Stoornissen in het gebruik van middelen

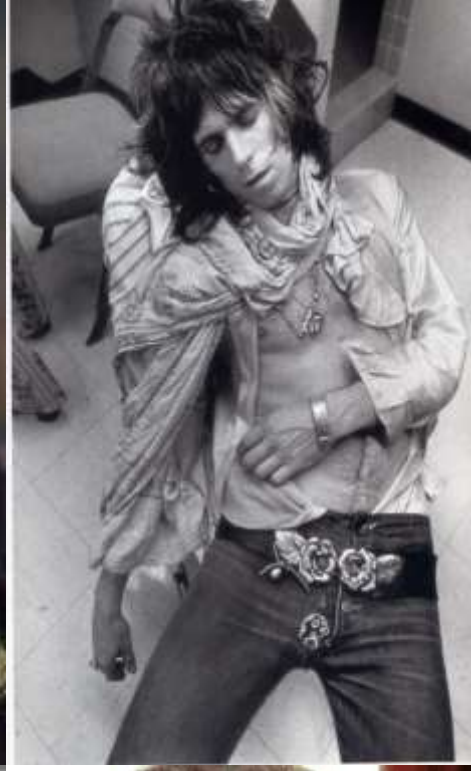
"Nieuwe behandelvormen"

Geert.dom@uantwerpen.be

Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen / Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld • ***Honorarium of andere (financiële) vergoeding*** • Aandeelhouder • Andere relatie, namelijk …	• • Lundbeck/GSK/ Astra Zeneca/ Eli Lilly / Merck/Janssen / Reckitt Benckiser Pharmaceuticals • •

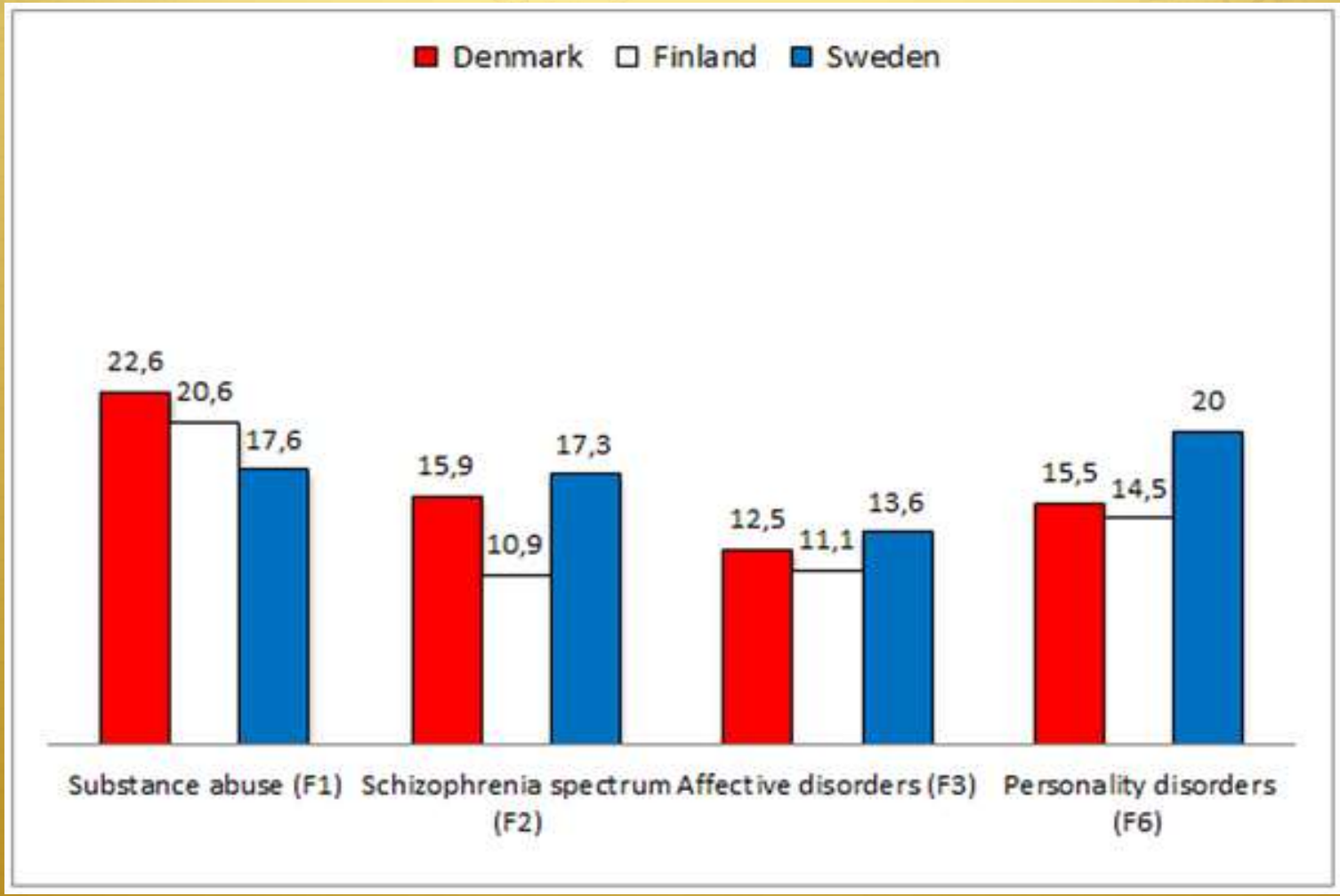


NASA


Waarom hebben we nieuwe behandelingen en/of andere aanpak nodig?

Figure 2. Difference in life expectancy among 124,971 women with recent onset mental illness in Denmark, Finland and Sweden compared to the general population.



Nordentoft M, Wahlbeck K, Hällgren J, Westman J, et al. (2013) Excess Mortality, Causes of Death and Life Expectancy in 270,770 Patients with Recent Onset of Mental Disorders in Denmark, Finland and Sweden. PLoS ONE 8(1): e55176. doi:10.1371/journal.pone.0055176
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0055176

De problemen

- We bereiken onvoldoende de potentiele patienten.
- >> oplossing: bereik verhogen
- Als we ze bereiken blijft de effectiviteit van de behandeling matig.
- >> oplossingen:
  - targetting subgroepen betere respons
  - Uitgaan van onderliggende neurobiologische defecten.

Table 7. First and Second Line Pharmacological Treatments in Addictive Disorders

Disorder	First Line Treatment	Second Line Treatment
Nicotine Dependence	varenicline bupropion NRT	nortryptiline clonidine
Alcohol Dependence	naltrexone acamprosate disulfiram	topiramate baclofen?*
Opioid Dependence	methadone buprenorphine heroin	naltrexone (XR)#
Cocaine Dependence	bupropion dexamphetamine disulfiram? modafinil? methadone high dose?	topiramate? vigabatrin? bacolfen? ondansetron? cabergoline? aripiprazole? methamphetamine?
Cannabis Dependence	naltrexone? buspirone? atomoxetine? dronabinol?	
Pathological Gambling	naltrexone nalmefene	paroxetine??^

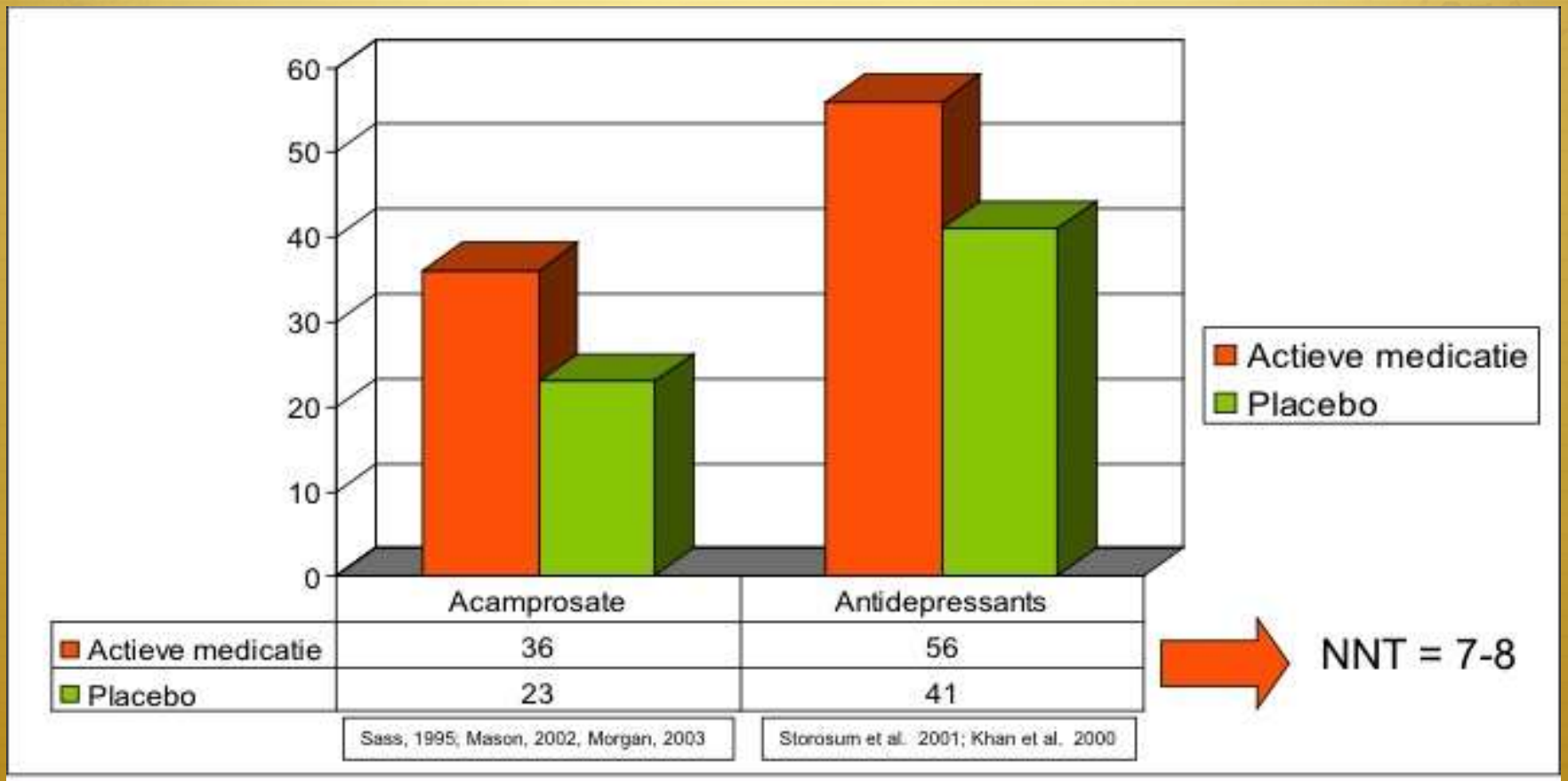
*? = indications but no proof of efficacy.
#XR = extended release.
^?? = inconsistent findings.

Medications tested in phase II Clinical Trials for reducing drinking severity
(without taking into account pharmacogenetic heterogenity)

Transmittor system	Medication	Primary molecular target	Effect size
Opioid	Naltrexone	M-opioidreceptor antagonist	Small
GABA	Baclofen	GABA-B agonist	Mixed effects
Glutamate, GABA	Acamprosate	NMDA antagonist GABA-A agonist	Small
Serotonin	Sertraline	5-HT transporter	Small-medium
Serotonin	Ondansetron	5HT3 antagonist	Small-medium
GABA, glutamate	Topiramate	GABA-A antagonist	medium

Small effect size: 0.2-0.3 Medium: around 0.5; Large effect-size: > 0.8

After Bankole Johnson



	Acamprosate	Antidepressants
Actieve medicatie	36	56
Placebo	23	41
	Sass, 1995; Mason, 2002; Morgan, 2003	Storosum et al. 2001; Khan et al. 2000

NNT = 7-8

Acamprosaat is bewezen effectieve interventie met een beperkte effectgrootte:
Ongeveer 40% abstinent na 6-12 maanden en een NNT van 7-8

Leucht et al. BJP 201

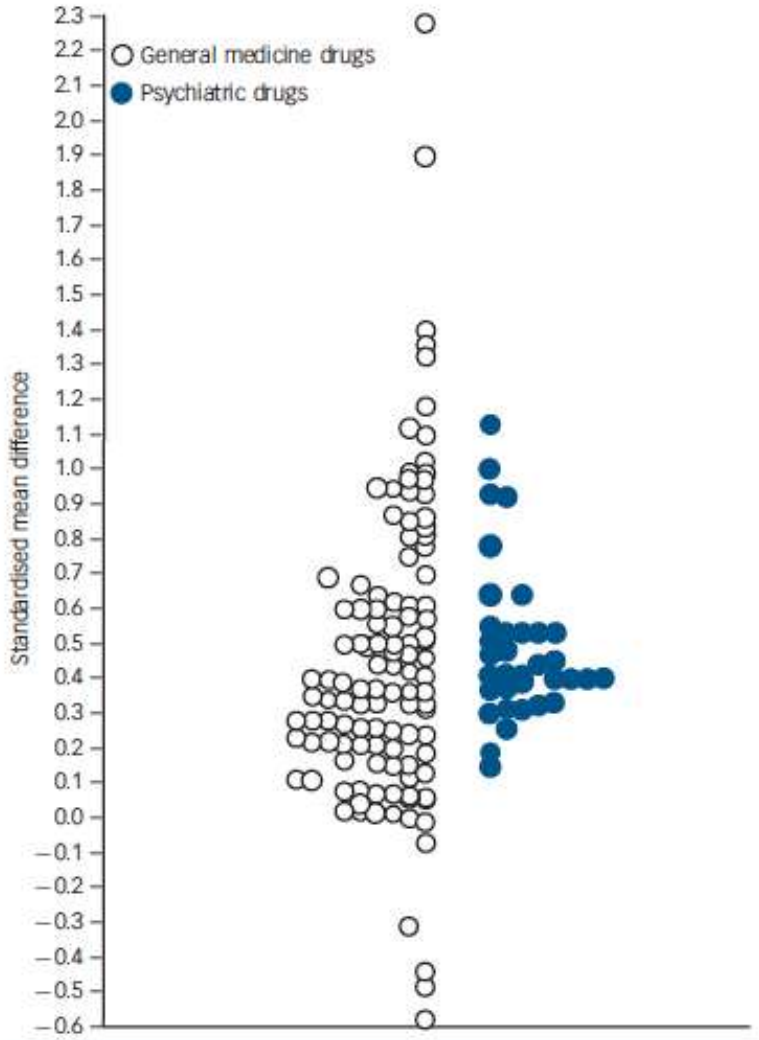


Fig. 1 Summary of effect sizes.

All effect sizes in online Tables DS3 and DS4 are presented except for duplicates (e.g. effect size on dichotomous response and continuous reduction of severity in schizophrenia). Online Fig. DS25 identifies which dot corresponds to which result, and Figs DS26–29 present the results of dichotomous outcomes as relative and absolute risk/responder differences. Data on older meta-analyses from Table DS1 are not included. Effect sizes of dichotomous outcomes were converted to standardised mean differences expressed as Hedges' *g*. Effect sizes of general medicine medication are presented on the left-hand side (median 0.37, mean 0.45, 99% CI 0.37–0.53) and psychiatric drugs on the right-hand side (median 0.41, mean 0.49, 95% CI 0.41–0.57).

Middel	Jaarprevalentie gebruikers		Jaarprevalentie verslaafden		Verslavingszorg		Verslaafden in huisartsenpraktijk	
	% 12+	Aantal 12+	%18+	Aantal 18+	Aantal	% van ver-slaafden	Per 2500	Per 150
Tabak	34	4.400.000	17	2.000.000	Nihil	Nihil	425	25
Alcohol	73	9.800.000	3,7	280.000	28.000	10	90	6
Benzodia-zepinen	4	500.000	3,3	250.000	Nihil	Nihil	80	5
Cannabis	3	400.000	0,5	35.000	3.500	9	10	< 1
XTC	0,3	65.000	?	?	< 300	?	?	?
Heroïne	0,2	28.000	0,3	25.000	17.500	70	5-10	< 1
Cocaïne	> 0,4	> 50.000	> 0,3	> 20.000	7.000	< 30	> 10	1

Use of mental health services in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project

Proportion of individuals consulting any type of formal health services in the previous 12 months, according to 12-month mental disorder status

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

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

CI=confidence interval

Alonso et al. Acta Psychiatr Scand Suppl 2004; 420: 47–54

Oorzaken van 'treatment gap' bij alcoholproblematiek

Treatments[1-3]

- Lack of efficacious treatments
- Complicated treatment regimens with abstinence as the only pharmacological treatment goal

Society[2]

- Low public awareness of alcohol dependence as a brain disease
- Low public awareness of the burden of alcohol consumption and dependence

Physicians[4-7]

- Preference for psychosocial intervention
- Limited screening, diagnosing and treatment skills in primary care
- Lack of motivation due to difficult and time-consuming patients and no efficacious treatment options
- Social stigma

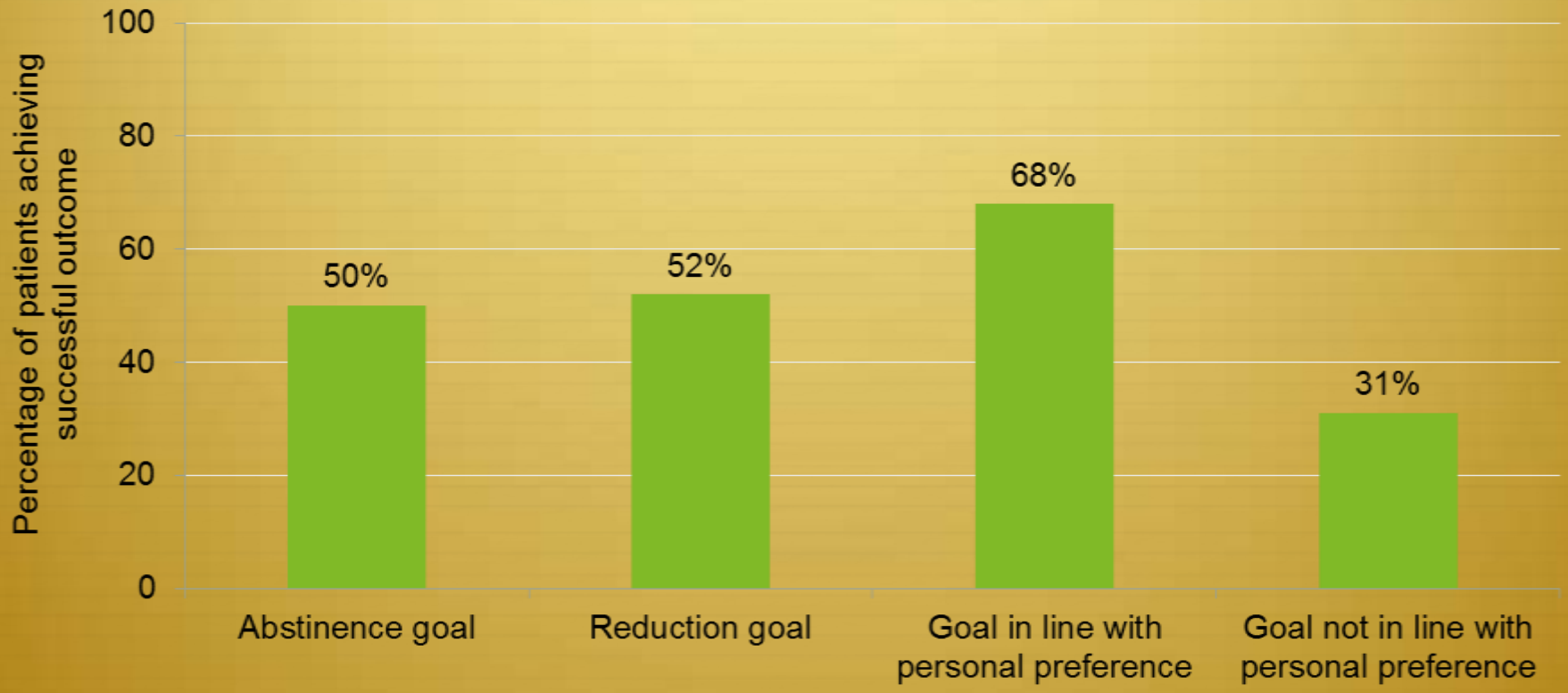
Patients[8]

- Low treatment-seeking behaviour due to:
  - Stigma
  - Negative beliefs or experiences with treatment/treatment goals
  - Treatment would not solve the problem
  - Privacy issues
  - Denial of problem severity

1. VisionGain. The global anti-addiction market, 2008–2023, 2008;
2. Decision Resources. Addiction Disorders, January 2007;
3. Decision Resources. Spectrum. Therapeutic Markets: Opportunities and Pipeline Analysis, 2010;
4. Informed. GP Segment Research, 2010; 5. Zaicom. Evaluating the nalmefene business opportunity in EU, 2011;
6. GP Segmentation Research, 2012; 7. Alonso. Acta Psychiatr Scand 2004:109(Suppl. 420):47–54; 8. Sobell et al. Addiction 2000;95(5):749–764

Betrokkenheid van patiënten bij behandeldoelen

12-month follow-up status by actual treatment received

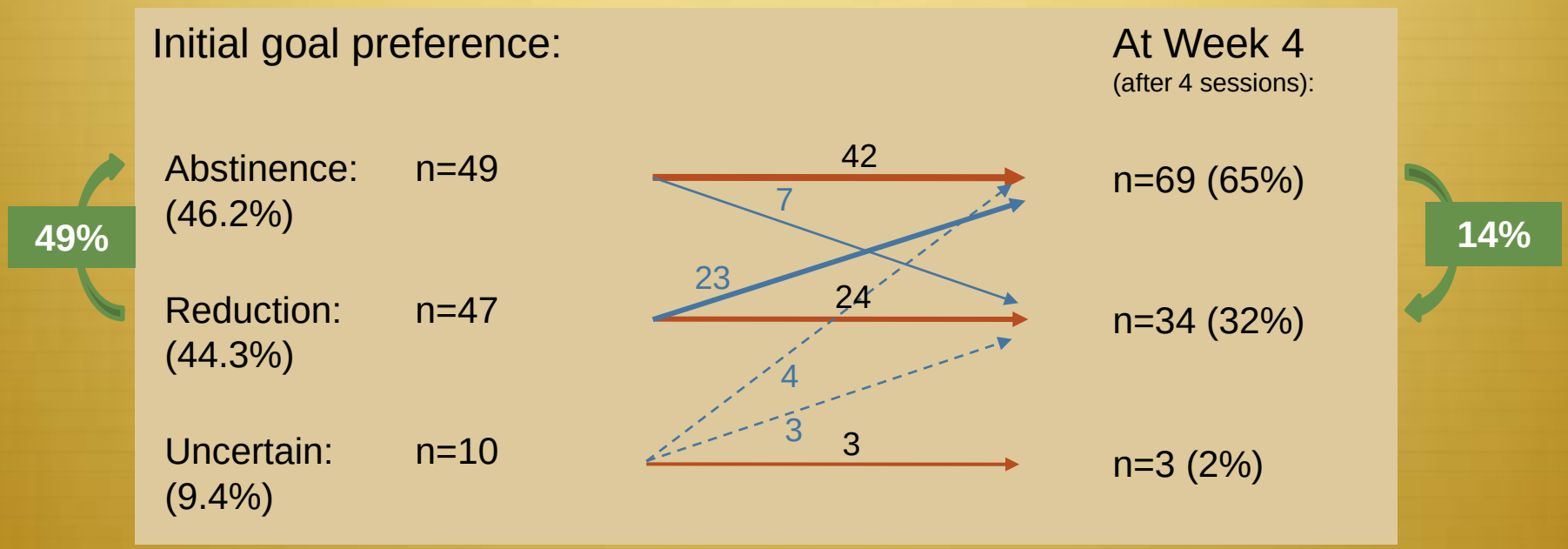


Patiënten mee laten beslissen over de behandeldoelen verhoogt de kans op een gunstige uitkomst

Orford & Keddie. Br J Addict 1986;81(4):495–504

Evolutie in behandeldoelen

Initiële doelstelling en veranderingen na 4 weken



49% van patiënten met initiële voorkeur voor reductie schoven op naar abstinentie na vier weken

Een aantal patiënten die initieel voor reducite opteren, beslissen na eerste ervaring met 'minder drinken' naar abstinentie als behandeldoel

Hodgins et al. Addict Behav 1997;22(2):247–255

Voordelen van reductie als een bijkomende doelstelling voor alcoholafhankelijke patiënten

Veel patiënten verkiezen reductie als behandeldoel[3-4]

Reductie biedt een laagdrempelige, niet gestigmatiseerde en flexiebele behandeloptie[5]

Reductie gerichte behandelingen is zo effectief als abstinentie gerichte behandeling[2,6]

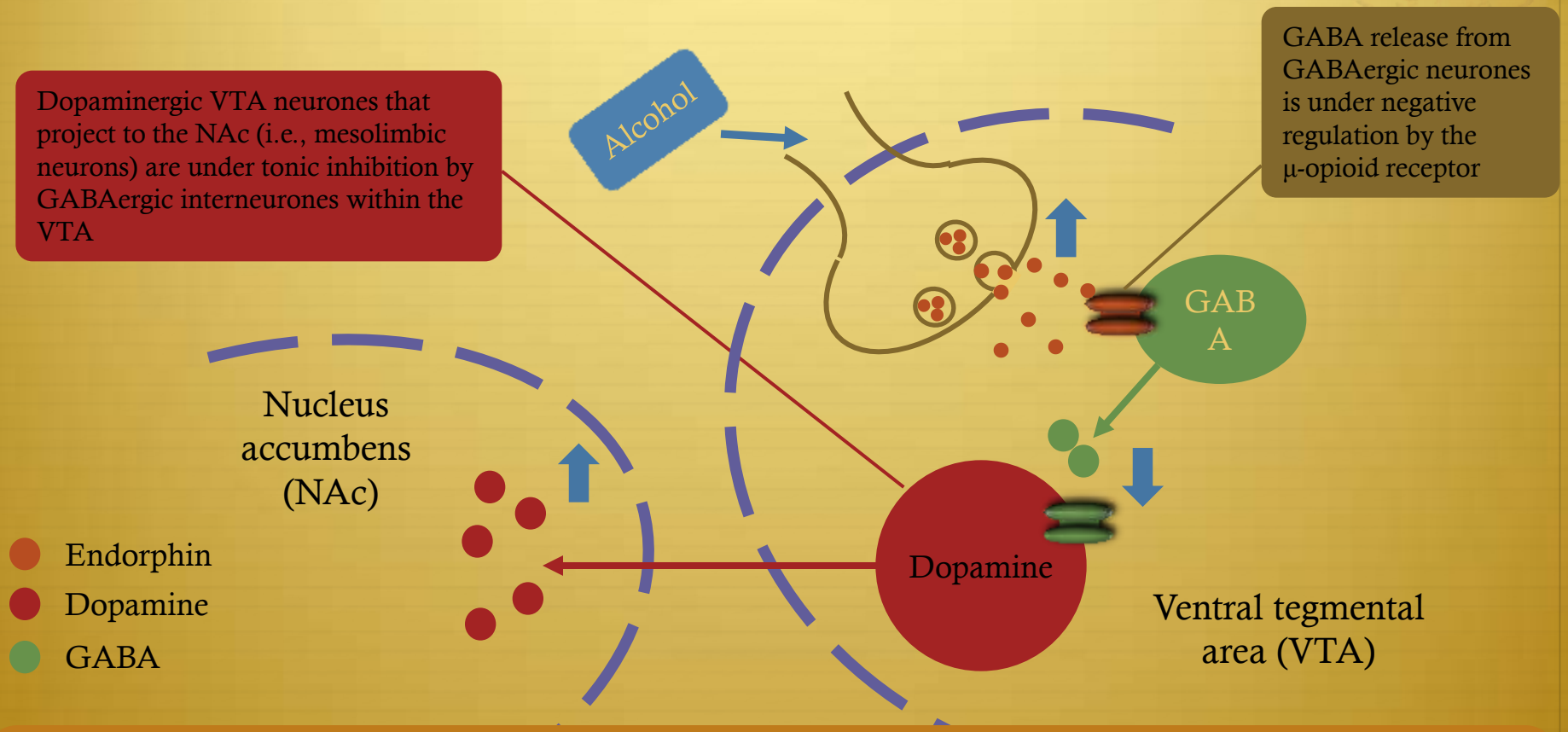
Reductie is in een aantal gevallen een intermediaire doelstelling op weg naar abstinentie[4]

Er is risicovermindering, zonder volledige alcoholstop[2]

Reductie is een praktisch en pragmatisch alternatief voor abstinentie gerichte behandeling[1]

1. Gastfriend et al. J Subst Abuse Treat 2007;33:71-80; 2. Marlatt & Witkiewitz, Addict Behav 2002;27:867-86; 3. Heather et al. Alcohol Alcohol 2010;45:128-35; 4. Hodgins et al. Addict Behav 1997;22(2):247-55; 5. van Amsterdam et al. J Psychopharmacol 2013;27(3):248-55; 6. Sobell & Sobell. Behav Res Ther 1976;14(3):195-215

Alcoholconsumptie leidt tot een transiënte toename van dopamine door endorfine vrijzetting

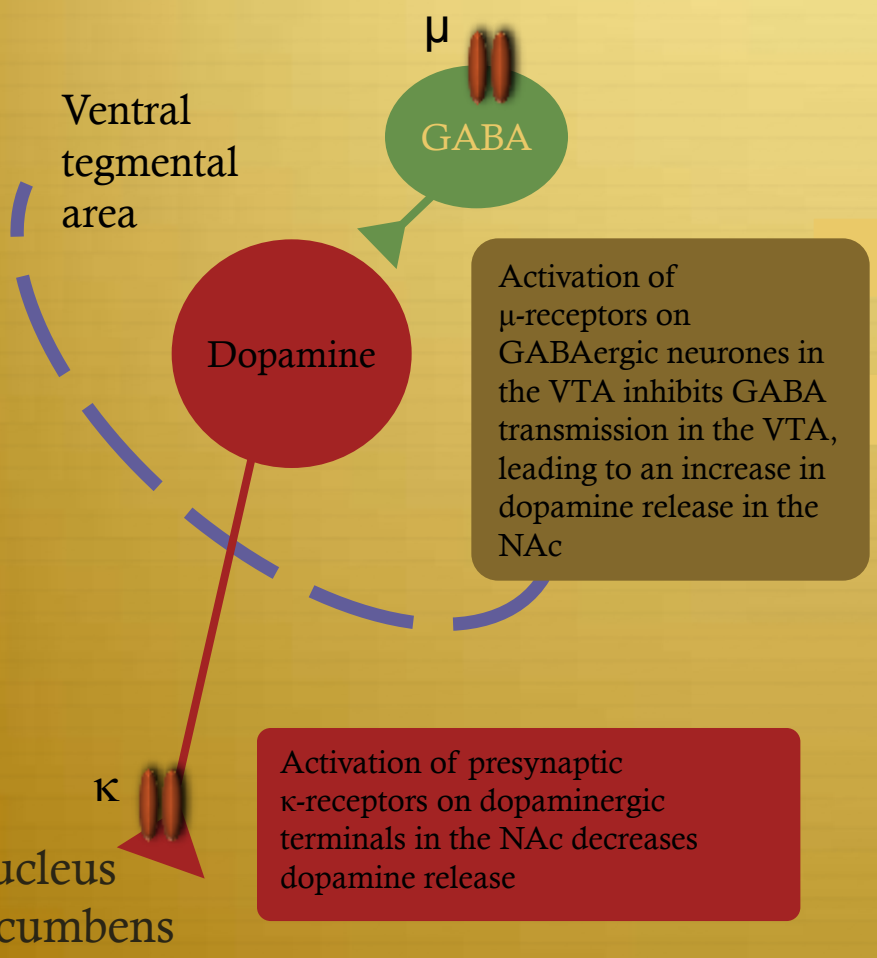


- **Acute alcoholinname inducesert endorfine vrijzetting, die GABA vrijzetting in de VTA inhibeert, waardoor de inhitoire tonus op de dopamine cellen vermindert**
- **Dit leidt tot een toegenomen dopamine vrijzetting in de NAc**

Heilig et al. Nat Rev Neurosci 2011;12(11):670–684;
Clapp et al. Alcohol Res Health 2008;31(4):310–339

Dynorphin/endorphin systems are opposing systems

Neurobiology



Function

Opposing or opposite actions mediated by μ- and κ-opioid receptors

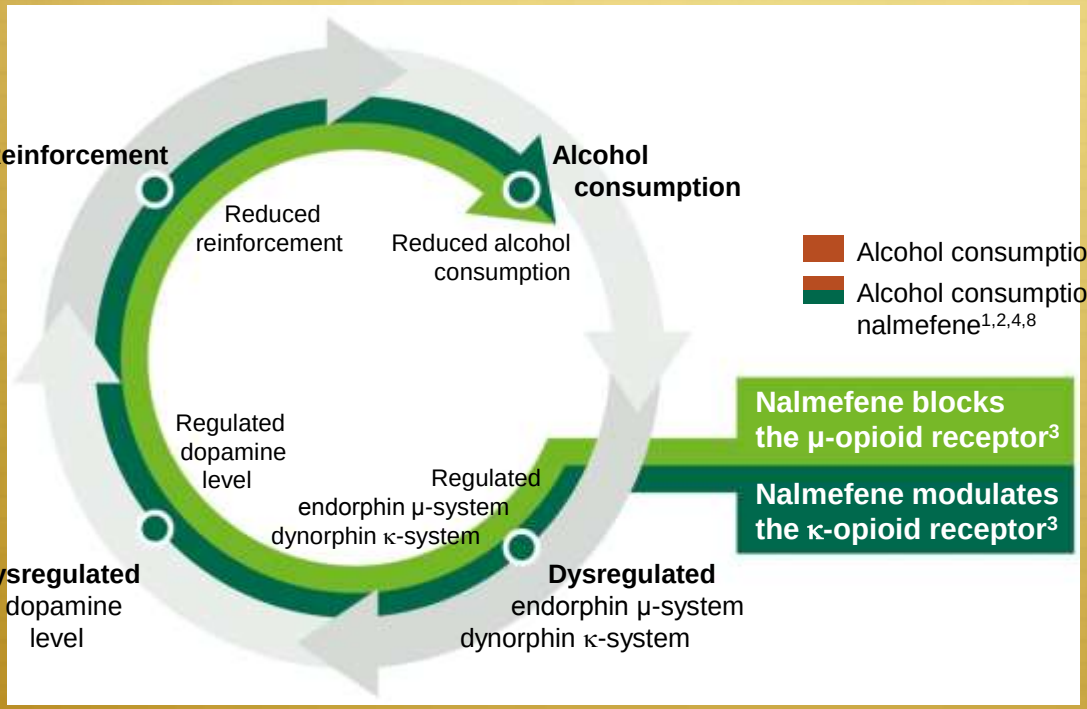
Function	μ	κ
Reward	+	-
Mesolimbic dopamine level	Increase	Decrease
Subjective effects	Euphoria and preference	Dysphoria and aversion

+=mediating the opioid function;
-=antagonising the μ-receptor-mediated function

Spanagel et al. Proc Natl Acad Sci U S A 1992;89(6):2046–2050; Pan. Trends Pharmacol Sci 1998;19(3):94–98

Nalmefene breaks the cycle of continuous drinking[1,2]

Nalmefene is a unique,[3] dual-acting,[4] opioid system modulator

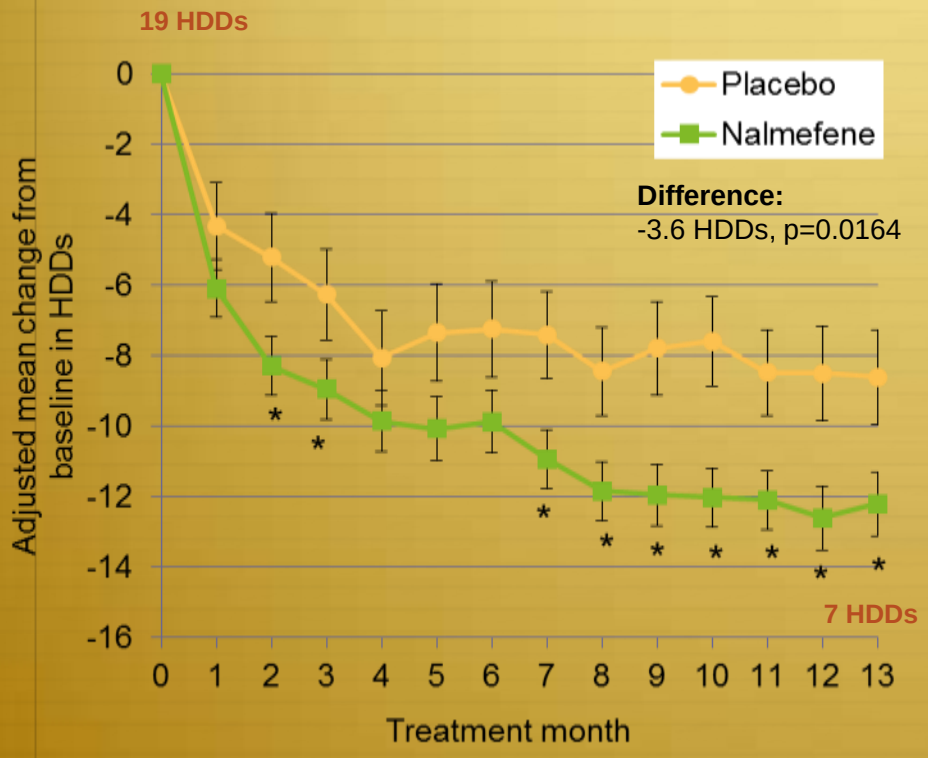


- Nalmefene is a dual-acting modulator because it acts on both the μ/δ- and κ-opioid receptors
- It therefore helps to restore the balance of a dysregulated motivational system, which reduces the urge to drink alcohol[2,4,5,8]

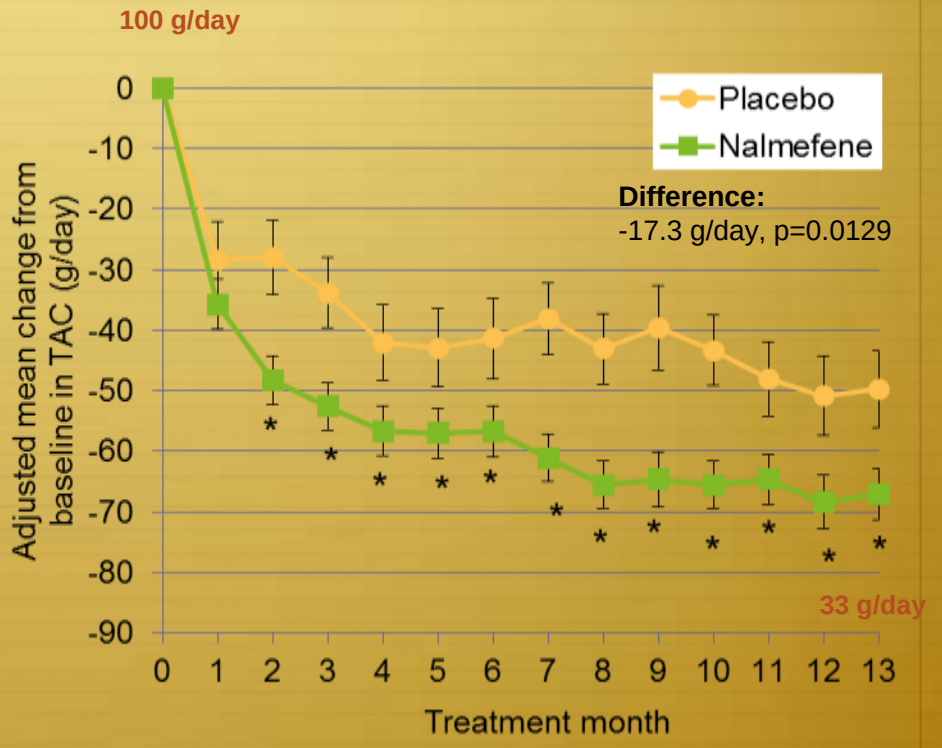
1. Mann et al. Biol Psychiatry 2013;73(8):706–713;
2. Walker & Koob. Neuropsychopharmacology 2008;33(3):643–652; 3. Michel et al. Meth Find Exp Clin Pharmacol 1985;7:175–177;
4. Hillemacher et al. Expert Opin Investig Drugs 2011;20(8):1073–1086; 5. Volkow et al. Jour of Clin Inv 2003;111(10):1444–1451;
6. Clapp et al. Alcohol Res Health 2008;31(4):310–339; 7. Sirohi et at. Front Mol Neurosci 2012: Epub ahead of print;
8. Nealey et al. Neuropharmacology 2011;61(1-2):35–42;

HDD/TAC: change from baseline in the 1-year study: Patients with at least high DRL at baseline and randomisation

SENSE: change in HDDs



SENSE: change in TAC

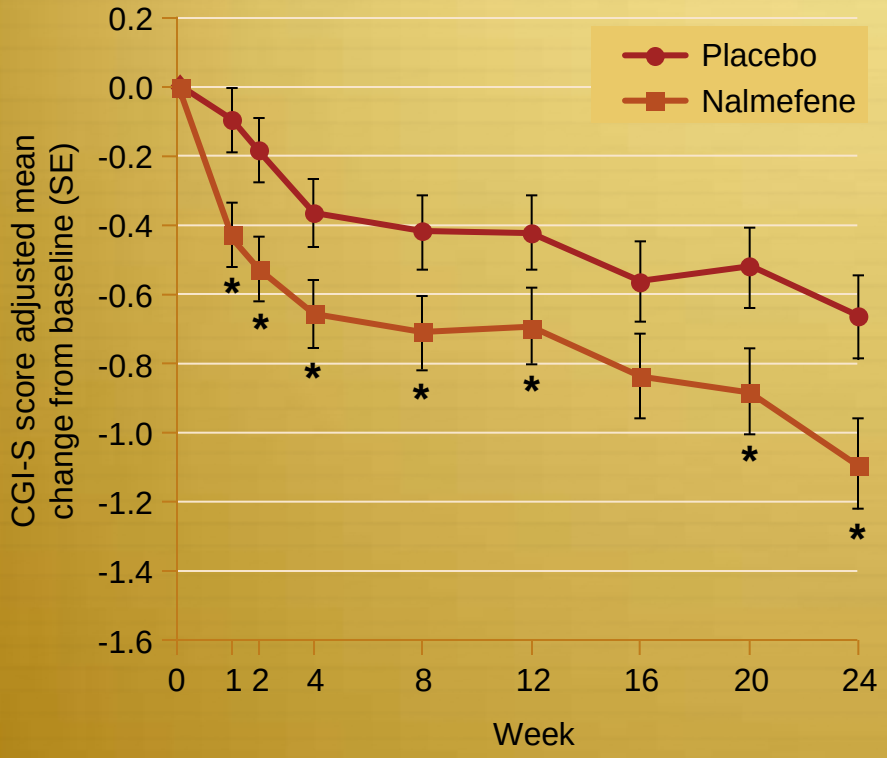


MMRM (OC) FAS estimates and SE; *p<0.05;
MMRM=mixed-effect model repeated measure;
OC=observed cases; FAS=full analysis set; SE=standard error

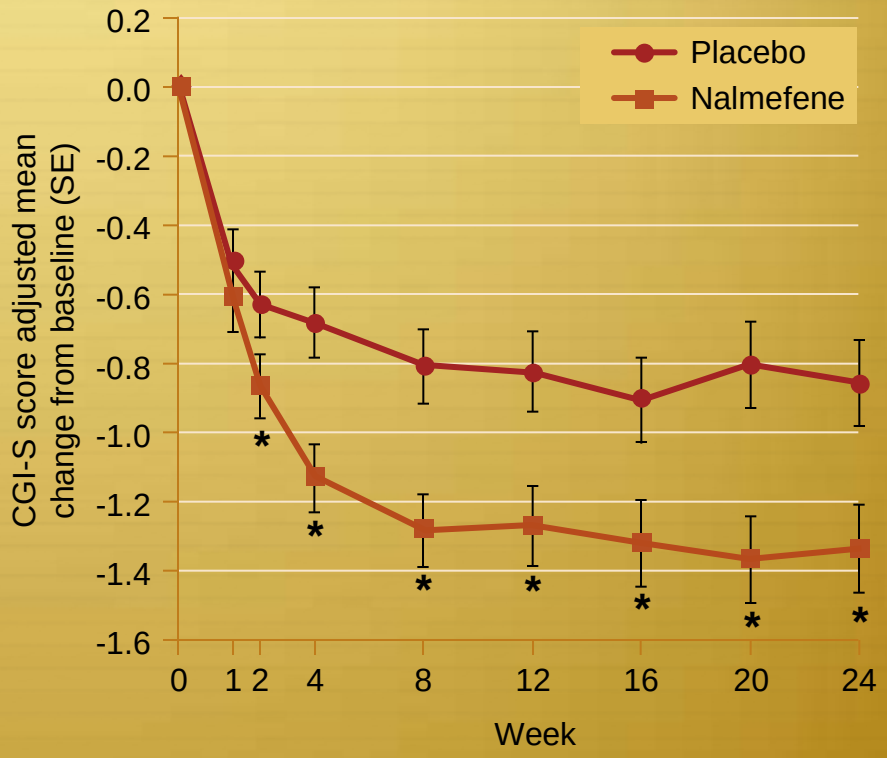
van den Brink et al. SENSE. Poster at EPA 2013
van den Brink et al. J Psychopharmacol, in press

Clinical Global Impression-Severity (CGI-S): change from baseline in the 6-month studies: Patients with at least high DRL at baseline and randomisation

ESENSE 1



ESENSE 2



FAS (full analysis set), MMRM; *p<0.05;
Baseline values for ESENSE 1: placebo 4.2, nalmefene 4.1;
Baseline values for ESENSE 2: placebo 4.3, nalmefene 4.4

van den Brink et al. Alcohol Alcohol 2013;48(5):570-8

Responder analysis: Pooled ESENSE 1 & 2 data at Month 6

Responder analysis	Odds ratio	95% CI	NNT
2-category downward shift in DRL	1.87	1.35–2.59	7
Downward shift to low DRL	1.79	1.27–2.53	9
70% reduction in TAC	1.88	1.32–2.70	9

*p<0.05; MMRM analysis
CI=confidence interval; NNT=number needed to treat

Nutt et al Poster at ECNP 2013

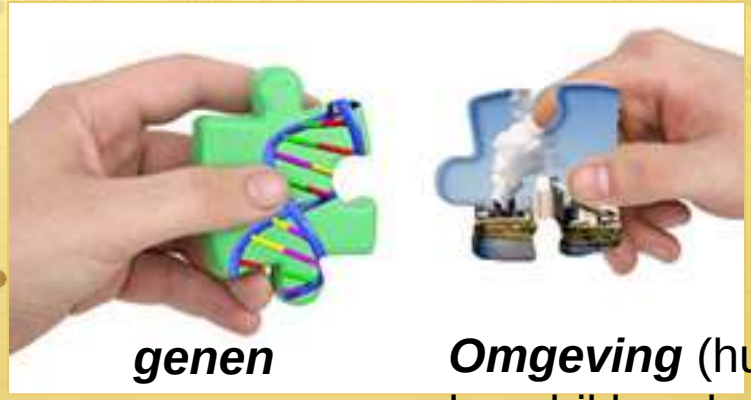
De problemen

- We bereiken onvoldoende de potentiele patienten.
- >> oplossing: bereik verhogen
- ***Als we ze bereiken blijft de effectiviteit van de behandeling matig.***
- ***>> oplossingen:***
  - ***targetting subgroepen betere respons***
  - ***Uitgaan van onderliggende neurobiologische defecten.***

Where in the brain is addiction localised?

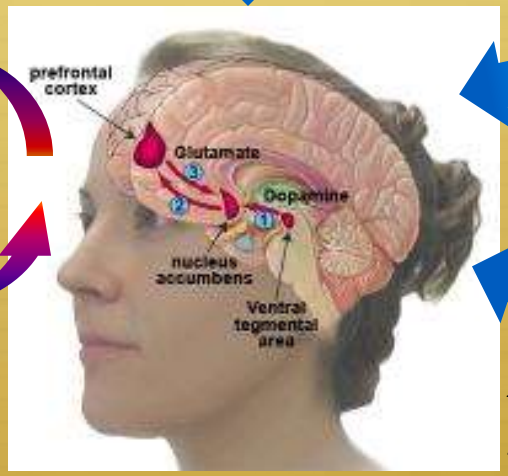
- Different areas of the brain subserve different functions
- PET/SPECT and fMRI scanning can now test these theories

startleeftijd



genen

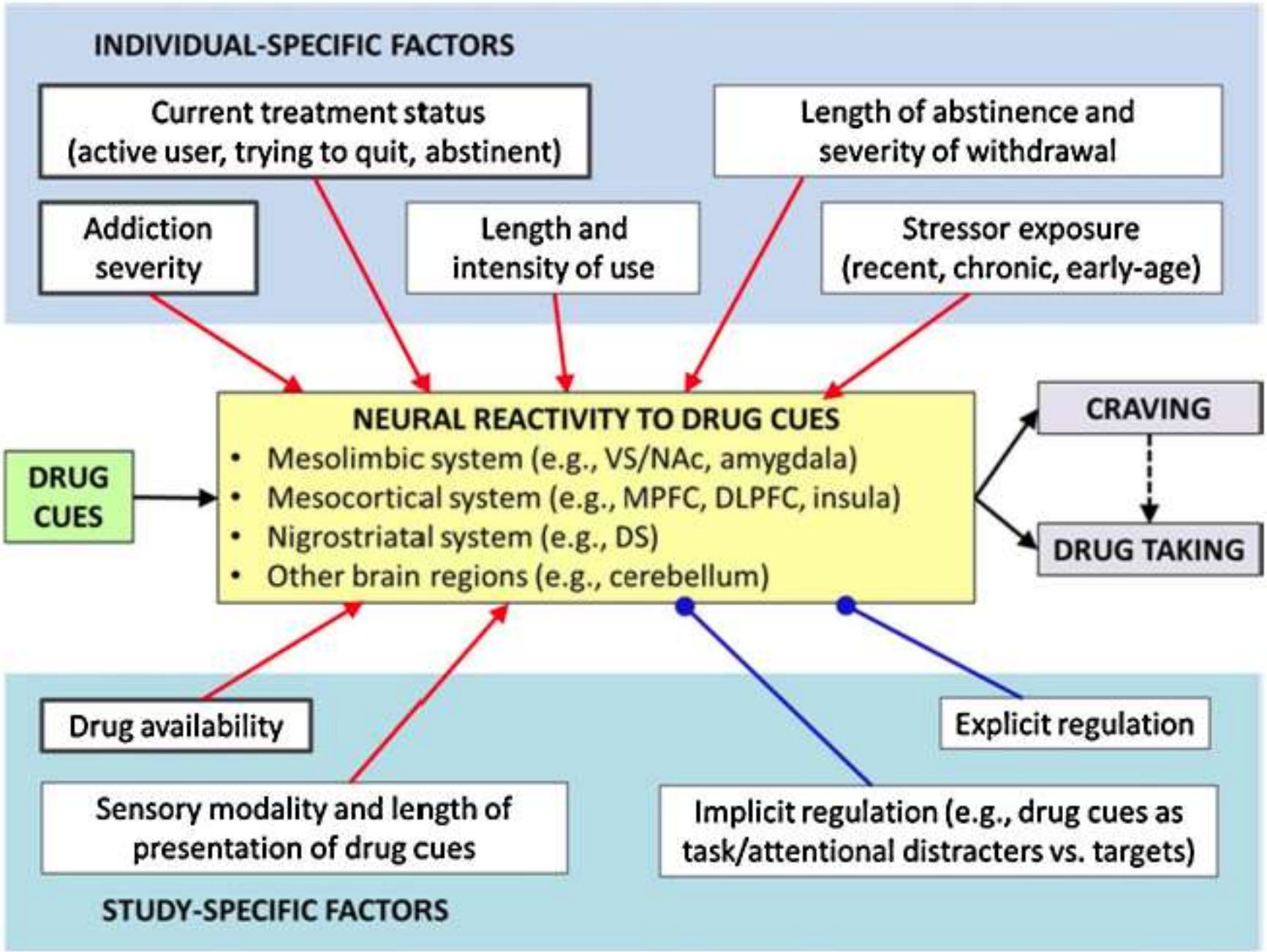
Omgeving (huidig en vroeger): beschikbaarheid, kansarmoede,… ***stress***)

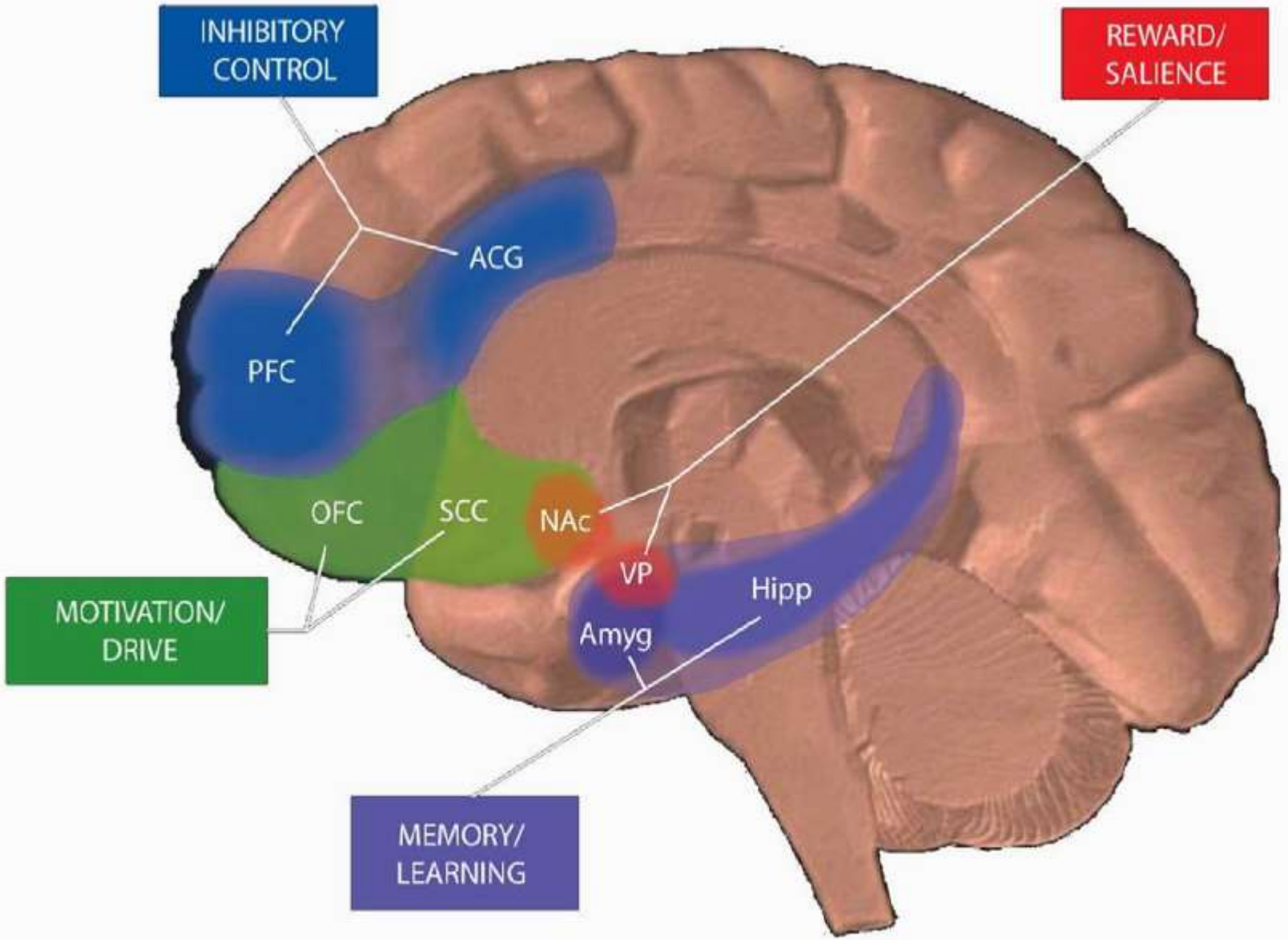


hersenmechanismen

Psychologische / psychiatrische stoornissen

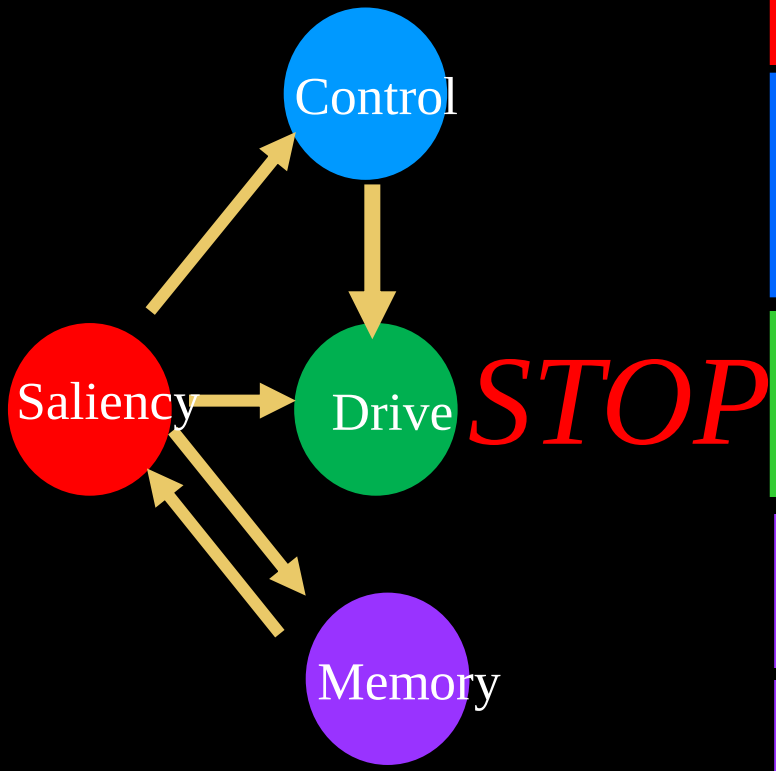
verslaving


INDIVIDUAL-SPECIFIC FACTORS
Current treatment status (active user, trying to quit, abstinent)
Length of abstinence and severity of withdrawal
Addiction severity
Length and intensity of use
Stressor exposure (recent, chronic, early-age)
NEURAL REACTIVITY TO DRUG CUES
• Mesolimbic system (e.g., VS/NAc, amygdala)
• Mesocortical system (e.g., MPFC, DLPFC, insula)
• Nigrostriatal system (e.g., DS)
• Other brain regions (e.g., cerebellum)
DRUG CUES
CRAVING
DRUG TAKING
Drug availability
Sensory modality and length of presentation of drug cues
Explicit regulation
Implicit regulation (e.g., drug cues as task/attentional distracters vs. targets)
STUDY-SPECIFIC FACTORS

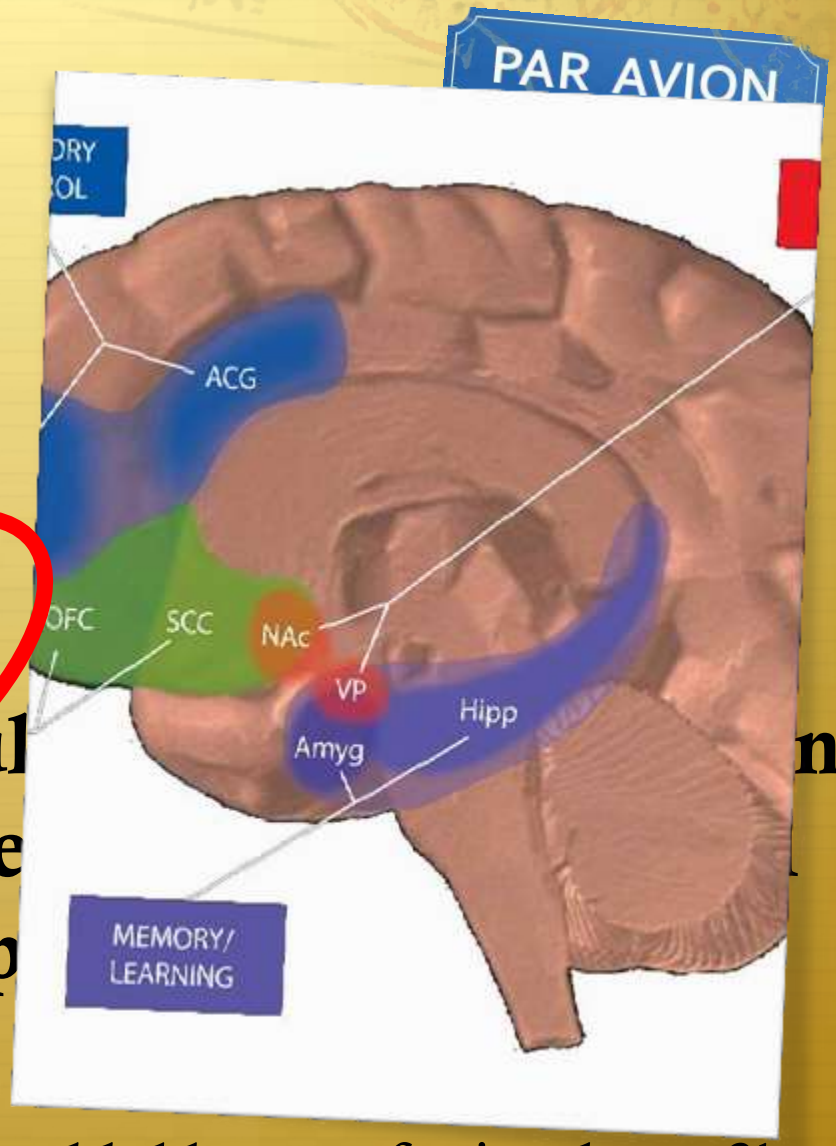

INHIBITORY CONTROL
REWARD/ SALIENCE
ACG
PFC
OFC
SCC
NAc
VP
Hipp
Amyg
MOTIVATION/ DRIVE
MEMORY/ LEARNING

Medications for Relapse Prevention

Non-Addicted Brain



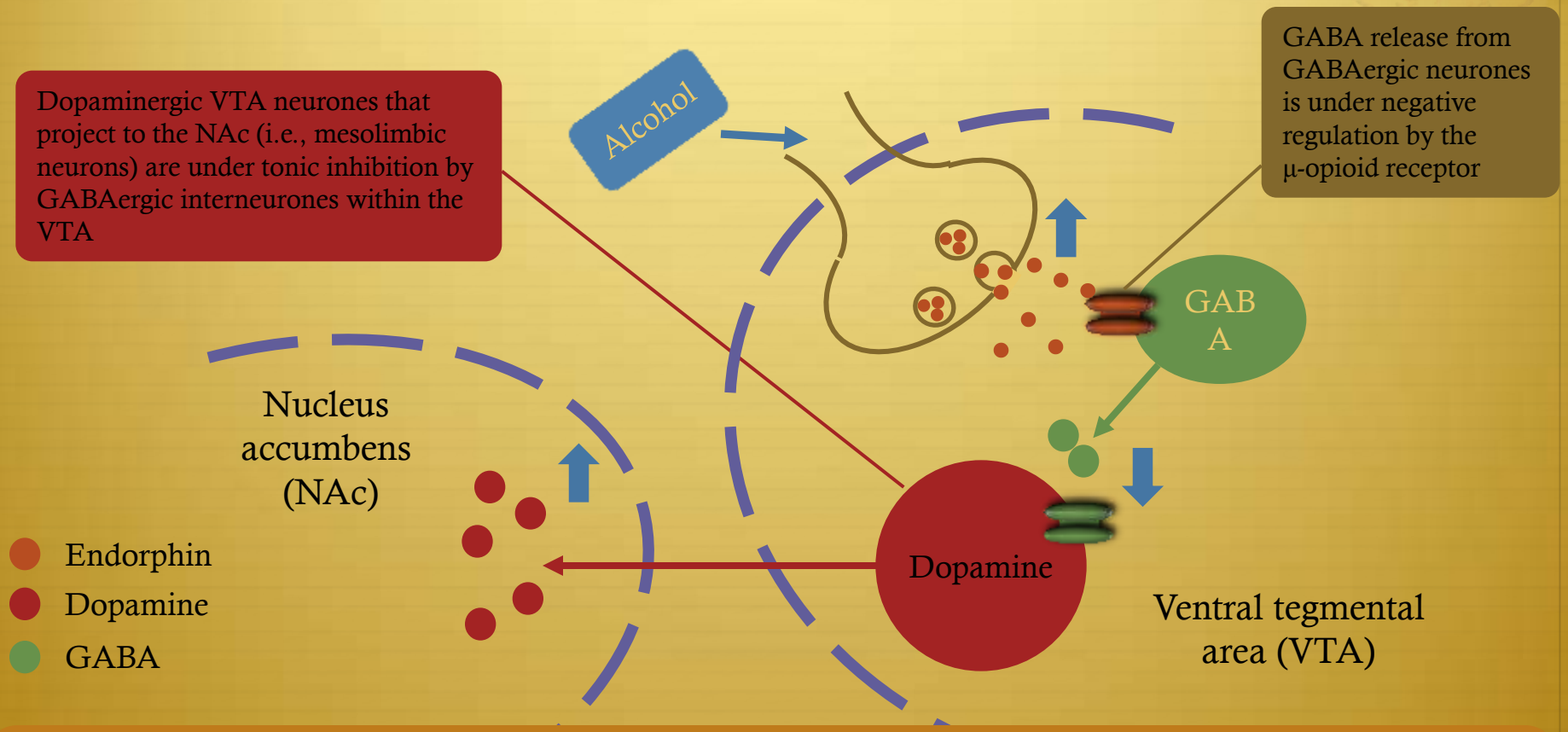
Interfere with drug's reinforcing effects	*Vaccines* *Enzymatic degredation* *Naltrexone* *DA D3 antagonists* *CB_1 antagonists*
Executive function/ Inhibitory control	*Biofeedback* *Modafinil* *Bupropion* *Stimulants*
Strengthen prefrontal-striatal communication	*Adenosine* *A2 antagonists* *DA D3 antagonists*
Interfere with conditioned memories (craving)	*Antiepileptic GVG* *N-acetylcysteine*
Teach new memories	*Cycloserine*
Counteract stress responses that lead to relapse	*CRF antagonists* *Orexin antagonists*



Improving impul n
important targe
dep

Modulatie beloningssyteem: blokkeren of stimuleren ?!

Alcohol, opiaten leiden tot een transiënte toename van dopamine door endorfine vrijzetting



- **Acute alcoholinname inducesert endorfine vrijzetting, die GABA vrijzetting in de VTA inhibeert, waardoor de inhitoire tonus op de dopamine cellen vermindert**
- **Dit leidt tot een toegenomen dopamine vrijzetting in de NAc**

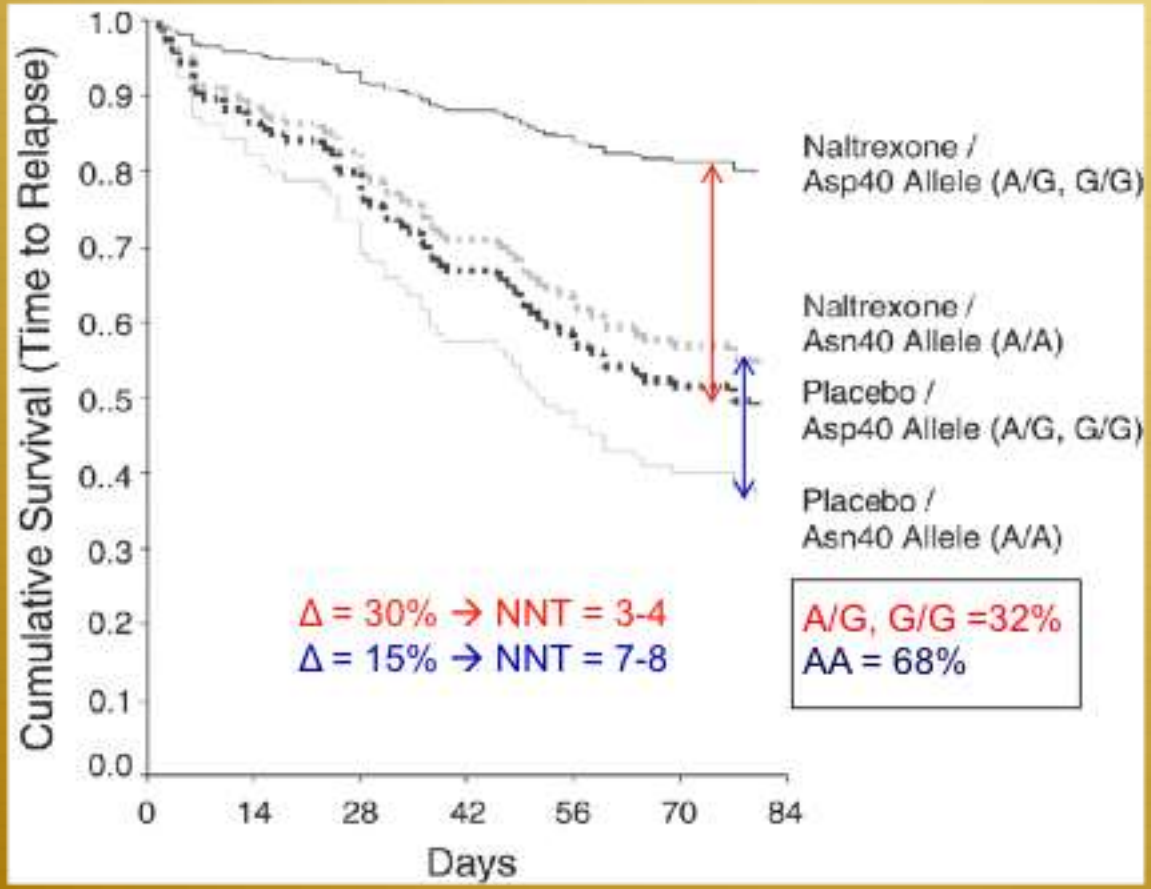
Heilig et al. Nat Rev Neurosci 2011;12(11):670–684;
Clapp et al. Alcohol Res Health 2008;31(4):310–339

Moduleren van opioide transmissie

- Behandeling alcohol: nalorex – nalmefene
- Behandeling opiaat afhankelijkheid:
  - Blokkeren: nalorex
  - Stimuleren: methadone
  - Agonist/antagonist: buprenorphine

Maar werkt dit voor iedereen ??

Farmacogenomics



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	-

GENETISCHE TYPERING

NS

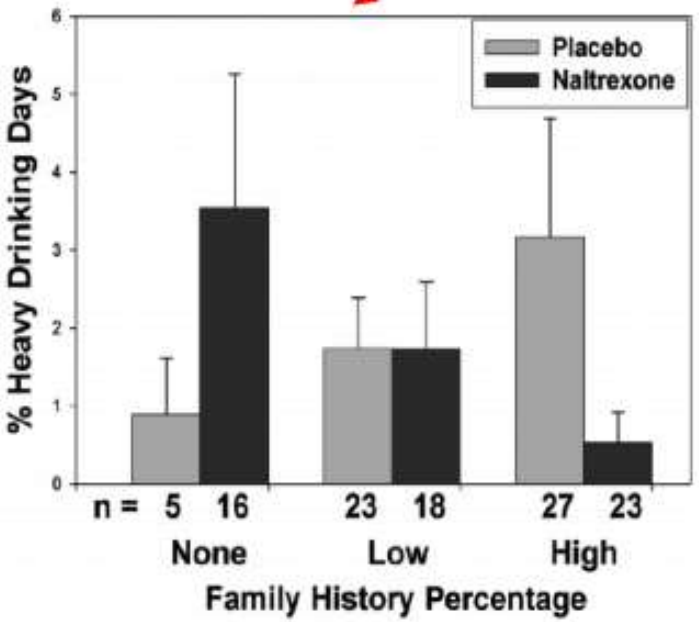


Figure 1. Percentage of heavy drinking days during 6-month follow-up by medication (naltrexone vs. placebo) and percentage of family members with a history of problem drinking (0%, <20%, or ≥20% relatives with problems). The interaction of family history percentage and medication was significant using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

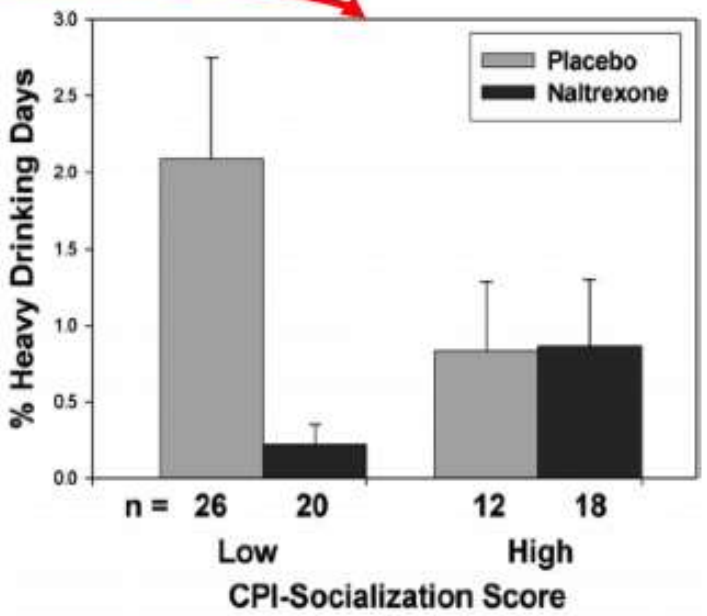


Figure 2. Among patients compliant with ≥70% of medication doses, percentage of heavy drinking days during 6-month follow-up by medication (naltrexone vs. placebo) and socialization (California Personality Inventory-Socialization scale [CPI-So] score ≤24 or >24). The interaction of CPI-Socialization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

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

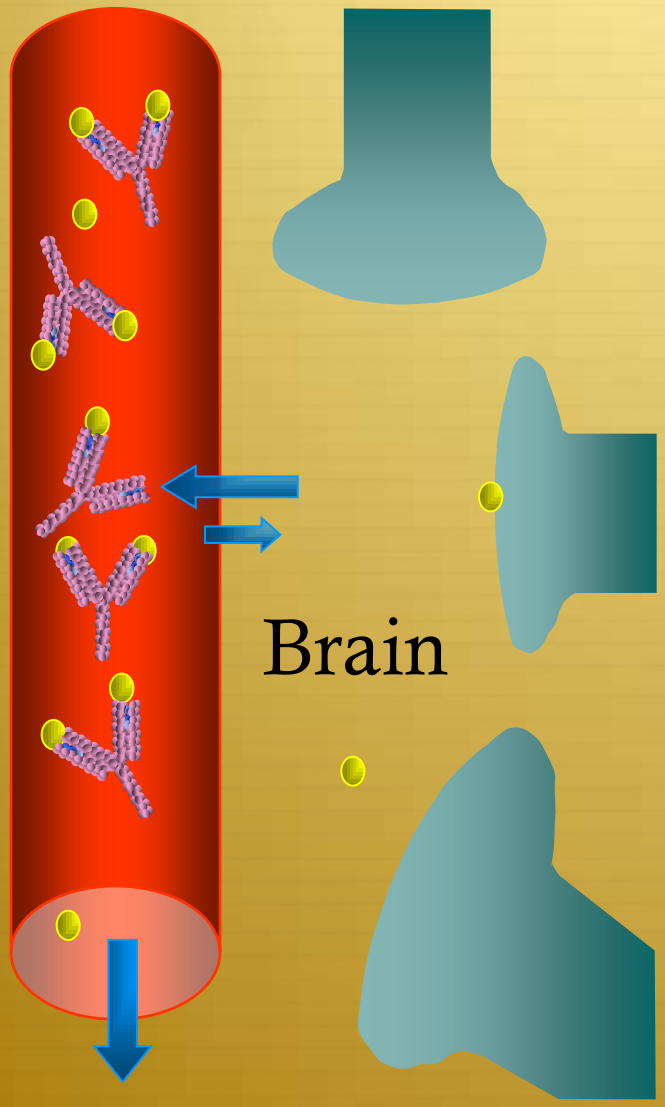
Damaris J. Rohsenow
Providence Veterans Affairs Medical Center and Brown University School of Medicine

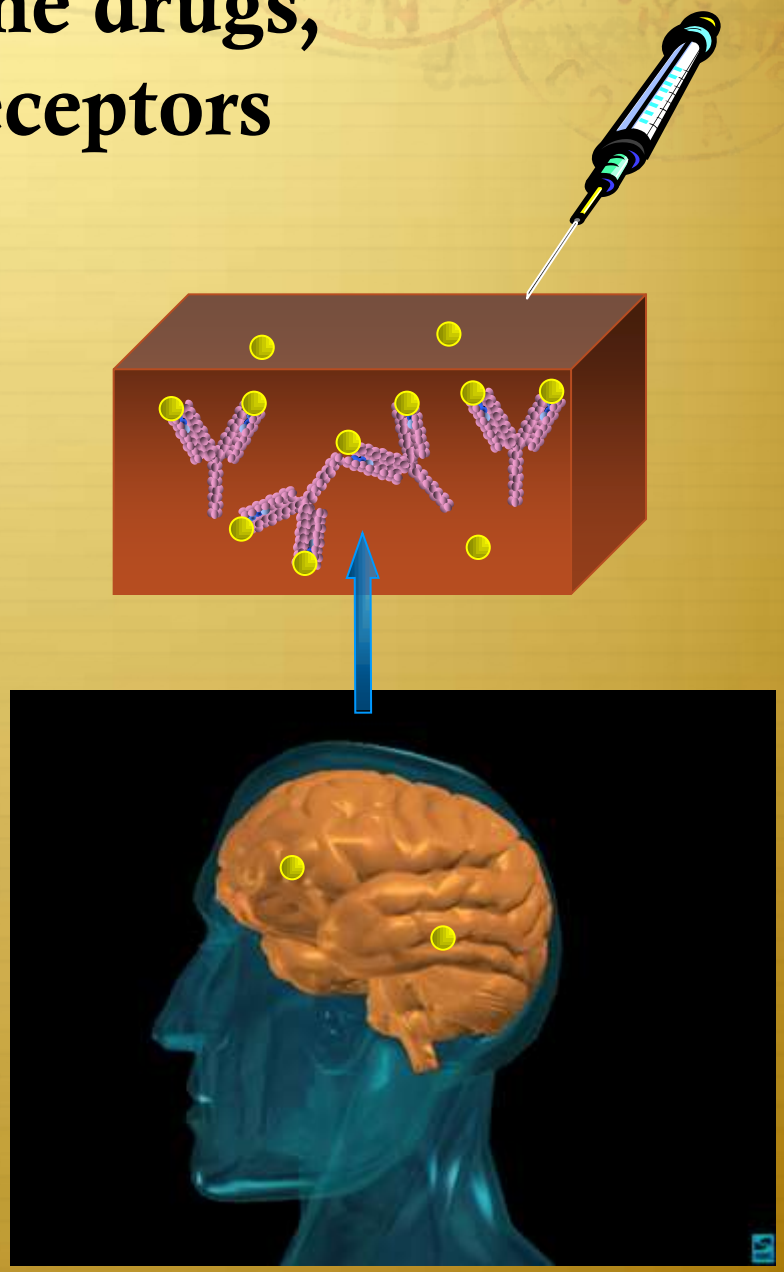
Robert Miranda Jr.
Brown University School of Medicine

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

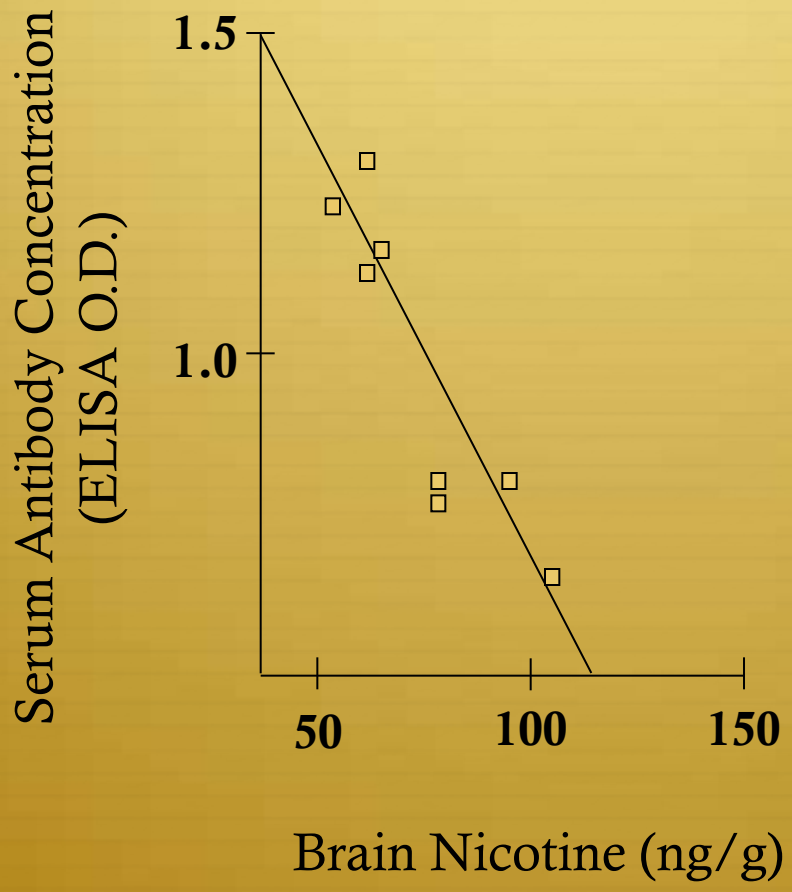
Targeting the drugs, not the receptors

Capillary
Blood Flow





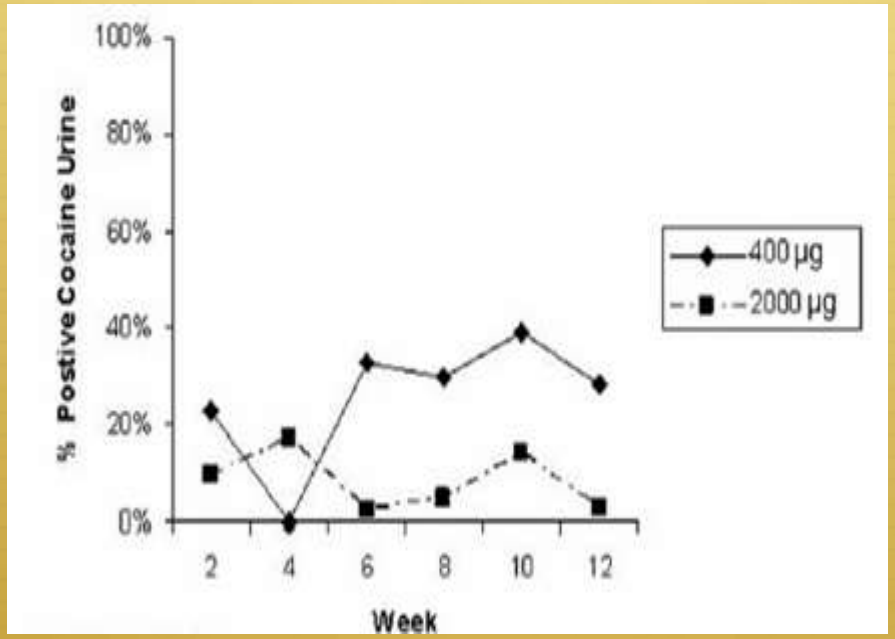
Effects of Antibody Titer on Brain Nicotine Concentration



Two nicotine vaccines in phase 3 trials

Vaccination against cocaine

- Phase 2 trials for cocaine
  - reduced cocaine +ve urines (*Martell et al 2005*)



- Feasible for most other drugs

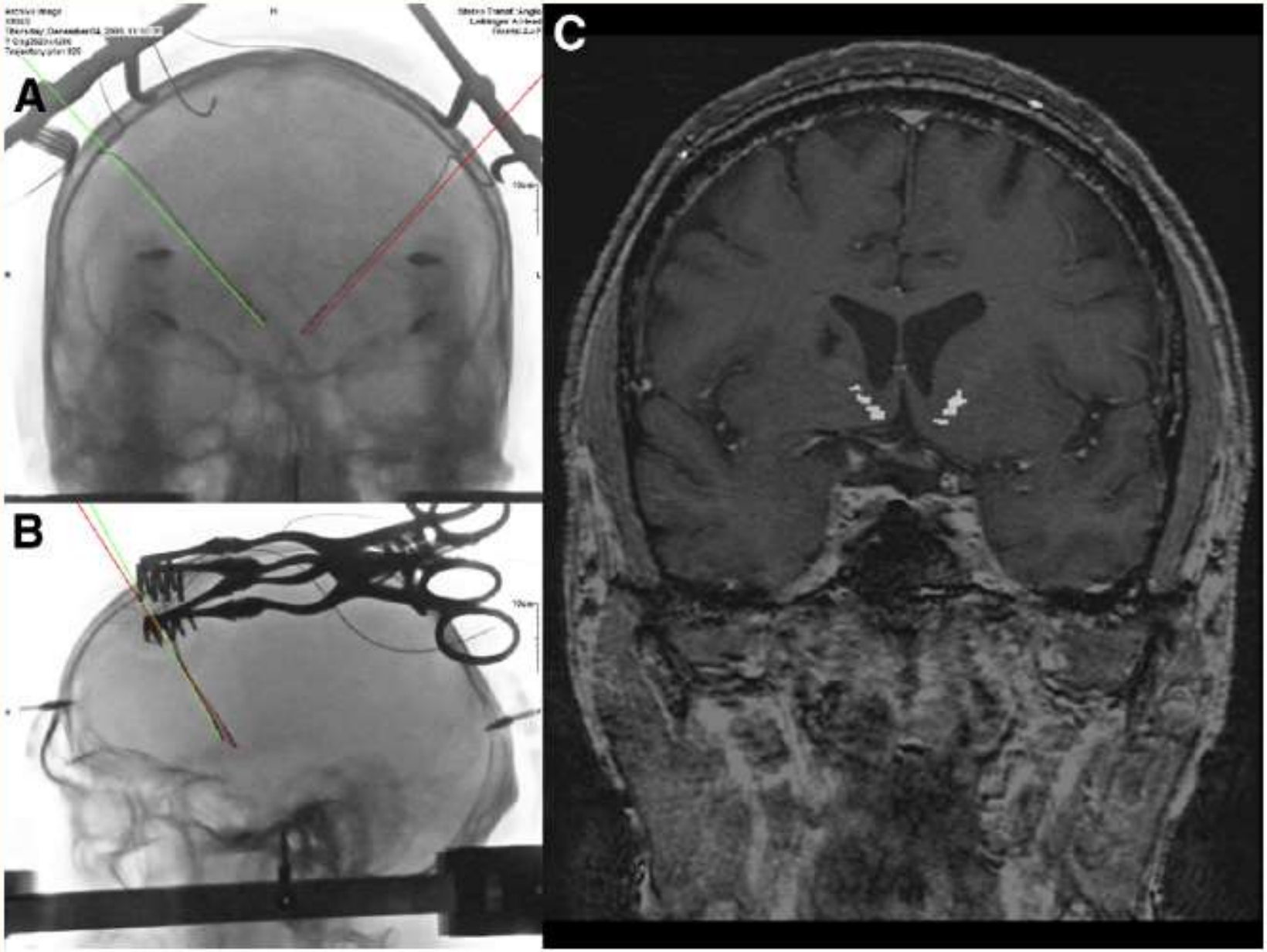
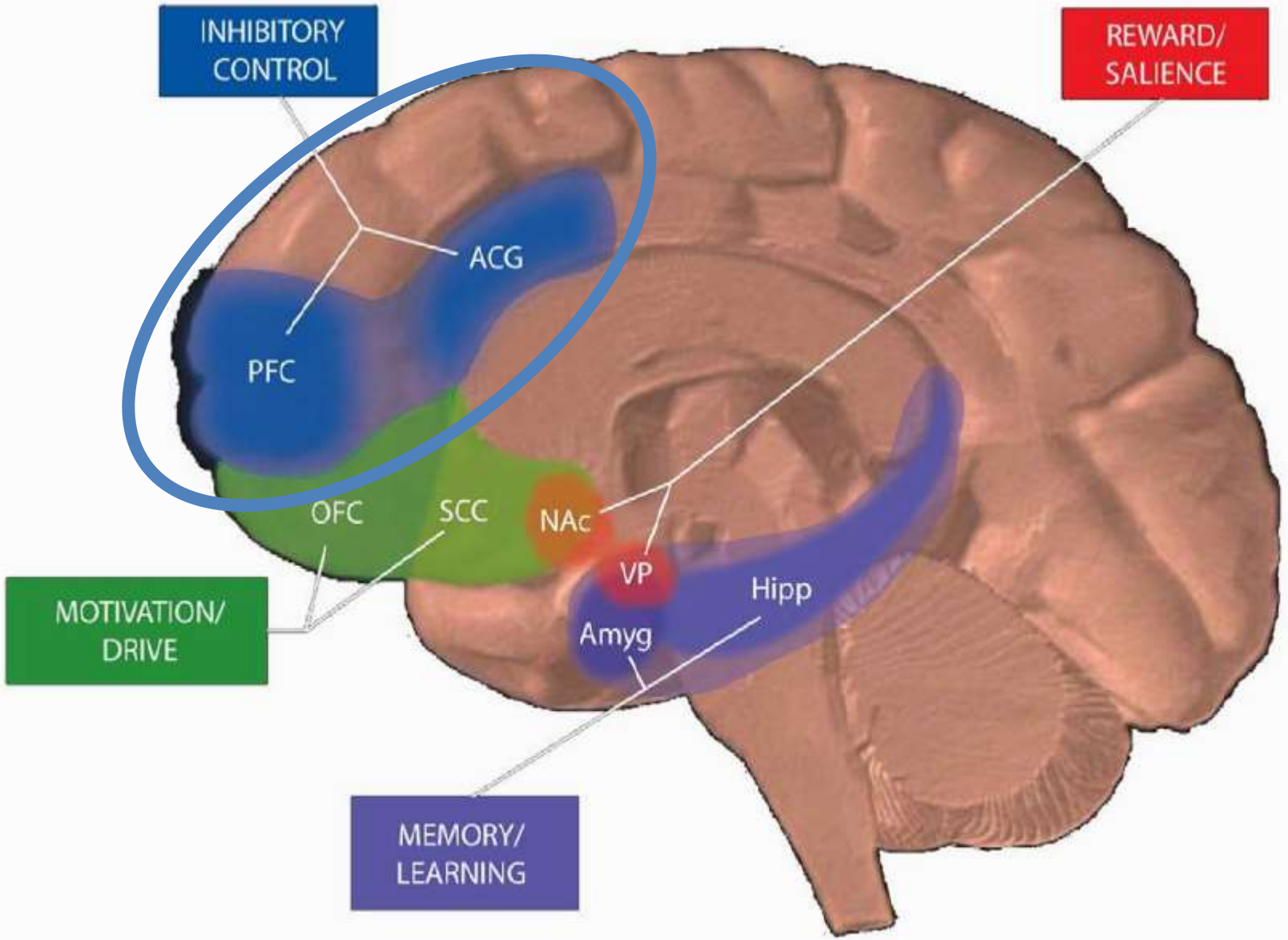


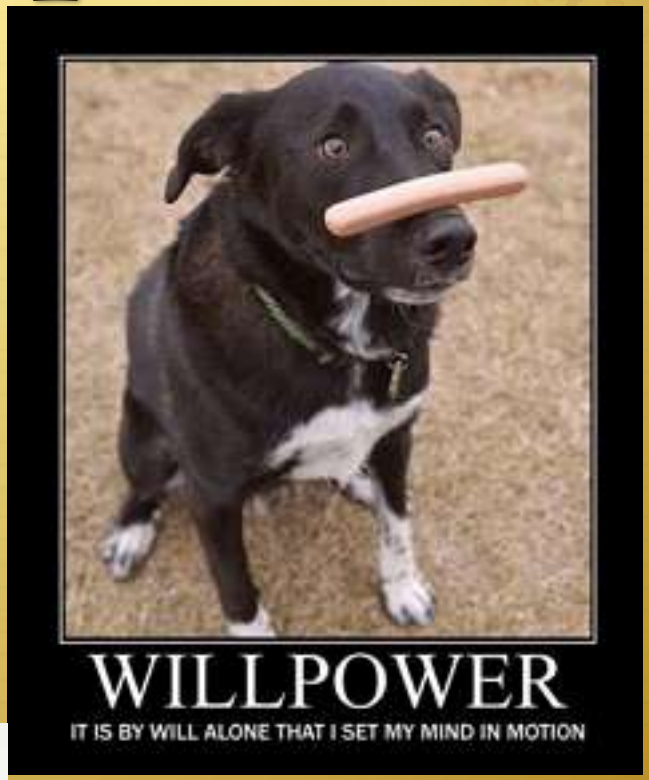
Figure 1. Displayed are intraoperative stereotactic x-ray images of the skull (**A**, **B**) and the postoperative computed tomographic (CT) examination of case 6 after transformation into the preoperative treatment planning magnetic resonance imaging series (**C**). The latter shows the distal contacts (CT, bone window) of the implanted leads in projection onto the nucleus accumbens (NAc) shell and NAc core as intended.

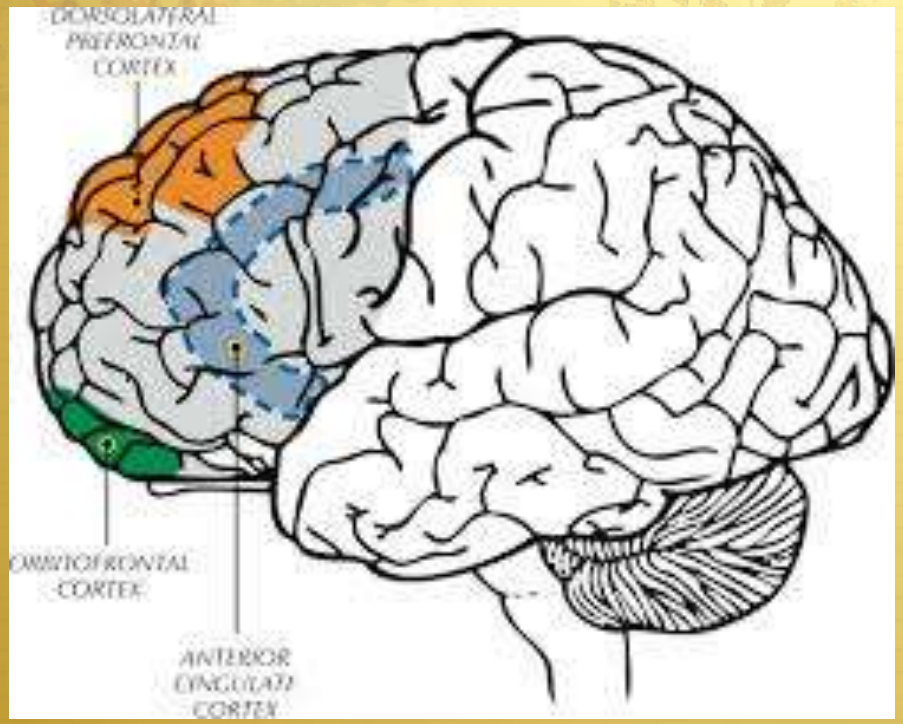
Muller et al., 2013 Ann NY Acad Sci

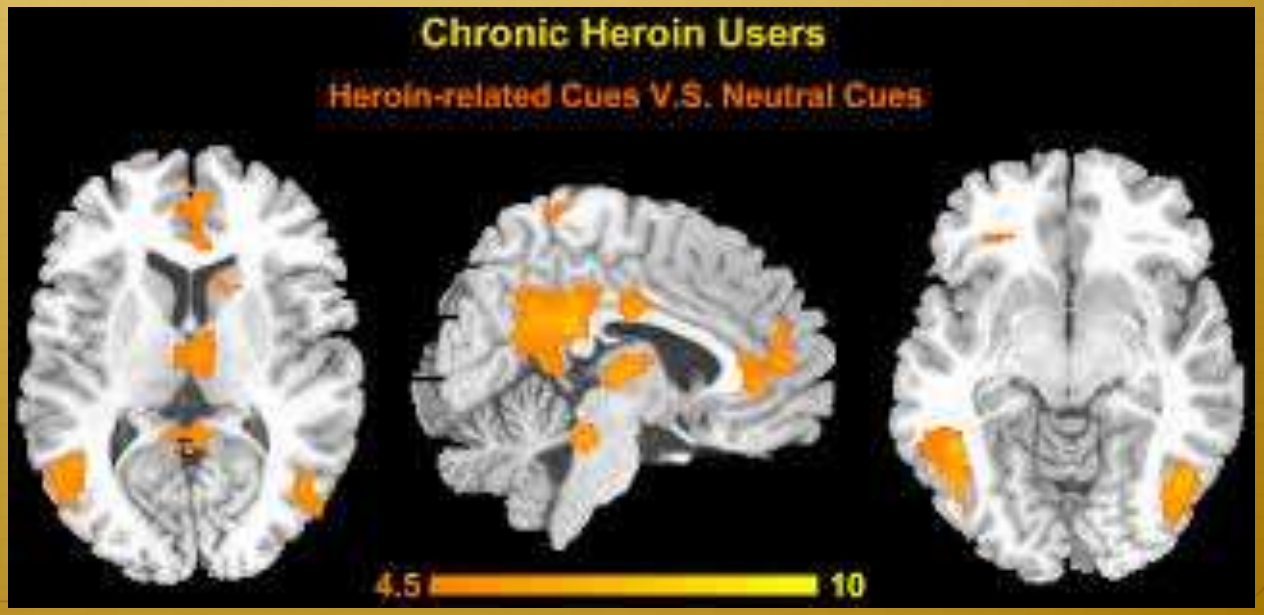
Study	Number of patients	Substance	Reason for DBS	Time of follow-up	Benefit/outcome
Kuhn *et al.*[9]	1	Alcohol	Anxiety	12 months	Remission
Kuhn *et al.*[59]	10	Nicotin	Varies but no substance abuse		3 Unaided smoking cessations (30%)
Kuhn *et al.*[11]	1	Alcohol	Alcohol addiction	12 months	Remission
Mantione *et al.*[61]	1	Nicotine	OCD	24 months	Unaided cessation
Müller *et al.*[10]	5	Alcohol	Alcohol addiction	Up to 48 months	Marked reduction in 3, remission in 2
Zhou *et al.*[64]	1	Heroine	Heroine addiction	2.5 months active stimulation plus 3.5 months off stimulation	Remission for entire time (six years)
Valencia-Alfonso *et al.*[65]	1	Heroine	Heroine addiction	Six months	Remission


INHIBITORY CONTROL
REWARD/ SALIENCE
ACG
PFC
OFC
SCC
NAc
VP
Hipp
Amyg
MOTIVATION/ DRIVE
MEMORY/ LEARNING

Zelfregulatie <> Impulsiviteit




DORSOLATERAL
PREFRONTAL
CORTEX
ORBITOFRONTAL
CORTEX
ANTERIOR
CINGULATE
CORTEX


Chronic Heroin Users
Heroin-related Cues V.S. Neutral Cues
4.5
10

A

B

C

D

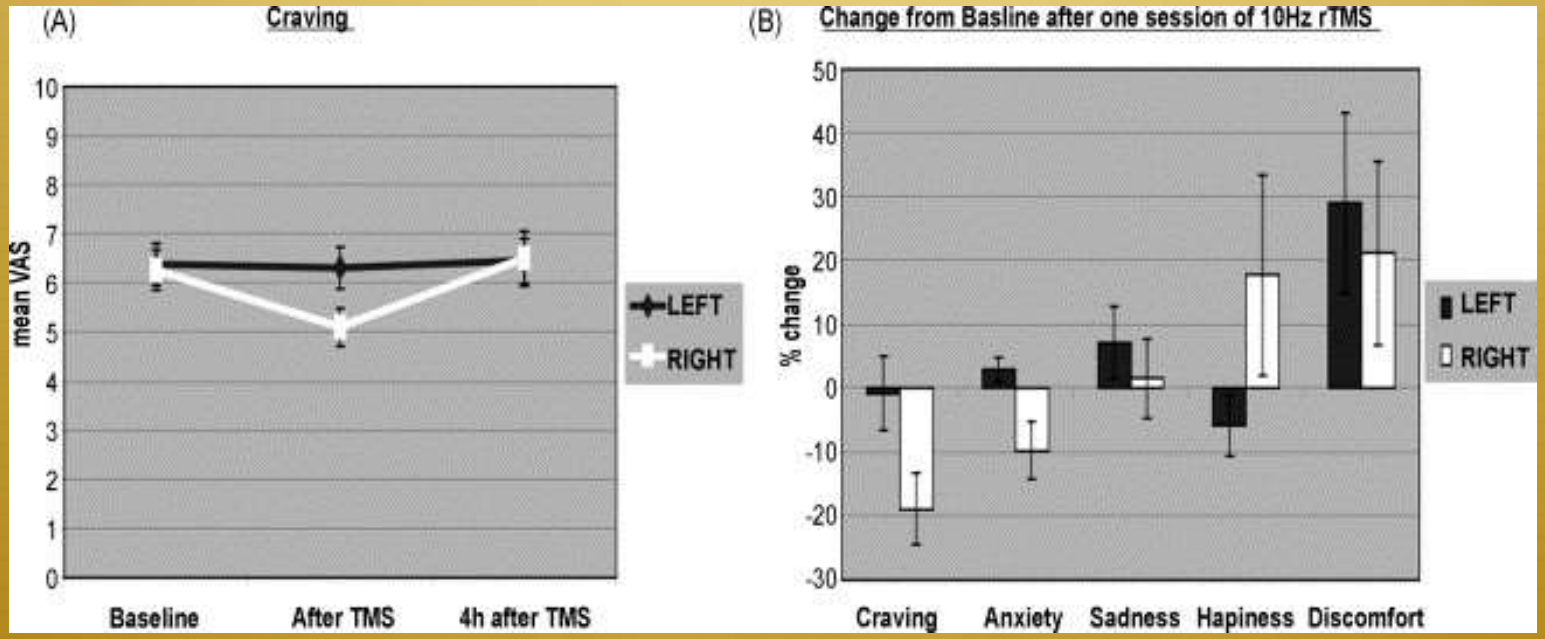
Transcraniele Magnetische Stimulatie bij Cocaineverslaafden

Available online at www.sciencedirect.com
ScienceDirect
Drug and Alcohol Dependence xxx (2006) xxx–xxx
DRUG and ALCOHOL DEPENDENCE
www.elsevier.com/locate/drugalcdep
ELSEVIER

Short communication

One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving

Joan Albert Camprodon [a], José Martínez-Raga [b], Miguel Alonso-Alonso [a], Mei-Chiung Shih [c], Alvaro Pascual-Leone [a,*]



Substance	Drug status	Modality	Target	Stim./inh.	Nr. of subjects	Study design	Parameters	Duration stimulation	Assessment	Follow up	Findings
Nicotine	Abstinent 12 h	rTMS	left DLPFC	Stim.	14	randomized sham controlled cross-over	20 Hz, 20 trains, 50 pulses, 90% MTH	Two sessions	VAS craving Cigarettes smoked	6h	reduction cigarettes smoked no efect on craving
Food	Abstinent 45 min	rTMS	left DLPFC	Stim.	28	randomized sham controlled	10 Hz, 20 trains, 50 pulses, 110% MTH	One session	VAS craving Food consumption	45 min	reduction food craving no effect on food consumption
Cocaine	Abstinent ?	rTMS	left and right DLPFC	Stim.	6	randomized sham controlled cross-over	10 Hz, 20 trains, 100 pulses, 90% MTH	One session	VAS craving, anxiety, sadness, happiness, discomfort	4h	reduction in craving by right side stimulation reduction in anxiety, increase in hapiness by right side stimulation increase in sadness by left side stimulation increase in discomfort by left and right side stimulation
Nicotine	Abstinent 1.5 h	tDCS	left and right DLPFC	Stim.	24	randomized sham controlled cross-over	2 mA, 20 min.	One session	VAS craving VAS mood domains	-	craving increases over time cue exposure increases craving left and right stimulation reduces craving left and right stimulation reduces cue elicited craving
Alcohol	Abstinent 10 d	tDCS	left and right DLPFC	Stim.	13	randomized sham controlled cross-over	2 mA, 20 min.	One session	Alcohol Urge Questionnaire (AUQ) VAS mood domains	-	left stimulation increases "worried" no effect on mood domains alcohol cues increase craving left and right stimulation reduce craving no cue induced craving after left and right stimulation
Cocaine	Abstinent ?	rTMS	left DLPFC	Stim.	36	cohort study	15 Hz, 20 trains, 30 pulses, 100% MTH	Ten sessions	Symptoms of craving	-	reduction in cocaine craving effect increases over time
Nicotine	Abstinent ?	tDCS	left DLPFC	Stim.	27	randomized sham controlled cross-over	2 mA, 20 min.	Five sessions	VAS craving (5 items) VAS mood domains Cigarettes smoked	-	cue exposure increases craving stimulation reduces craving after cue exposure decrease in cigarettes smoked no changes in mood domains effect increases over time
Nicotine	Abstinent ?	rTMS	left DLPFC	Stim.	48	randomized sham controlled	10 Hz, 20 trains, 50 pulses, 100%MTH	Ten sessions	Fagerström Test for Nicotine Dependence (mFTND) VAS craving Short version of the Tobacco Craving Questionnaire (sTCQ) Cigarettes smoked Urine level cotinine	6 months	reduction in amount of colinine in urine reduction of cigarttes smoked in all groups reduction in cigarettes smoked larger in stimulation groups reduction of mFTND score after stimulation stimulation reduces VAS craving after cue exposure reduction in sTCQ scores after stimulation
Marijuana	Abstinent 24 h	tDCS	left and right DLPFC	Stim./ Inh.	25	randomized sham controlled	2 mA, 10 min.	One seesion	VAS craving Risk Task	-	sham stimulation chose more low-risk option right side stimulation reduces craving
Alcohol	Abstinent 10 d	rTMS	right DLPFC	Stim.	45	randomized sham controlled	10 Hz, 20 trains, 50 pulses, 110% MTH	Ten sessions	Alcohol Craving Questionnaire; total and factor scores (ACQ-NOW)	4 weeks	improvement on ACQ-NOW total score effect on six out of seven factor scores reduction in relapse rate
Nicotine	Abstinent ?	rTMS	bilateral superior frontal gyrus	Stim./inh.	15	randomized sham controlled cross-over	1 Hz or 10 Hz, 150 or 1500 pulses, 90% MTH	Ten sessions	Brief version of Shiffman-Jarvik questionnaire Cigarette evaluation questionnaire	-	increase in craving after smoking cue exposure greater in 10 Hz SFG stimulation decrease in craving after neutral cue exposure in 10 Hz SFG stimulation decrease in craving reduction effect of smoking a cigarette in 10 Hz SFG stimulation reduction in chest sensations after smoking cigarette in 10 Hz SFG stimulation chest sensations of smoking a cigarette reduce craving
Alcohol	Abstinent 14 d	rTMS	left DLPFC	Stim.	19	randomized sham controlled	20 Hz, 20 trains, 50 pulses, 90% MTH	One session	German version of Obsessive Compulsive Drinking Scale Attentional blink	-	reduction in craving in all groups during study detection of alcohol related pictures worse after real stimulation improvement in detection of neutral , positive and negative pictures in both group
Alcohol	Active, but sober	rTMS	bilateral dACC	Inh.	1	case report	1 Hz, 600 pulses, 90% machine output	Fifteen sessions	VAS craving Brain activity by LORETA EEG Functional connectivity by LORETA EEG	3 months	craving induces increase in beta activity in ACC and PCC craving increases connectivity between ACC and PCC exposure to alcohol cues activates already hyperactive ACC and PCC rTMS reduces craving craving absent: decreased activity in ACC, insula, PCC and nucleus accumbens after rTMS no activation in ACC, PCC and nucleus accumbens after cue exposure
Alcohol	Mean abstinence 12 d	rTMS	right DLPFC	Stim.	31	randomized sham controlled cross-over	20 Hz, 40 trains, 40 pulses, 110% MTH	One seesion	Obsessive Compulsive Drinking Scale; 5 items related to craving	3 days	no effect on craving no effect on cue induced craving
Nicotine	Abstinent ?	rTMS	left DLPFC	Inh.	10	randomized sham controlled cross-over	1 Hz, 1800 pulses	One session	VAS craving	-	immediate cigarette availability increases craving TMS eliminates the effect of cigarette availability craving correlates with hyperactivity in mOFC, left DLPFC and ventral striatum
Cocaine	Mean abstinence 16 d	tDCS	left and right DLPFC	Stim. right/ inh. left	13	randomized sham controlled	2 mA; 20 min	One session	Brain activity by LORETA EEG	-	ACC activity increases after cue exposure reduction in activity of ACC during exposure to cocaine-related cues after stimulati

Psychological Medicine, Page 1 of 12. © Cambridge University Press 2014
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ORIGINAL ARTICLE

Neural substrates of impulsive decision making modulated by modafinil in alcohol-dependent patients

L. Schmaal[1,2*], A. E. Goudriaan[1,3], L. Joos[4], G. Dom[4,5], T. Pattij[6], W. van den Brink[1] and D. J. Veltman[2]

[1] *Amsterdam Institute for Addiction Research, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*
[2] *Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands*
[3] *Arkin Mental Health Institute, Amsterdam, The Netherlands*
[4] *Collaborative Antwerp Psychiatric Research Institute (CAPRI), Department of Psychiatry, University of Antwerp, Antwerp, Belgium*
[5] *Psychiatric Center Alexian Brothers, Boechout, Belgium*
[6] *Department of Anatomy and Neurosciences, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands*

Background. Impulsive decision making is a hallmark of frequently occurring addiction disorders including alcohol dependence (AD). Therefore, ameliorating impulsive decision making is a promising target for the treatment of AD. Previous studies have shown that modafinil enhances cognitive control functions in various psychiatric disorders. However, the effects of modafinil on delay discounting and its underlying neural correlates have not been investigated as yet. The aim of the current study was to investigate the effects of modafinil on neural correlates of impulsive decision making in abstinent AD patients and healthy control (HC) subjects.

Method. A randomized, double-blind, placebo-controlled, within-subjects cross-over study using functional magnetic resonance imaging (fMRI) was conducted in 14 AD patients and 16 HC subjects. All subjects participated in two fMRI sessions in which they either received a single dose of placebo or 200 mg of modafinil 2 h before the session. During fMRI, subjects completed a delay-discounting task to measure impulsive decision making.

Results. Modafinil improved impulsive decision making in AD pateints, which was accompanied by enhanced recruitment of frontoparietal regions and reduced activation of the ventromedial prefrontal cortex. Moreover, modafinil-induced enhancement of functional connectivity between the superior frontal gyrus and ventral striatum was specifically associated with improvement in impulsive decision making.

Conclusions. These findings indicate that modafinil can improve impulsive decision making in AD patients through an enhanced coupling of prefrontal control regions and brain regions coding the subjective value of rewards. Therefore, the current study supports the implementation of modafinil in future clinical trials for AD.

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Schmaal et al. 2014 Psycholog Medic

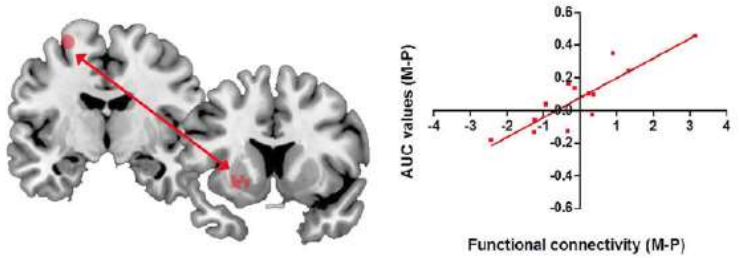


Fig. 3. Correlation between increased functional connectivity and reduction in discounting after modafinil administration in alcohol dependence. Results of the regression analysis of modafinil-induced changes in effective connectivity against changes in discounting behaviour [area under the curve (AUC) values] revealed a significant effect of connectivity between the left superior frontal gyrus (SFG) (left brain slice) and left striatum (right brain slice). Improvement in delay-discounting behaviour was associated with an enhanced functional coupling between the left SFG and left (ventral) striatum. M, Modafinil; P, placebo.

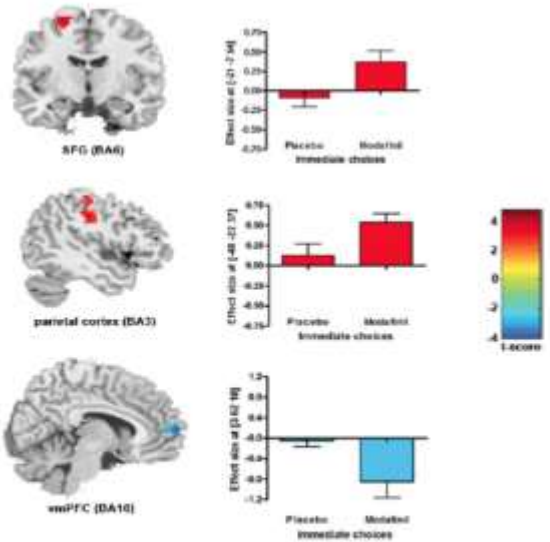


Fig. 2. Modafinil-induced changes in brain activation during immediate choices in alcohol dependence (AD). Differences in neural activity between modafinil and placebo conditions during choices for immediate rewards in the AD group (statistical parametric maps and effect sizes at the peak voxels). Activity in regions displayed in red [left superior frontal gyrus (SFG) and parietal region] significantly increased after modafinil administration. Activity in the ventromedial prefrontal cortex (vmPFC) in blue significantly decreased after modafinil administration. The colour bar represents voxel *T* value. Coordinates on y axes are Montreal Neurological Institute coordinates. BA, Brodmann area.

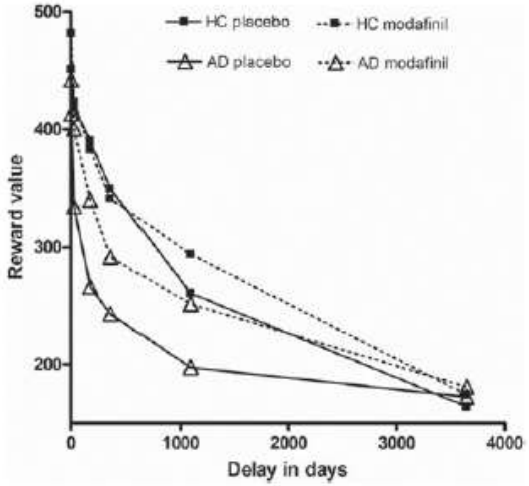


Fig. 1. Delay discounting in alcohol-dependent (AD) and healthy control (HC) subjects, separate for placebo and modafinil. Indifference points were plotted for each delay (in days) for AD and HC groups, separate for the placebo and modafinil conditions. There was a significant treatment × group interaction effect ($F_{1,20}=4.94$, $p=0.04$) on area under the curve (AUC) values. *Post-hoc* tests revealed that this effect was driven by a significant increase in AUC values (i.e. reduced delay discounting) in the AD group, whereas modafinil had no effect in the HC group.

BIOL PSYCHIATRY 2013;73:211–218

ARCHIVAL REPORT

Effects of Modafinil on Neural Correlates of Response Inhibition in Alcohol-Dependent Patients

Lianne Schmaal, Leen Joos, Marte Koeleman, Dick J. Veltman, Wim van den Brink, and Anna E. Goudriaan

Background: Impaired response inhibition is a key feature of patients with alcohol dependence. Improving impulse control is a promising target for the treatment of alcohol dependence. The pharmacologic agent modafinil enhances cognitive control functions in both healthy subjects and in patients with various psychiatric disorders. However, very little is known about the underlying neural correlates of improvements in response inhibition following modafinil.

Methods: We conducted a randomized, double-blind, placebo-controlled, crossover study using functional magnetic resonance imaging with a stop signal task to examine effects of a single dose of modafinil (200 mg) on response inhibition and underlying neural correlates in abstinent alcohol-dependent patients (AD) ($n = 16$) and healthy control subjects ($n = 16$).

Results: Within the AD group modafinil administration improved response inhibition (reflected by the stop signal reaction time [SSRT]) in subjects with initial poor response inhibition, whereas response inhibition was diminished in better performing subjects. In AD patients with initial poor response inhibition, modafinil-induced SSRT improvement was accompanied by greater activation in the thalamus and supplementary motor area (SMA) and reduced connectivity between the thalamus and the primary motor cortex. In addition, the relationship between baseline response inhibition and modafinil-induced SSRT improvement was mediated by these changes in thalamus and SMA activation.

Conclusions: These findings indicate that modafinil can improve response inhibition in alcohol-dependent patients through its effect on thalamus and SMA function but only in subjects with poor baseline response inhibition. Therefore, baseline levels of response inhibition

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

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]

[a]*Collaborative Antwerp Psychiatric Research Institute (CAPRI), University of Antwerp, Universiteitsplein 1, B-2610 Wilrijk, Belgium*
[b]*Amsterdam Institute for Addiction Research, Academic Medical Centre, University of Amsterdam, Department of Psychiatry, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands*
[c]*Arkin, Mental Health Care, P.O. Box 75848, 1070 AV Amsterdam, The Netherlands*
[d]*StatUA, Center for Statistics, University of Antwerp, Prinsstraat 13, B-2000 Antwerpen, Belgium*
[e]*Psychiatric Centre Alexian Brothers, Provinciesteenweg 408, B-2530 Boechout, Belgium*

Received 24 May 2012; received in revised form 30 August 2012; accepted 5 October 2012

Method: design

- Randomized, double-blind, placebo-controlled study

- Treatment with modafinil (or placebo): 10 weeks
  - Dose: max 300mg/day, intake in the morning
  - Population (N=83):
    - Having a diagnosis of current alcohol dependency according to DSM-IV
    - Recently detoxified and abstinent
    - 18-60 year (both men and women)
    - NOT dependent on other substances than alcohol, except for nicotine and cannabis
    - NOT taking any psycho-active medication

Results: Primary outcome measures

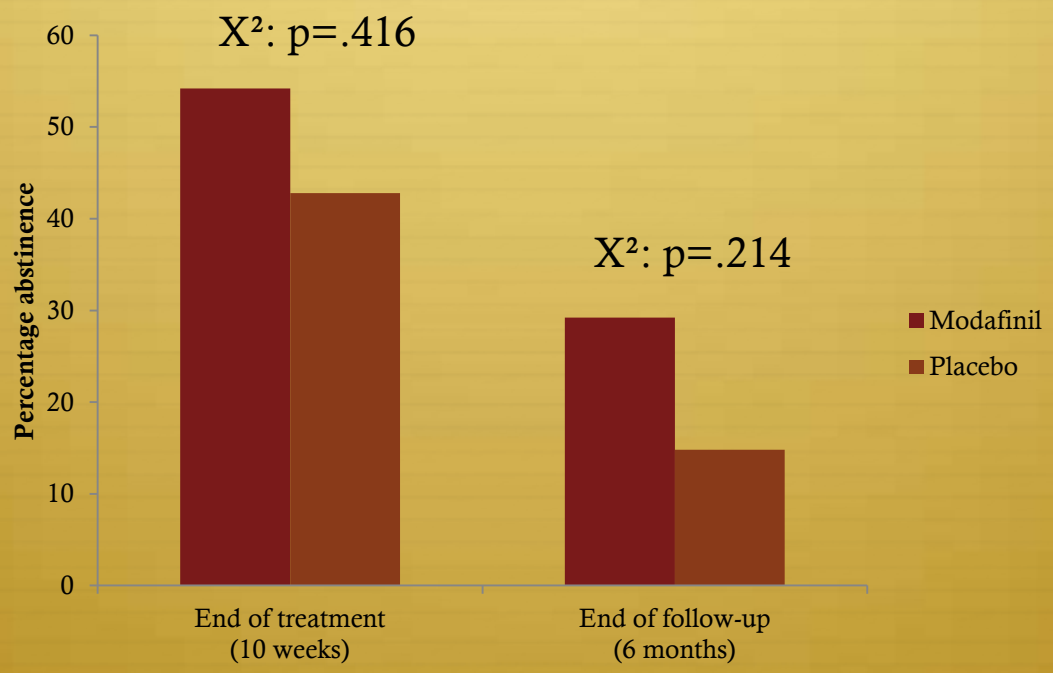
- Primary outcome measures:
  - Alcohol use
    - % abstinent days
    - % heavy drinking days*
  - Impulsivity
    - Self-reported state impulsivity
    - Response inhibition (SST)
    - Delay discounting (DDT)

*≥ 5 standard drinks for men; ≥ 4 standard drinks for women

Results: Complete abstinence

Groups did not significantly differed in abstinence rates

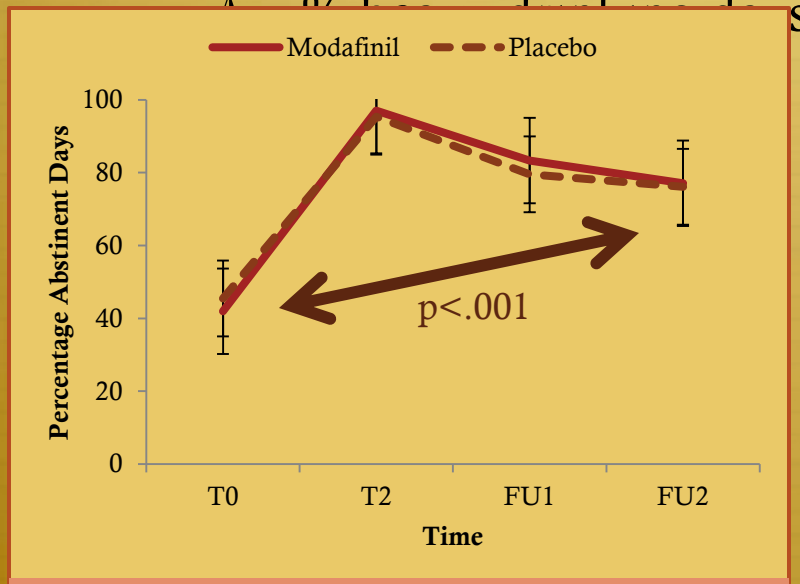
- Abstinence rates



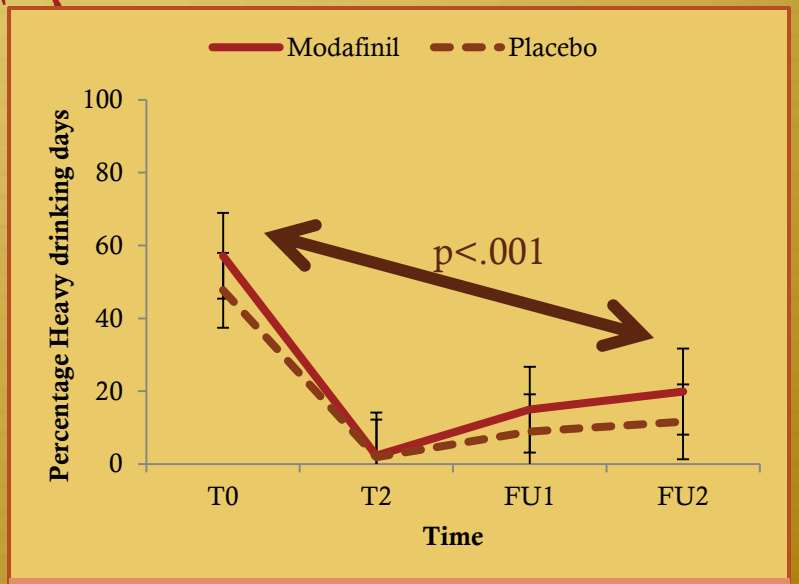
Results: Primary outcome measures

Alcohol use variables changed over time, but no significant effect of treatment

- Primary outcome measures:
  - Alcohol use ↓
    - % abstinent days (T ↑)
    - % [illegible] days (T ↓)



MMRM: time by treatment: p=.756

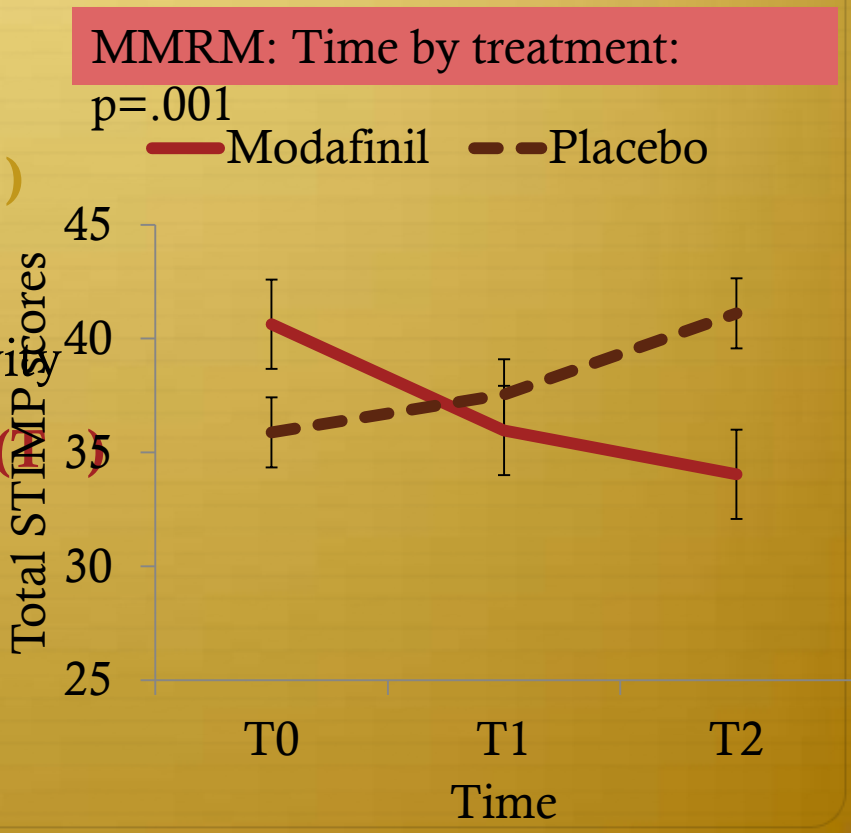


MMRM: time by treatment: p=.113

Results: Primary outcome measures

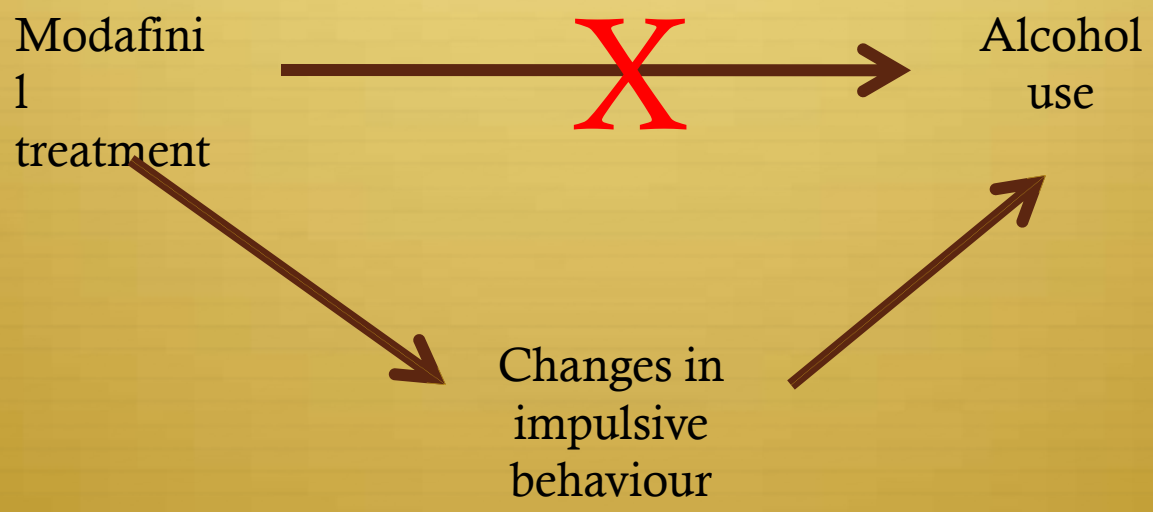
Modafinil improved self-reported state impulsivity

- Primary outcome measures:
  - Alcohol use ↓
    - % abstinent days (T ↑)
    - % heavy drinking days (T)
  - Impulsivity ↓
    - Self-reported state impulsivity
    - Response inhibition (SST) (↑)
    - Delay discounting (DDT)



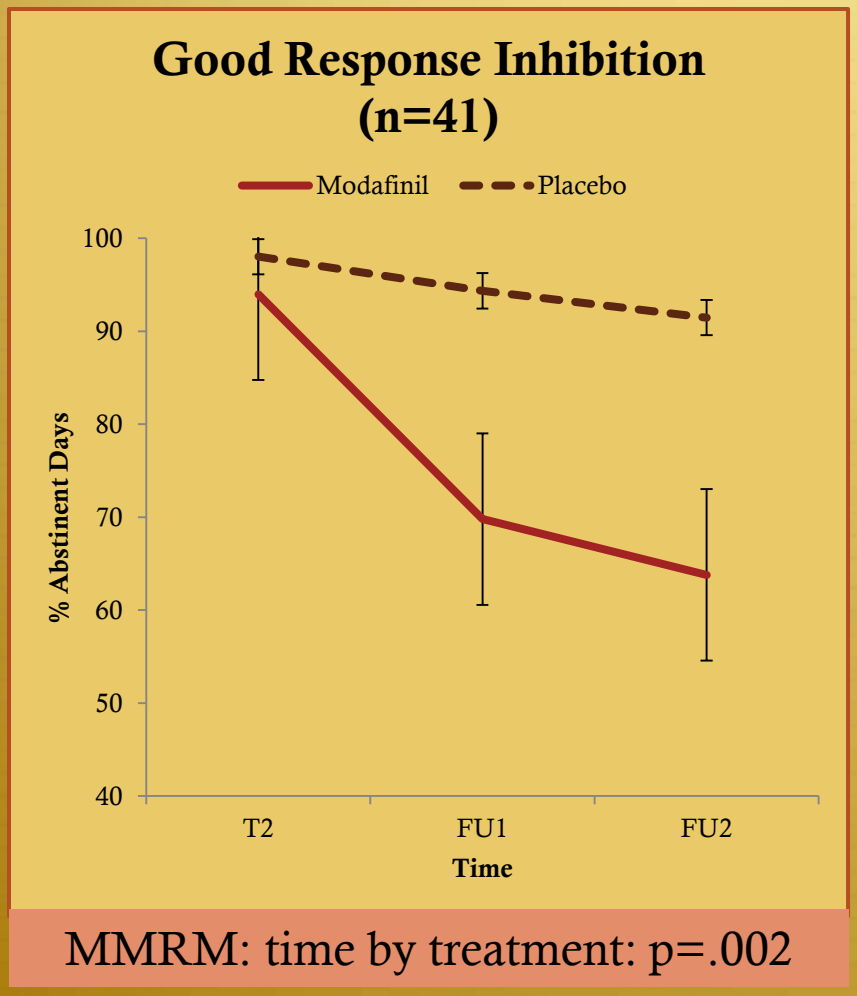
Results: mediation analyses

Redundant

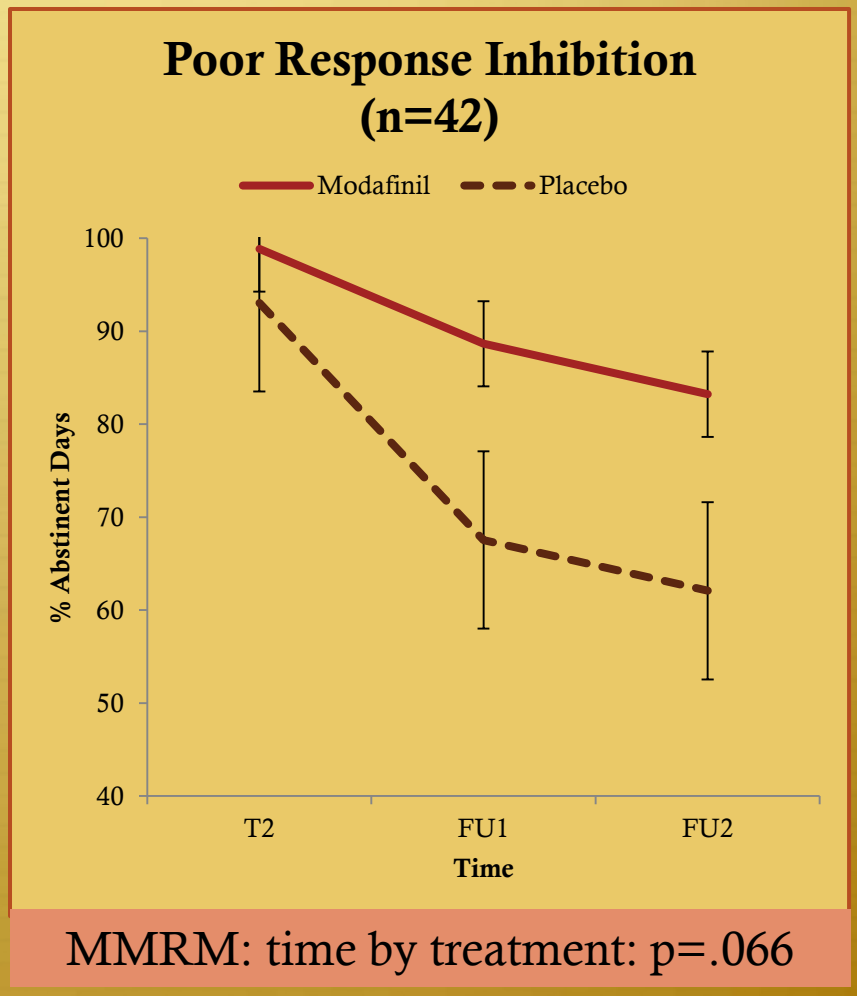


Bi-directional effects in subgroups

Percentage Abstinent Days (MMRM 3-way: **p<.001**)



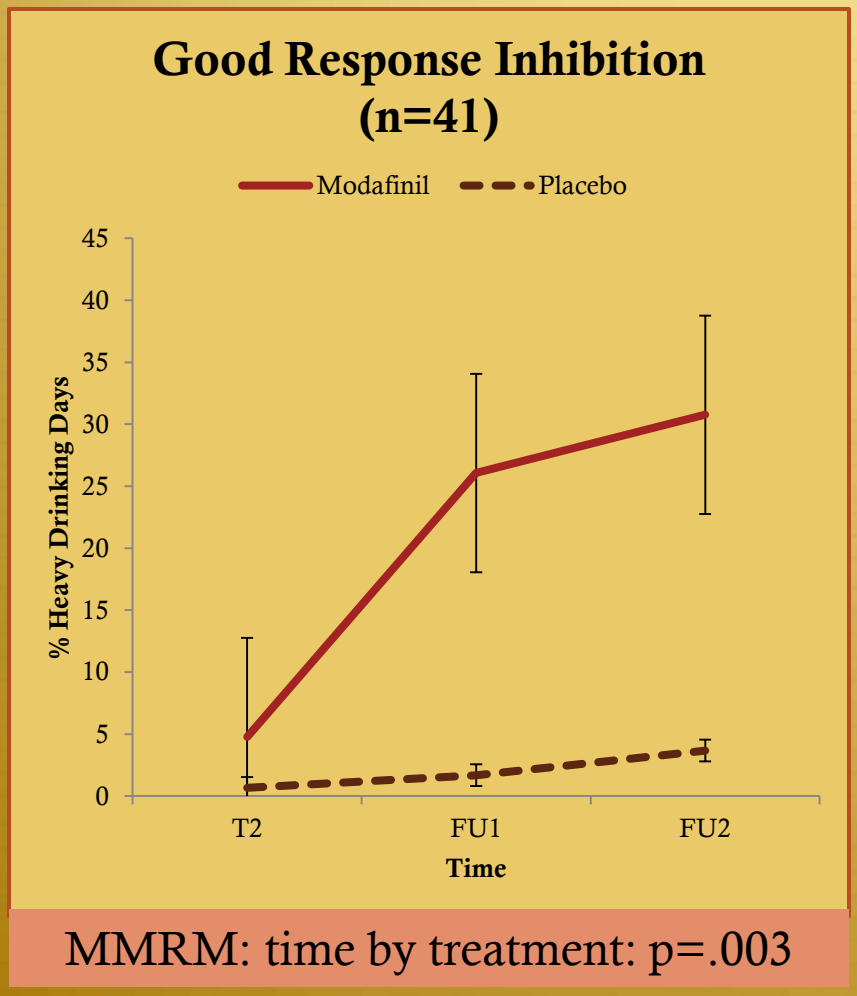
MMRM: time by treatment: p=.002



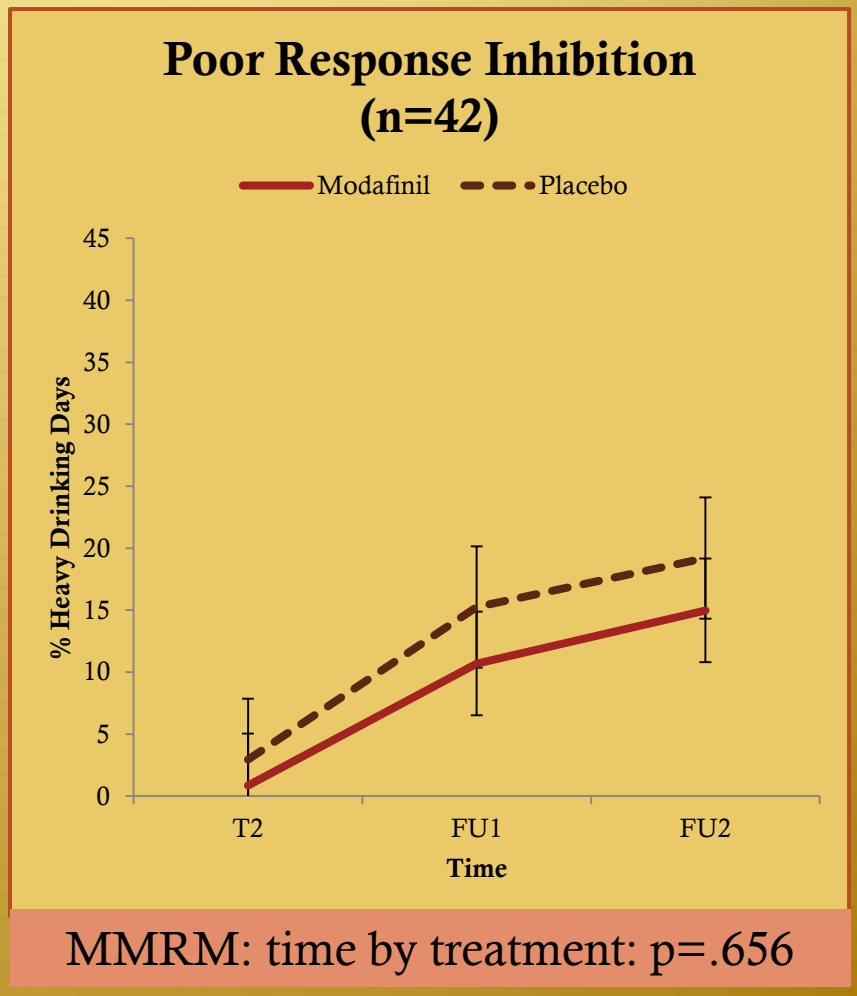
MMRM: time by treatment: p=.066

Bi-directional effects in subgroups

Percentage Heavy Drinking Days (MMRM 3-way: **p=.001**)



MMRM: time by treatment: p=.003



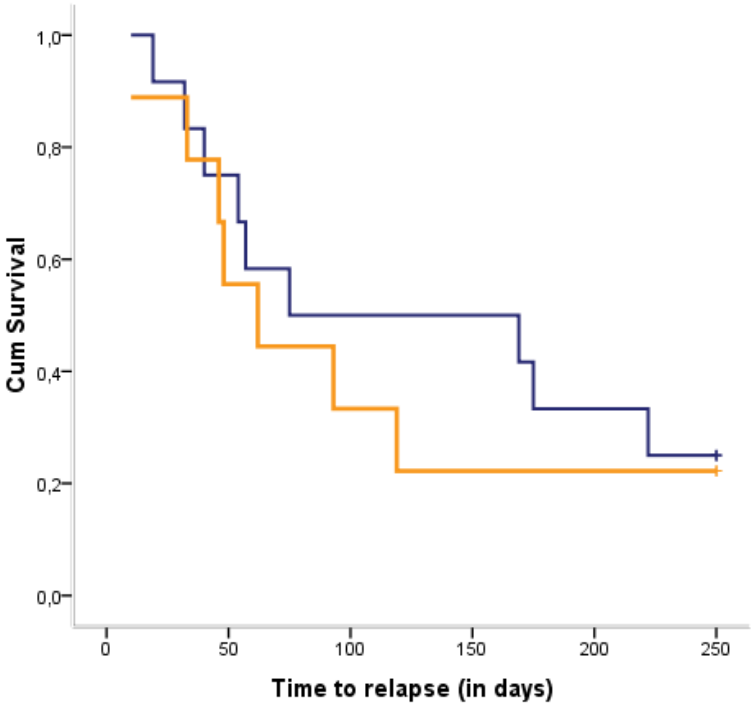
MMRM: time by treatment: p=.656

Bi-directional effects in subgroups

Postponed relapse in ADP with poor response inhibition with MOD

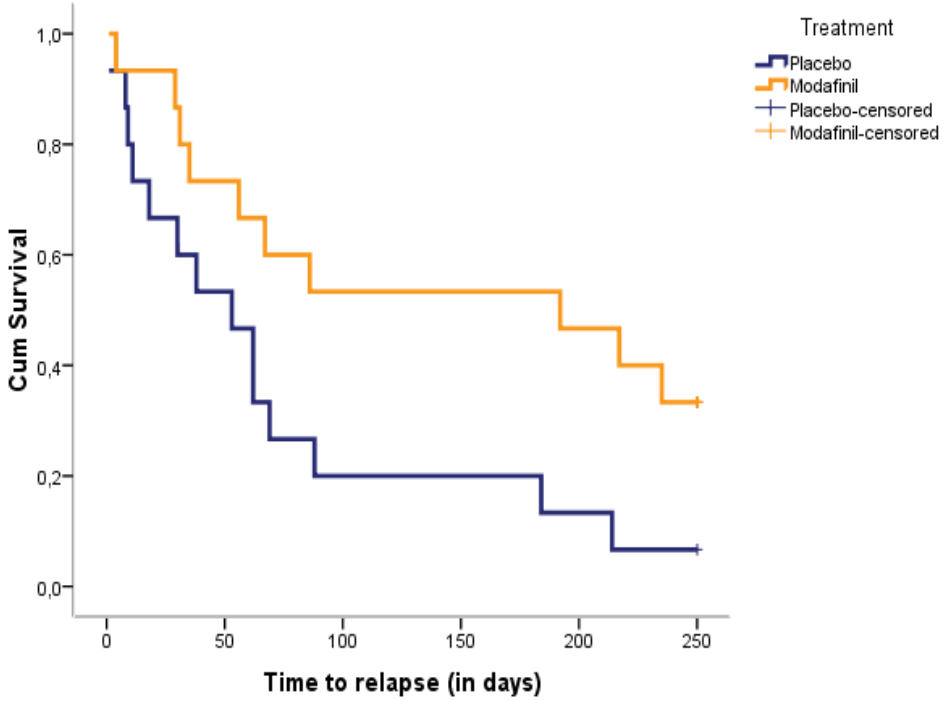
Only completers were included

Good Response Inhibition (n=21)



Log Rank (Kaplan-Meier): p=.708

Poor Response Inhibition (n=30)



Log Rank (Kaplan-Meier): p=.022

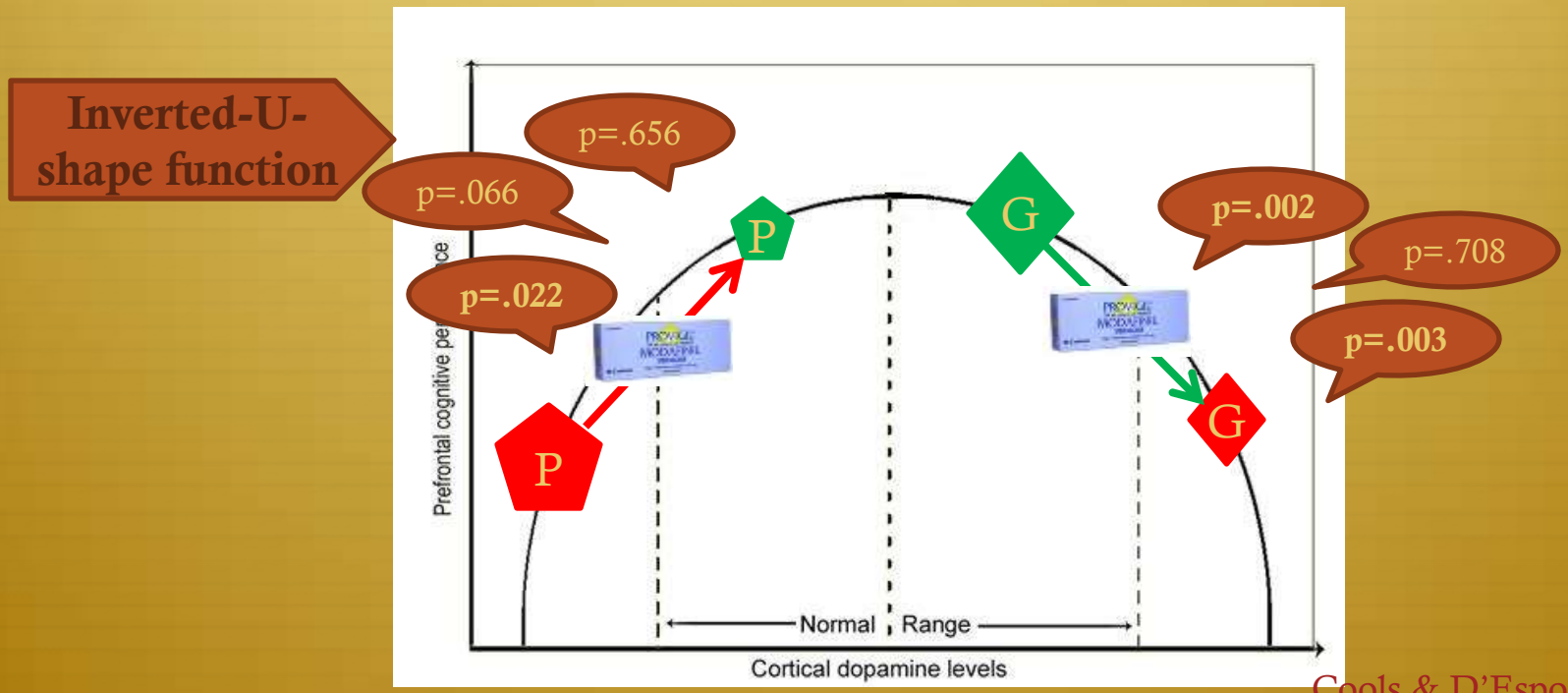
Discussion

Results summary:

- ✓ Modafinil was well tolerated in alcohol dependent patients.
- ✓ Patients **felt** less impulsive with MOD compared to PLAC.
- ✓ BUT: This did not result in less drinking or impulsive behaviour.
- ✓ **Patients with poor response inhibition at baseline** might benefit from modafinil.
- ✓ ***Detrimental effects might occur in patients with good baseline response inhibition.***

Discussion: bi-directional effects

- **Patients with poor response inhibition at baseline** might benefit from modafinil.
- D**etrimental effects** might occur in patients with good baseline response inhibition.



Cools & D'Esposito, 2011

Praten of Pillen of…trainen?

Gecontroleerd:

> STOP!

Automatische processen: Neem!

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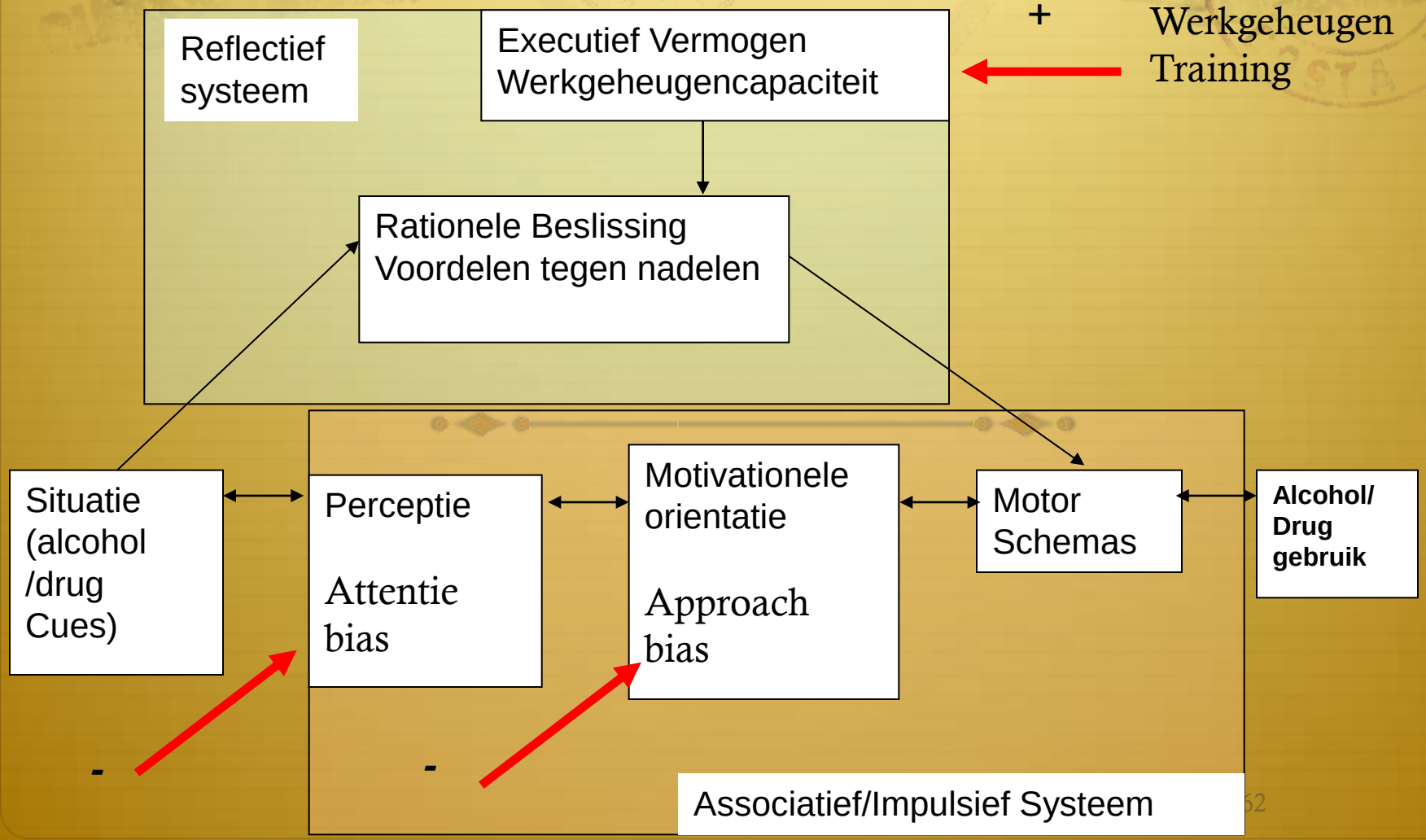
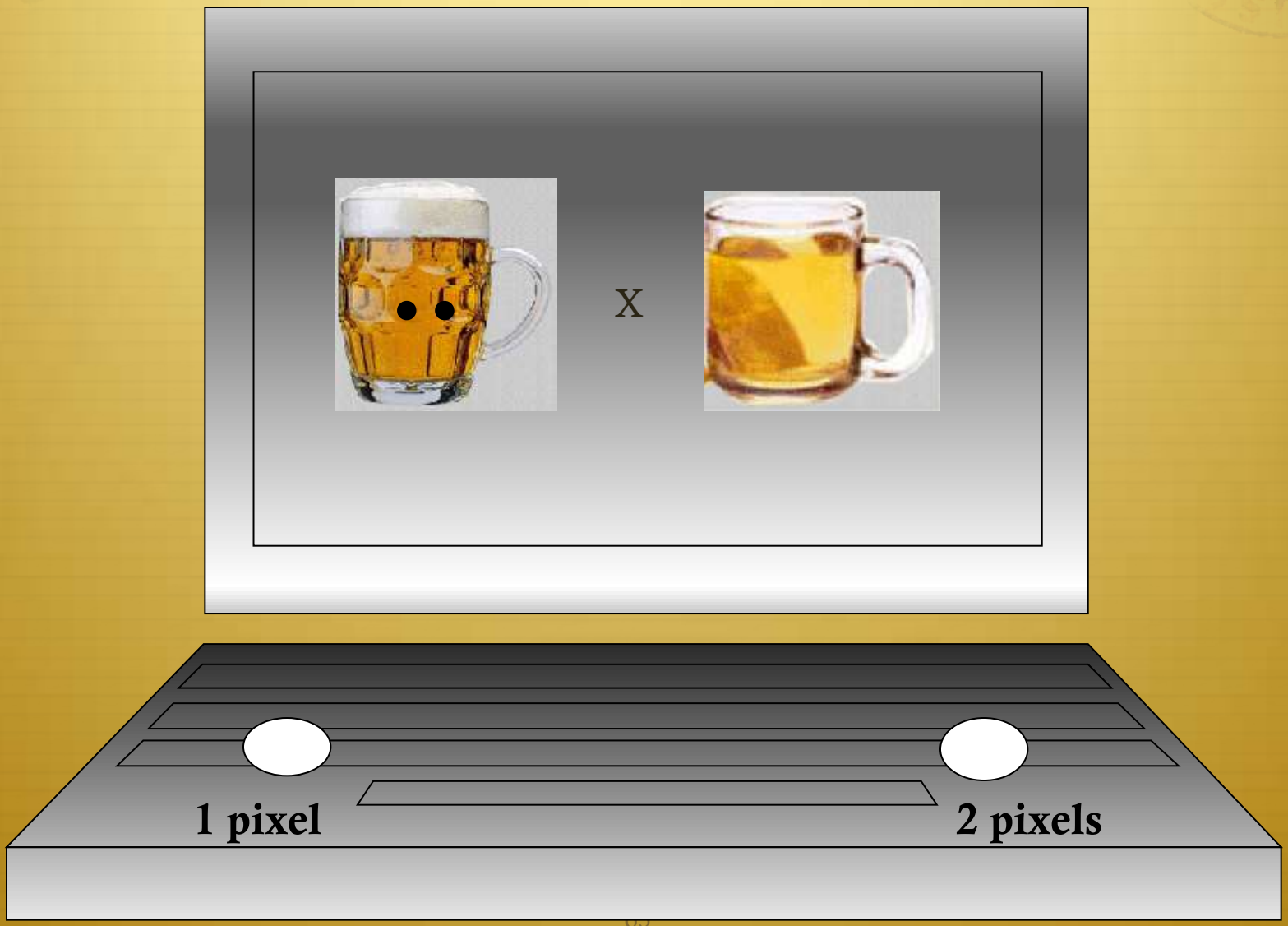
Modelgestuurde Nieuwe interventies



Alcohol trial

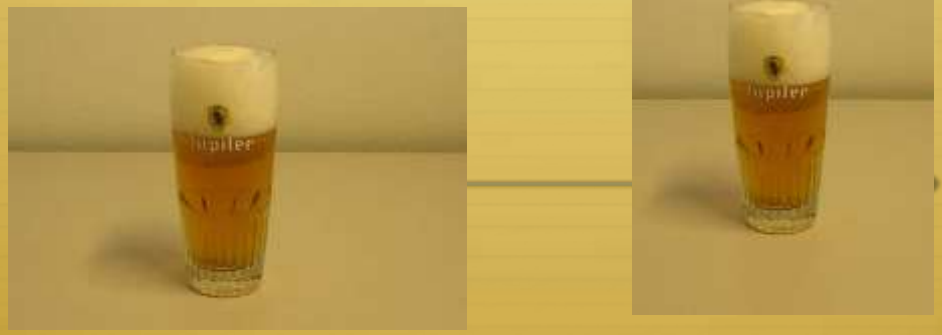


Nieuw: Retraining actie-tendens

Vorm bepaalt actie

Liggend: duwen

rechtop: trekken



Cognitive online training: Wiers et al. ?

(met Mike Rinck, RUN e.a.)

Praten of Pillen samen met trainen?

Gecontroleerd:

> STOP!

Automatische processen: Neem!

67

European Neuropsychopharmacology (2014) 24, 529–539

ELSEVIER

www.elsevier.com/locate/euroneuro

Modafinil combined with cognitive training is associated with improved learning in healthy volunteers – A randomised controlled trial ☆

J. Gilleen[a,*], P.G. Michalopoulou[a], A. Reichenberg[a], R. Drake[b], T. Wykes[a], S.W. Lewis[b], S. Kapur[a]

[a]*Institute of Psychiatry, King's College, London SE5 8AF, United Kingdom*
[b]*Institute of Brain, Behaviour and Mental Health, University of Manchester, United Kingdom*

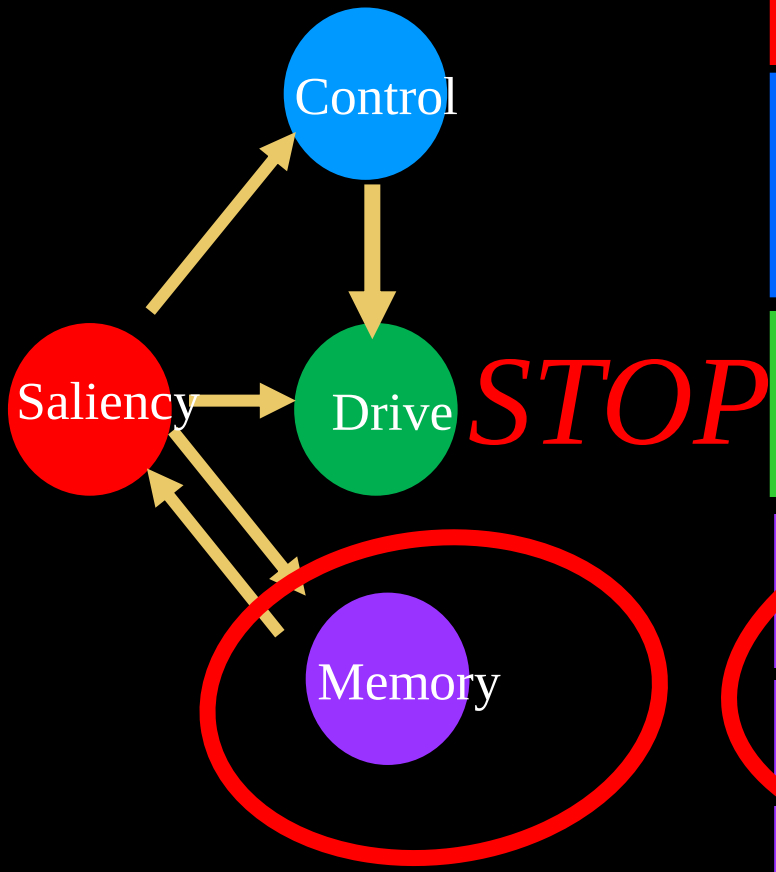
Received 28 June 2013; received in revised form 6 January 2014; accepted 7 January 2014

Gilleen et al., 2014

- Rate of new-language learning was significantly enhanced with modafinil, and effects were greatest over the first five sessions. Modafinil improved within-day learning rather than between-day retention.
- No enhancement of gains with modafinil was observed in working memory nor rate of verbal learning. Gains in all tasks were retained post drug administration, but transfer effects to broad cognitive abilities were not seen.
- ??

Medications for Relapse Prevention

Non-Addicted Brain



Interfere with drug's reinforcing effects	*Vaccines* *Enzymatic degredation* *Naltrexone* *DA D3 antagonists* *CB_1 antagonists*
Executive function/ Inhibitory control	*Biofeedback* *Modafinil* *Bupropion* *Stimulants*
Strengthen prefrontal-striatal communication	*Adenosine A2 antagonists* *DA D3 antagonists*
Interfere with conditioned memories (craving)	*Antiepileptic GVG* *N-acetylcysteine*
Teach new memories	*Cycloserine*
Counteract stress responses that lead to relapse	*CRF antagonists* *Orexin antagonists*

Pharmacology, Biochemistry and Behavior 100 (2012) 801–810

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

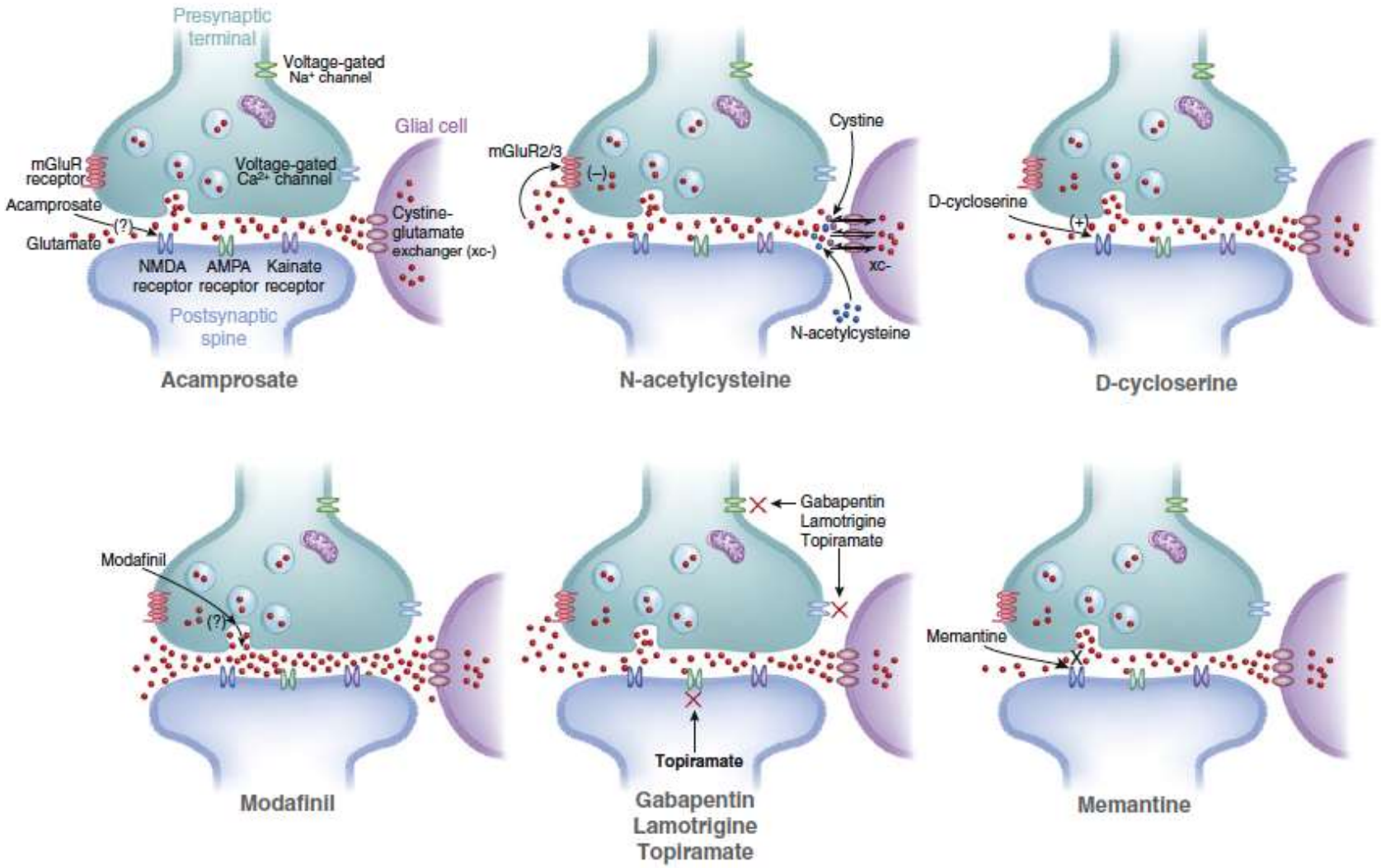
journal homepage: www.elsevier.com/locate/pharmbiochembeh

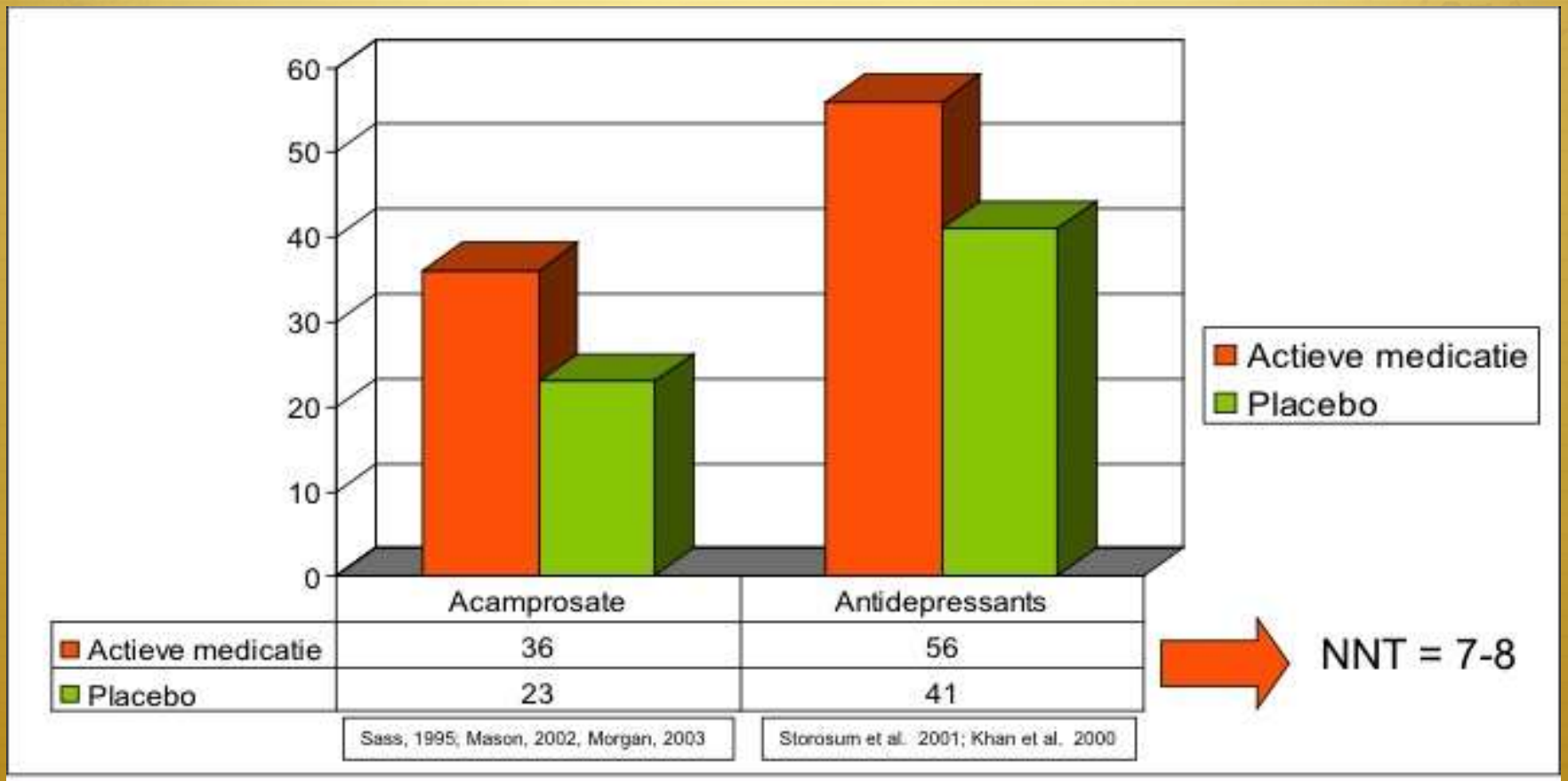
Review

Glutamatergic medications for the treatment of drug and behavioral addictions

M. Foster Olive [a,*], Richard M. Cleva [a], Peter W. Kalivas [b], Robert J. Malcolm [c]

[a] Department of Psychology, Arizona State University, Tempe, AZ 85287, USA
[b] Department of Neurosciences, Medical University of South Carolina, Charleston, SC 29425, USA
[c] Center for Drug and Alcohol Programs, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC 29425, USA


Presynaptic terminal
Voltage-gated Na+ channel
Glial cell
mGluR receptor
Voltage-gated Ca2+ channel
Acamprosate
(?)
Glutamate
Cystine-glutamate exchanger (xc-)
NMDA receptor
AMPA receptor
Kainate receptor
Postsynaptic spine
Acamprosate
mGluR2/3
(–)
Cystine
xc-
N-acetylcysteine
N-acetylcysteine
D-cycloserine
(+)
D-cycloserine
Modafinil
(?)
Modafinil
Gabapentin
Lamotrigine
Topiramate
Topiramate
Gabapentin
Lamotrigine
Topiramate
Memantine
Memantine



	Acamprosate	Antidepressants
Actieve medicatie	36	56
Placebo	23	41
	Sass, 1995; Mason, 2002; Morgan, 2003	Storosum et al. 2001; Khan et al. 2000

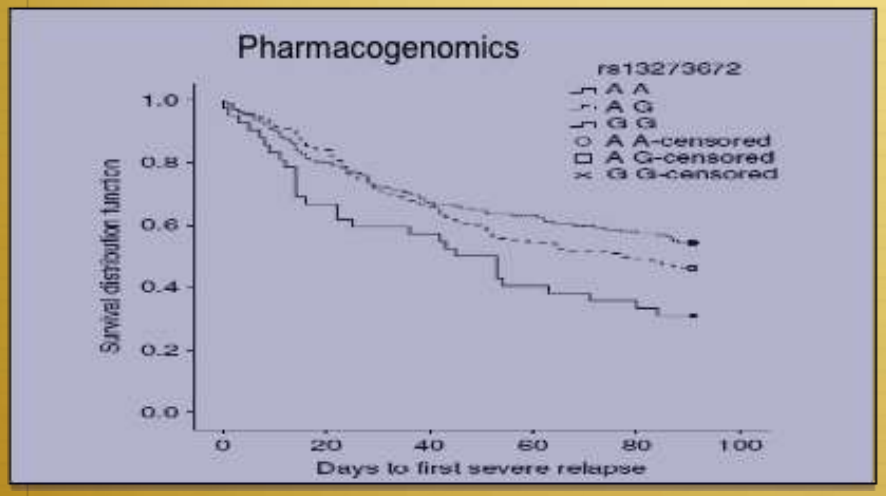
NNT = 7-8

Acamprosaat is bewezen effectieve interventie met een beperkte effectgrootte:
Ongeveer 40% abstinent na 6-12 maanden en een NNT van 7-8

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.



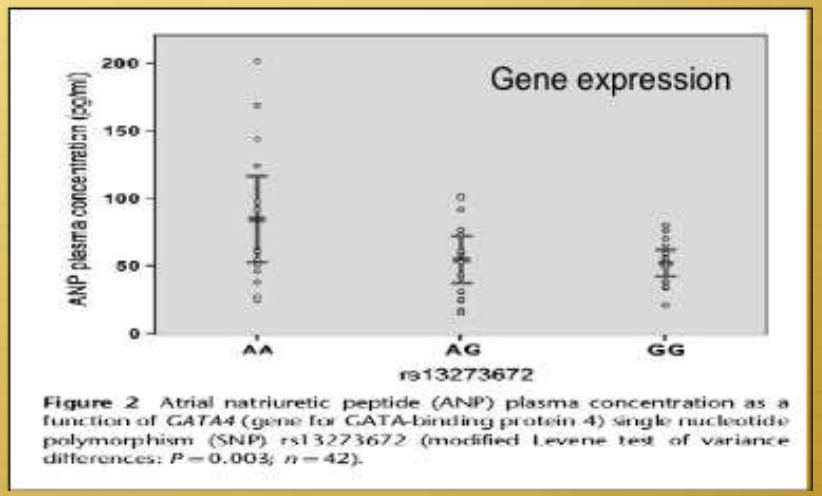


Figure 2 Atrial natriuretic peptide (ANP) plasma concentration as a function of *GATA4* (gene for GATA-binding protein 4) single nucleotide polymorphism (SNP) rs13273672 (modified Levene test of variance differences: $P = 0.003$; $n = 42$).

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

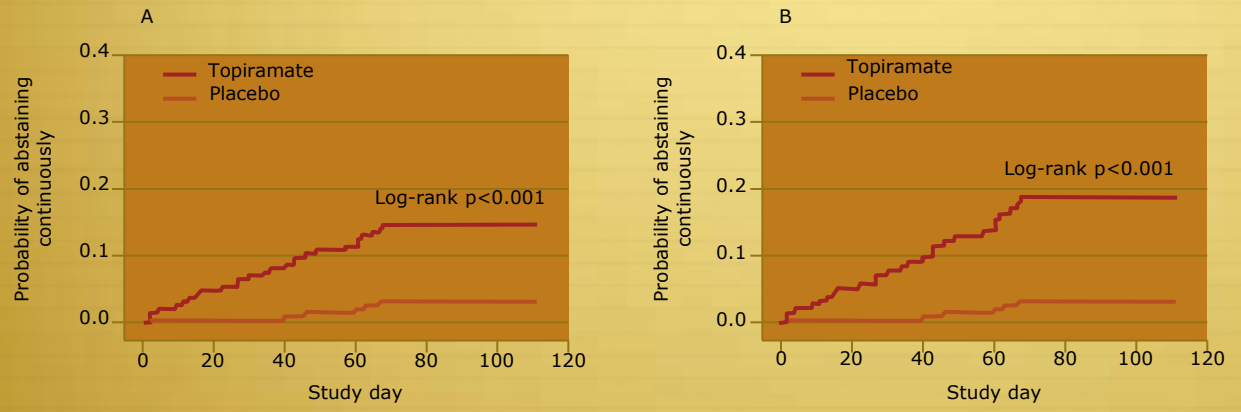
F Kiefer[1,12], SH Witt[2,12],
J Frank[2], A Richter[1], J Treutlein[2]

Topiramaat

- Topiramaat (Topamax®) is een anti-epilepticum waarvan, zoals voor de meeste anti-epileptica, het volledige werkingsmechanisme nog niet is opgeklaard. Vermoedelijk stimuleert topiramaat de GABA(A) receptoren, remt het de werking van glutamaat en leidt het tot een verminderde afgifte van dopamine in het striatum.
- Enkele grotere RCT's toonden een positief effect van topiramaat zowel wat betreft het bereiken van abstinentie als het verminderen van alcoholgebruik en alcoholgerelateerde schade (Johnson e.a., 2004; 2007).
- Een behandeling met topiramaat vraagt een intensieve medische begeleiding. Allereerst moet er opgebouwd worden van een startdosis van 25 mg naar een maximale dosis van 300 mg over een periode van ongeveer 8 weken.
- Daarnaast kent het product relatief frequente bijwerkingen zoals sufheid en concentratieverlies, eetlustverlies, paresthesieën en een slechte smaak.
- Vooral deze bijwerkingen, met een hoge drop-out uit behandeling, maken topiramaat geen eerste keuze product.
- Momenteel is het ook nog niet geregistreerd in België voor de indicatie alcoholafhankelijkheid.

Topiramate for treating alcohol dependence: a randomised controlled trial

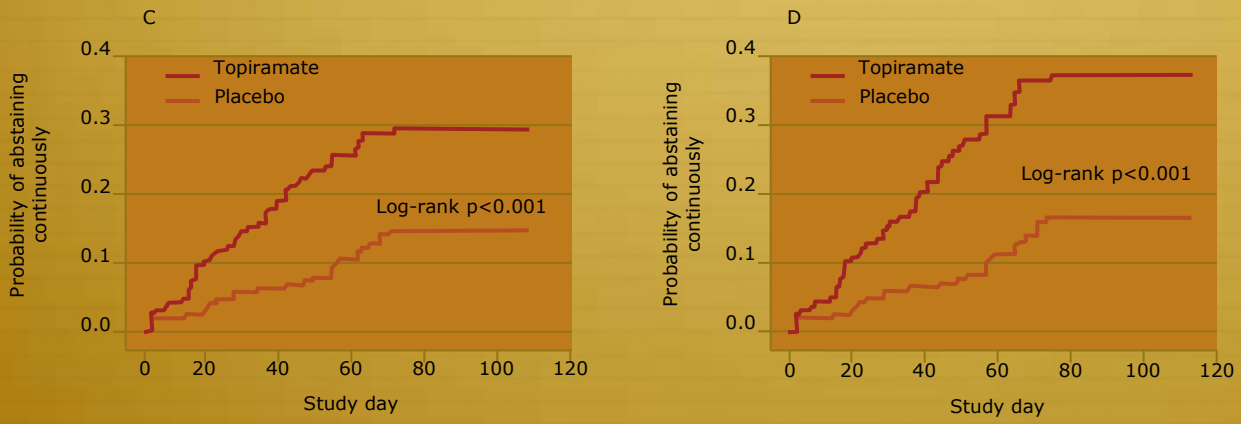
Time to first day of 28 or more days of continuous abstinence, (A) the primary analytic approach of imputing missing data with the baseline value; (B) the prespecified approach of not imputing missing data



Number of participants at risk

Topiramate	183	174	168	162	156	156	179	150	123	104	92	33
Placebo	188	187	187	185	182	182	185	181	175	156	143	50

Time to first day of 28 or more days of continuous non-heavy drinking, (C) the primary analytic approach of imputing missing data with the baseline value; (D) the prespecified approach of not imputing missing data



Number of participants at risk

Topiramate	183	163	148	136	129	129	179	139	103	79	68	22
Placebo	188	180	176	168	160	160	185	174	164	139	121	39

At least 28 days with continuous abstinence: 4% vs. 14%

At least 28 without HDDs: 15% vs. 29%

Reduced-risk drinking as outcome doubles success rate!

Johnson et al. JAMA 2007; 298 (14): 1641–1651

A Double-Blind Randomized Controlled Trial of *N*-Acetylcysteine in Cannabis-Dependent Adolescents

Kevin M. Gray, M.D.

Matthew J. Carpenter, Ph.D.

Nathaniel L. Baker, M.S.

Stacia M. DeSantis, Ph.D.

Elisabeth Kryway, P.A.-C.

Karen J. Hartwell, M.D.

Aimee L. McRae-Clark, Pharm.D.

Kathleen T. Brady, M.D., Ph.D.

Objective: Preclinical findings suggest that the over-the-counter supplement *N*-acetylcysteine (NAC), via glutamate modulation in the nucleus accumbens, holds promise as a pharmacotherapy for substance dependence. The authors investigated NAC as a novel cannabis cessation treatment in adolescents, a vulnerable group for whom existing treatments have shown limited efficacy.

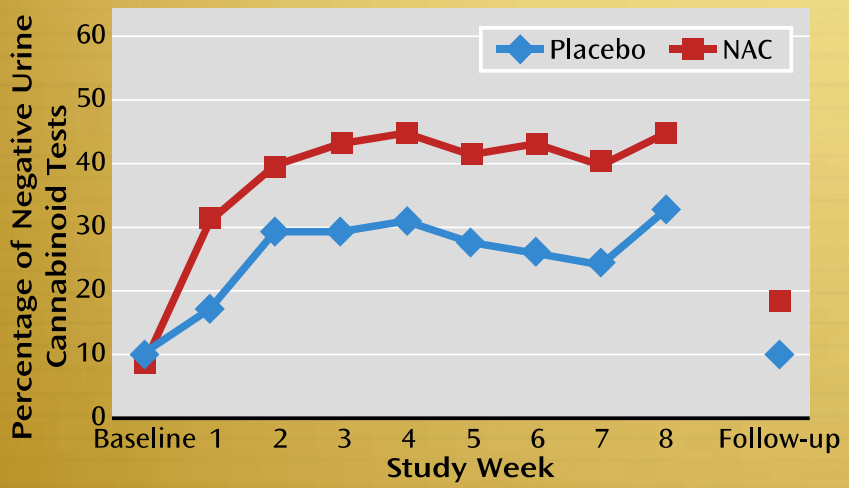
Method: In an 8-week double-blind randomized placebo-controlled trial, treatment-seeking cannabis-dependent adolescents (ages 15–21 years; N=116) received NAC (1200 mg) or placebo twice daily as well as a contingency management intervention and brief (<10 minutes) weekly cessation counseling. The primary efficacy measure was the odds of negative weekly urine cannabinoid test results during treatment among participants receiving NAC compared with those receiving placebo, in an intent-to-treat analysis. The primary tolerability measure was frequency of adverse events, compared by treatment group.

Results: Participants receiving NAC had more than twice the odds, compared with those receiving placebo, of having negative urine cannabinoid test results during treatment (odds ratio=2.4, 95% CI=1.1–5.2). Exploratory secondary abstinence outcomes favored NAC but were not statistically significant. NAC was well tolerated, with minimal adverse events.

Conclusions: This is the first randomized controlled trial of pharmacotherapy for cannabis dependence in any age group to yield a positive primary cessation outcome in an intent-to-treat analysis. Findings support NAC as a pharmacotherapy to complement psychosocial treatment for cannabis dependence in adolescents.

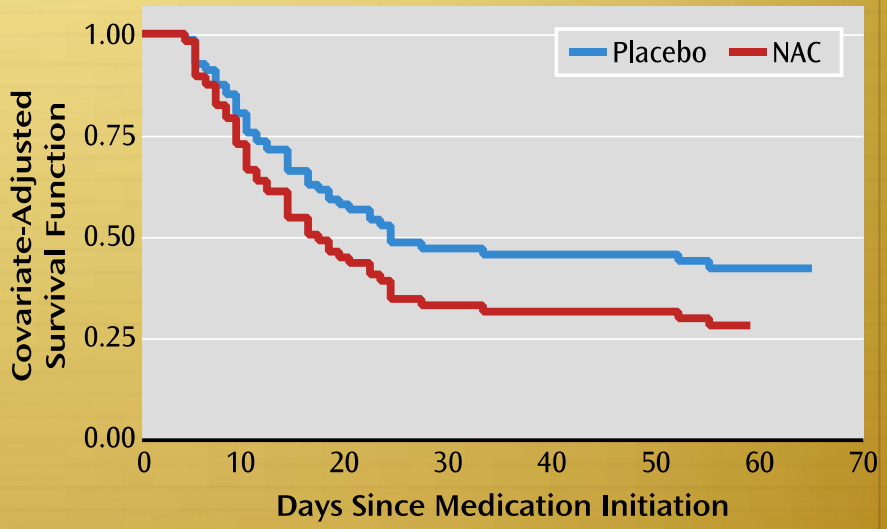
(Am J Psychiatry 2012; 169:805–812)

FIGURE 1. Proportion of Negative Urine Cannabinoid Tests Over Time Among Cannabis-Dependent Adolescents in a Randomized Controlled Trial of *N*-Acetylcysteine (NAC)[a]



[a] In this intent-to-treat analysis, all randomized participants (N=116) were included, and urine cannabinoid tests were assumed to be positive for all missed visits. With adjustment for years of cannabis use, baseline urine cannabinoid test results, and major depressive disorder, odds ratio=2.4, 95% CI=1.1–5.2; χ^2=4.72, p=0.029.

FIGURE 2. Survivorship Function for Time to First Negative Urine Cannabinoid Test Among Cannabis-Dependent Adolescents in a Randomized Controlled Trial of *N*-Acetylcysteine (NAC)[a]



[a] The graph shows the estimated survival function for NAC compared with placebo participants, adjusted for years of cannabis use and baseline urine cannabinoid test results.

Samenvatting 1

- Verslaving complexe & multiple pathogenese
- Behandeling beter aansluiten bij de onderliggende, individuele, neurobiologische ziekte processen (b.v. beloning versus zelfcontrole problemen,..)
- Gepersonaliseerde geneeskunde

Het zoeken naar gepersonaliseerde psychiatrie

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- Over het tijdschrift
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A Simple Risk Scoring System for Prediction of Relapse after Inpatient Alcohol Treatment

Mads Uffe Pedersen, PhD, Morten Hesse, PhD

Center for Alcohol and Drug Research, Aarhus University, Århus C, Denmark

2009

TABLE 2. Variables Included in the RARS = Risk of Alcohol Relapse Scale

	Code	Value in the original construction sample: Mean or percentage (relapsers)	Mean or percentage (abstainers)	Probability*
Standard units of alcohol per day during intensive periods	One if >20	23.0	17.2	0.003
Economic problems (EuropASI Composite Score)	One if >0	0.66	0.54	0.04
Treatment on the initiative of the clients, their families or workplace	One if false	58%	75%	0.001
Treatment paid by the client and/or the clients family	One if false	18%	31%	0.02
Treated for alcohol problems before	One if true	74%	62%	0.047
Prescribed psychopharmacological medicine	One if true	44%	30%	0.04
Contemplated suicide	One if true	29%	16%	0.03
Attempted suicide	One if true	8%	2%	0.048
Troubled with social problems/conflicts	One if>2	1.42	0.92	0.03
Need for help physical problems	One if>2	1.40	0.96	0.04

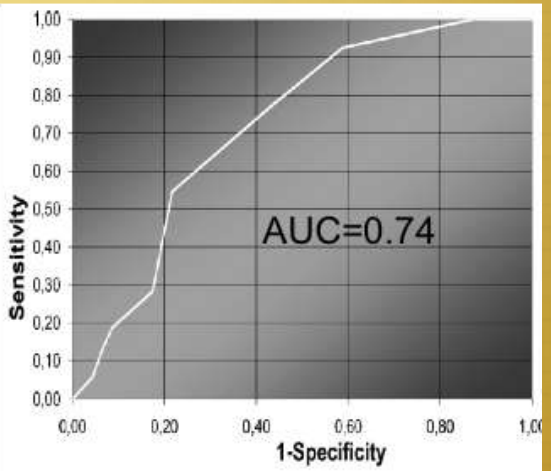


FIGURE 1. Receiver operating characteristics curve for validation sample 1 (RARS as a predictor of uncontrolled drinking during 6 months follow-up).

Voorspellers behandeluitkomst:

* ernst (alcoholconsumptie)
* sociale problemen (geld, conflicten)
* psychiatrische comorbiditeit
* somatische problemen
* motivatie voor behandeling
* eerdere alcoholbehandelingen

Addiction Biology

REVIEW

doi:10.1111/j.1369-1600.2010.00287.x

Pharmacogenetics of alcohol, nicotine and drug addiction treatments

Jessica E. Sturgess[1], Tony P. George[2,3], James L. Kennedy[1,3], Andreas Heinz[4] & Daniel J. Müller[1,3]

Pharmacogenetics Research Clinic, Neurogenetics Section, Centre for Addiction and Mental Health, Canada[1], Addiction Psychiatry Program, Department of Psychiatry, University of Toronto, Schizophrenia Program, Centre for Addiction and Mental Health, Canada[2], Schizophrenia Program, Centre for Addiction and Mental Health, Canada[3] and Department of Psychiatry, University Medicine Berlin, Charité Campus Mitte, Germany[4]

Addictive Behaviors 38 (2013) 1691–1698

Contents lists available at SciVerse ScienceDirect

Addictive Behaviors

Predictive validity of treatment allocation guidelines on drinking outcome in alcohol-dependent patients

Maarten J.M. Merkx [a,*], Gerard M. Schippers [a], Maarten W.J. Koeter [a], Pieter Jelle Vuijk [a], Mariana Poch [b], Hans Kronemeijer [c], Wim van den Brink [a]

[a] *Amsterdam Institute for Addiction Research, Academic Medical Center, University of Amsterdam, The Netherlands*
[b] *Jellinek/Arkin, Amsterdam, The Netherlands*
[c] *Arkin, Amsterdam, The Netherlands*

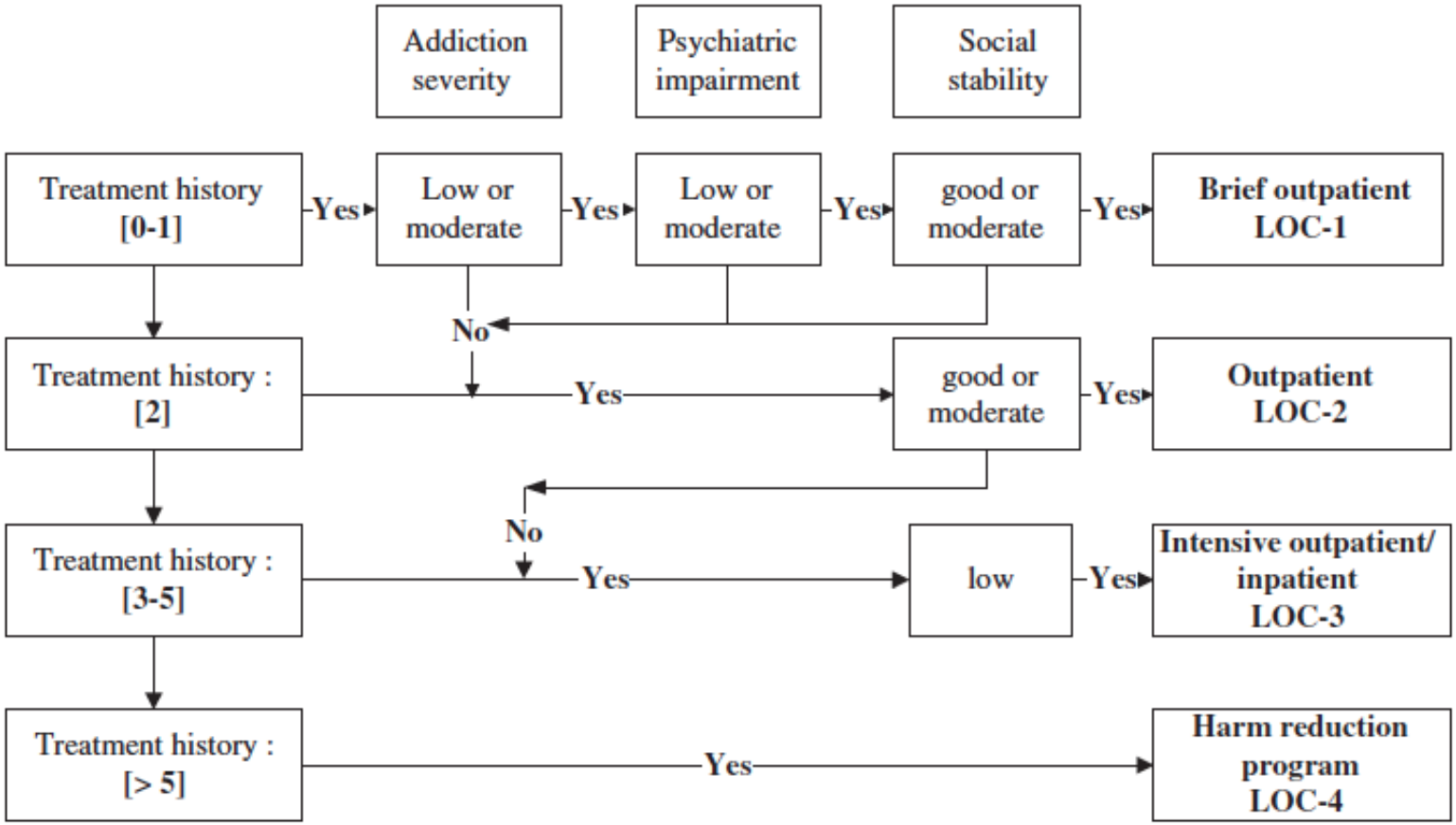


Fig. 2. Allocation guidelines for matching and referral.

Merkx et al., 2013

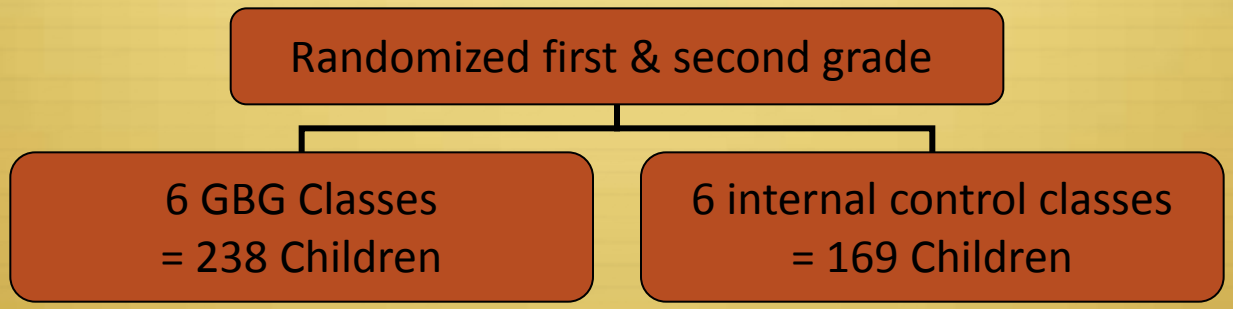
- The results were not in line with our hypotheses.
- Patients treated at a more intensive level of care than recommended had favorable outcomes compared to patients treated at the recommended level of care (55.5% vs. 43.9% success).
- Patients allocated to the recommended level of care did not have better outcomes than those treated at a less intensive level of care (43.9% vs 38.3% success).

Maar ook vroeg ingrijpen !!

May 2008 - Vol. 103 s1, Destiny Matters: Childhood and Adolescent Prediction of Adult Alcohol Use and Abuse in Six Multi-decade Longitudinal Studies Page 1-109

A classroom playing the Good Behavior Game in Denver.

Design



2 year GBG implementation

Results after 1 year = diminishment
aggressive/disruptive behavior boys.

Follow-up 19-21 years

randomly assigned to intervention or control.

Results: By young adulthood significant impact was found among males, particularly those in first grade who were more aggressive, disruptive, in reduced drug and alcohol abuse/dependence disorders, regular smoking, and antisocial personality disorder. These results underline the value of a first-grade universal prevention intervention.

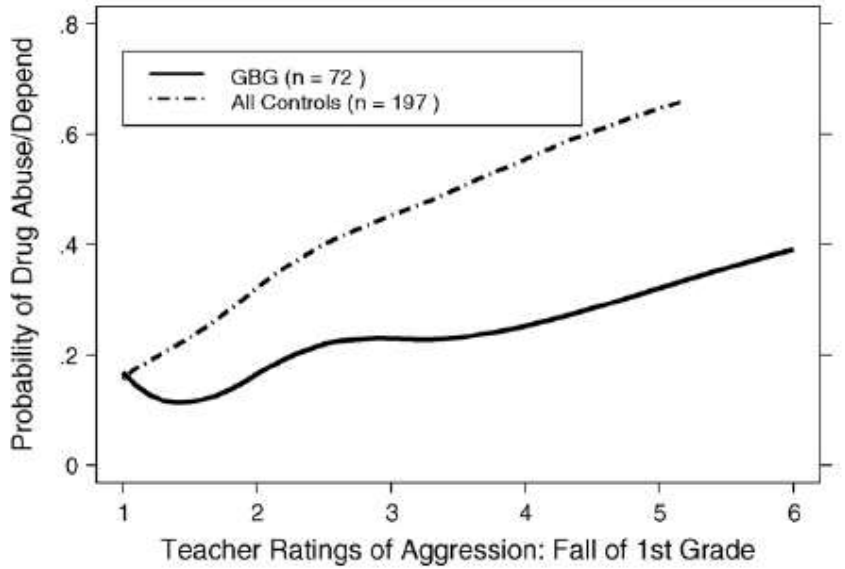


Fig. 2. Impact of GBG vs. all three controls combined on lifetime drug abuse/dependence disorders by baseline aggressive, disruptive behavior among Cohort 1 males.

OUTCOMES	GROUP	GBG CLASSROOM	STANDARD CLASSROOM
Drug abuse and dependence disorders	All males	19 percent	38 percent
	Highly aggressive males	29 percent	83 percent
Regular smoking	All males	6 percent	19 percent
	Highly aggressive males	0 percent	40 percent
Alcohol abuse and dependence disorders	All males and females	13 percent	20 percent
Antisocial personality disorder (ASPD)	Highly aggressive males	40 percent	100 percent
Violent and criminal behavior (and ASPD)	Highly agressive males	34 percent	50 percent
Service use for problems with behavior, emotions, drugs, or alcohol	All males	25 percent	42 percent
Suicidal thoughts	All females	9 percent	19 percent
	All males	11 percent	24 percent

Conclusie

- Verslaving complex
- Huidig behandel bereik nog te beperkt
- Huidige behandeling beperkte effectiviteit
- Naar de toekomst (en stukje heden):
  - > beter aansluiten op neurobiologische individuele kenmerken
  - > gepersonaliseerde aanpak
  - > stagering en profilering

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