Treatment of Alcohol Use Disorders
New Options for Better Outcomes

Wim van den Brink, MD PhD
Amsterdam University Medical Centers, location AMC
Amsterdam, The Netherlands

Amsterdam UMC
Universitair Medische Centra

amC

Nordic Reform Conference 2019
Oslo, 20 September 2019

NORDIC REFORM CONFERENCE

Disclosure

Interest	Name of organization
Grants	Alkermes
Honoraria	Lundbeck, Merck Serono, Eli Lilly, Indivior, Pfizer, Angelini
Advisory Board/Consultant	Lundbeck, Merck Serono, Indivior, Mundipharma, D&A Pharma, Bioproject, Novartis, Kinnov Therapeutics, Opiant Pharmaceuticals, Takeda

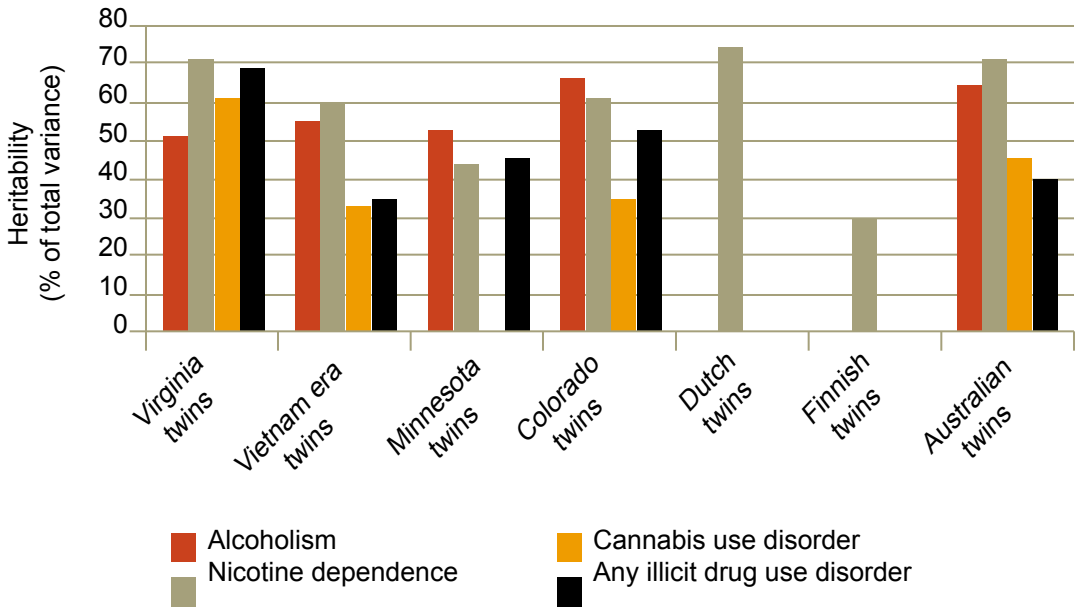
Content

- Addiction a treatable brain disorder
- Many new neurobiological and psychological treatments
- New treatment goals
- Role of substitution treatment
- Compliance, polypharmacy, and precision medicine
- New paradigms
- Conclusions

Addiction a Treatable Brain Disorder

Heritability estimates

Heritability estimates for alcohol dependence, nicotine dependence, cannabis and other illicit drug use disorders across samples of twins



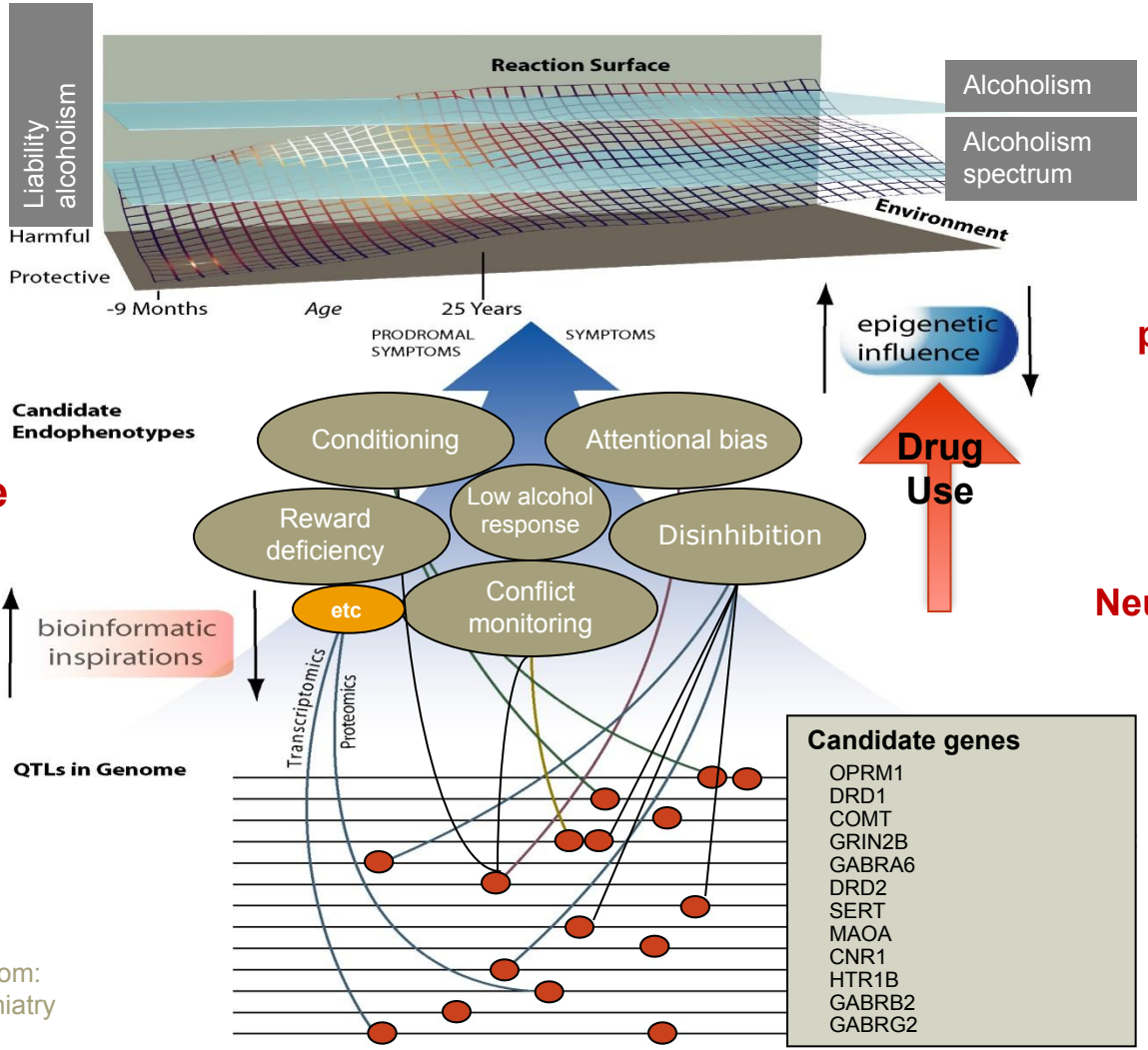
Type of dependence	Heritability
Alcohol	50–70%
Nicotine	50–75%
Cannabis	35–75%
Cocaine	35–80%
Heroin	40–60%

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

Phenotype

Endophenotype

Genotype



Social support

Insight-oriented psychotherapy

CBT

Medication Neuromodulation

Pharmaco-genetics

Gene therapy

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

Neurobiology of addiction

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, Hippocampus Thalamus Prefrontal cortex (OFC, ACC)	Dynorphins (κ-receptors) Dopamine CRH Glutamate
Attentional bias/ salience	OFC VMPFC	Dopamine
Habit formation	Putamen, Nc caudatus (dorsal striatum)	Dopamine
Withdrawal	Locus coeruleus	Noradrenalin, CRH Glutamate

Naive

Experimenting
moderate use

Binging

Abuse

Dependence
(craving)

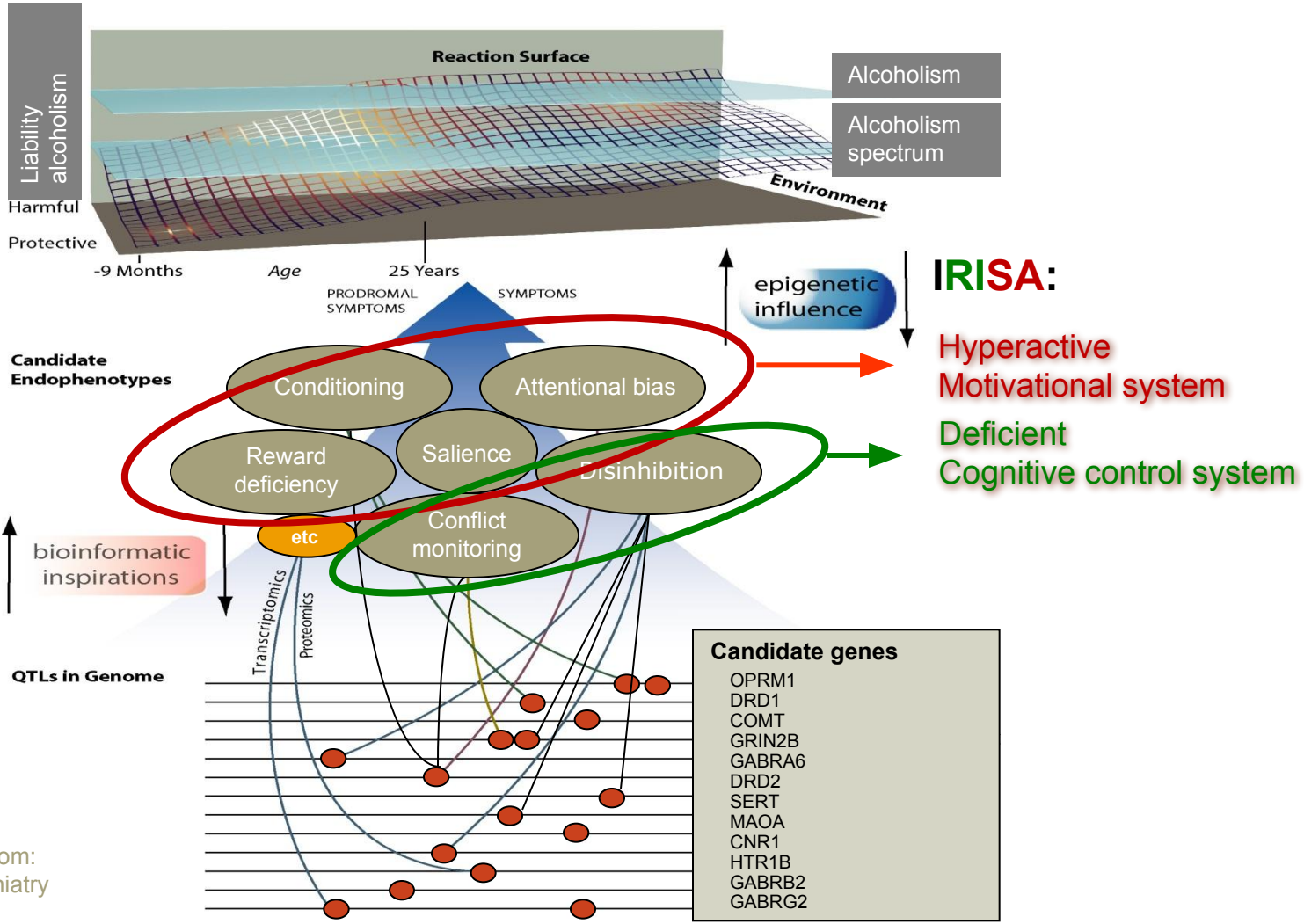
Addiction
(compulsive use)

Van Ree. 2002; de Vries & Schippenberg. 2002; Kreek et al. 2002; Van den Brink. 2006; Volkow. 2004; Koob & Volkow. 2010

Fenotype

Endofenotype

Genotype



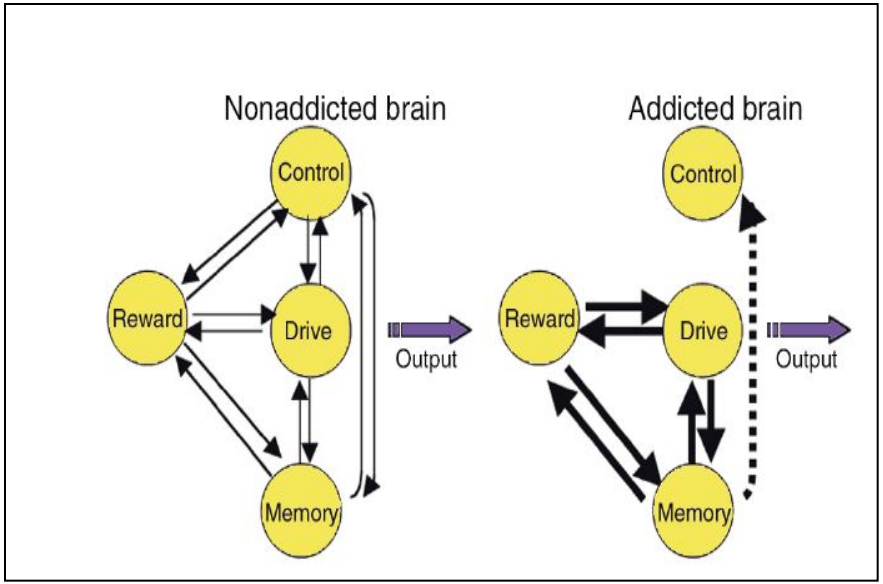
Ooteman et al (2006) adapted from:
Gottesman & Gould. Am J Psychiatry 2003;160:636–645

Brain Structures and Functions in Addiction

The addicted human brain: insights from imaging studies

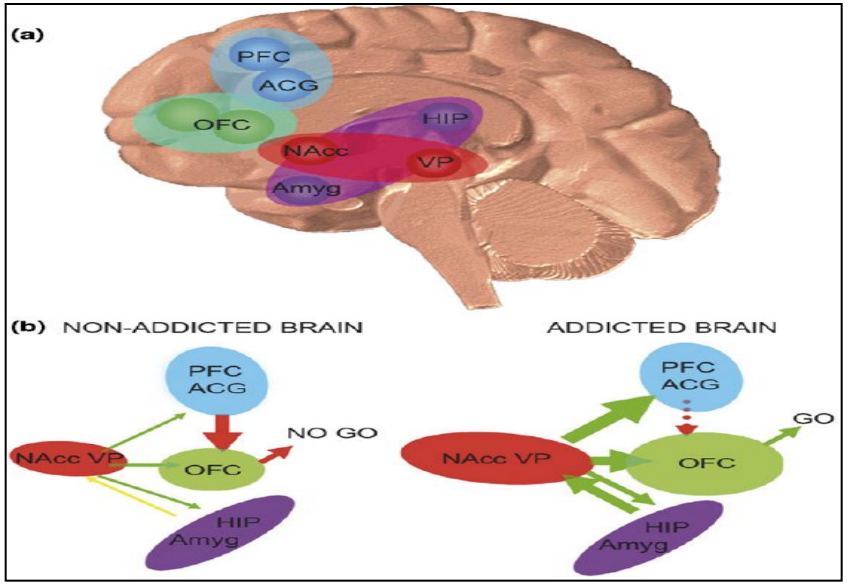
J. Clin. Invest. **111**:1444–1451 (2003)

Nora D. Volkow,[1,2] Joanna S. Fowler,[3] and Gene-Jack Wang[1]



Drug addiction: the neurobiology of disrupted self-control 2006

Ruben D. Baler and Nora D. Volkow *TRENDS in Molecular Medicine* Vol.12 No.12



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

Neurobiology of addiction

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Dependence
(craving)

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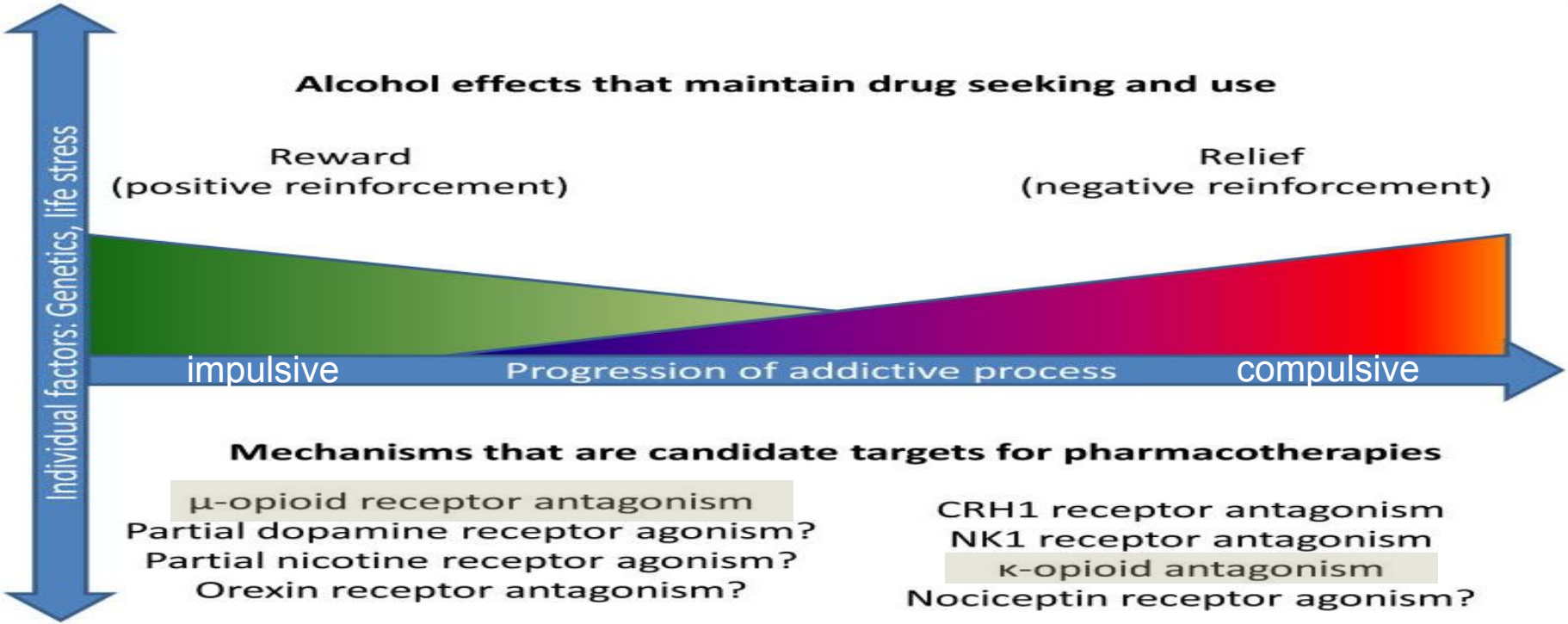
(compulsive use)

Van Ree. 2002; de Vries & Schippenberg. 2002; Kreek et al. 2002; Van den Brink. 2006; Volkow. 2004; Koob & Volkow. 2010

From reward to relief and from impulsive to compulsive



Adapted from Heilig et al., 2010

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

Conceptual Treatment Models Pharmacological Tx

Model for Pharmacotherapy of Addiction

Repeated reward

Antagonist

Attentional bias → Cue-reactivity

Stress

Drug-related stimulus

Anti-stress medication

Detection threshold

Anti-craving medication

Craving

Inhibition

Cognitive enhancer

Agonist

Relapse

Conflict registration

Pharmacotherapy Alcohol Use Disorder

Repeated reward

Antagonist

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

Attentional bias → Cue-reactivity

Drug-related stimulus

Stress

Anti-stress drug

doxazosine

Detection threshold

Anti-craving drug

- **Acamprosate**
- Topiramate?
- LD Baclofen
- Varenicline??

Craving

Inhibition

Cognitive enhanc

- Modafinil?
- LSD/Psilocybin?

Agonist

- HD Baclofen?
- Sodium Oxybate?
- Gabapentin?
- C_2H_5OH (alcohol)

Relapse

Conflict

Problems with potentially new medications

- Many of the new medications are already out of patent
- Testing new compounds for AUDs is risky for pharmaceutical industry
- Not very likely that all these promising medications will be EMA/FDA registered

- New role for professional, patient and political organisations
- **Non-registered medications with “enough” scientific support in guidelines!**
- **Reimburse off-label prescriptions by specialist as off-label prescriptions!**
- **Monitor the use, outcomes and potential adverse events!**

Conceptual Treatment Models
Psychological Tx

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

Neuroimaging the Effectiveness of Substance Use Disorder Treatments

Elizabeth A. Cabrera[1] · Corinde E. Wiers[1] · Elsa Lindgren[1] · Gregg Miller[1] · Nora D. Volkow[1,2] · Gene-Jack Wang[1]

J Neuroimmune Pharmacol (2016) 11:408–433

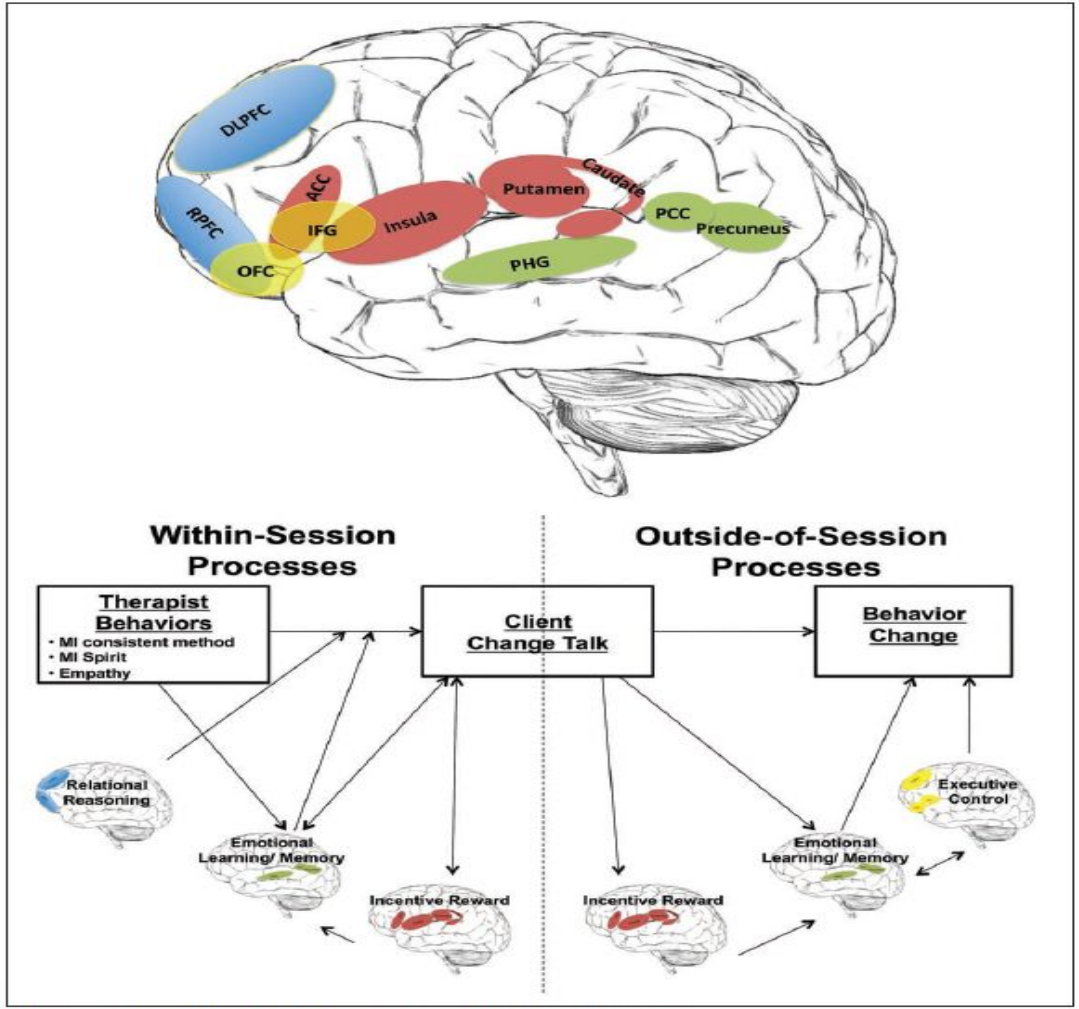
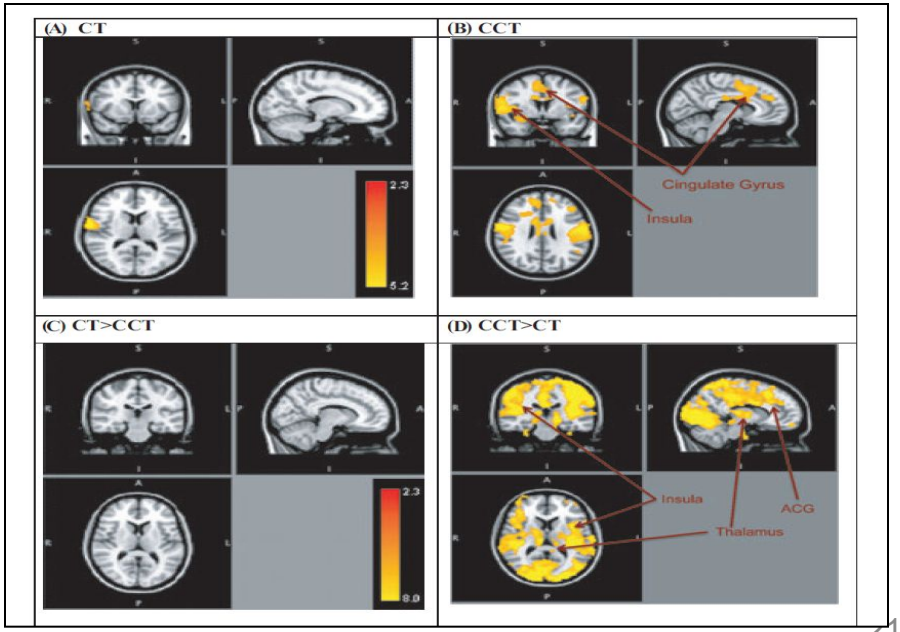


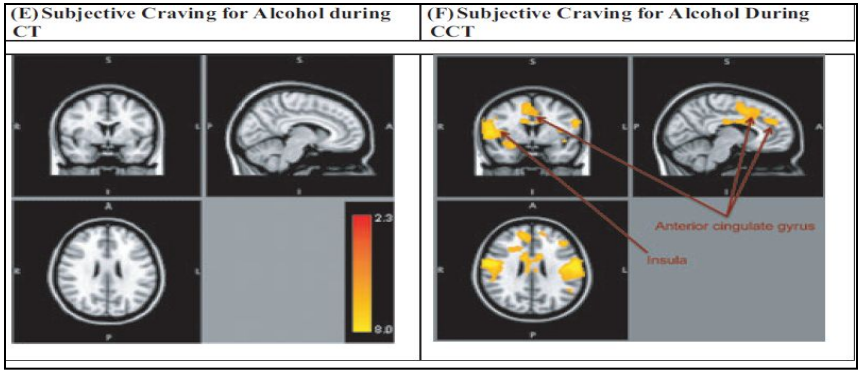
FIGURE 2. Neural circuitry associated with the proposed model; MI – motivational interviewing

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

Model for Psychotherapy of Addiction

Repeated reward

Counterconditioning

Attentional bias → Cue-reactivity

Drug-related stimulus

Stress

CBT
Mindfulness

Detection threshold

CET
(+DCS)
Act
MBRP
EMDR?

Craving

Inhibition

MET
Working
Memory
Training

CM
CRA

Relapse

Conflict registration

Conclusions and remaining issues

- Many pharmacological interventions for alcohol (nicotine and opioid) dependence
- Very few pharmacological interventions for stimulant and cannabis dependence
- Many psychological interventions for all addictions

- **BUT**

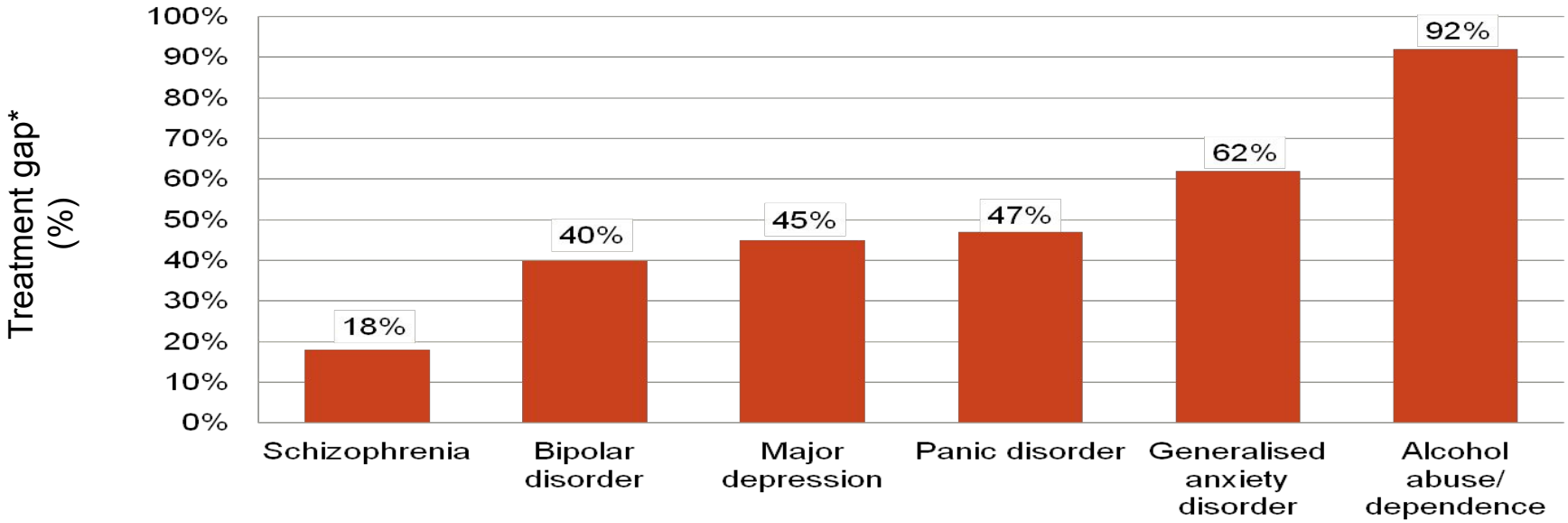
- Do patients and therapists want all these treatments?
  * abstinence vs. reduced/controlled drinking
  * agonists (often liked by patients) vs. antagonists (often liked by therapists)
  * change vs. acceptance of craving

- How effective are these interventions?
  * compliance, polypharmacy, precision medicine

- New paradigms ?

New Treatment Goals

Treatment gap in alcohol dependence

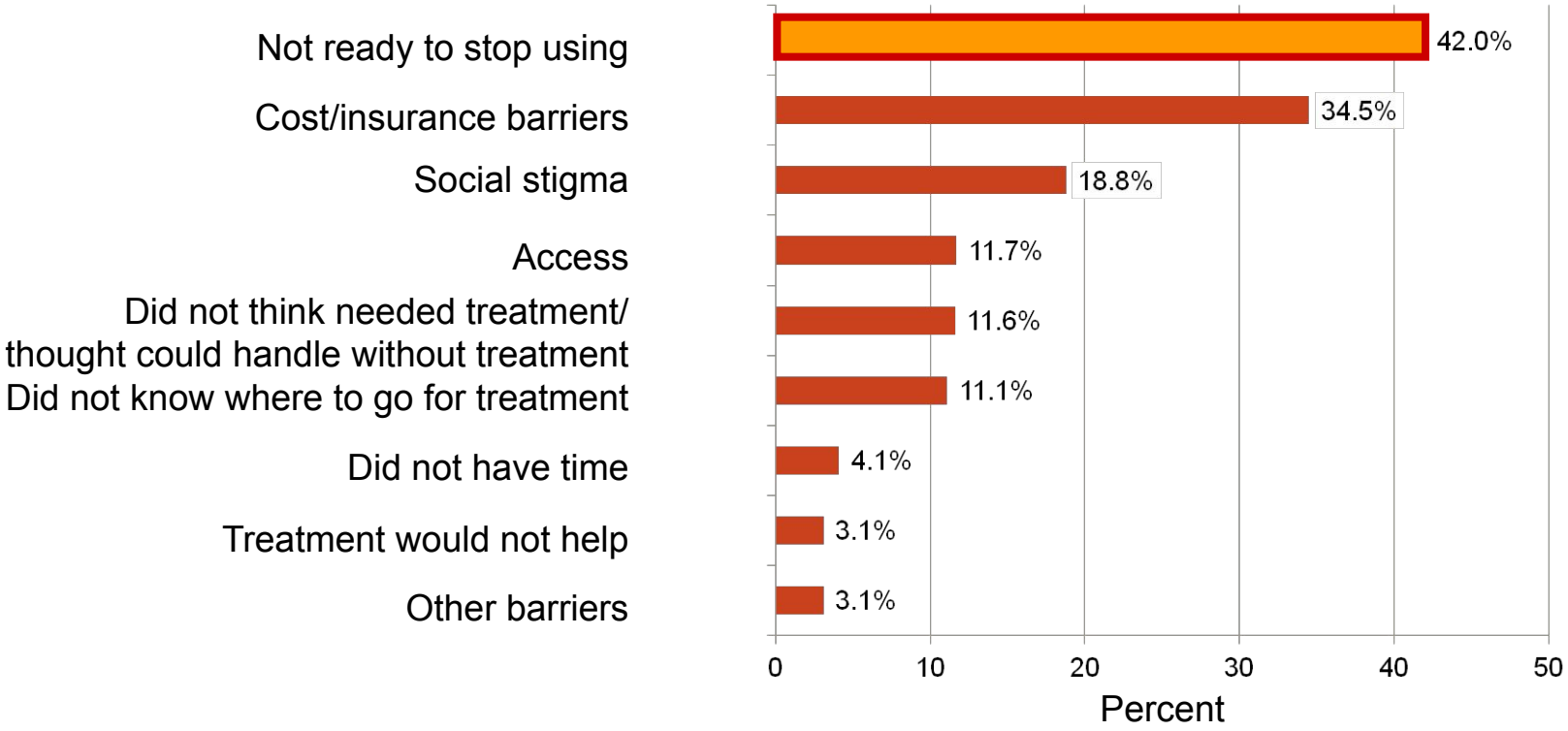


Alcohol abuse and dependence have the widest treatment gap among all mental disorders – less than 10% of European patients with alcohol abuse and dependence are treated

Kohn et al. Bull World Health Organ 2004;82:858–866

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

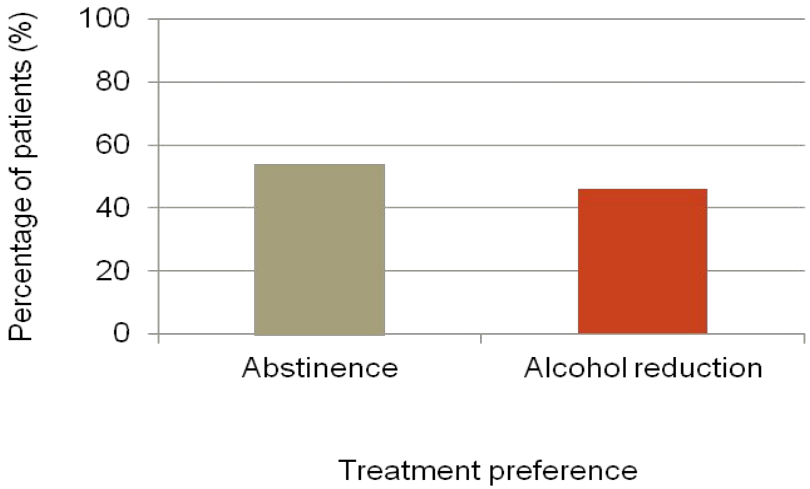
Reasons for not seeking AD treatment



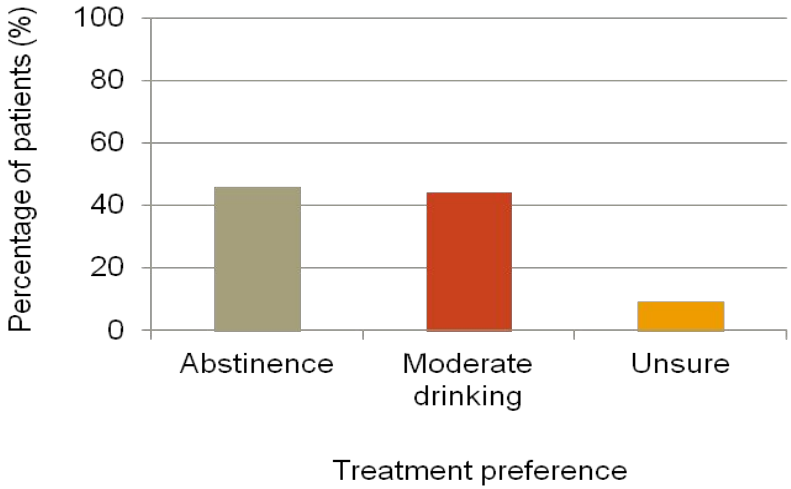
SAMHSA 2007, National Survey on Drug Use and Health (NSDUH)

Treatment Preference (UK & Canada)

UK survey of patients with alcohol problems (n=742)
Heather et al. Alcohol Alcohol 2010;45(2):128–135



Canadian study of patients with chronic alcoholism (n=106)
Hodgins et al. Addict Behav 1997;22(2):247–255



Need for alcohol reduction intervention

Effective Pharmacotherapy Alcohol Dependence

Treatment Goal	1st Choice	2nd Choice	3rd Choice
Abstinence ↕ Reduced Drinking	**Acamprosate** (NNT=11) **Naltrexone??** (NNT=20)	**Disulfiram** (NNT=25; NS)*	Baclofen? Sodium Oxybate?
Abstinence ↕ Reduced Drinking	**Naltrexone#** (NNT=11) **Nalmefene?**	Topiramate?	Gabapentin? Modafinil?? Varenicline? Doxasozine??

* no supervision
# off-label

First choice registered reduced drinking medication?
(and many 2nd and 3rd choice medications)

Review

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

Jan van Amsterdam* and Wim van den Brink[1]

Psychopharm

Journal of Psychopharmacology
27(11) 987–997

DOI: 10.1177/0269881113495320
jop.sagepub.com
SAGE

Maintenance of World Health Organization Risk Drinking Level Reductions and Posttreatment Functioning Following a Large Alcohol Use Disorder Clinical Trial

Katie Witkiewitz, Daniel E. Falk, Raye Z. Litten, Deborah S. Hasin, Henry R. Kranzler, Karl F. Mann, Stephanie S. O'Malley, and Raymond F. Anton

Alcohol Clin Exp Re, Vol **, No *, 2019: pp 1–9

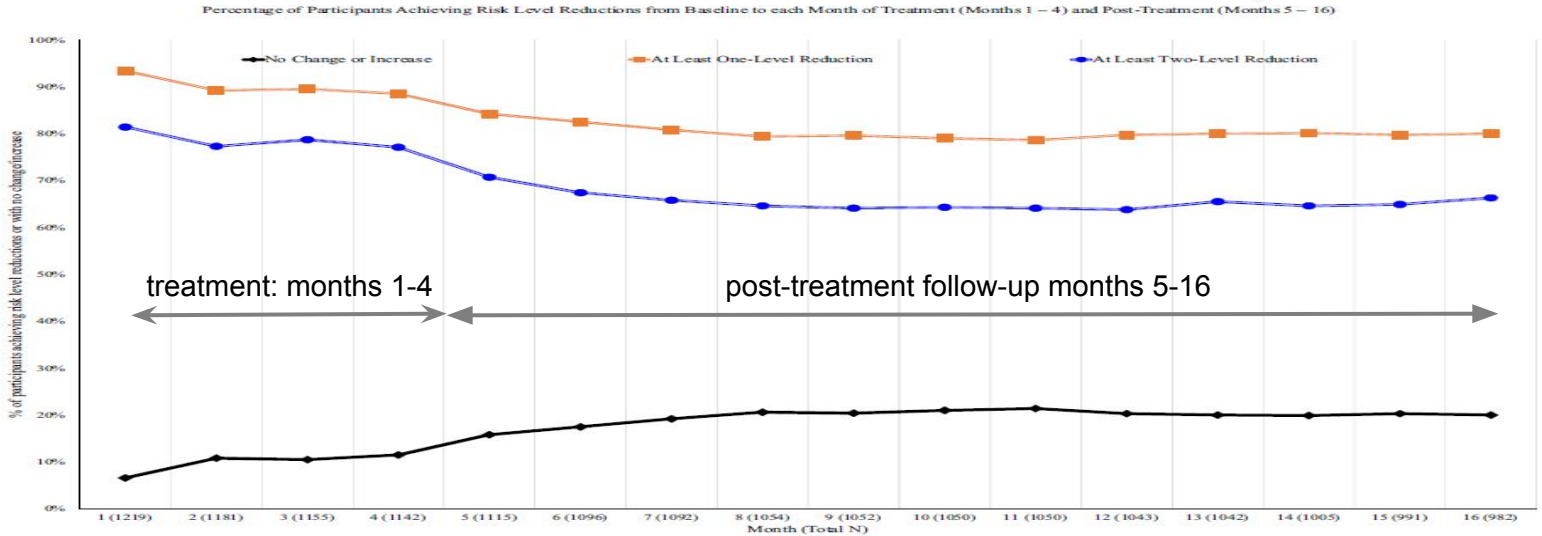
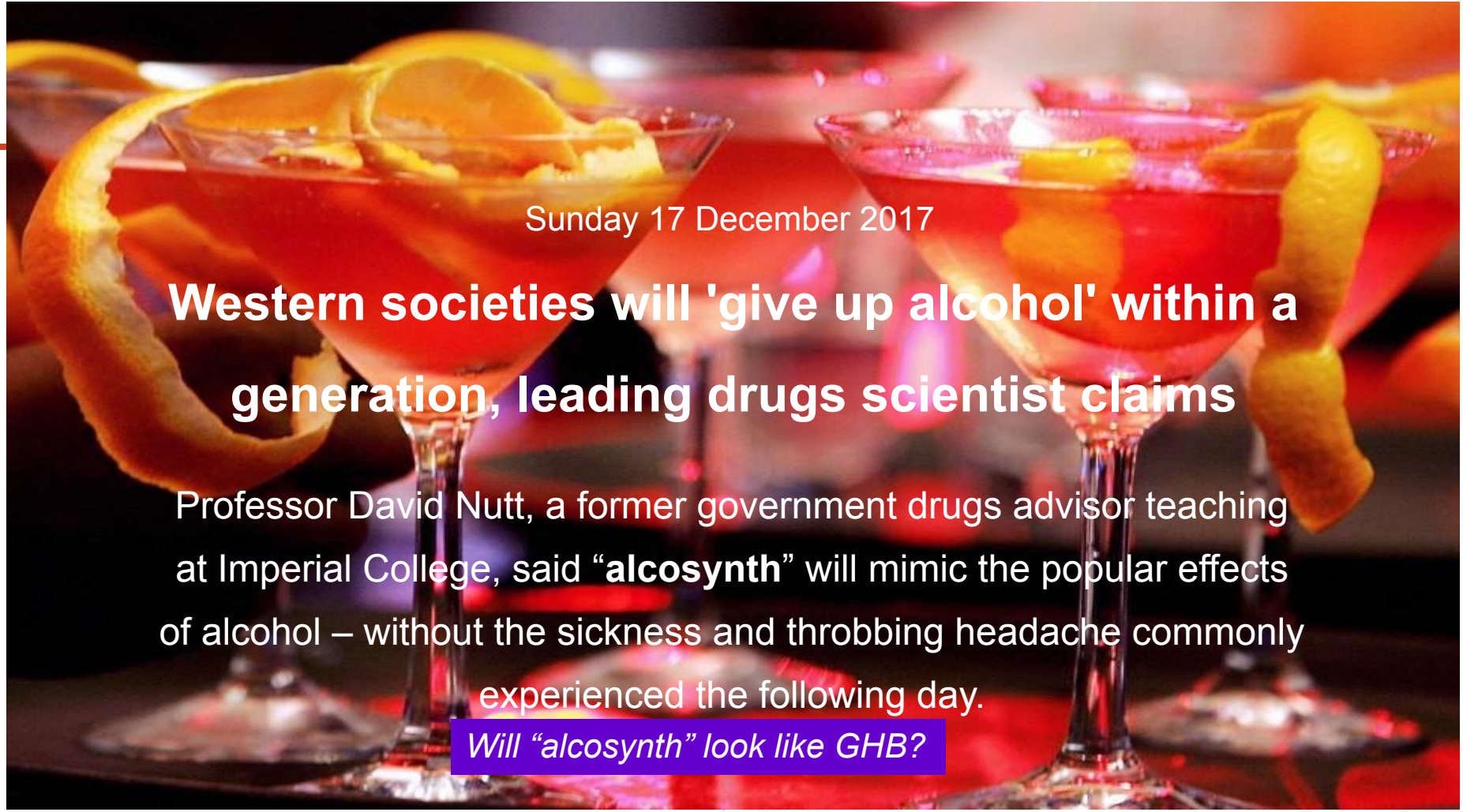


Fig. 2. Percentage of participants achieving WHO risk level reductions from baseline to each month of treatment (months 1 to 4) and posttreatment (months 5 to 16).

Witkiewitz et al., in press (Addiction): sustainability of reduced drinking independent of baseline severity

Role of Substitution Treatment



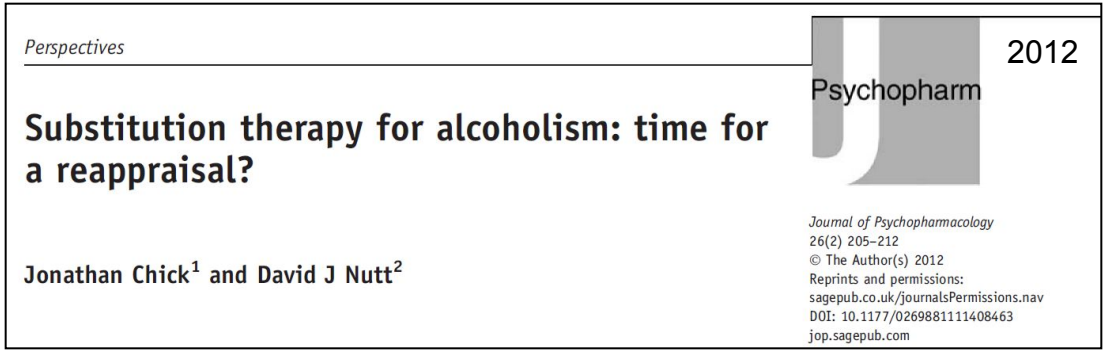
Sunday 17 December 2017

Western societies will 'give up alcohol' within a generation, leading drugs scientist claims

Professor David Nutt, a former government drugs advisor teaching at Imperial College, said “**alcosynth**” will mimic the popular effects of alcohol – without the sickness and throbbing headache commonly experienced the following day.

Will “alcosynth” look like GHB?

Position papers



Perspectives

2012

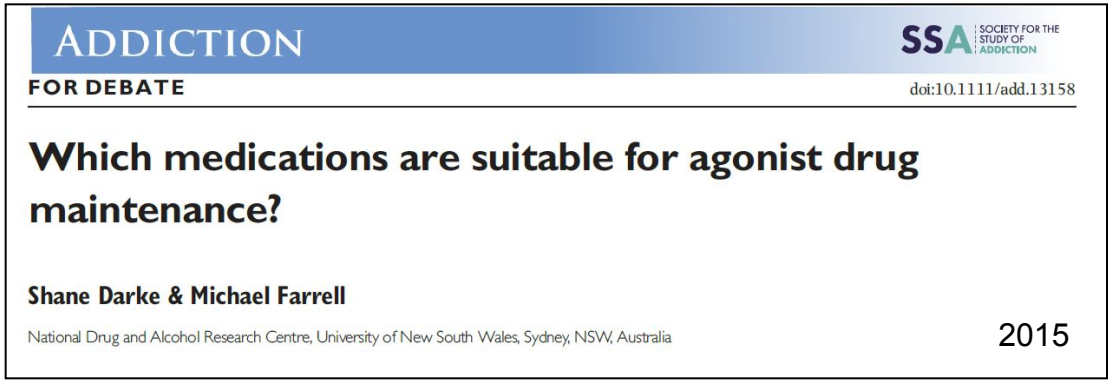
Substitution therapy for alcoholism: time for a reappraisal?

Psychopharm

Jonathan Chick[1] and David J Nutt[2]

Journal of Psychopharmacology
26(2) 205–212

DOI: 10.1177/0269881111408463
jop.sagepub.com



ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

FOR DEBATE

doi:10.1111/add.13158

Which medications are suitable for agonist drug maintenance?

Shane Darke & Michael Farrell

National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW, Australia

2015

Requirements:

* Agonist (effect)
* Oral use with longer effect
* Low toxicity

Safety measures

* Tx setting: specialist+support
* Combine with psychosocial
* Define outcomes

Effective Pharmacotherapy Alcohol Dependence

Treatment Goal	1st Choice	2nd Choice	3rd Choice
Abstinence ↕ Reduced Drinking	**Acamprosate** (NNT=11) **Naltrexone??** (NNT=20)	**Disulfiram** (NNT=25; NS)*	**Baclofen?** **Sodium Oxybate?**
	Naltrexone# (NNT=11) **Nalmefene?**	Topiramate?	**Gabapentin?** Modafinil?? Varenicline? Doxasozine??

* no supervision
# off-label

Third choice substitution medications

New Issues in treatment of AD

Addiction Biology
SSA SOCIETY FOR THE STUDY OF ADDICTION
ORIGINAL ARTICLE
doi:10.1111/adb.12645

Efficacy and safety of sodium oxybate in alcohol-dependent patients with a very high drinking risk level

Wim van denBrink[1], Giovanni Addolorato[2], Henri-Jean Aubin[3,4], Amine Benyamina[4], Fabio Caputo[5], Maurice Dematteis[6], Antoni Gual[7], Otto-Michael Lesch[8], Karl Mann[9], Icro Maremmani[10], David Nutt[11], François Paille[12], Pascal Perney[13], Jürgen Rehm[14,15,16], Michel Reynaud[17], Nicolas Simon[18], Bo Söderpalm[19], Wolfgang H. Sommer[9,20], Henriette Walter[8] & Rainer Spanagel[20]

Addict Biol. 2018 Jul;23(4):969-986.

Sodium oxybate (GHB)

Baclofen (LD/HD)

The Use of Baclofen as a Treatment for Alcohol Use Disorder: A Clinical Practice Perspective

Renaud de Beaurepaire[1], Julia M. A. Sinclair[2], Mathis Heydtmann[3], Giovanni Addolorato[4,5], Henri-Jean Aubin[5,7,8,9], Esther M. Beraha[10], Fabio Caputo[11], Jonathan D. Chick[12,13], Patrick de La Selle[14], Nicolas Franchitto[15], James C. Garbutt[16], Paul S. Haber[17,18], Philippe Jaury[19], Anne R. Lingford-Hughes[20], Kirsten C. Morley[21], Christian A. Müller[22], Lynn Owens[23], Adam Pastor[24,25], Louise M. Paterson[20], Fanny Pélissier[26], Benjamin Rolland[27,28], Amanda Stafford[29], Andrew Thompson[23], Wim van den Brink[30], Lorenzo Leggio[31,32,33] and Roberta Agabio[34]

Front Psychiatry. 2019 Jan 4;9:708.

Baclofen for the treatment of alcohol use disorder: the Cagliari Statement

*Roberta Agabio, Julia MA Sinclair, Giovanni Addolorato, Henri-Jean Aubin, Esther M Beraha, Fabio Caputo, Jonathan D Chick, Patrick de La Selle, Nicolas Franchitto, James C Garbutt, Paul S Haber, Mathis Heydtman, Philippe Jaury, Anne R Lingford-Hughes, Kirsten C Morley, Christian A Müller, Lynn Owens, Adam Pastor, Louise M Paterson, Fanny Pélissier, Benjamin Rolland, Amanda Stafford, Andrew Thompson, Wim van den Brink, Renaud de Beaurepaire, Lorenzo Leggio

Lancet Psychiatry. 2018 Dec;5(12):957-960.

A meta-analysis of the efficacy of gabapentin for treating alcohol use disorder

ADDICTION

2019

Henry R. Kranzler[1,2], Richard Feinn[3], Paige Morris[1] & Emily E. Hartwell[1,2]

Table 2 Meta-analysis results.

Outcome	*Number of studies*	*Number of subjects*	*Effect[a] size*	*95% CI*	*P-value*
Complete abstinence	6	673	1.33	0.84–2.10	0.23
Relapse to heavy drinking	6	673	0.80	0.57–1.13	0.21
Percentage of days abstinent	4	476	0.26	−0.16 – 0.69	0.23
Percentage of heavy drinking days	7	730	−0.64	−1.22 – −0.06	0.03
Drinks/day	5	652	−0.15	−0.64 – 0.35	0.56
GGT concentration	4	352	−0.12	−0.37 – 0.13	0.39

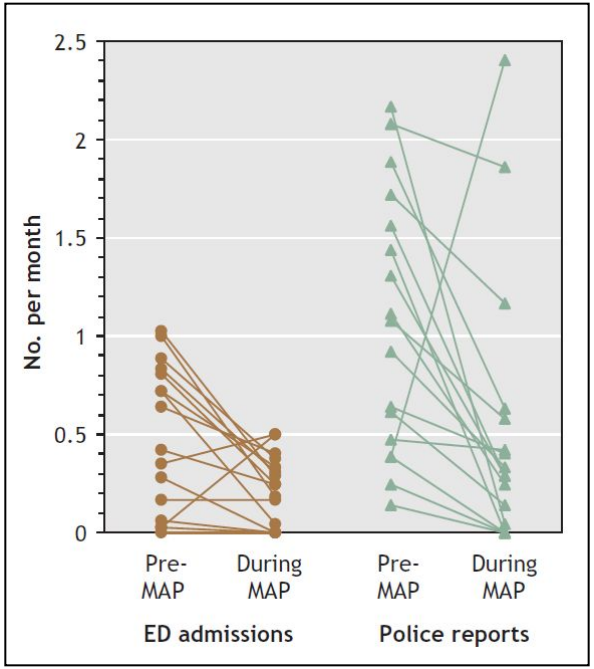
Gabapentin probably only effective in reducing the % of heavy drinking days

Shelter-based managed alcohol administration to chronically homeless people addicted to alcohol

CMAJ

Tiina Podymow, Jeff Turnbull, Doug Coyle, Elizabeth Yetisir, George Wells

CMAJ · JANUARY 3, 2006 · 174(1)



Lower total alcohol intake

Fewer emergency room admissions

Fewer police reports

Does managing the consumption of people with severe alcohol dependence reduce harm? A comparison of participants in six Canadian managed alcohol programs with locally recruited controls

TIM STOCKWELL[1,2], BERNIE PAULY[1,3], CLIFTON CHOW[1], REBEKAH A. ERICKSON[1,2], BONNIE KRYSOWATY[1], AUDRA ROEMER[1,2], KATE VALLANCE[1], ASHLEY WETTLAUFER[4] & JINHUI ZHAO[1]

Drug and Alcohol REVIEW

Drug and Alcohol Review (2017)

Effectiveness of Addiction Tx

Effectiveness of Addiction Tx Medication

Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings
A Systematic Review and Meta-analysis

JAMA May 14, 2014 Volume 311, Number 18

Daniel E. Jonas, MD, MPH; Halle R. Amick, MSPH; Cynthia Feltner, MD, MPH; Georgiy Bobashev, PhD; Kathleen Thomas, PhD; Roberta Wines, MPH; Mimi M. Kim, PhD; Ellen Shanahan, MA; C. Elizabeth Gass, MPH; Cassandra J. Rowe, BA; James C. Garbutt, MD

Systematic review with 123 RCTs (n=22.803)
Meta-analysis with 95 RCTs,
including N=27 acamprosate RCTS (n=7.519) and N=53 naltrexone RCTs (n=9.140)

Results

Acamprosate:	Abstinence	RD=9% □	**NNT=11**
	Heavy drinking	RD=5% □	**NNT=20**
Naltrexone:	Abstinence	RD=1% (ns)	
	Heavy drinking	RD=9% □	**NNT=11**

In direct comparison no difference between acamprosate and naltrexone

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

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]

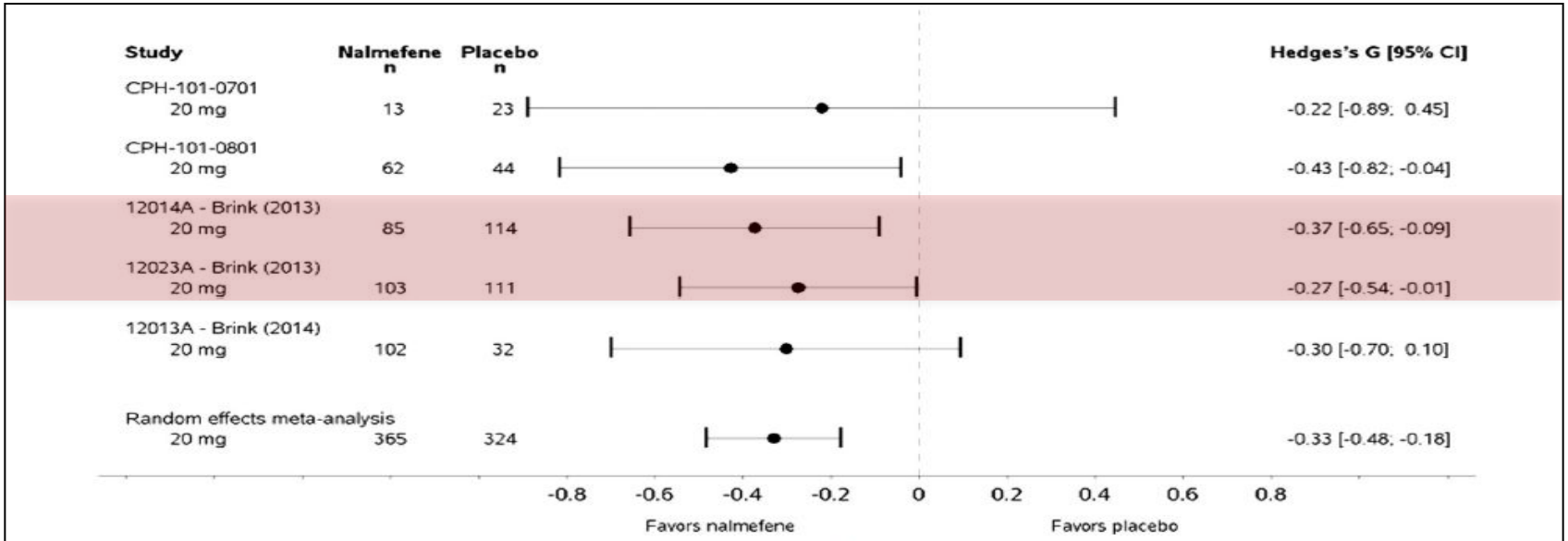


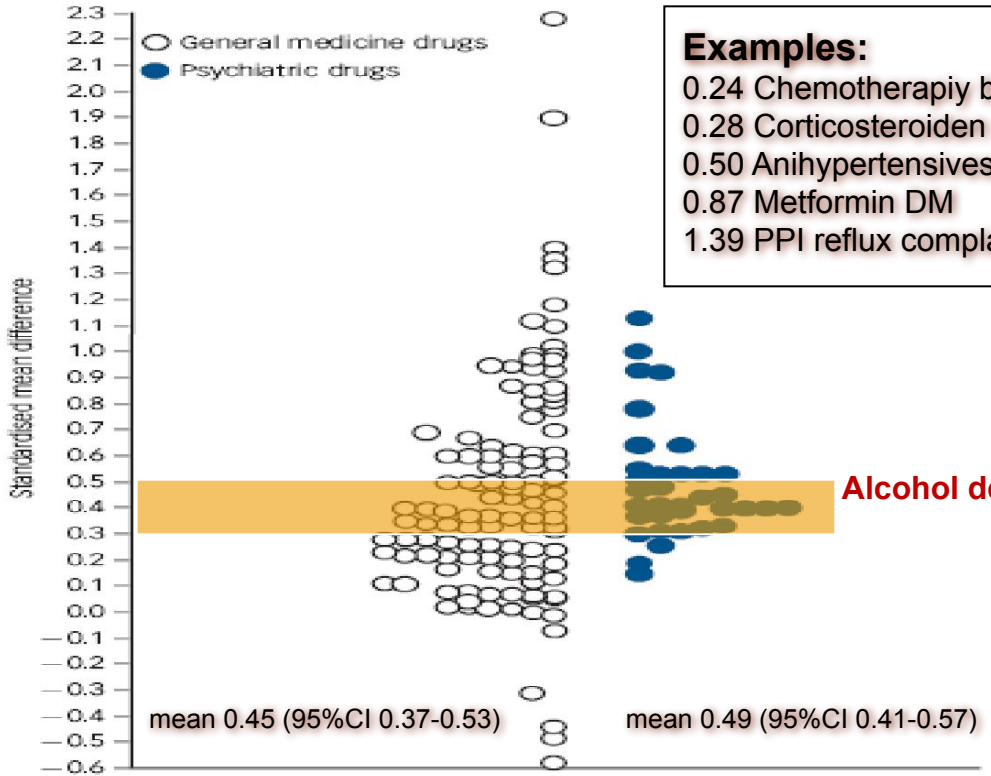
Figure 3 Meta-analysis of change from baseline in monthly HDDs; nalmefene versus placebo - Target Population. N: The number of patients at endpoint assessment.

Comparing Effect-Sizes of Alcohol Medications

	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.

Effectiveness compared to general medicine



Examples:

0.24 Chemotherapiy breast cancer
0.28 Corticosteroiden COPD
0.50 Anihypertensives
0.87 Metformin DM
1.39 PPI reflux complaints

Examples:

0.35 Antidepressives depression
0.40 Lithium bipolar disorder
0.50 Antipsychotics psychosis
0.78 Methylfenidata ADHD
0.40 Anti-alcohol medication

Alcohol dependence medication (abstinence/reduction)
d=0.30-0.45 NNT=7-10

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

Effectiveness of Addiction Tx Psychotherapy

Cognitive-Behavioral Treatment With Adult Alcohol and Illicit Drug Users: A Meta-Analysis of Randomized Controlled Trials*

MOLLY MAGILL, PH.D.,† AND LARA A. RAY, PH.D.†

JOURNAL OF STUDIES ON ALCOHOL AND DRUGS / JULY 2009

TABLE 2. Main treatment effect by primary drug, type of CBT treatment, and type of comparison condition

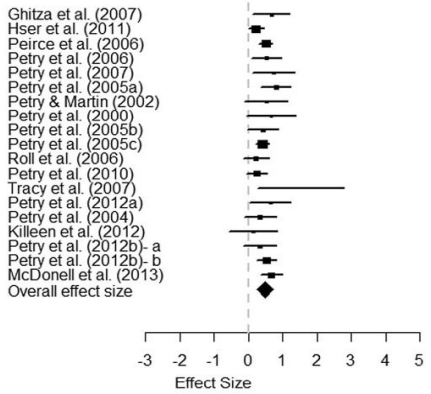
Variable	Alcohol	Marijuana	C/S/O	Polydrug	CBT	CBT + psychosoc.	CBT + pharm.	Vs active treatment	Vs passive treatment	Vs no treatment	Vs no adjunct
Fixed effects	0.067[a]	0.513[b§]	0.126[c*]	0.116	0.165[d§]	0.329[e*]	0.208[f§]	0.129[g*]	0.116[§]	0.848[§]	0.089[h]
95% CI	-0.002, 0.136	0.375, 0.651	0.011, 0.242	-0.007, 0.239	0.085, 0.245	0.238, 0.421	0.070, 0.346	0.041, 0.217	0.052, 0.180	0.692, 1.010	-0.066, 0.244
Range	-0.670, 1.209	0.225, 0.824,	-0.845, 0.626	-0.442, 0.642	-0.644, 0.626	-0.239, 1.210	-0.451, 0.867	-0.644, 0.626	-0.451, 0.867	0.288, 1.210	-0.845, 0.523
N	23	6	13	11	21	19	13	17	32	6	7
Q (df)	34.20 (22)*	10.53 (5)	40.39 (12)[§]	10.96 (10)	37.80 (20)*	64.23 (18)[§]	18.53 (12)	20.09 (16)	34.10 (31)	18.66 (5)[§]	35.21 (6)[§]
I^2	35.67*	52.53	70.29	8.72	47.09	71.97	35.25	20.38	31.26	73.21	82.96
Random effects	0.088	0.470[§]	0.133	0.113	0.172*	0.305[§]	0.199*	0.133*	0.152[§]	0.796[§]	-0.054
95% CI	-0.018, 0.194	0.259, 0.681	-0.084, 0.350	-0.020, 0.246	0.053, 0.292	0.116, 0.493	0.021, 0.376	0.029, 0.238	0.062, 0.242	0.454, 1.140	-0.455, 0.348

Meta-analysis: 53 RCTs and mean of 18 sessions of CBT:
Effect of CBT generally significant but small (overall g=0.17; range g=0.09-0.47)
Best results in cannabis and in combination with psychosocial support

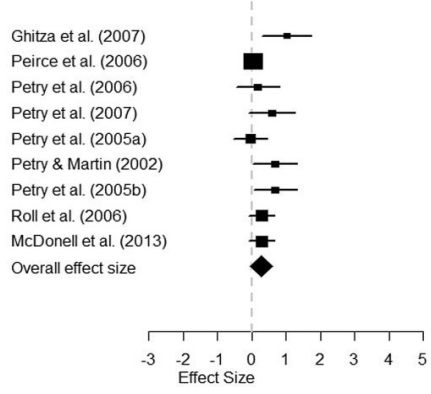
Prize-based contingency management for the treatment of substance abusers: a meta-analysis

Addiction 2014

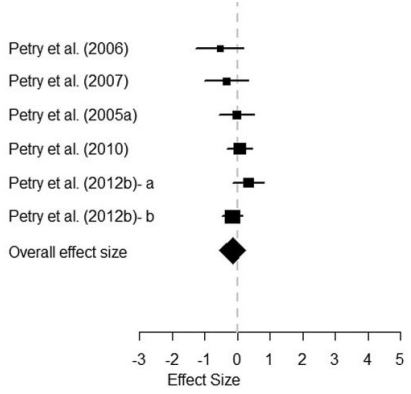
Lois A. Benishek[1,2], Karen L. Dugosh[1], Kim C. Kirby[1,2], Jason Matejkowski[1,3], Nicolle T. Clements[1,4], Brittany L. Seymour[1] & David S. Festinger[1,2]



End of Tx: d=0.46



Short-term FU: d=0.33



6 months FU: d=0.09 (ns)

CM probably only more effective than CBT at the short by not the long-term

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

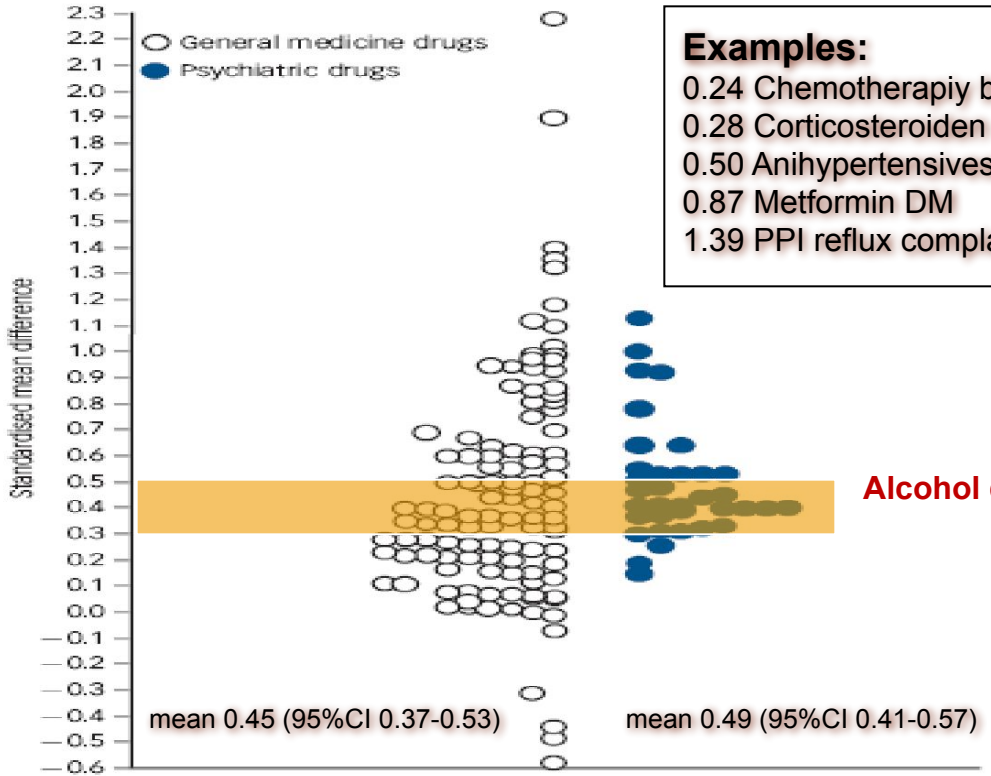
Christopher Sundström[1] · Matthijs Blankers[2,3,4] · Zarnie Khadjesari[5,6]

2016

Results E-Health interventions

* consistent, maar small effect (d=0.10-0.30): reduction 2-3 glasses/**week**
* effect gets smaller with time and probably no effect > 6 months
* effect on binge drinking en damage not proven
* no effect of therapeutic model
* possibly some effect of duration of intervention
* Some indication that "blended intervention" (e-health + chat/f2f) works

Effectiveness compared to general medicine



Examples:

0.24 Chemotherapiy breast cancer
0.28 Corticosteroiden COPD
0.50 Anihypertensives
0.87 Metformin DM
1.39 PPI reflux complaints

Examples:

0.35 Antidepressives depression
0.40 Lithium bipolar disorder
0.50 Antipsychotics psychosis
0.78 Methylfenidata ADHD
0.40 Anti-alcohol medication

Alcohol dependence psychotherapy (abst/reduction)
d=0.10-0.45 NNT=7-20

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

Conclusion Effectiveness Interventions

- Interventions are consistently effective at the group level, but effect sizes are small to moderate at best and NNTs are generally >7-10
- This means that many patients in treatment continue to suffer from excessive alcohol/drug use and the side-effects related to treatments
- **The question is whether we can do better and how?**

Improving Treatment Effectiveness

How can we do better?

Possible solutions

- Improve compliance: psychotherapy, long-acting formulations
- Combine pharmacotherapy with psychotherapy: e.g. CET+DCS
- Combine different medications: polypharmacy
- New medications: based on basic science or via “repurposing”
- **Patient-treatment matching: precision/personalized medicine**

  *** phenotype, endophenotype, genotype, tx process**

- New treatment modalities, e.g. neuromodulation

Precision/Personalized Medicine
Pharmacotherapy
Alcohol Dependence
Phenotype

A meta-analysis of the efficacy of gabapentin for treating alcohol use disorder

ADDICTION

2019

Henry R. Kranzler[1,2], Richard Feinn[3], Paige Morris[1] & Emily E. Hartwell[1,2]

Table 2 Meta-analysis results.

Outcome	*Number of studies*	*Number of subjects*	*Effect[a] size*	*95% CI*	*P-value*
Complete abstinence	6	673	1.33	0.84–2.10	0.23
Relapse to heavy drinking	6	673	0.80	0.57–1.13	0.21
Percentage of days abstinent	4	476	0.26	−0.16 – 0.69	0.23
Percentage of heavy drinking days	7	730	−0.64	−1.22 – −0.06	0.03
Drinks/day	5	652	−0.15	−0.64 – 0.35	0.56
GGT concentration	4	352	−0.12	−0.37 – 0.13	0.39

Gabapentin only effective in reducing the % of heavy drinking days

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

2005

	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 differential treatment effect

Baclofen for the Treatment of Alcohol Dependence and Possible Role of Comorbid Anxiety

K.C. Morley[1,*], A. Baillie[2], S. Leung[3], G. Addolorato[4], L. Leggio[5,6,7] and P.S. Haber[1,8]

Alcohol and Alcoholism Vol. 49, No. 6, pp. 654–660, 2014

Table 3. Intention to treat outcomes

	Placebo ($n = 14$)	Baclofen 30 mg/day ($n = 14$)	Baclofen 60 mg/day ($n = 14$)
Primary outcomes			
Days to lapse[+]	3.14 (1.90–4.39)	13.14 (2.79–23.49)	17.64 (3.45–31.84)
Days to relapse[+]	7.07 (2.37–11.77)	23.79 (9.62–37.95)	19.17 (4.91–34.52)
Drinks per drinking day[x]	2.82 (0.01–5.65)	5.86 (2.80–8.92)	5.64 (3.20–8.08)
Heavy drinking days per week[x]	1.36 (0.32–3.04)	2.07 (0.26–3.88)	1.89 (0.43–3.34)
Secondary outcomes:			
STAI State Anxiety[x]	32.44 (22.59–42.29)	33.18 (24.13–42.22)	36.61 (28.24–44.98)
OCDS Obsessive[x,*]	4.66 (2.20–7.12)	4.08 (1.63–6.52)[c]	4.47 (2.53–6.42)
OCDS Compulsive[x]	6.98 (2.70–11.26)	6.93 (2.67–11.19)	8.22 (4.87–11.56)
Stratified for comorbid anxiety[xx]			
Days to lapse[+,**]			
Absence of comorbid anxiety	3.57 (1.31–5.83)	5.29 (0.00–13.36)	15.27 (0.00–30.78)
Presence of comorbid anxiety	2.71 (1.53–3.90)	21.00 (3.12–38.88)[a]	26.33 (0.00–65.70)
Days to relapse[+,**]			
Absence of comorbid anxiety	9.14 (0.00–18.36)	17.14 (0.00–37.63)	15.09 (0.56–29.62)
Presence of comorbid anxiety	5.00 (2.70–7.30)	30.43 (10.68–50.18)[a]	36.67 (0.00–33.10)[b]

Small study with strong interaction effect and significant effects of baclofen only in the subgroup with a life-time anxiety disorder (also: CC genotype of GABAB1 receptor gene).

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

Figure 2. Effect of Naltrexone Hydrochloride or Placebo on Percentage of Heavy Drinking Days

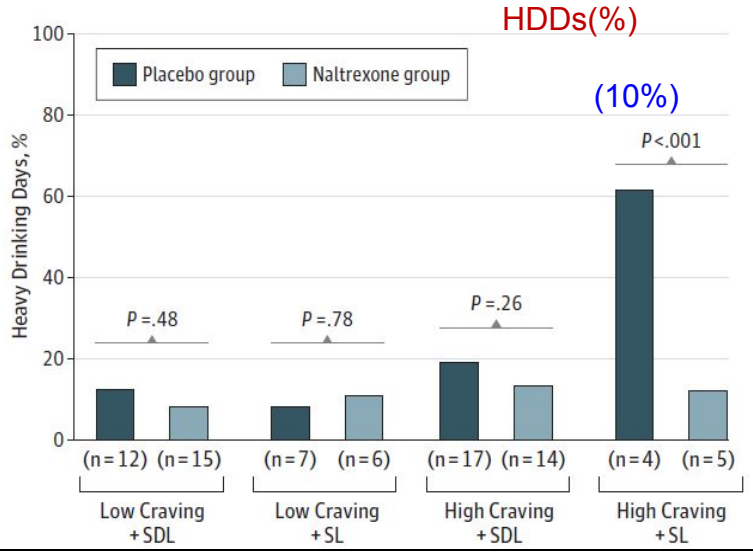
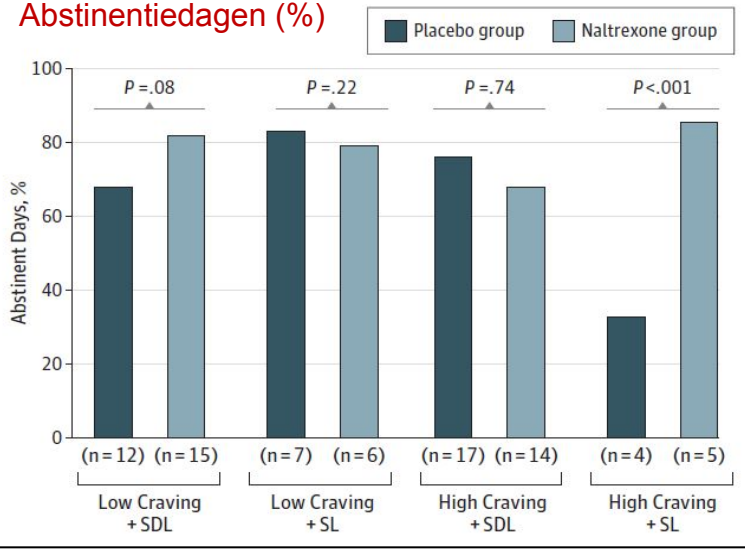


Figure 3. Effect of Naltrexone Hydrochloride or Placebo on Percentage of Abstinent Days



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

0145-6008/03/2711-1743$03.00/0
Alcoholism: Clinical and Experimental Research
Vol. 27, No. 11
November 2003

Family History of Alcoholism and Response to Sweets

Alexey B. Kampov-Polevoy, James C. Garbutt, and Elena Khalitov

Precision/Personalized Medicine
Pharmacotherapy
Alcohol Dependence
Endophenotype

Effects of the atypical stimulant modafinil on a brief gambling episode in pathological gamblers with high vs. low impulsivity

M Zack *Clinical Neuroscience, Centre for Addiction and Mental Health, Toronto, Ontario, Canada.*
CX Poulos *Department of Psychology, University of Toronto, Toronto, Ontario, Canada.*

2009

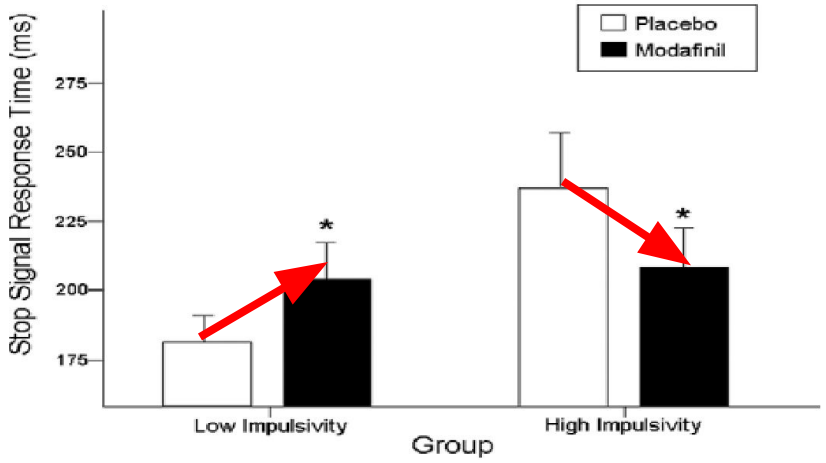


Figure 4 Mean (SEM) stop signal response time (SSRT; ms) on Stop Signal Task in pathological gamblers. Larger scores indicate poorer inhibitory control (more disinhibition). *$P < 0.05$ for simple effect of modafinil vs. placebo for each group.

In PG:

Low baseline impulsivity modafinil results in more impulsivity and craving

High baseline impulsivity modafinil results in less impulsivity and craving

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]

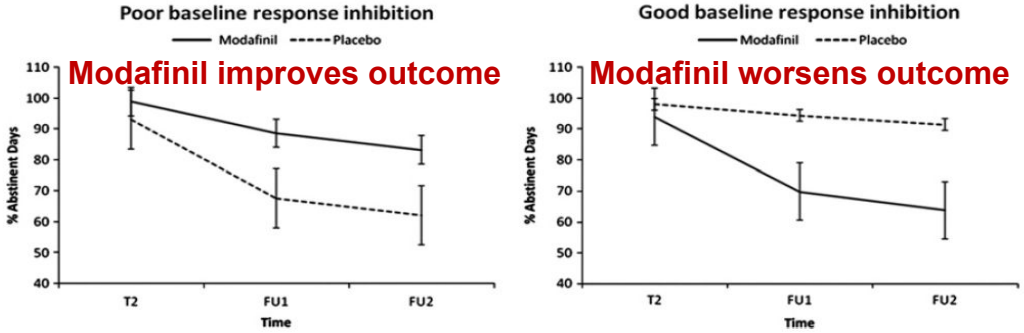


Figure 4 Time × treatment (modafinil vs. placebo) interaction based on MMRM for percentage abstinent days in subgroups of alcohol dependent patients with poor baseline response inhibition (n=30 (sample at T2); SSRT > 233.22) versus alcohol dependent patients with good baseline response inhibition (n=22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

Predicting Naltrexone Response in Alcohol-Dependent Patients: The Contribution of Functional Magnetic Resonance Imaging

ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH 2014

Karl Mann, Sabine Vollstädt-Klein, Iris Reinhard, Tagrid Leménager, Mira Fauth-Bühler, Derik Hermann, Sabine Hoffmann, Ulrich S. Zimmermann, Falk Kiefer, Andreas Heinz, and Michael N. Smolka

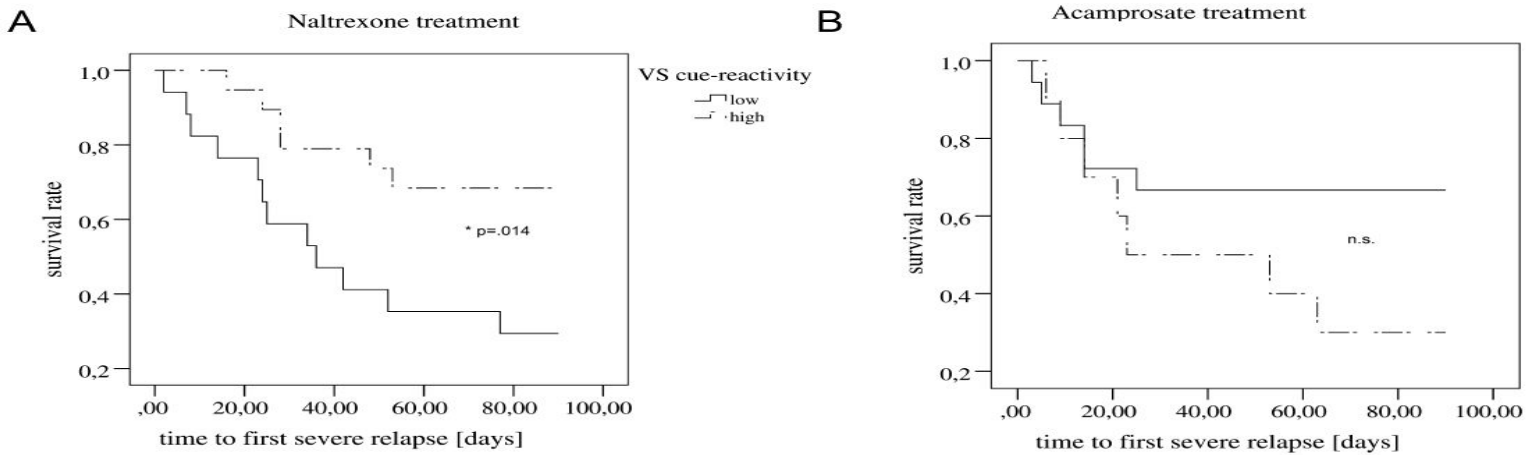


Fig. 3. Association between pretreatment ventral striatum (VS) cue reactivity and days until first severe relapse (median split for illustration purposes): Kaplan–Meier estimates of survival rates in patients with low versus high cue reactivity in (**A**) patients receiving naltrexone (n = 17 low cue reactivity, n = 19 high cue reactivity) or (**B**) acamprosate (n = 18 low cue reactivity, n = 10 high cue reactivity).

Patients with high pre-Tx VS activity during visual cues-exposure do better with NTX

Precision/Personalized Medicine
Pharmacotherapy
Alcohol Dependence
Genotype

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

2007

NS

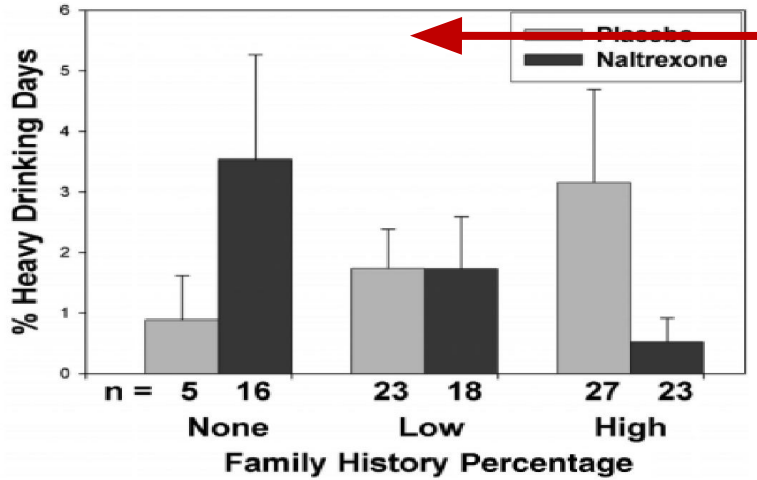


Figure 1. Percentage of heavy drinking days during 6-month follow-up by medication (naltrexone vs. placebo) and percentage of family members with a history of problem drinking (0%, <20%, or ≥20% relatives with problems). The interaction of family history percentage and medication was significant using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

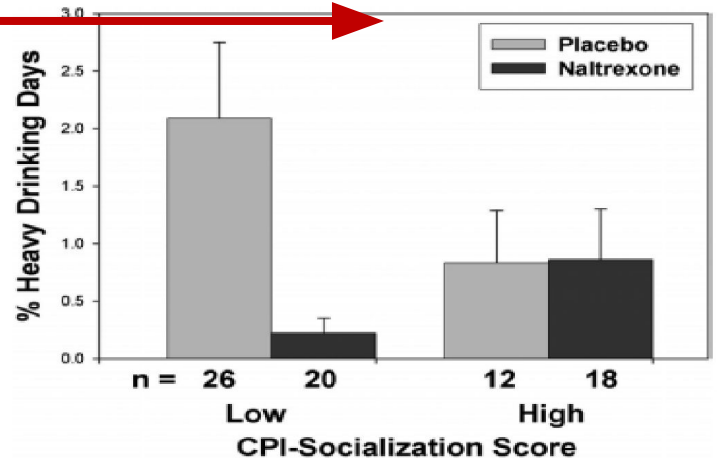
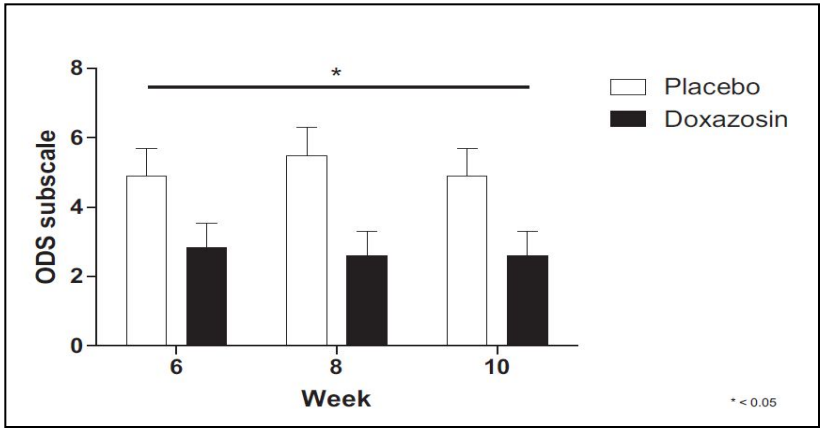


Figure 2. Among patients compliant with ≥70% of medication doses, percentage of heavy drinking days during 6-month follow-up by medication (naltrexone vs. placebo) and socialization (California Personality Inventory-Socialization scale [CPI-So] score ≤24 or >24). The interaction of CPI-Socialization 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.

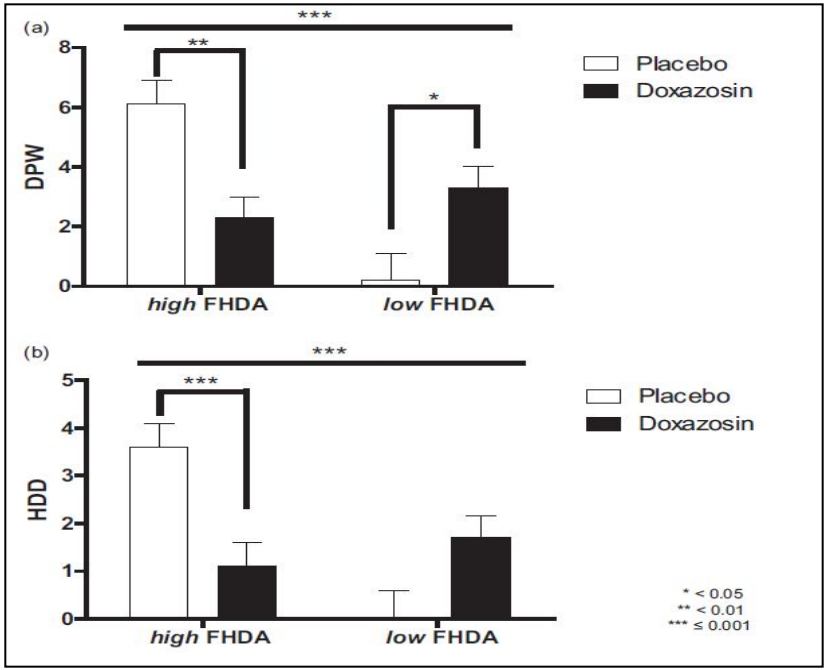
Role of the α_1 blocker doxazosin in alcoholism: a proof-of-concept randomized controlled trial

2016

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]



Doxazosin reduces alcohol craving, but effect on drinking outcomes dependent on FHAD, with pos. effect in FHAD+ and neg. effect in FHAD- patients.



Predicting response to opiate antagonists and placebo in the treatment of pathological gambling

Jon E. Grant · Suck Won Kim · Eric Hollander · Marc N. Potenza

2008

Psychopharmacology (2008) 200:521–527

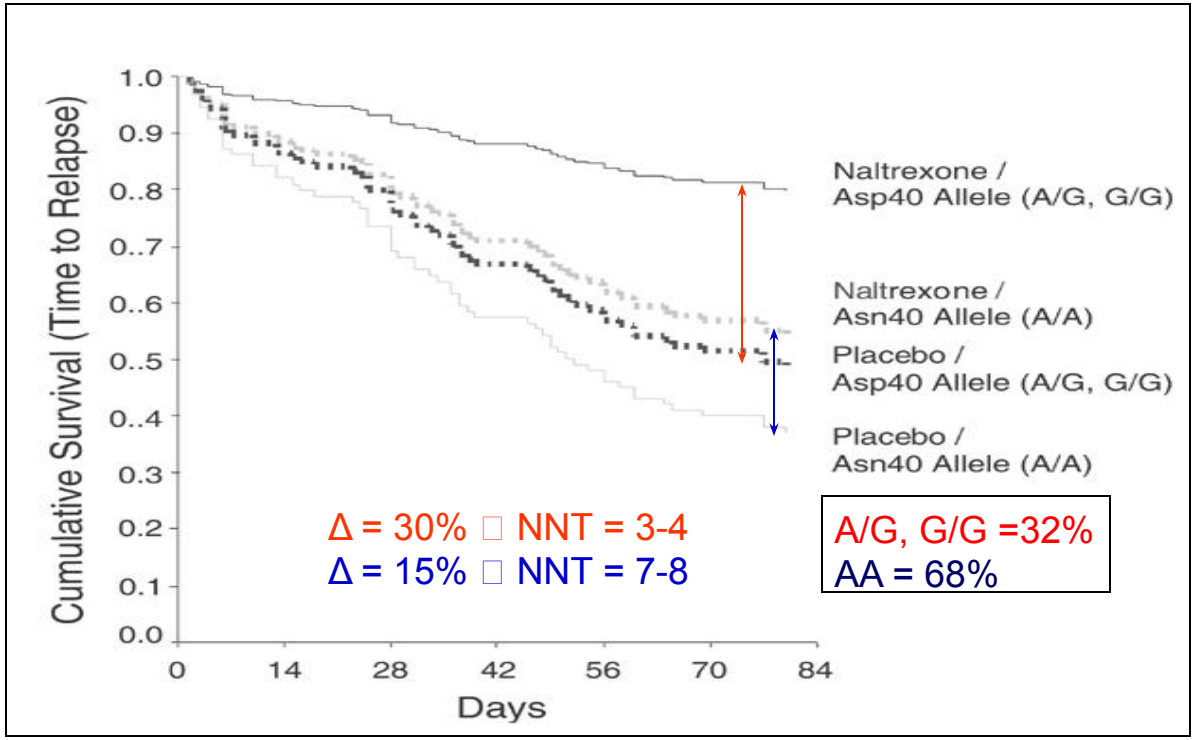
Table 2 Relationship between demographic and clinical variables and response to opiate antagonists in 214 subjects with pathological gambling who received active medication

Baseline variable	Parameter estimate	SE	Wald χ^2	p value	Hazard ratio	HR 95% CI
Age	0.04	0.09	0.15	0.699	1.04	0.79–1.07
Gender	0.01	0.20	<0.01	0.952	1.01	0.75–1.48
Race/ethnicity	0.01	0.27	<0.01	0.965	1.01	0.81–2.07
Marital status	0.12	0.20	0.36	0.549	1.13	0.67–1.34
Education	0.42	0.25	2.79	0.094	1.52	0.85–1.95
PG-YBOCS total	−0.02	0.03	0.74	0.390	0.98	0.94–0.99
PG-YBOCS urges/thoughts	0.02	0.06	0.12	0.729	1.02	0.91–1.14
PG-YBOCS behavior	−0.04	0.03	1.73	0.189	0.96	0.91–1.01
Sheehan Disability Scale	−0.02	0.03	0.49	0.485	0.98	0.93–1.01
HAM-D	0.02	0.03	0.25	0.620	1.02	0.97–1.08
HAM-A	−0.01	0.03	<0.01	0.983	1.00	0.95–1.05
Positive family history of alcohol use disorders	0.55	0.20	7.53	0.006	1.74	1.17–2.58
Prior treatment for pathological gambling	−0.04	0.27	0.02	0.882	0.96	0.64–1.58

PG-YBOCS Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling, *HAM-D* Hamilton Depression Rating Scale, *HAM-A* Hamilton Anxiety Rating Scale

In PG, familiy history of alcohol use disorder predicts response to NMF/NTX

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	-
ETC.	

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]

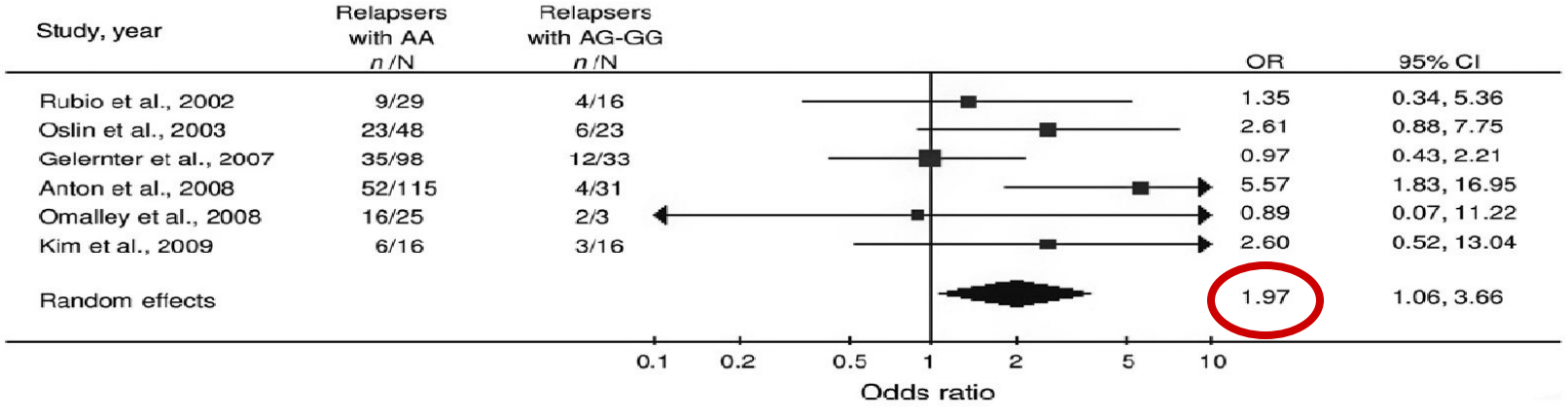


Figure 2 Meta-analysis of the association of A118G opioid μ-receptor polymorphism with relapse rates after naltrexone treatment in patients with alcohol dependence. Naltrexone-treated patients with AA genotype (cases) are compared with those with G allele (controls) under a random-effects model ($Z = 2.14$, $P = 0.03$). 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

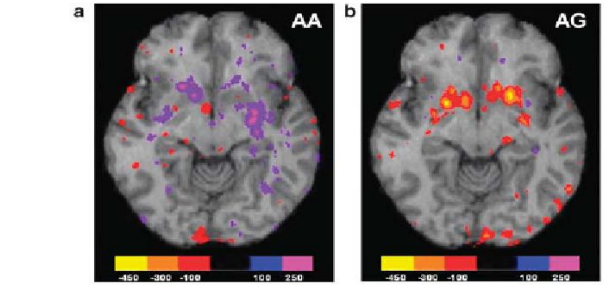
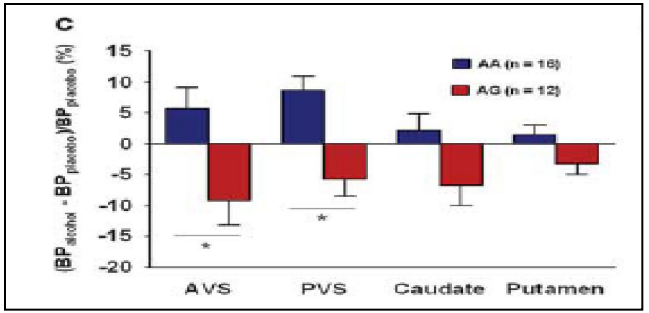


Figure 1 Human PET study. Axial view of group maps showing change of [^{11}C]-raclopride binding potential (ΔBP; nCi ml^{-1}) between placebo and alcohol sessions in **(a)** AA individuals and **(b)** AG individuals. Color bars indicate corresponding ΔBP values. Reduction in raclopride binding is attributed 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

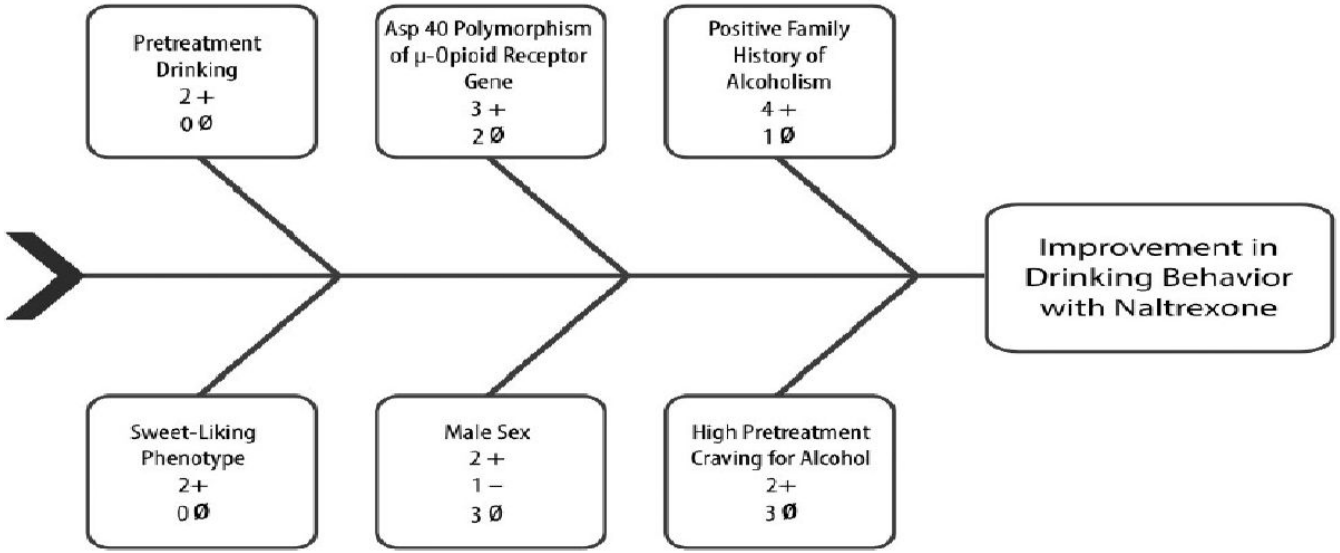


Figure 2 Fishbone diagram of possible moderators of response to naltrexone in alcohol dependence. For each bone, we provide the number of studies that indicate a positive (+) or negative (–) association or mixed/neutral evidence (ø) between the moderator and naltrexone response

BUT .....

Original Investigation

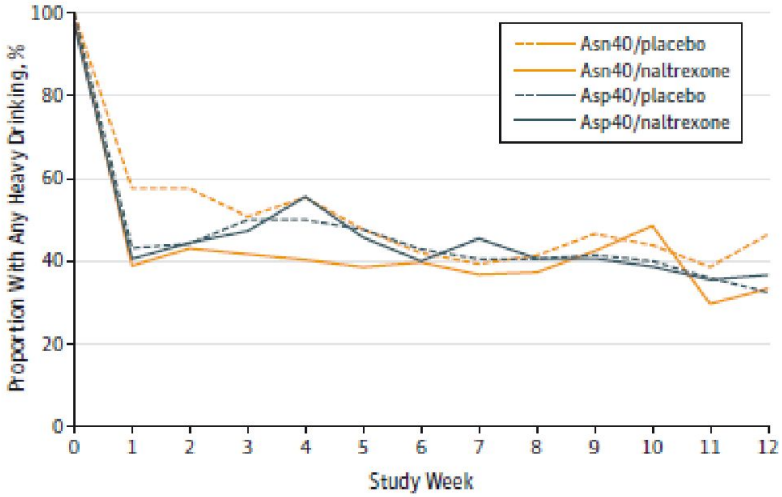
Naltrexone vs Placebo for the Treatment of Alcohol Dependence
A Randomized Clinical Trial

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.

Alcoholism: Clinical and Experimental Research

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June 2014

Critical Review

A Meta-Analysis of Topiramate's Effects for Individuals with Alcohol Use Disorders

Janet C. Blodgett, A. C. Del Re, Natalya C. Maisel, and John W. Finney

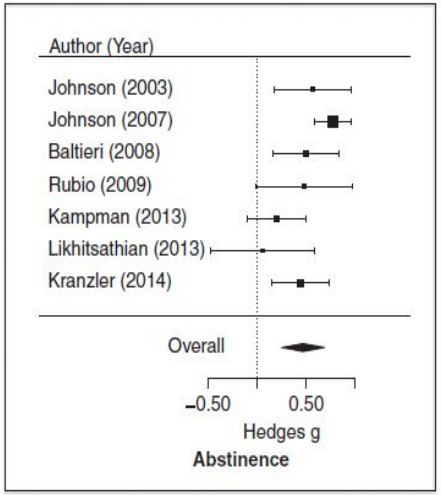
Background: Influenced by several trials and reviews highlighting positive outcomes, topiramate is increasingly prescribed as a treatment for alcohol use disorders (AUDs). The only previously published meta-analysis of topiramate for AUDs was limited by a sample of only 3 randomized, placebo-controlled trials (RCTs).

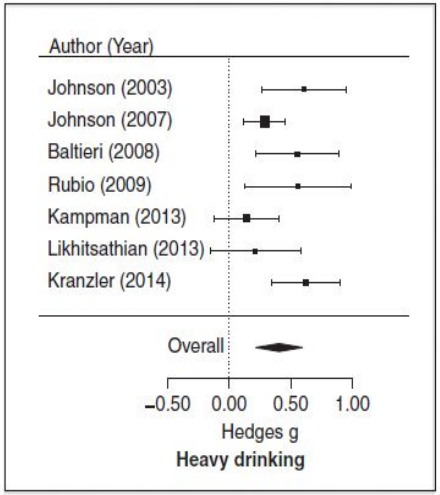
Methods: A systematic search identified 7 RCTs (including a total of 1,125 participants) that compared topiramate to placebo for the treatment for AUDs. This meta-analysis estimated the overall effects of topiramate on abstinence, heavy drinking, craving, and γ-glutamyltranspeptidase (GGT) outcomes and included several sensitivity analyses to account for the small sample of studies.

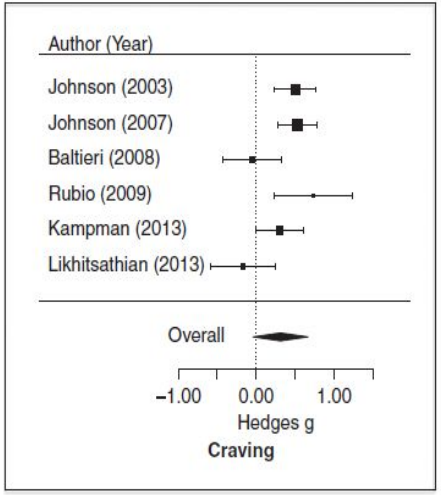
Results: Overall, the small to moderate effects favored topiramate, although the effect on craving was not quite significantly different from 0. The largest effect was found on abstinence ($g = 0.468$, $p < 0.01$), followed by heavy drinking ($g = 0.406$, $p < 0.01$), GGT ($g = 0.324$, $p = 0.02$), and craving ($g = 0.312$, $p = 0.07$) outcomes. Sensitivity analyses did not change the magnitude or direction of the results, and tests did not indicate significant publication bias. The small sample size did not allow for examination of specific moderators of the effects of topiramate.

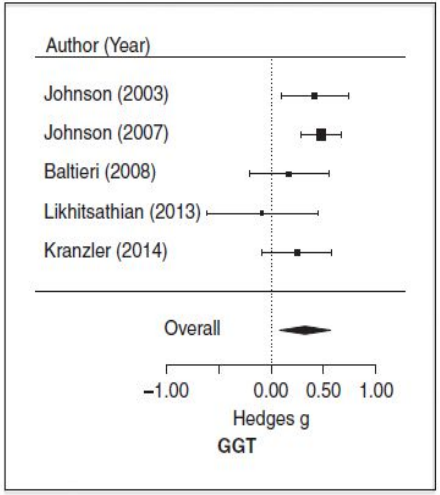
Conclusions: Topiramate can be a useful tool in the treatment of AUDs. Its efficacy, based on the current sample of studies, seems to be of somewhat greater magnitude than that of the most commonly prescribed medications for AUDs (naltrexone and acamprosate). Further research will help to identify the contexts in which topiramate is most beneficial (e.g., dose, concurrent psychotherapy, patient characteristics).

Key Words: Topiramate, Meta-Analysis, Alcohol Use Disorders, Treatment.









A Meta-Analysis of Topiramate's Effects for Individuals with Alcohol Use Disorders

Janet C. Blodgett, A. C. Del Re, Natalya C. Maisel, and John W. Finney

Alcohol & Alcoholism, 2014

7 studies with 1,125 participants
Doses: 100-300 mg/day

Abstinence	g=0.468 (p<0.01)
Heavy drinking	g=0.406 (p<0.01)
CGT	g=0.324 (p=0.02)
Craving	g=0.312 (p=0.07)

Kampman:
* AUD + cocaine use disorder

Likhisathian
* Add-on to intensive psychotherapy

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.

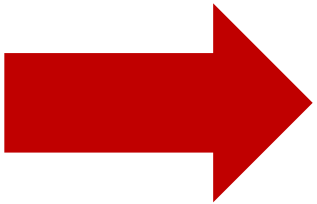
Objective: Topiramate has been shown to reduce drinking and heavy drinking in individuals with alcohol dependence whose goal was to stop drinking. The authors evaluated the efficacy and tolerability of topiramate in heavy drinkers whose treatment goal was to reduce drinking to safe levels.

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.

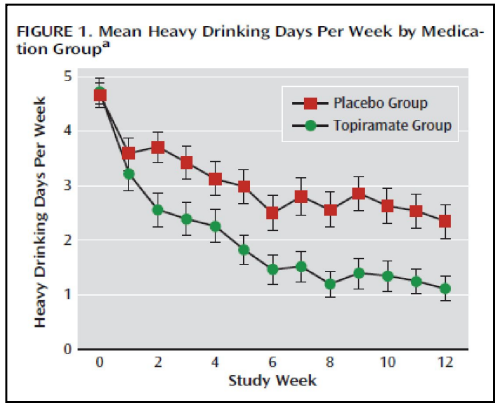
Conclusions: These findings support the use of topiramate at a daily dose of 200 mg to reduce heavy drinking in problem drinkers. The moderator effect of rs2832407, if validated, would facilitate the identification of heavy drinkers who are likely to respond well to topiramate treatment and provide an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

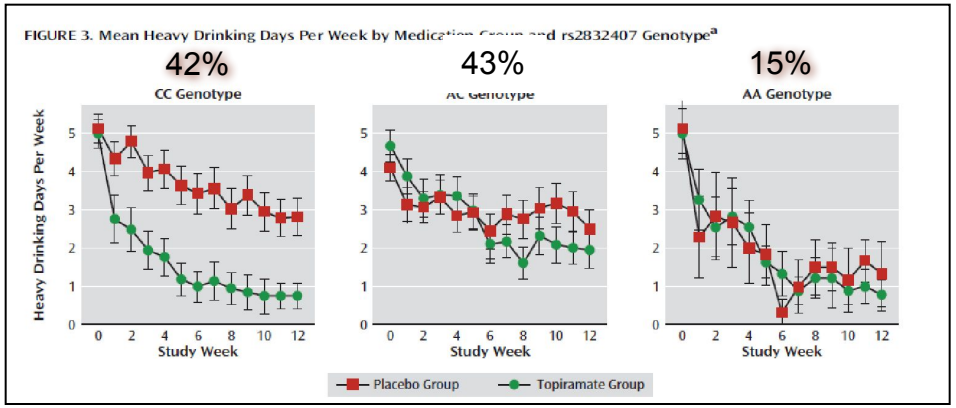
(Am J Psychiatry 2014; 171:445–452)



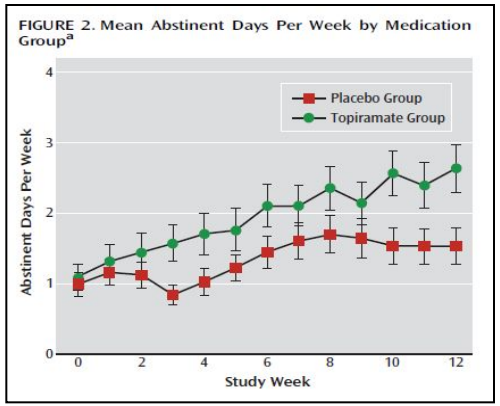
Candidate Genes: Topiramate (200mg) and GRK1

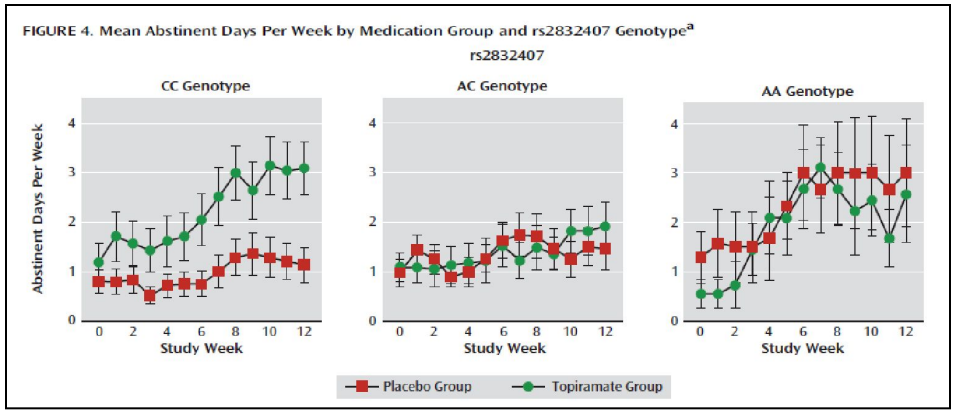
HDDs per week





Abstinence days/week

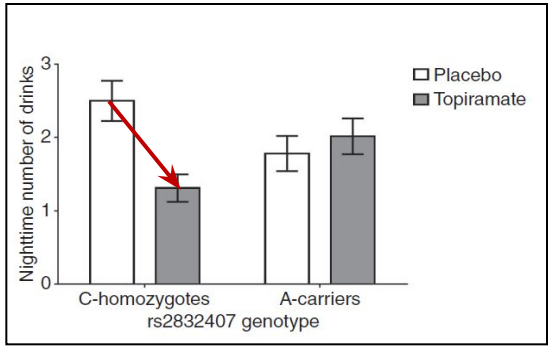


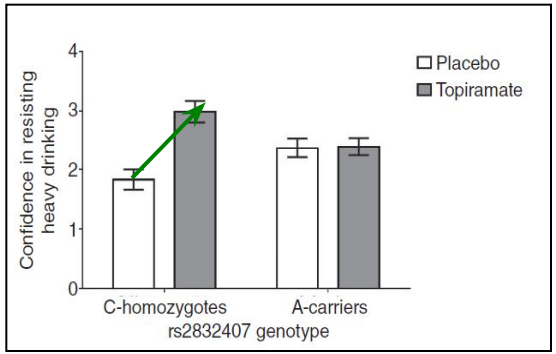


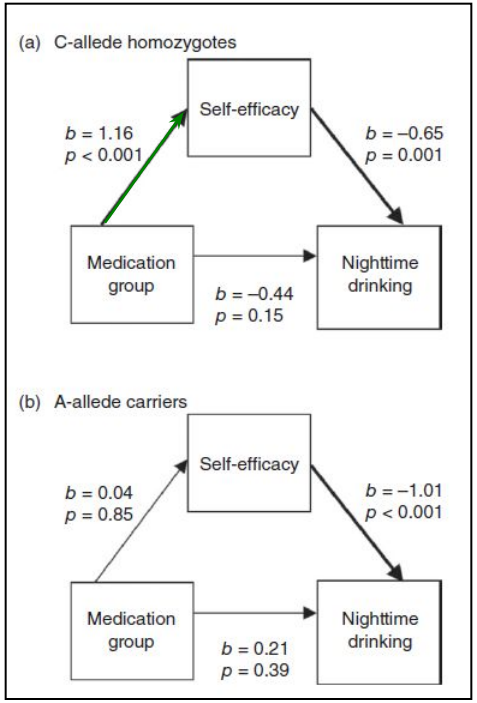
Self-efficacy mediates the effects of topiramate and *GRIK1* genotype on drinking

Addiction Biology 2014

Henry R. Kranzler[1,2]*, Stephen Armeli[3]*, Reagan Wetherill[1], Richard Feinn[4], Howard Tennen[5], Joel Gelernter[6,7], Jonathan Covault[8] & Timothy Pond[1]







Only CC group shows effect of topiramate on night time drinking

Only CC group shows effect of topiramate on self-efficacy

Effect of topiramate on night-time drinking in CC group mediated by effect topiramate on self-efficacy!!

Explanation?

Baclofen and GABA-B receptor subunit 1 gene

Article Title: **Moderation of baclofen response by a GABAB receptor polymorphism: Results from the BacALD study**

Authors: Kirsten C Morley; Natasha Luquin; Andrew Baillie; Isabel Fraser; Ronald J Trent; Glenys Dore; Nghi Phung; Paul S Haber

Addiction. 2018 Dec;113(12):2205-2213

Abstract:

Background: Baclofen has been shown to reduce alcohol consumption in alcohol-dependent individuals, but there is marked heterogeneity in response. The present study evaluated whether the response to baclofen is moderated by a single nucleotide polymorphism (rs29220) in the GABAB receptor subunit 1 gene (GABBR1).

Methods: Alcohol dependent patients were treated for 12 weeks with 30 mg/day of baclofen, 75 mg baclofen or placebo. Predefined primary outcomes included survival time to lapse (any drinking) and relapse (> 5 drinks per day in men and > 4 in women), and the composite outcomes of drinks per drinking day, number of heavy drinking days, and percentage days abstinent.

Results: We observed significant medication x genotype interaction effect for time to relapse (OR: 3.40, 95% CI:1.01-11.46) and a near significant interaction effect for time to lapse (OR: 3.29, 95% CI:0.98-11.06). Patients with the CC genotype demonstrated increased percentage days abstinent and a greater time to relapse following baclofen treatment (80% vs 36%; 50.55 days vs 9.71 days), while those with the G- genotype showed no medication differences (57% vs 59%; 27.21 days vs 28.88 days). Patients with the CC genotype reported significantly less dizziness than the G- carriers (24% vs 0% for CC and G- respectively, $P < 0.01$).

Conclusion: Our study is the first demonstration that the GABBR1 rs29220 polymorphism is associated with response to baclofen in the treatment of alcohol dependence which may have important implications for treatment selection.

Relatively small study showing strong interaction effect with baclofen only being effective in patients with CC genotype of GABAB1 gene (or lifetime anxiety disorder?)

Genome-wide Association Study of Alcohol Dependence

GWAS

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]

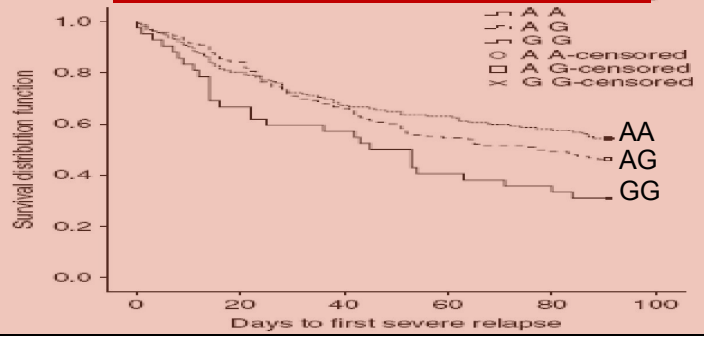
PREDICT Study 2010

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.

Effect of acamprosate by sr13273672



Jorde et al.

Genetic variation in the atrial natriuretic peptide transcription factor GATA4 modulates amygdala responsiveness in alcohol dependence.

Personalized or Precision Pharmacotherapy

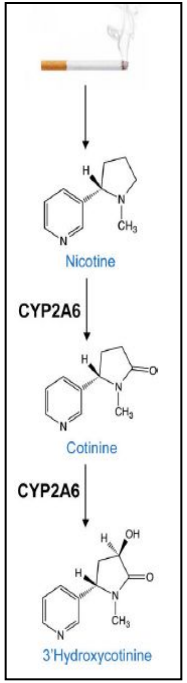
Treatment Goal	1st Choice	2nd Choice	3rd Choice
Abstinence ↕ **Reduced Drinking**	**Acamprosaat** (anxiety, withdrawal, GATA4) **Naltrexon??** (ASPD, SL+, FH+, OPRM1)	**Disulfiram** (partner)	Baclofen (anxiety, GABBR1) (GHB??) (VH DRL)
	Naltrexon# (ASPD, SL+, FH+, OPRM1) **Nalmefene** (dysphoria??)	Topiramate (GRIK1, PTSD?)	Modafinil (impulsivity) Gabapentin (sleep problems) Varenicline (smoking?) Doxasozine (FH+/RR↑)

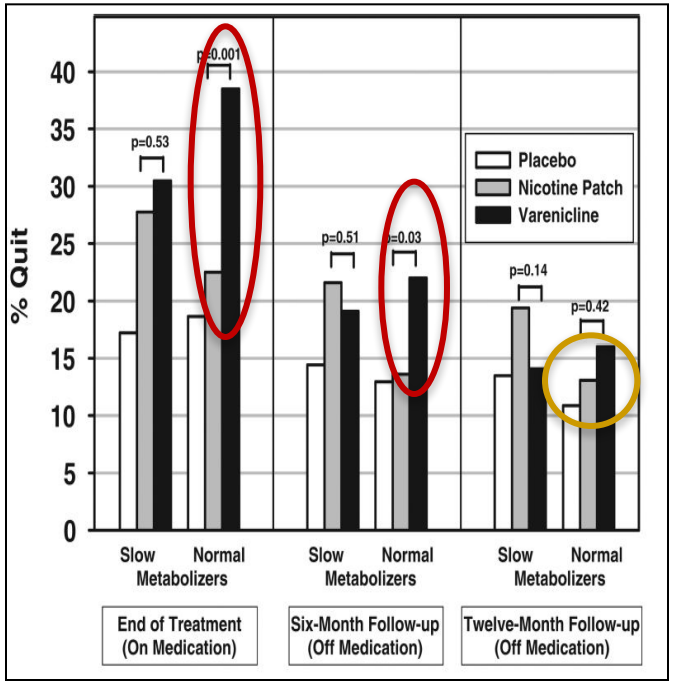
off-label

Precision/Personalized Medicine
Pharmacotherapy
Nicotine Dependence
Phenotype

A Randomized Placebo-controlled Trial to Test a Genetically-informed Biomarker ForPersonalizing Treatment for Tobacco Dependence

Caryn Lerman, Ph.D.[1], Robert A. Schnoll, Ph.D.[2], Larry W. Hawk Jr., Ph.D.[3], Paul Cinciripini, Ph.D.[4], Tony P. George, M.D.[5], E. Paul Wileyto, Ph.D.[6], Gary E. Swan, Ph.D.[7], Neal I. Benowitz, M.D[8], Daniel F. Heitjan, Ph.D.[6], Rachel F. Tyndale, Ph.D.[5,9], and on behalf of the PGRN-PNAT Research Group*





Lancet Respir Med. 2015 February ; 3(2): 131–138.

CYP2A6 influences nicotine metabolism, which influences nicotine metabolite ratio (NMR)

Compared to slow metabolizers (NMR <0.31), normal (and fast) metabolizers did better with varenicline than with NRT at end of Tx and 6 months FU (NNT NM: NRT=4.9 vs Var=26.0) No interaction at 12 month FU!

Also bupropion (e.g. Patterson et al. 2008)

Precision/Personalized Medicine
Pharmacotherapy
Nicotine Dependence
Genotype

Genetic variants in the serotonin transporter influence the efficacy of bupropion and nortriptyline in smoking cessation

2012

Marieke Quaak[1,2], Constant P. van Schayck[2], Dirkje S. Postma[3], Edwin J. Wagena[2]* & Frederik J. van Schooten[1]

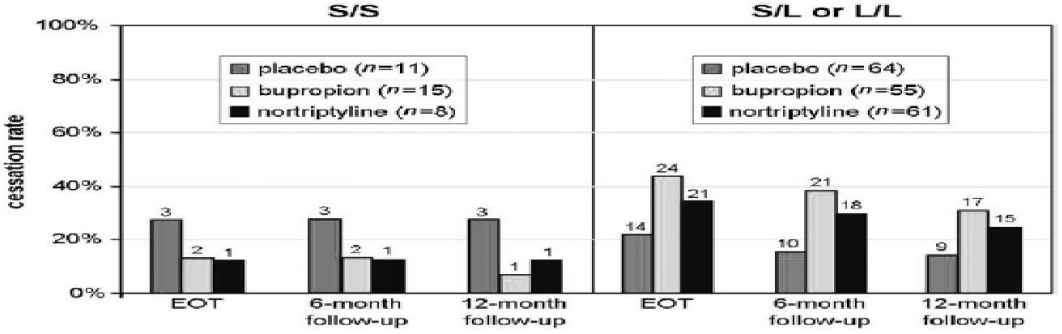


Figure 1 Prolonged abstinence by 5-HTTLPR genotype and treatment group. The number of participants abstinent in the treatment groups is presented. Participants in the S/L or L/L group derive more benefit from antidepressant therapy compared with placebo. EOT: end-of-treatment

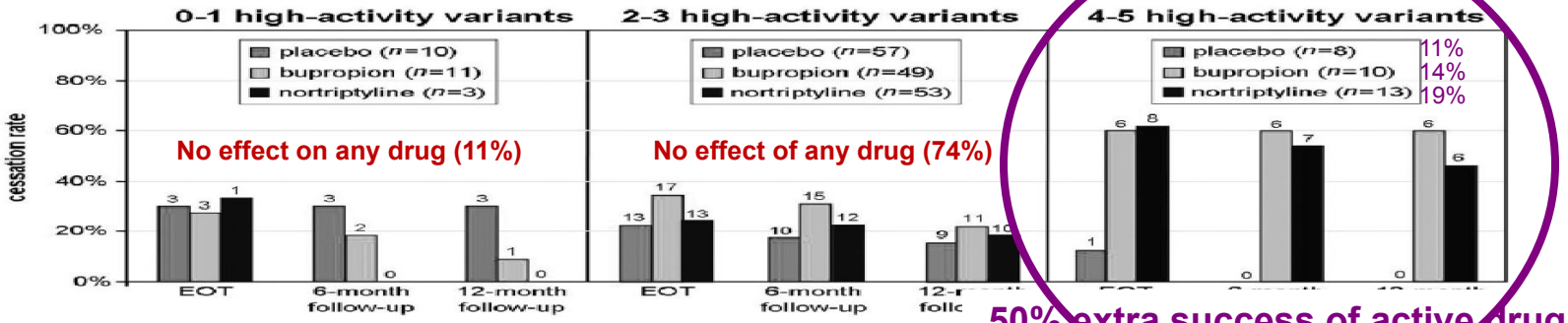


Figure 2 Prolonged abstinence by a combination of high-activity alleles and treatment ; treatment groups is presented. Participants with four to five high-activity variants derive sig compared with placebo. For those with zero to one or two to three high-activity variar EOT: end-of-treatment

Serotonergic gene variation in substance use pharmacotherapy: a systematic review

Pharmacogenomics. 2015 July ; 16(11): 1–8.

Isabelle E Bauer[1], **David P Graham**[2], **Jair C Soares**[1], and **David A Nielsen**[*,2]

Executive summary

- Pharmacogenetics is a promising field that has the potential to improve patient care and reduce healthcare costs related to drug addiction.
- Genetic variability of the serotonergic biosynthesis enzyme tryptophan hydroxylase 2 (*TPH2*) and the serotonin transporter (*SLC6A4*) genes mediates the efficacy of several addiction treatments, such as ondansetron, disulfiram and the antidepressants bupropion, sertraline and nortriptyline.
- More research is needed to identify additional serotonergic gene variants that predict the success of treatments, their clinical outcomes and potential side effects of therapeutic interventions for drug addiction.

ORIGINAL ARTICLE

Molecular Genetics of Successful Smoking Cessation

Convergent Genome-Wide Association Study Results

George R. Uhl, MD, PhD; Qing-Rong Liu, PhD; Tomas Drgon, PhD; Catherine Johnson, MSc; Donna Walther, MSc; Jed E. Rose, PhD; Sean P. David, MD; Ray Niaura, PhD; Caryn Lerman, PhD

2010

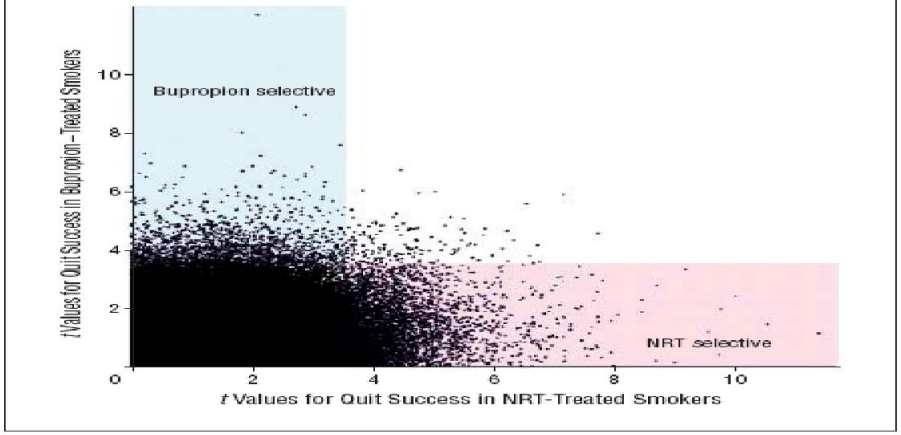


Figure 1. Scatterplot of the distributions of *t* values for comparisons between individuals with successful vs unsuccessful attempts to quit smoking in pooled samples from those receiving nicotine replacement therapy (NRT) (x-axis) vs bupropion hydrochloride (y-axis) for secondary analyses seeking candidate genes with treatment-specific effects. If no genes provided treatment-specific effects, values would cluster on a 45° line from the origin. We highlight single-nucleotide polymorphisms (SNPs) that provide NRT-selective (pink shading) or bupropion-selective (blue shading) effects (see also eTable 4). The *t* values of 3.6 and 3.7 for NRT and bupropion, respectively, correspond to $P < .005$. These data combine individuals from samples 1 and 2 who received NRT and individuals from samples 1 and 3 who received bupropion.

GWAS:

133 SNPs predictive of smoking cessation in 550 treated smokers

41 SNPs specific for NRT

66 SNPs non-specific

26 SNPs specific for bupropion

Precision/Personalized Medicine
Psychotherapy
Alcohol Dependence

Matching Alcoholism Treatments to Client Heterogeneity: Treatment Main Effects and Matching Effects on Drinking during Treatment*

PROJECT MATCH RESEARCH GROUP†

ABSTRACT. *Objective:* This article examines client drinking and related psychosocial functioning during the course of alcoholism treatment. It focuses on (1) the main effects of the three Project MATCH treatments, (2) the prognostic value of client attributes employed in the matching hypotheses, and (3) the attribute by treatment interaction effects. *Method:* Clients recruited from outpatient settings (n = 952) or from aftercare settings (n = 774) were randomized to one of the following treatments: Motivational Enhancement Therapy (MET), Cognitive Behavioral Therapy (CBT) and Twelve-Step Facilitation (TSF). Alcohol consumption and psychosocial functioning during treatment were assessed at the end of the 12-week treatment phase. *Results:* During the treatment phase, small but statistically significant differences among treatments were found only in the outpatient arm on measures of alcohol consumption and alcohol-related negative consequences. Forty-one percent (41%) of CBT and TSF clients were abstinent or drank moderately without alcohol-related consequences, compared with 28% of MET clients. Tests of 10 a priori primary client-treatment matching hypotheses failed to find any interaction effects that had an impact on drinking throughout the treatment phase. *Conclusions:* In the outpatient setting there appears to be a temporary advantage to assigning individuals to CBT or TSF rather than MET. When there is a need to quickly reduce heavy drinking and alcohol-related consequences, it appears that CBT or TSF should be the treatment of choice. (*J. Stud. Alcohol* **59:** 631-639, 1998)

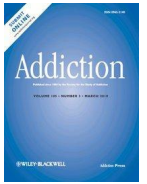
Large study (n=1,726) comparing the effect of 3 different types of psychotherapy (MET, CBT, TSF) and testing 10 a priori matching hypotheses using phenotypic patient characteristics

* No clinically relevant differences in the effect of the 3 different interventions
* No clinically meaningful patient-treatment matching effects

UK Alcohol Treatment Trial: client–treatment matching effects

UKATT Research Team*

School of Psychology and Sport Sciences, Northumbria University, Newcastle upon Tyne, UK



2007

Table 2 Tests of matching hypotheses at 3 and 12 months follow-up that were statistically significant ($P < 0.05$) or approached statistical significance ($P < 0.1$).

Follow-up interval	*Outcome variable*	*Matching variable*	*Treat β β (95% CI)*	*Matching β β (95% CI)*	*Int β MET* Matching β (95% CI)*	*P-value interaction*	R^2
3 months	DDD_t	NAEQ distal	−5.071 (−10.450, 0.309)	−0.141 (−0.220, −0.062)	0.098 (0.001, 0.195)	0.047	0.321
3 months	DDD_t	GHQ	2.997 (−1.132, 7.127)	0.072 (−0.004, 0.148)	−0.085 (−0.183, 0.013)	0.090	0.302
3 months	DDD_t	LDQ	2.790 (−0.899, 6.480)	0.377 (0.215, 0.539)	−0.183 (−0.393, 0.026)	0.086	0.336
3 months	APQ common	GHQ	1.549 (−0.253, 3.352)	0.057 (0.022, 0.091)	−0.037 (−0.08, 0.006)	0.089	0.285
12 months	LDQ	NAEQ prox	−3.637 (−7.085, −0.189)	−0.479 (−0.817, −0.140)	0.403 (−0.036, 0.843)	0.072	0.155
12 months	LDQ	NAEQ distal	−5.539 0−9.905, −1.173)	−0.108 −0.174, −0.042)	0.093 0.014, 0.171)	0.021	0.160

*(opposite direction)

*(opposite direction)

*Social and behaviour network therapy (SBNT) = 0, motivational enhancement therapy (MET) = 1. High score more severe—drinks per drinking day in the total follow-up sample (DDD_t). Alcohol Problems Questionnaire (APQ). Leeds Dependence Questionnaire (LDQ). General Health Questionnaire (GHQ). Low score more severe: Negative Alcohol Expectancy Questionnaire (NAEQ).

UK Alcohol treatment trial (UKATT): N=742 with 2 interventions (MET, SBNT)

130 interactions: 13 matching variables, 5 outcomes, and 2 assessment points

* Of these 130 interactions 4 p<0.10 and 2 p<0.05* (none for both assessments)

* Conclusion: Observed interactions most likely chance findings!

Precision/Personalized Medicine
Psychotherapy
Cannabis Dependence

Cannabis Dependence: CBT of MDFT?

Treatment of adolescents with a cannabis use disorder: Main findings of a randomized controlled trial comparing multidimensional family therapy and cognitive behavioral therapy in The Netherlands

Vincent Hendriks[a,b,*], Evelien van der Schee[a], Peter Blanken[a,b]

[a] Parnassia Addiction Research Centre (PARC), Brijder Addiction Treatment, Parnassia Bavo Group, PO-Box 53002, 2505 AA, The Hague, The Netherlands
[b] Central Committee on the Treatment of Heroin Addicts (CCBH), Utrecht, The Netherlands

2011

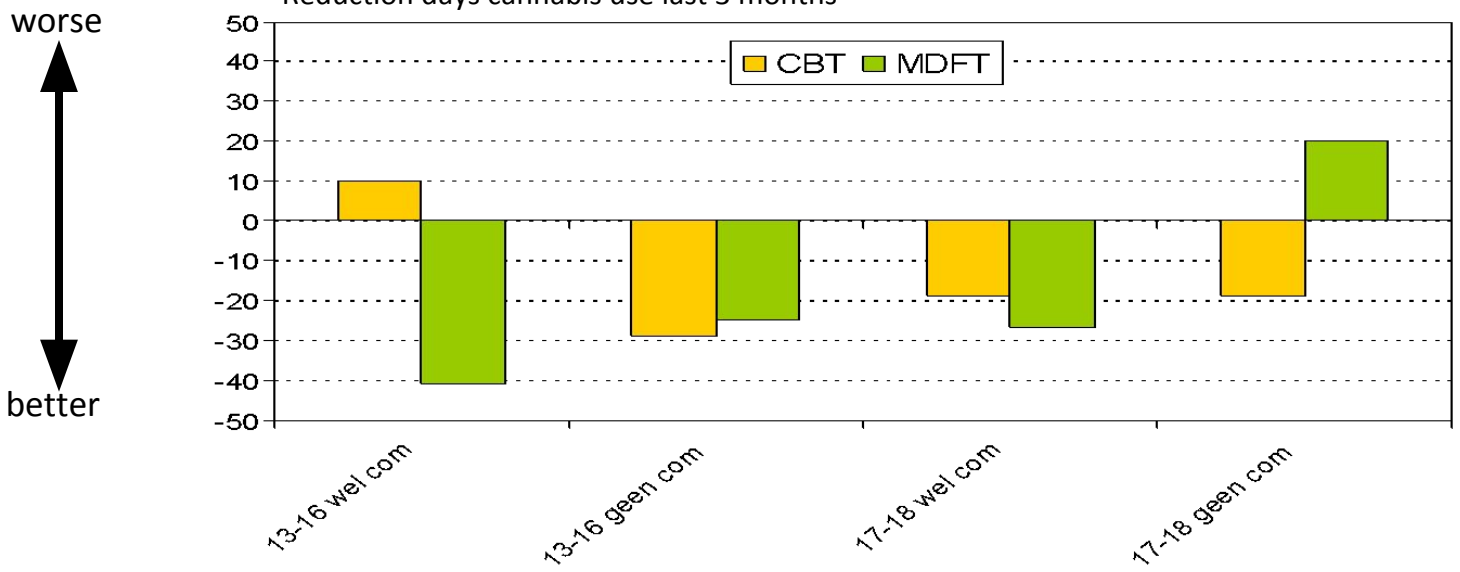
Overall CBT just as effective as MDFT in treatment adolescents with cannabis dependence

2012

Matching adolescents with a cannabis use disorder to multidimensional family therapy or cognitive behavioral therapy: Treatment effect moderators in a randomized controlled trial

Vincent Hendriks*, Evelien van der Schee, Peter Blanken

2012



PREFERRED	MDFT	CBT	CBT	CBT

Working alliance and outcome in youth addiction and MH Tx

Van Benthem et al., in preparation

Prospective study of 127 adolescents inj addiction and MH Tx
* pre-Tx asessment with Working Alliance Inventory for therapists and patients
* outcomes in terms of Sxx and drug use
Results:

Youth	Therapist	Responders
Weak	Weak	26 %
Weak	Strong	45 %
Strong	Weak	35 %
Strong	Strong	74 %

Outcome much better if mutual working alliance strong training and/or swich!

Conclusions

Conclusions

- Addiction is (also) a treatable brain disease
- New pharmacological treatments with limited effect size
- Polypharmacy and/or personalized treatments are needed
- Interesting precision/personalized medicine findings in alcohol and nicotine dependence that can be used for patient-treatment matching in clinical practice
- Larger (replication) studies with well-designed treatments and control for multiple comparison are needed.

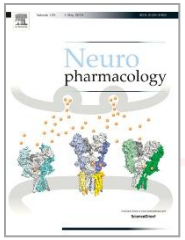
Thank You

Wim van den Brink: w.vandenbrink@amc.uva.nl

Psychiatry & the psychedelic drugs. Past, present & future

James J.H. Rucker [a, b, d, *], Jonathan Iliff [c], David J. Nutt [d]

Neuropharmacology 142 (2018) 200–218



Alcoholisme 1940-1970

Studies: N=8; 6 RCTs, 1 gecontroleerde studie, 1 open studie; n=30-176 patiënten

Medicatie: LSD (meestal zonder psychotherapie; wel prettige omgeving)

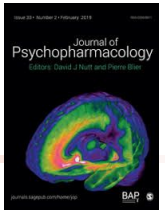
Uitkomst: wisselend, met kleine significante – niet beklijvende - effecten

Formele meta-analyse van de 6 RCTs studies: Krebs & Johansen, 2012 □

Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials

Teri S Krebs[1,2] and Pål-Ørjan Johansen[1,2]

Journal of Psychopharmacology
26(7) 994–1002



2012

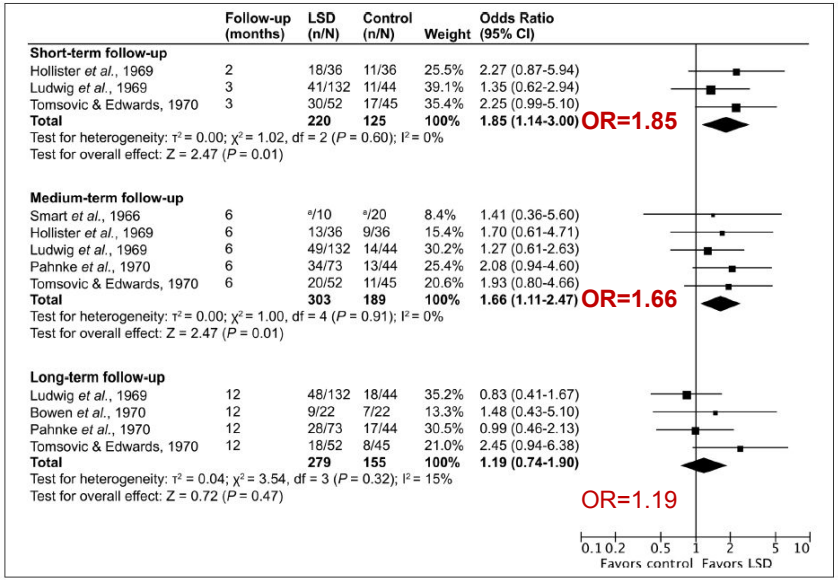


Figure 3. Improvement in alcohol misuse at short-, medium- and long-term follow-up after LSD versus control treatments.
[a]Continuous outcome data.

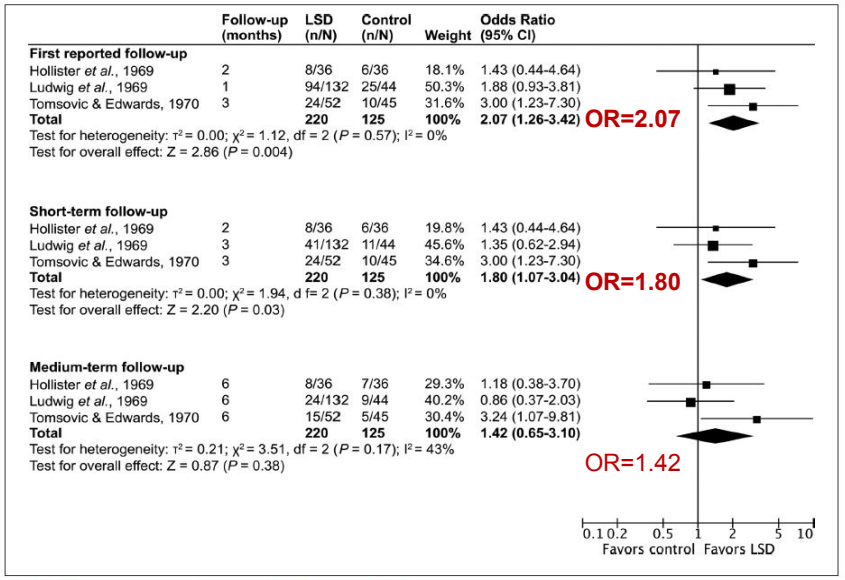


Figure 4. Maintained abstinence from alcohol after LSD versus control treatments.

Substantiële effecten LSD (3-6 maanden) op minder drinken en blijvende abstinentie

Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials

Teri S Krebs[1,2] and Pål-Ørjan Johansen[1,2]

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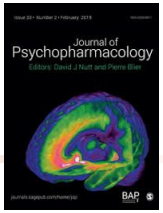
26(7) 994–1002



2012

Table 3. Data from recent meta-analyses of randomized controlled clinical trials on the effectiveness of LSD, naltrexone, acamprosate and disulfiram for alcoholism or alcohol dependence.

Outcome	LSD, single dose		Naltrexone, daily		Acamprosate, daily		Disulfiram, daily	
	Benefit difference (95% CI)	NNT	Benefit difference (95% CI)	NNT	Benefit difference (95% CI)	NNT	Benefit difference (95% CI)	NNT
Improvement on alcohol misuse, or return to heavy drinking	16% (8%, 25%)	6	11% (7%, 15%)	9	1% (-2%, 5%)	100	Not reported	
Maintained abstinence, or return to any drinking	15% (4%, 25%)	7	3% (1%, 6%)	33	11% (7%, 15%)	9	11% (-1%, 22%)	9

LSD outcomes are at first follow-up after single dose and are compared to no drug or active placebo. Naltrexone and acamprosate outcomes are during daily drug treatment and are compared to placebo. Disulfiram outcomes are during daily unsupervised drug treatment and are compared to other or no treatment. Data on naltrexone, acamprosate and disulfiram extracted from published meta-analyses (Rösner et al., 2010a, 2010b; Krampe and Ehrenreich, 2010). Pooled benefit differences calculated using a random-effects, inverse variance method. Benefit difference = % patients with beneficial outcome in experimental – % patients with beneficial outcome in control. Number needed to treat (NNT) = 1/(benefit difference).

Eenmalig LSD effectiever dan doorgaande behandeling met NTX, ACP, Disulfiram

Efficacy of Ketamine in the Treatment of Substance Use Disorders: A Systematic Review

Jennifer L. Jones [1], Camilo F. Mateus [1], Robert J. Malcolm [1], Kathleen T. Brady [1,2] and Sudie E. Back [1,2]*

frontiers in Psychiatry

2018

Systematisch review

Studies: N=7 studies: 3 RCT parallel, 2 RCTs cross-over, 1 case-controle, 1 ??

Diagnose: 2 cocaïne (Dakwar 2014, 2017), 3 opioïd (Krupitsky 2002, 2007; Jovaisa 2006), 2 alcohol (Krupitsky 1997; Wong, 2015)

Medicatie: ketamine i.v. of i.m.

Uitkomst: vermindering onthouding, vergroting motivatie, vermindering craving, toename (langdurige) abstinentie

The Effects of Subanesthetic Ketamine Infusions on Motivation to Quit and Cue-Induced Craving in Cocaine-Dependent Research Volunteers

Elias Dakwar, Frances Levin, Richard W. Foltin, Edward V. Nunes, and Carl L. Hart

2014

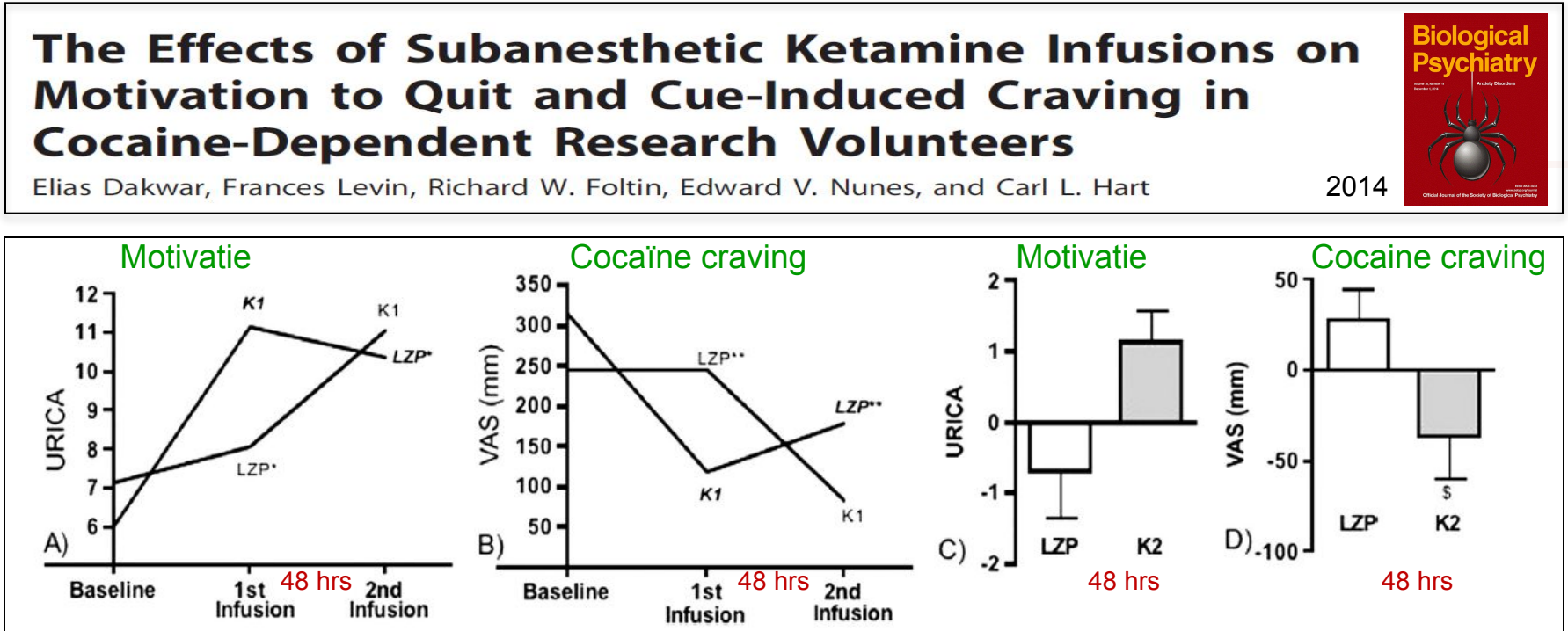


Figure 2. Persistent (>72-hour) K1 effects; ketamine .71 mg/kg (K2) effects, 24 hours postinfusion. **(A, B)** Baseline and postinfusion URICA and VAS scores by infusion order (first or second) for LZP ($n = 3$) and K1 ($n = 3$). **(C, D)** Difference from preceding assessment, LZP vs. K2, in subjects who received K1 in the first infusion ($n = 5$) (mean values and SEMs shown; median values are provided in the Results section). **(A)** URICA assessments for LZP were significantly different when LZP was administered first or second, $^{*}p = .047$, suggesting a post-K1 carry-over effect. **(B)** LZP order effects with sum VAS scores, $^{**}p = .1$. **(C)** Paired within-subject comparison of URICA by condition, K2 vs. LZP, in those who received K1 in the first condition ($n = 5$); nonsignificant, $p = .11$. **(D)** Paired within-subject comparison of sum VAS scores by condition in those who received K1 in the first infusion ($n = 5$), K2 vs. LZP, $^{\$}p = .046$. Abbreviations as in Figure 1.

Randomized cross-over studie: ketamine geeft motivatie en verminderd cocaïne-craving

Mogelijke schadelijkheid Psychelica

Ranking the Harm of Alcohol, Tobacco and Illicit Drugs for the Individual and the Population

Jan van Amsterdam[a] Antoon Opperhuizen[a] Maarten Koeter[b, c]
Wim van den Brink[b, c]

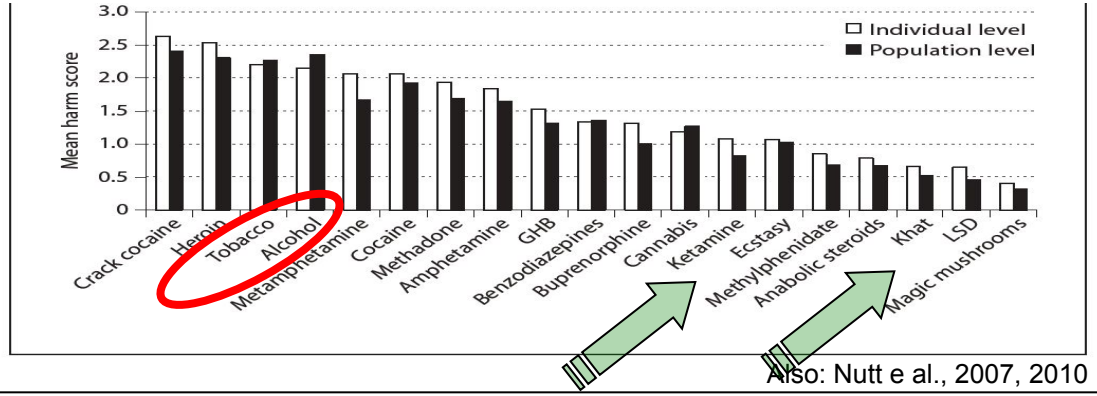


Fig. 1. Mean harm score of drugs at individual (user) level and population level. Mean harm is defined as the averaged value of the scores for toxicity, dependence and social harm (either at individual or population level) of the drugs.

Also: Nutt e al., 2007, 2010

Van alle psychedelica worden paddostoelen en LSD als minst schadelijk gezien en worden ecstasy en ketamine slechts een beperkt risisco toegedicht.

Internationale overeenstemming relatieve schadelijkheid

Drug harms in the UK: a multicriteria decision analysis

David J Nutt, Leslie A King, Lawrence D Phillips, on behalf of the Independent Scientific Committee on Drugs

THE LANCET

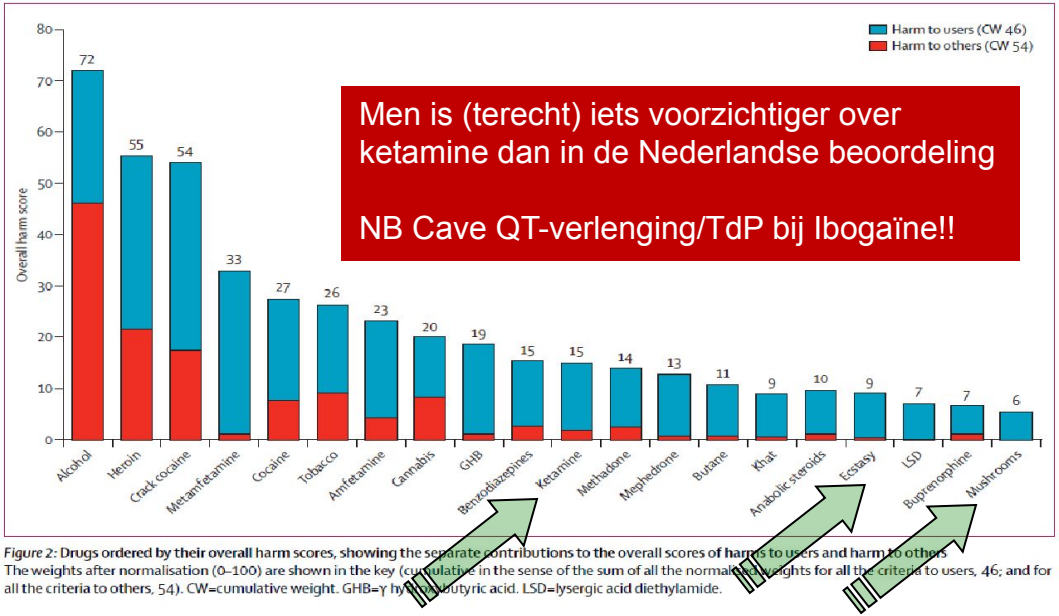


Figure 2: Drugs ordered by their overall harm scores, showing the separate contributions to the overall scores of harms to users and harm to others. The weights after normalisation (0–100) are shown in the key (cumulative in the sense of the sum of all the normalised weights for all the criteria to users, 46; and for all the criteria to others, 54). CW=cumulative weight. GHB=γ hydroxybutyric acid. LSD=lysergic acid diethylamide.

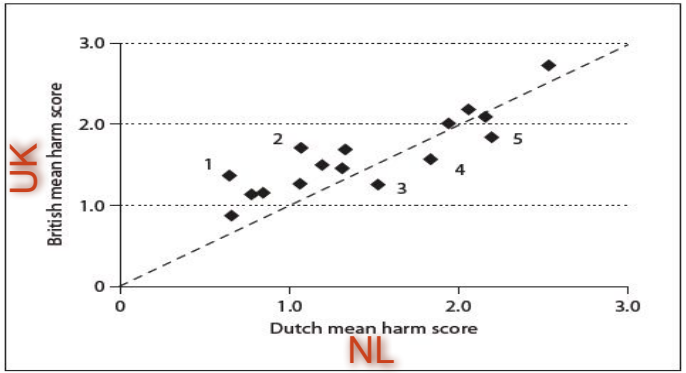


Fig. 2. Correlation between the mean harm scores of 16 drugs given by Dutch and British experts. Correlation coefficient is 0.87. Drugs which were scored differently by Dutch experts as compared with the British experts, i.e. deviating from the dashed reference line, were LSD (1), ketamine (2), GHB (3), amphetamine (4), and tobacco (5).