-based	Smokefree.gov	3 month	222	45.05 (13.35)	62	92.5	ACT: 46.0 TAU: 46.9
Gifford et al. (2004)	Smoking	Face-to-face Smoking Cessation Clinic	Nicotine replacement treatment	6 and 12 month	76	43.00 (11.68)	59	72	ACT: 21.0 TAU: 16.0
Gifford et al. (2011)	Smoking	Face-to-face Clinic	Bupropion	6 and 12 month	303	45.99 (12.50)	58.7	86.8	ACT: 40.8 TAU: 48.0
Hayes et al. (2004)	Opiates	Face-to-face Clinic	Intensive 12-Step Facilitation Therapy	6 month	138	42.20 (NA)	51	87	ACT: 42.9 ITFS: 40.9
Luoma et al. (2012)	Polydrug abuse	Face-to-face Residential program	Treatment as usual: 12-step, process groups, skill training	4 month	133	33.60 (NA)	45.86	86	ACT: 11.8 TAU: 18.5
Menéndez et al. (2014)	Polydrug abuse	Face-to-face group Women's prison	CBT	6, 12, and 18 month	37	33.50 (17.15)	100	NA	ACT: 0 TAU: 0
Smout et al. (2010)	Methamphetamine	Face-to-face Clinic	CBT	3 month	104	30.90 (6.50)	40	NA	ACT: 72.5 TAU: 67.9
Stotts et al. (2012)	Opiates	Face-to-face Clinic	Drug counseling	None	56	39.85 (9.70)	37	82.5	ACT: 40.0 TAU: 53.9

Overall effect ACT: 10 RCTs

Study name	Outcome	Time point	Statistics for each study				
			Hedges's g	Lower limit	Upper limit	Z-Value	p-Value
Bricker (2013)	Self-report (30 day quit rate)	3 month Follow-up	0.542	-0.037	1.120	1.834	0.067
Bricker (2014a)	Self-report (Smoking cessation)	2 month Follow-up	0.297	-0.264	0.858	1.038	0.299
Bricker (2014b)	Self-report (Smoking cessation)	6 month Follow-up	0.255	-0.192	0.702	1.119	0.263
Gifford (2004)	Objective (Expired CO)	12 month Follow-up	0.611	0.105	1.117	2.365	0.018
Gifford (2011)	Objective (Expired CO)	12 month Follow-up	0.427	-0.028	0.882	1.838	0.066
Hayes (2004)	Objective (Opiate abstinence)	6 month Follow-up	0.242	-0.418	0.903	0.719	0.472
Luoma (2012)	Randomized objective (Abstinence)	4 month Follow-up	0.610	0.081	1.139	2.260	0.024
Menendez (2014)	Randomized objective (Abstinence)	12 month Follow-up	0.811	-0.210	1.831	1.557	0.119
Smout (2010)	Objective (Abstinence)	3 month Follow-up	0.294	-0.681	1.269	0.591	0.555
Stotts (2012)	Objective (Abstinence)	Post-treatment	0.359	-0.180	0.899	1.305	0.192
			0.427	0.248	0.606	4.679	0.000

Hedge's g and 95% CI



Hedge's g = 0.427
Q=3.323, p=0.95; I^2 =0.000

Fig. 1. Treatment effects for substance abuse abstinence at the longest available follow-up assessment.

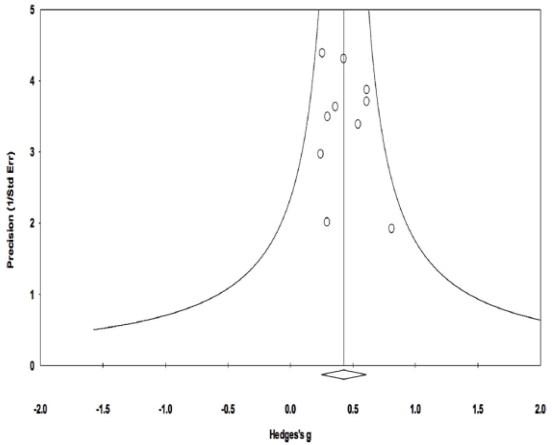


Fig. 2. Funnel plot of precision by hedge's g for measures of substance abstinence at the longest available follow-up assessment.

NB: Geen studies voor alcoholafhankelijkheid!

Psychotherapie voor alcoholafhankelijkheid CET + DCS tegen craving

Model voor Psychotherapie Verslaving

Repeated reward

Attentional bias → Cue-reactivity

Stress

Drug-related stimulus

Detection threshold

CET + DCS

Craving

Inhibition

Relapse

Conflict registration

D-cycloserine to enhance extinction of cue-elicited craving for alcohol: a translational approach

Transl Psychiatry (2015) **5**, e544; doi:10.1038/tp.2015.41

J MacKillop[1,2,3], LR Few[4], MK Stojek[5], CM Murphy[5], SF Malutinok[5], FT Johnson[5], SG Hofmann[6], JE McGeary[7,8,3], RM Swift[3,6] and PM Monti[3]

RCT:

* Double-blind
* N=30
* Group A: MET+CET+DCS
  Group B: MET+CET+Pla
* Dose DCS: 50 mg
  Timing DCS: 1 hr before CET
* Outcomes: craving, drinking
* FU: 3 weeks

Table 1. Participant characteristics

Variable	*%/Mean (s.d.)/Median (IQR)*		*P*
	DCS (n = 16)	*PBO (n = 14)*	
Sex	63% Male	43% Male	0.28
Age	41.88 (14.90)	42.79 (13)	0.86
Education (Years)	14.69 (2.68)	15.71 (2.37)	0.28
Income ($)	20 000–29 999 (0–9999 to >80 000)	30 000–39 999 (10 000–19 999 to 50 000–59 999)	0.83
Race	81% White; 13% Black; 6% Mixed Race	86% White; 14% Black	0.63
Hispanic ethnicity	6%	0%	0.34
% Drinking days	83.26% (14.97)	84.18% (21.09)	0.89
% Heavy drinking days	62.28% (28.81)	70.15% (28.14)	0.46
Drinks per day	5.317 (2.81)	7.870 (6.31)	0.16
AUD symptom count	5.06 (2.05)	5.86 (1.96)	0.29
Abuse/dependence	6%/94%	14%/86%	0.46
Smoker	50%	64%	0.45

Abbreviations: AUD, alcohol use disorder; DCS, D-cycloserine; IQR, interquartile range; PBO, placebo. Continuous variables were examined using *t*-tests, categorical variables were examined using χ^2 tests; heavy drinking days indicate consuming 5/4 drinks in a given day for males/females. Time frame for drinking refers to the last 28 days; time frame for AUD symptoms refers to the last year.

D-cycloserine to enhance extinction of cue-elicited craving for alcohol: a translational approach

J MacKillop[1,2,3], LR Few[4], MK Stojek[5], CM Murphy[5], SF Malutinok[5], FT Johnson[5], SG Hofmann[6], JE McGeary[7,8,3], RM Swift[3,6] and PM Monti[3]

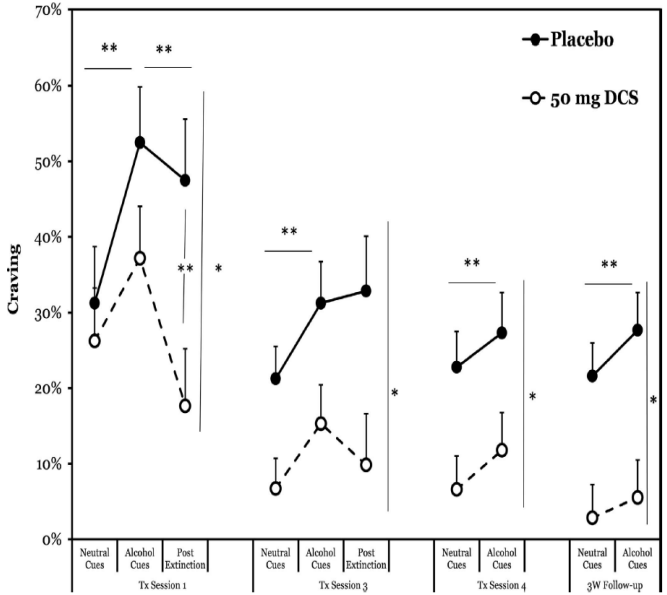


Figure 1. Effects of D-cycloserine (DCS) and placebo on craving for alcohol during cue reactivity and extinction across the study protocol. The DCS and placebo were administered 60 min before the cue exposure and extinction protocols in treatment (Tx) sessions 1 and 3. The initial cue exposure protocol lasted 14 min, including assessments; the extinction protocol comprised 63 min of subsequent active and passive exposure to personalized alcohol cues. Notations: horizontal bars with asterisks reflect significant within-subjects (time) main effects for a given interval; vertical bars with asterisks on the right reflect between-subjects (medication) main effects for the preceding epoch (including both epoch during session 3); vertical lines with asterisks between two time points reflect a significant difference in *post hoc* decomposition of an interaction effect; $^{*}P \leqslant 0.05$, $^{**}P \leqslant 0.01$.

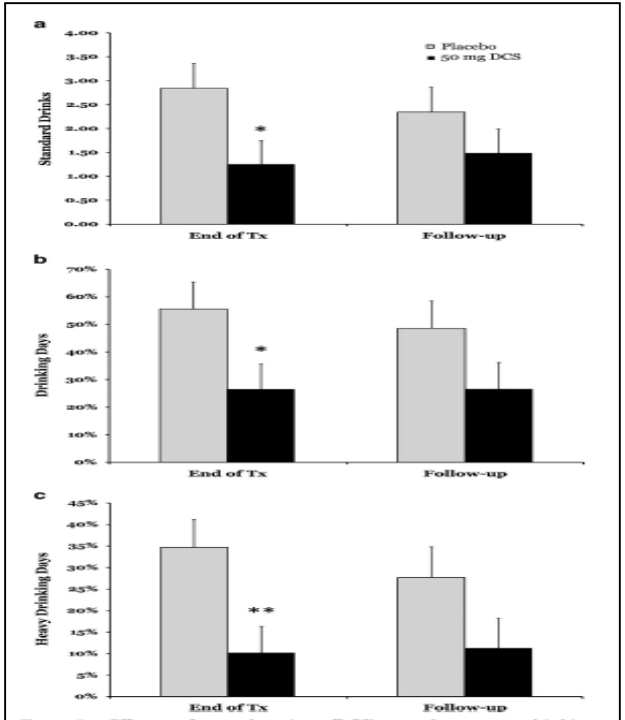


Figure 2. Effects of D-cycloserine (DCS) on short-term drinking outcomes at the conclusion of treatment (Tx) and 3-week follow-up. (**a**) Presents drinks per day, (**b**) presents percent drinking days and (**c**) presents percent heavy drinking days. Baseline drinking is covaried in all the analyses. $^{*}P \leqslant 0.05$, $^{**}P \leqslant 0.01$.

Maar … Kamboj et al., 2011 (125 mg DCS); Watson et al., 2011 (250 mg DCS)

Effects of D-cycloserine on extinction of mesolimbic cue reactivity in alcoholism: a randomized placebo-controlled trial

Falk Kiefer · Martina Kirsch · Patrick Bach · Sabine Hoffmann · Iris Reinhard · Anne Jorde · Christoph von der Goltz · Rainer Spanagel · Karl Mann · Sabine Loeber · Sabine Vollstädt-Klein

Psychopharmacology (2015)

RCT double-blind

* N=32 patients with alcohol cue-reactivity
* 7 sessions CET within 3 weeks
* DCS dose 50 mg

  DCS timing: 1 hr before CET
* Outcome: reduced cue-reactivity (fMRI)

Results:

DCS less cue-reactivity VS and DS →

DCS no effect on craving

DCS small (ns) effect on relapse

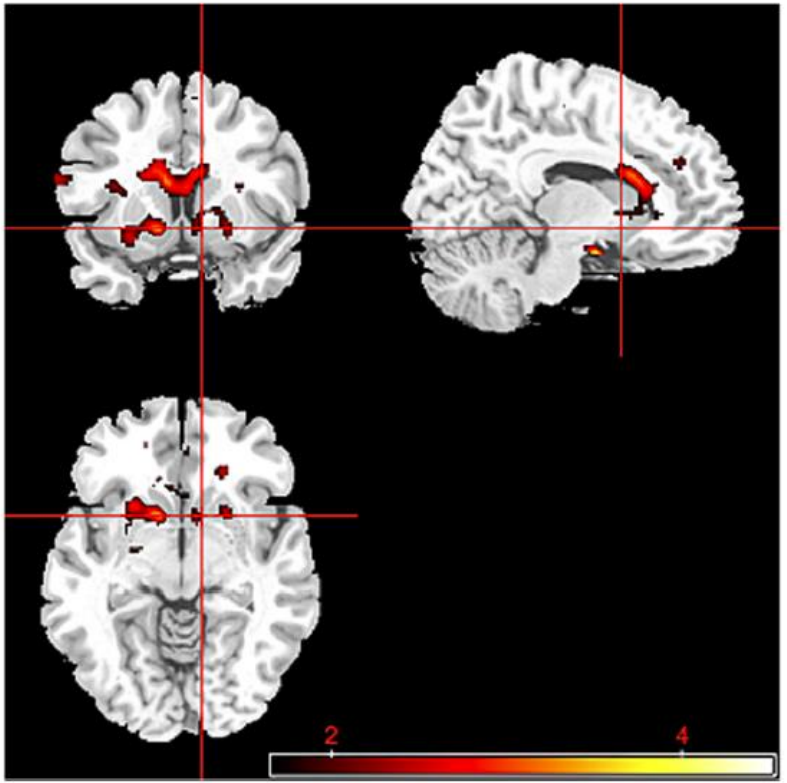


Fig. 3 Larger striatal cue-induced activation (contrast "alcohol-neutral stimuli") in alcohol-dependent patients after 3 weeks of treatment with CET and placebo (N=16) compared to treatment with CET and DCS (N=16), for illustration purposes; $p<0.05$ uncorrected; cluster size >20 voxels; (x, y, z)=(12, 10, −6)

Psychotherapie voor alcohol afhankelijkheid EMDR tegen craving

Model voor Psychotherapie Verslaving

Repeated reward

Attentional bias → Cue-reactivity

Stress

Drug-related stimulus

Detection threshold

EMDR?

Craving

Inhibition

Relapse

Conflict registration

EMDR Reprocessing of the Addiction Memory: Pretreatment, Posttreatment, and 1-Month Follow-Up

Michael Hase
Reha-Zentrum Berliner Tor, Hamburg, Germany

Sabine Schallmayer
Hannover Medical School, Hannover, Germany

Martin Sack
Technical University, Munich, Germany

Journal of EMDR Practice and Research, Volume 2, Number 3, 2008

RCT: open label, N=2x17

TAU vs TAU + 2 x 60 min EMDR

EMDR uitgevoerd door 1e auteur

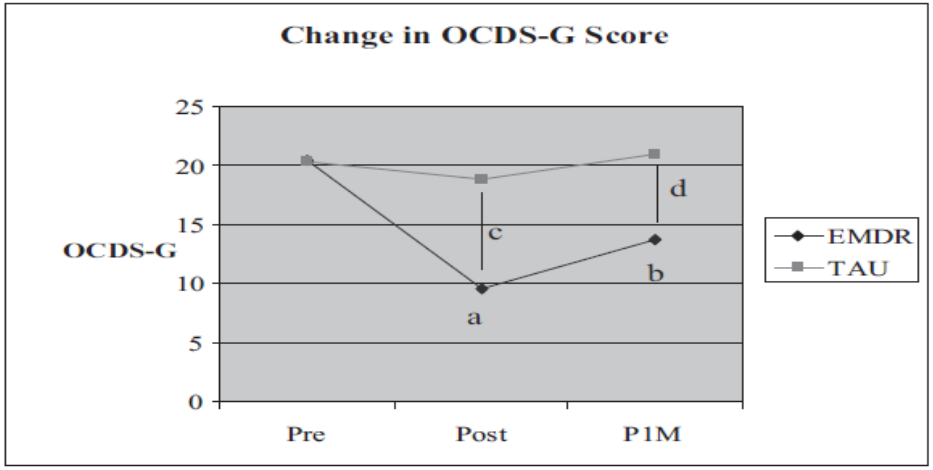


FIGURE 2. Changes in Obsessive–Compulsive Drinking Scale.

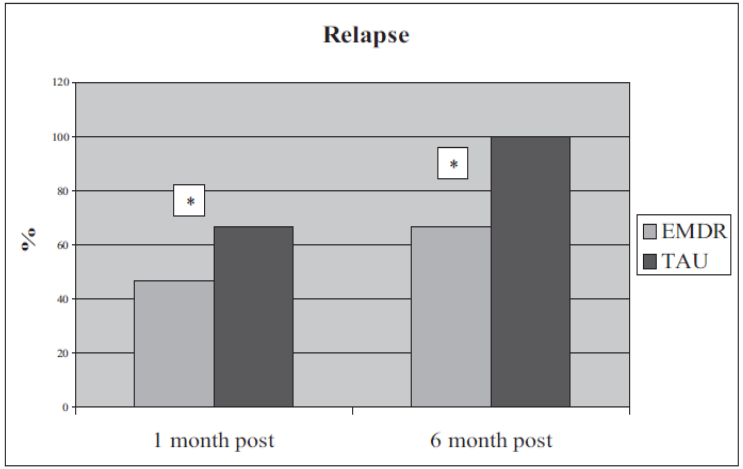


FIGURE 3. Number of relapses in EMDR and TAU.

Markus et al. BMC Psychiatry (2015) 15:51
DOI 10.1186/s12888-015-0431-z

BMC Psychiatry

STUDY PROTOCOL Open Access

A multi-site randomized study to compare the effects of Eye Movement Desensitization and Reprocessing (EMDR) added to TAU versus TAU to reduce craving and drinking behavior in alcohol dependent outpatients: study protocol

Wiebren Markus[1,2,3*], Gerdien H de Weert – van Oene[2,4], Eni S Becker[3] and Cor AJ DeJong[2]

RCT: 2 x 50 patiënten met alcoholafhankelijkheid

TAU vs tau + 7 sessies EMDR van elk 90 minuten

Primaire uitkomst: drinkgedrag

Secundaire uitkomsten: veiligheid, acceptatie, QoL

Resultaten:

Psychotherapie voor alcohol afhankelijkheid Online behandelingen Voorzorg

With few exceptions, across the systematic reviews eligible for this review, computer-based alcohol interventions are reported as being more effective in reducing alcohol consumption than control groups, albeit to different degrees. Effect sizes are mostly in the small range reflecting a weekly reduction of between two and three UK units or between one and 2.5 European units. Furthermore, effects seem to decay over time and may disappear completely after more than 12 months, although few studies include such long follow-ups. Interventions on students tend to render slightly smaller effects on alcohol consumption than interventions on adults/non-students. The impact of interventions on frequency of binge drinking and harm is not clear. Regarding moderators, there is at present no clear evidence for the superiority of one therapeutic orientation over another. There is mixed evidence of an association between length of intervention and outcome; some reviews found support for the hypothesis that the longer the length or duration of an intervention, the larger its effects, but not all. There is also mixed evidence for an added effect of guidance. Lastly, there is a lack of evidence regarding impact of trial engagement on outcome, with only one review addressing this issue quantitatively.

Computer-Based Interventions for Problematic Alcohol Use: a Review of Systematic Reviews

Christopher Sundström[1] · Matthijs Blankers[2,3,4] · Zarnie Khadjesari[5,6]

Int.J. Behav. Med. 2016

Bevindingen

* consistent, maar gemiddeld klein effect met vermindering van 2-3 glazen/week
* effect neemt af over de tijd en weinig aanwijzingen van effect > 6 maanden
* effect op binge drinking en schade nog niet overtuigend aangetoond
* geen voorkeur voor therapeutisch model
* mogelijk enig effect van duur interventie
* enige aanwijzingen dat “blended” werkt

Internet Therapy Versus Internet Self-Help Versus No Treatment for Problematic Alcohol Use: A Randomized Controlled Trial

Matthijs Blankers
Academic Medical Center, University of Amsterdam, and Arkin

Maarten W. J. Koeter
Academic Medical Center, University of Amsterdam

Gerard M. Schippers
Academic Medical Center, University of Amsterdam, and Arkin

2011

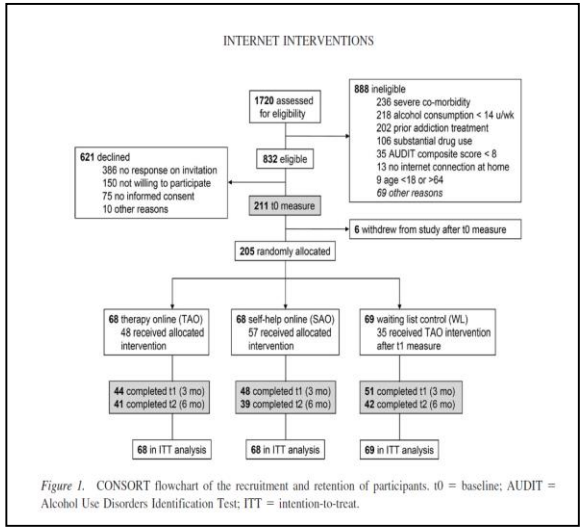
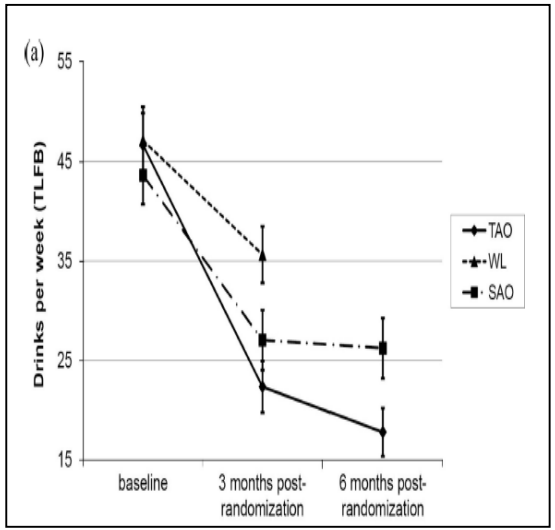
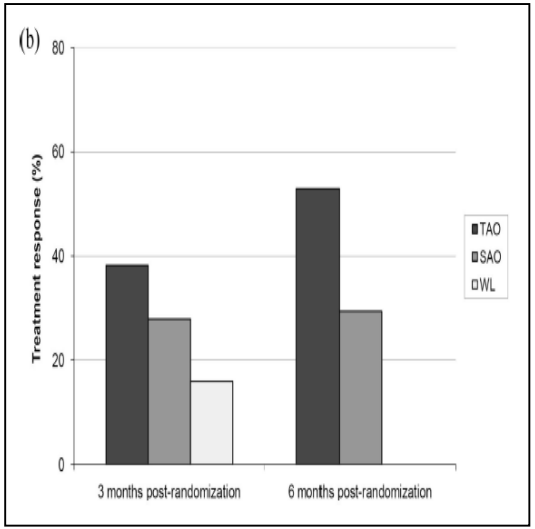


Figure 1. CONSORT flowchart of the recruitment and retention of participants. t0 = baseline; AUDIT = Alcohol Use Disorders Identification Test; ITT = intention-to-treat.





1720 gescreend, 832 geschikt, 205 (12%) gerandomiseerd

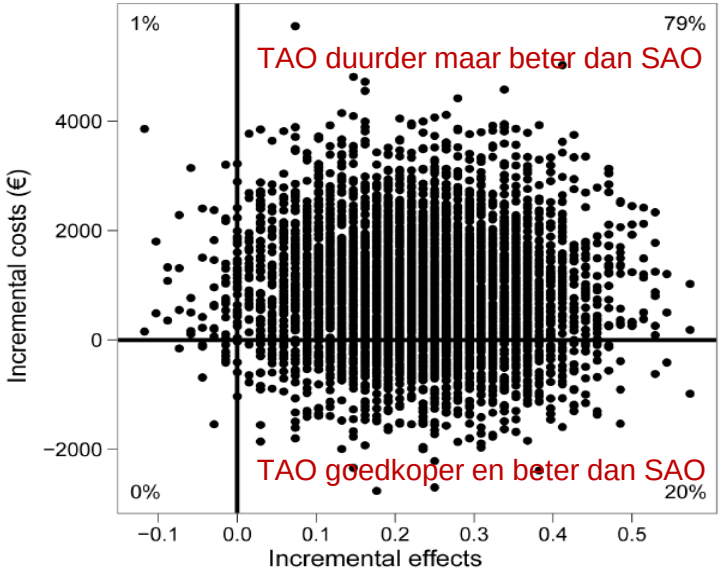
Internet-therapie (TAO = selfhelp + 7x40’ chats) is effectiever dan internet selfhelp (SAO) wat effectiever is dan wachtlijst (WL)

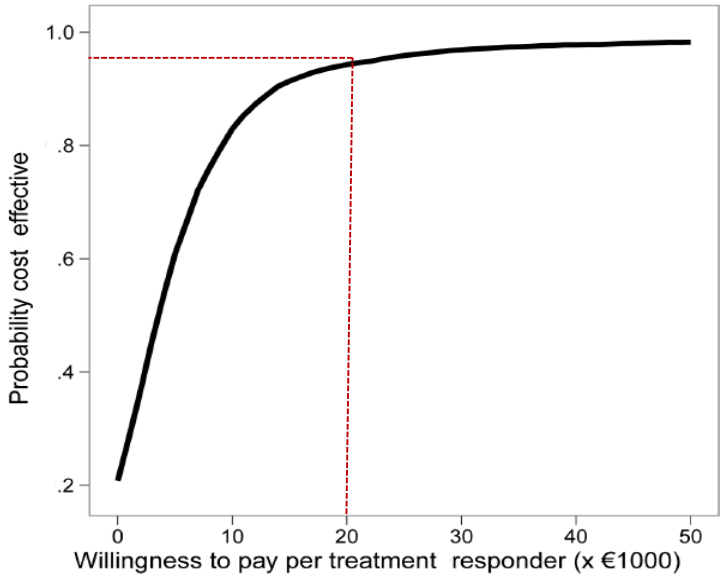
Economic Evaluation of Internet-Based Interventions for Harmful Alcohol Use Alongside a Pragmatic Randomized Controlled Trial

2012

Matthijs Blankers[1,2], PhD; Udo Nabitz[1], PhD; Filip Smit[3,4], PhD; Maarten WJ Koeter[2], PhD; Gerard M Schippers[2], PhD

Figure 2. Cost effectiveness plane (left) and cost effectiveness acceptability curve (right) with treatment response as the effect measure.





Guided and Unguided Internet-Based Treatment for Problematic Alcohol Use – A Randomized Controlled Pilot Trial

2016

Christopher Sundström[1]*, Mikael Gajecki[1], Magnus Johansson[1,2,3], Matthijs Blankers[4,5,6], Kristina Sinadinovic[1,3], Erik Stenlund-Gens[7], Anne H. Berman[1,3]

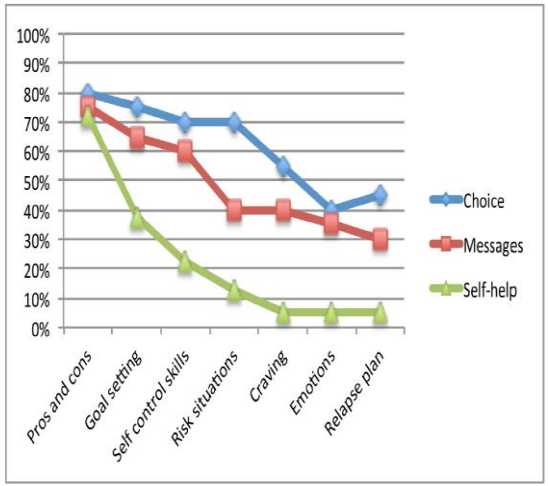


Fig 2. Proportion of participants completing each module in the two guidance groups (by choice or messages) and in the self-help group.

Table 2. Participant evaluations of the treatment at follow-up.

	Guidance: Choice (n = 16)	Guidance: Messages (n = 15)	Self-help (n = 19)
How did you like having contact with your counselor/treatment solely via the Internet? (scale 1–5) Was it…			
pleasant?	4.3 (SD = 1.1)	4.2 (SD = 3.7)	3.7 (SD = 1.4)
safe?	4.3 (SD = 1.1)	4.4 (SD = 0.8)	3.7 (SD = 1.8)
personal?	3.7 (SD = 1.0)	3.7 (SD = 1.4)	2.2 (SD = 1.6)
Did you miss (other kinds of) contact with your counselor, like through phone or face-to-face contact? Percent replying "yes"	25%	20%	65%
Do you consider the program an effective method for changing your drinking habit? Yes %	75%	80%	29%
Would you recommend the program to others? Yes %	81%	93%	47%
Did your willingness to seek professional help for your drinking problem in regular treatment increase during the program? Yes %	31%	20%	29%
Did you experience an increased insight into the following? Percent (%) answering "Yes"			
Your risk situations	94%	87%	65%
Your risk feelings	75%	73%	71%
Your risk thoughts	88%	87%	59%
The advantages of your alcohol consumption	56%	73%	41%
The disadvantages of your alcohol consumption	94%	93%	76%

Met SH+chats meer therapietrouw en meer tevreden dan met SH

Met SH+chats veel betere uitkomsten dan met SH en SH+berichten

Psychotherapie voor alcohol afhankelijkheid Online behandelingen Nazorg

Smartphone Nazorg

A Smartphone Application to Support Recovery From Alcoholism
A Randomized Clinical Trial

David H. Gustafson, PhD; Fiona M. McTavish, MS; Ming-Yuan Chih, PhD; Amy K. Atwood, PhD; Roberta A. Johnson, MA, MEd; Michael G. Boyle, MA; Michael S. Levy, PhD; Hilary Driscoll, MA; Steven M. Chisholm, MA; Lisa Dillenburg, MSW; Andrew Isham, MS; Dhavan Shah, PhD

JAMA Psychiatry. 2014;71(5):566-572. doi:10.1001/jamapsychiatry.2013.4642
Published online March 26, 2014.

Nazorg voor 349 patiënten met alcoholafhankelijkheid na klinische behandeling

* randomisatie nazorg: 8 maanden TAU vs. 8 maanden TAU+A-CHESS
* follow-up 4 maanden
* uitkomst: risky drinking days (4-5 glazen binnen 2 uur) laatste 30 dagen

A-CHESS = Addiction-Comprehensive Health Enhancement Support System

Smartphone Nazorg

Table 2. Group Differences on Risky Drinking Days Overall and by Month[a]

Effect	Mean (SE)		Mean Difference (95% CI)	t_{df}	*P* Value	*d*[b]	*h*
	Control	A-CHESS					
Analysis of all available data[c]							
Overall	2.75 (0.34)	1.39 (0.34)	1.37 (0.46 to 2.27)	$2.98_{287.69}$	.003	.23	.18
By month							
4	3.01 (0.48)	1.50 (0.47)	1.52 (0.24 to 2.80)	$2.32_{802.26}$	.02	.25	.19
8	2.65 (0.48)	1.54 (0.49)	1.11 (−0.20 to 2.42)	$1.67_{809.01}$	.10	.18	.15
12	2.60 (0.49)	1.13 (0.50)	1.47 (0.13 to 2.81)	$2.15_{819.05}$	.03	.24	.21

Table 3. Prevalence and Odds of Abstinence by Month[a]

Characteristic	Abstinence				OR (95% CI)	*P* Value[d]
	Prevalence, No. (%)[b]		Odds[c]			
	Control	A-CHESS	Control	A-CHESS		
Months						
4	105 (67.7)	118 (75.6)	2.10	3.11	1.48 (0.90-2.43)	.13
8	101 (66.9)	114 (78.1)	2.02	3.56	1.7 (1.05-2.96)	.04
12	95 (65.5)	107 (78.7)	1.90	3.69	1.94 (1.14-3.31)	.02
4, 8, and 12[e]	63 (39.6)	81 (51.9)	0.66	1.08	1.65 (1.05-2.57)	.03

Nazorg met TAU+A-CHESS leidt tov van TAU tot significante vermindering aantal “risky drinking days” (1.39 vs. 2.75; p=0.003) en tot grotere kans op continue abstinentie (51.9% vs. 39.6%, NNT=8, p=0.03)

Neuromodulatie voor alcohol afhankelijkheid

Retraining Automatic Action Tendencies Changes Alcoholic Patients' Approach Bias for Alcohol and Improves Treatment Outcome

Psychological Science
22(4) 490–497

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SAGE

2011

Reinout W. Wiers[1], Carolin Eberl[2], Mike Rinck[3], Eni S. Becker[3], and Johannes Lindenmeyer[2]
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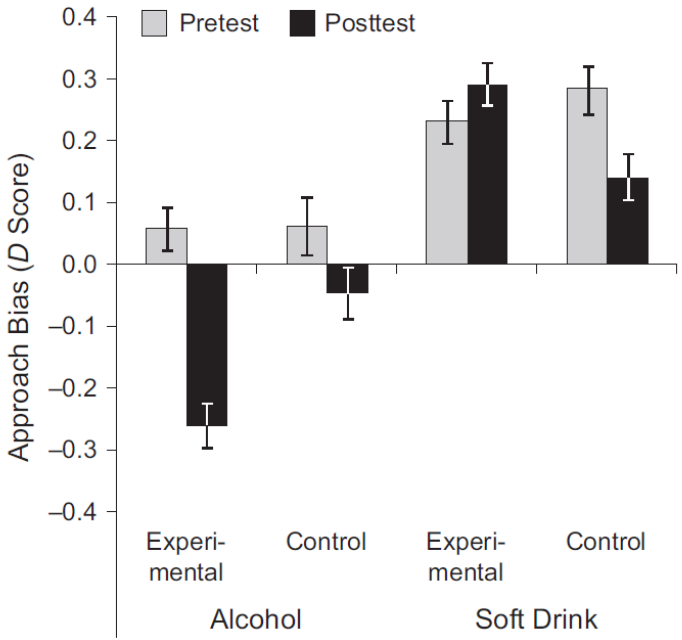


Table 2. Logistic Regression Results for Treatment Outcome 1 Year After Treatment Discharge

Variable	*b*	*SE b*	Wald *z*	*p*
Gender	0.880	0.358	6.03	.014
Duration of alcohol problem (years)	0.033	0.018	3.59	.058
Number of detoxifications	−0.028	0.027	1.05	.31
Alcohol problems (AUDIT score)	−0.026	0.020	1.61	.20
Duration of treatment (days)	0.008	0.009	0.82	.36
Depression (BDI score)	−0.025	0.022	1.25	.26
Mental burden (SCL-90-R score)	0.022	0.020	1.25	.26
Condition (experimental, control)	0.760	0.299	6.46	.011

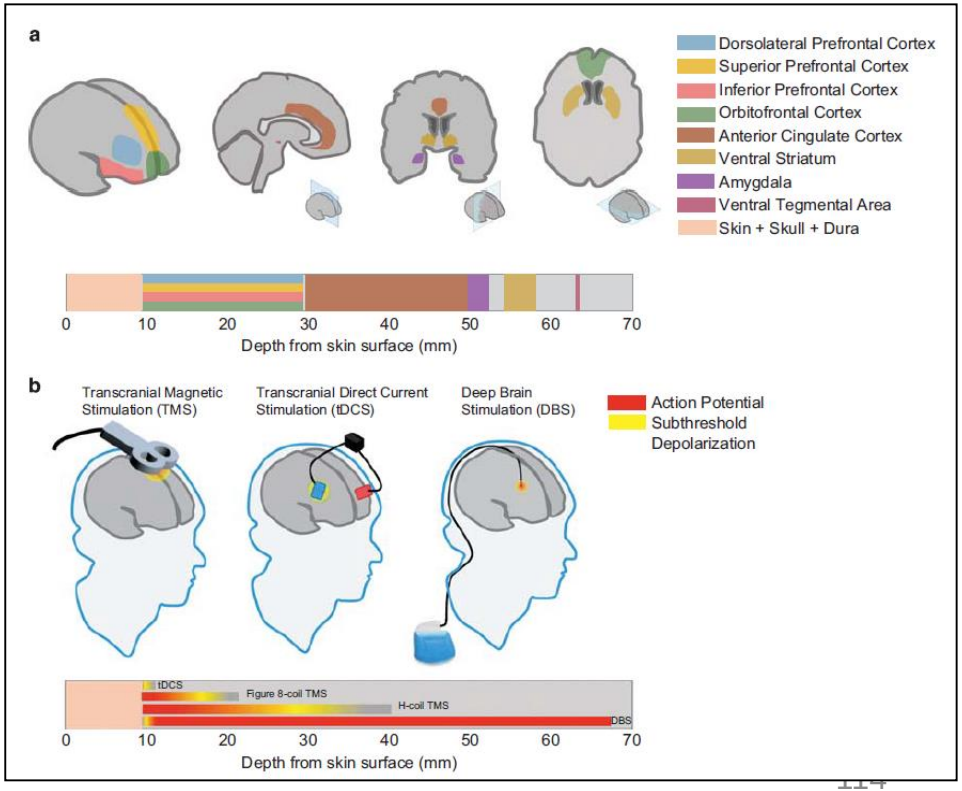
Review

Brain Stimulation in Addiction

Michael C Salling*,1 and Diana Martinez2,3

Neuropsychopharmacology (2016)

Alcoholafhankelijkheid



High Frequency rTMS

* 5 studies 8-coil, 2 studies H-coil
* 8-coil: inconsistent minder craving
* H-coil: minder craving

tDCS

* 4 studies
* inconsistent minder craving

DBS (ventraal striatum)

* 2 studies: 5 patiënten + 1 casus
* consistent minder craving
* 2-3/6 abstinent

Addiction

SSA SOCIETY FOR THE STUDY OF ADDICTION

EDITORIAL

doi:10.1111/add.12773

Is deep brain stimulation a treatment option for addiction?

2014

DBS is mogelijk effectief bij de behandeling van verslaafden, maar het lukt vooralsnog niet om in Europa voldoende grote studies uit te voeren om effectiviteit/veiligheid vast te stellen

JUDY LUIGJES[1,2], WIM van den BRINK[1,2], P. RICHARD SCHUURMAN[3], JENS KUHN[4] & DAMIAAN DENYS[1,2,5]

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Conclusies

Conclusions Behandeling Alcoholafhankelijkheid

- Nieuwe theoretische inzichten zorgen voor nieuwe behandelingen
- Er zijn veel nieuwe ontwikkelingen in de farmacotherapie, maar grote effecten blijven uit
- Polyfarmacie en personalized medicine hebben de (nabije) toekomst!
- Er zijn veel nieuwe ontwikkelingen in de psychotherapie, zowel in de vroege fase bij minder ernstig zieke patienten als in de nazorg
- Neuromodulatie staat nog in de kinderschoenen en het is onduidelijk wat de toekomst zal brengen.

Dank U voor Uw aandacht!

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