

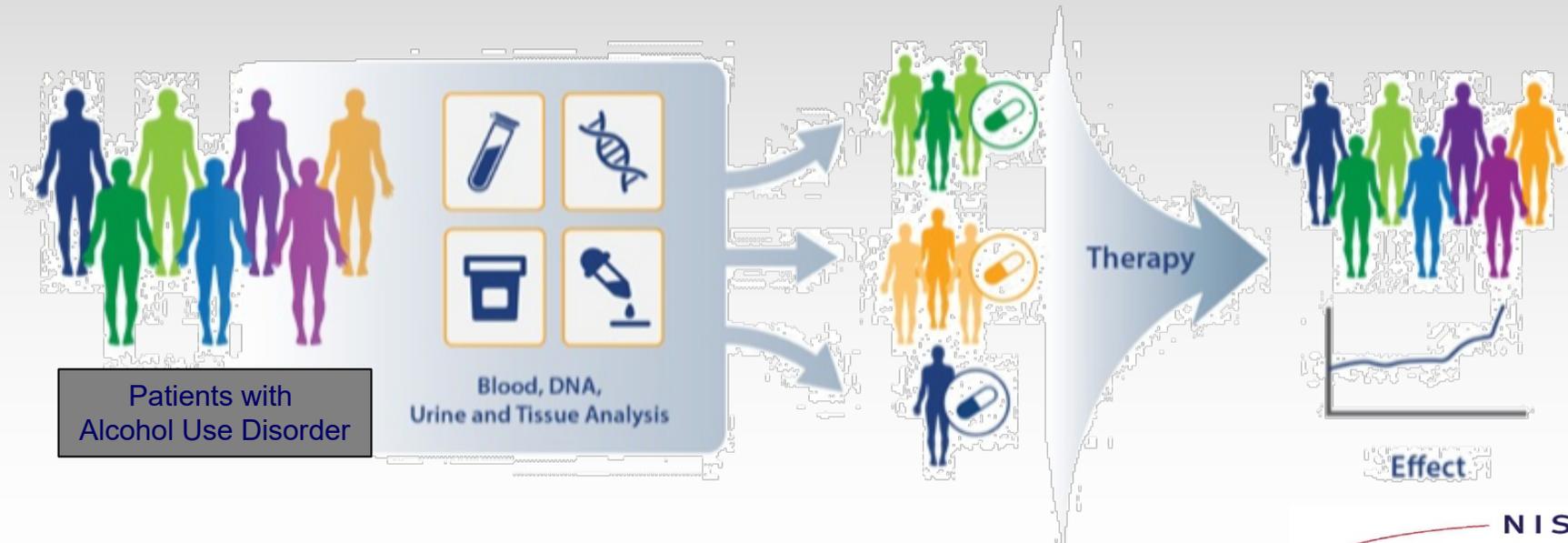
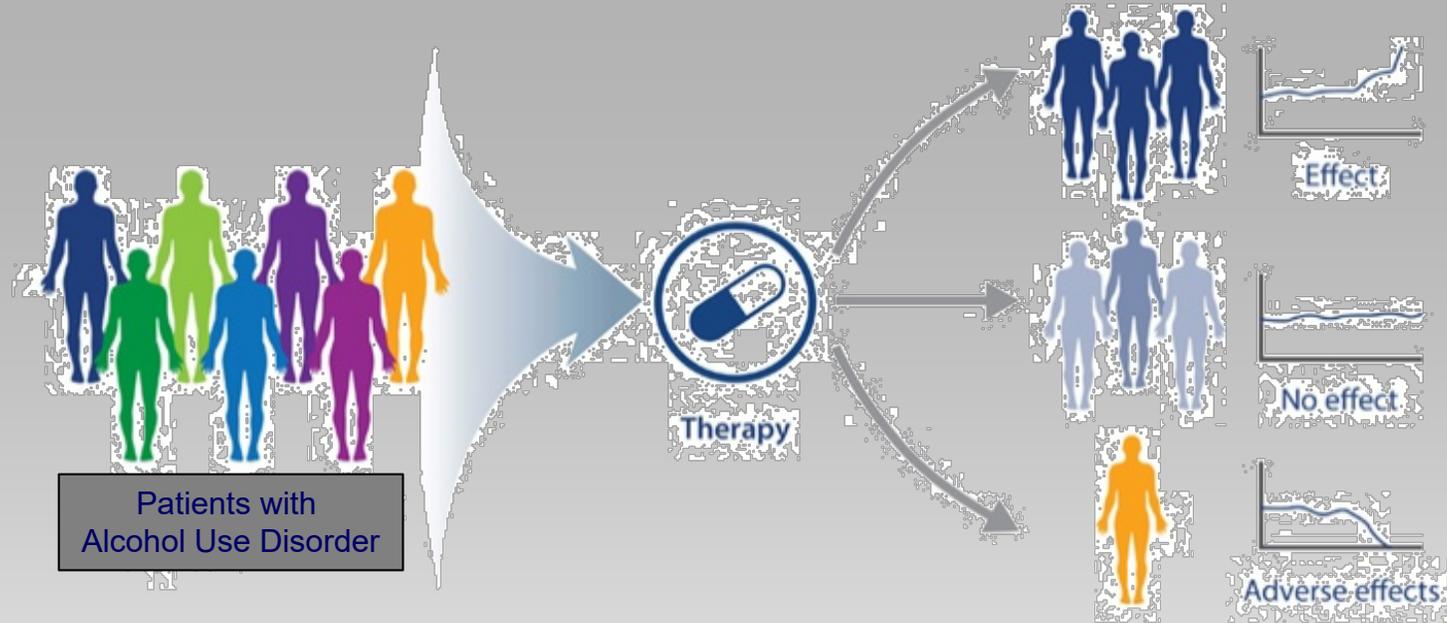


Op zoek naar de graal...?

Arnt Schellekens
Psychiater Radboudumc, PI Donders Institute
Wetenschappelijk Directeur NISPA





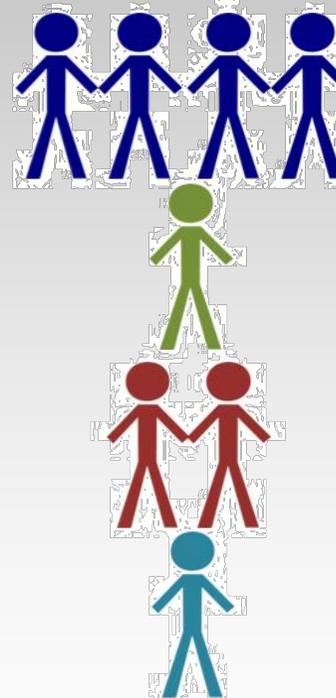




Generalized Medicine



Personalized Medicine



Personalized:

-*Pharmacotherapy*

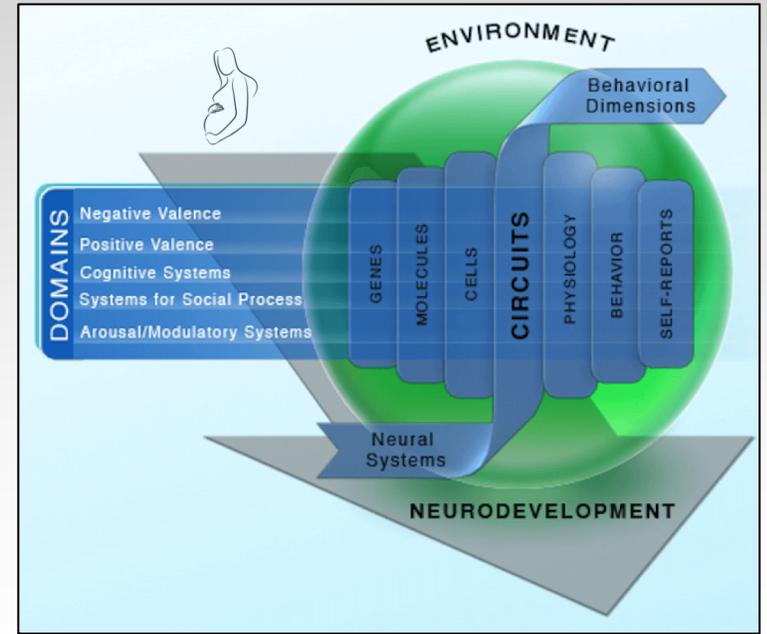
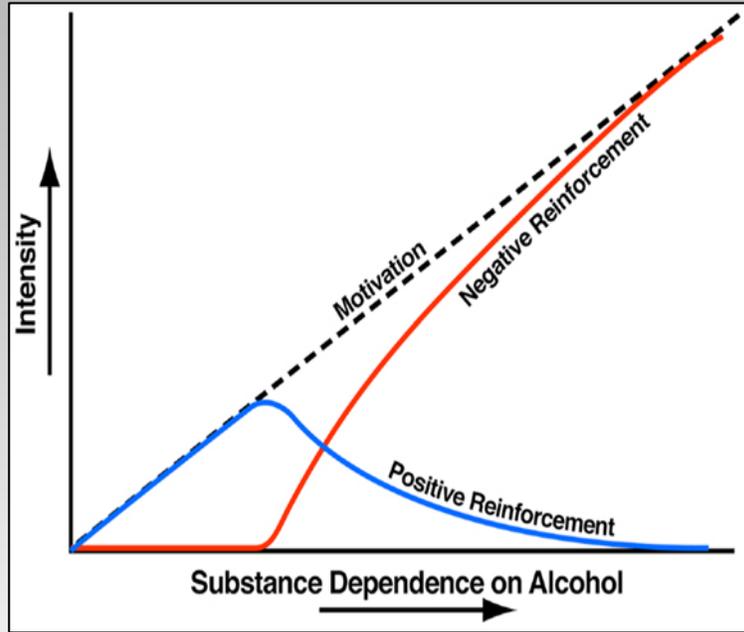
-Treatment goals

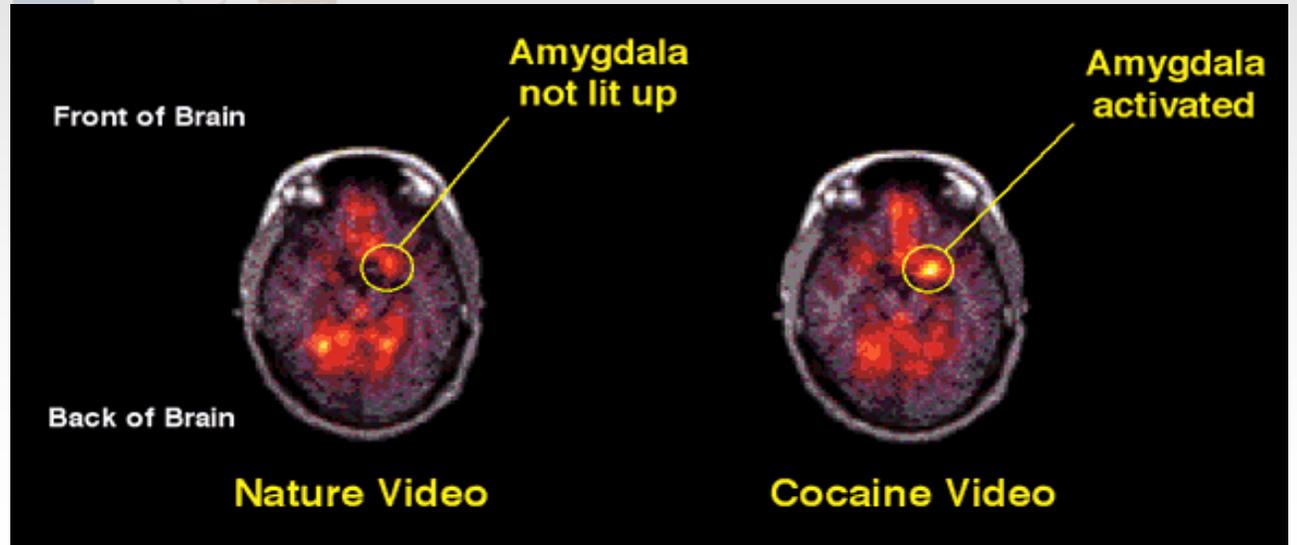
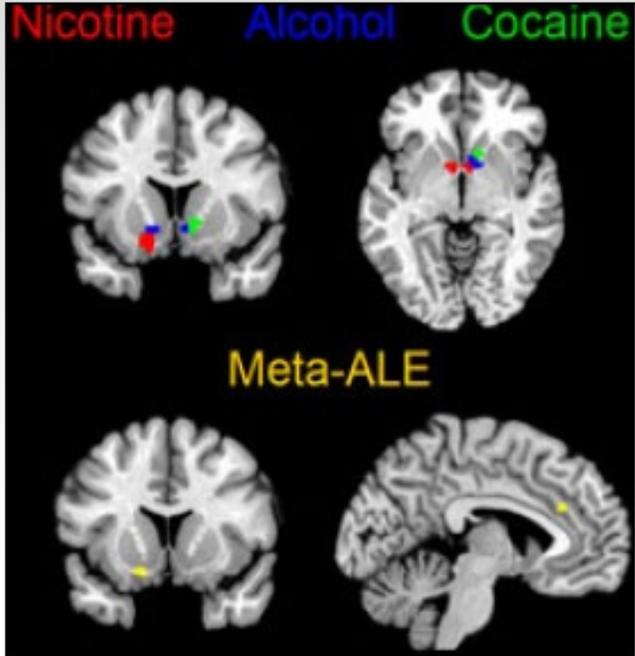
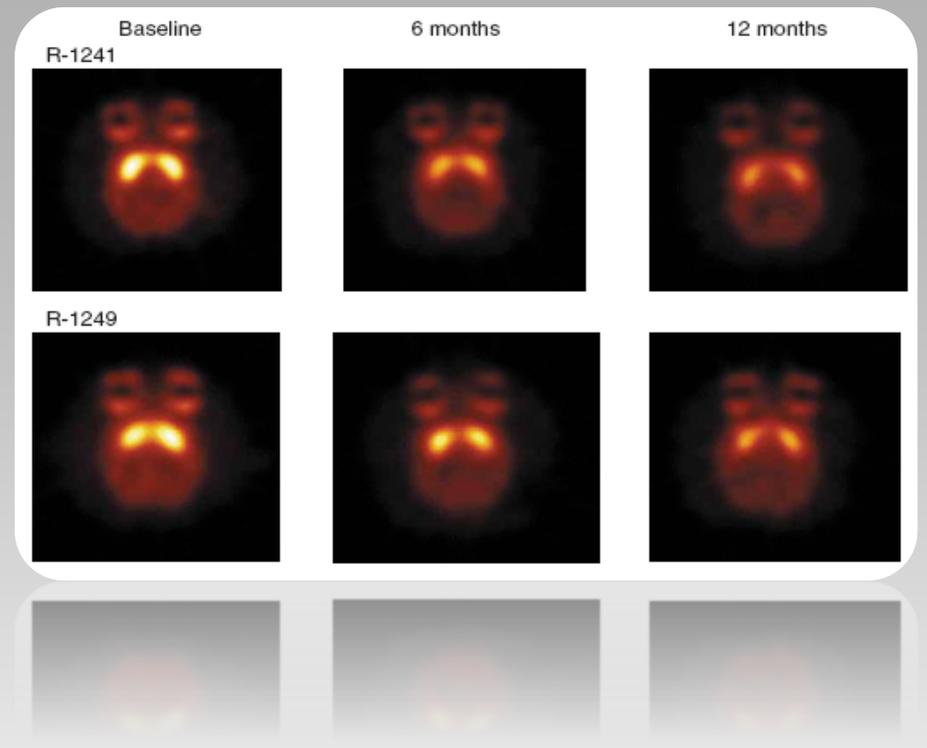
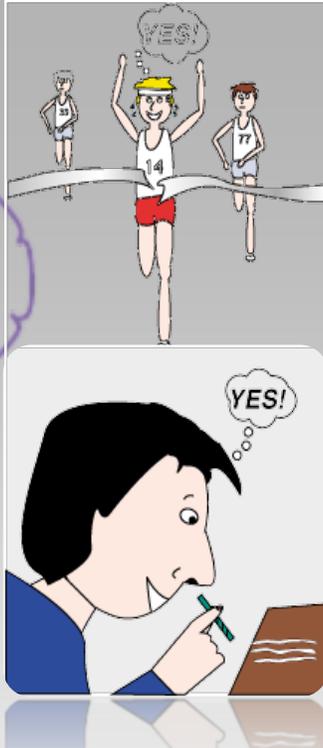
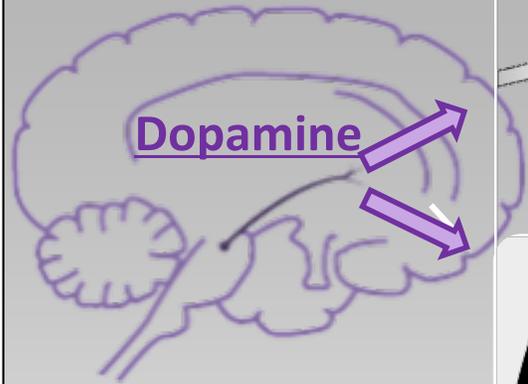
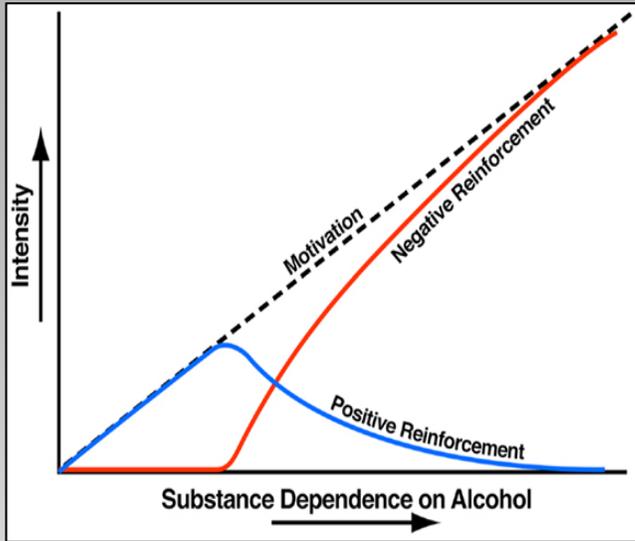
-Psychotherapy

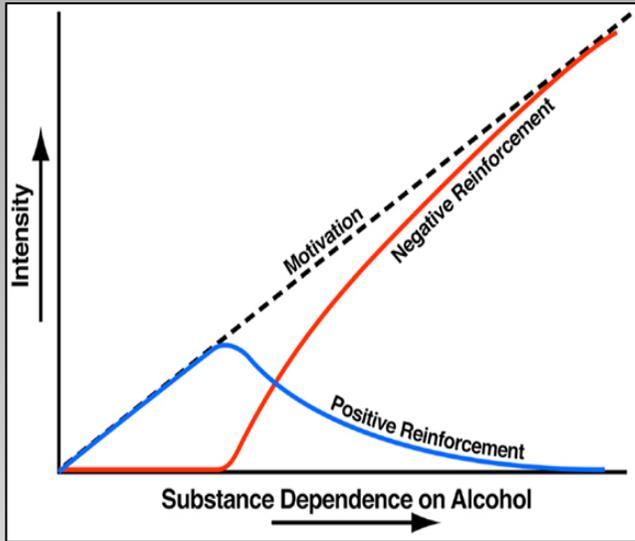
-Treatment intensity

-Neuromodulation

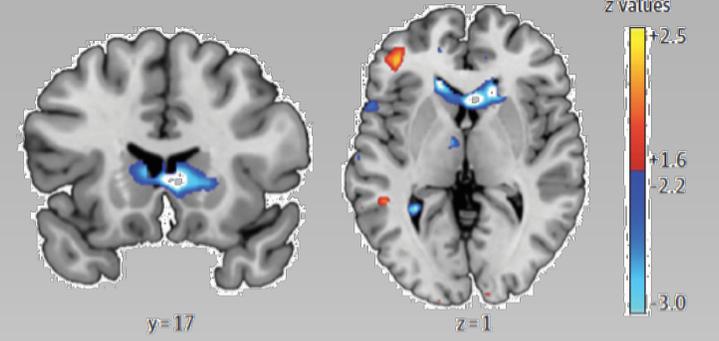
-eHealth



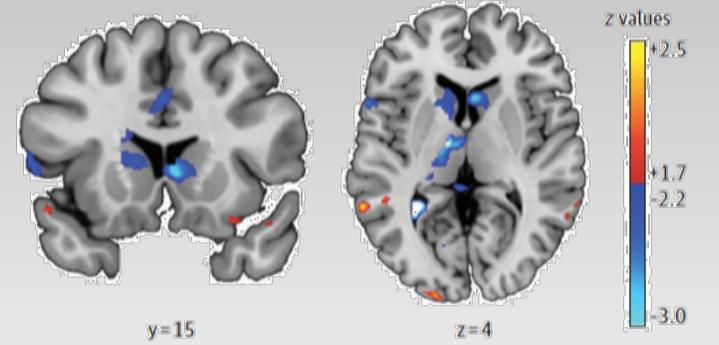




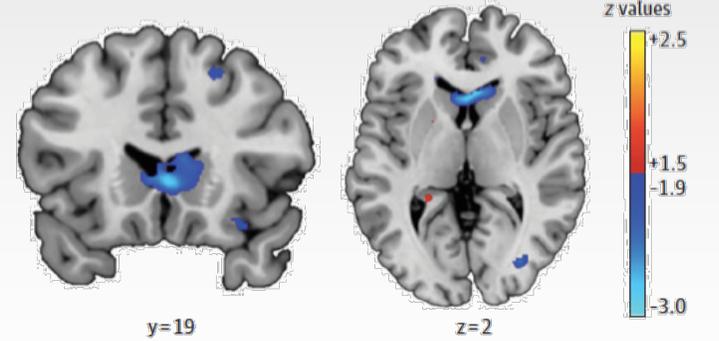
All addicted vs controls

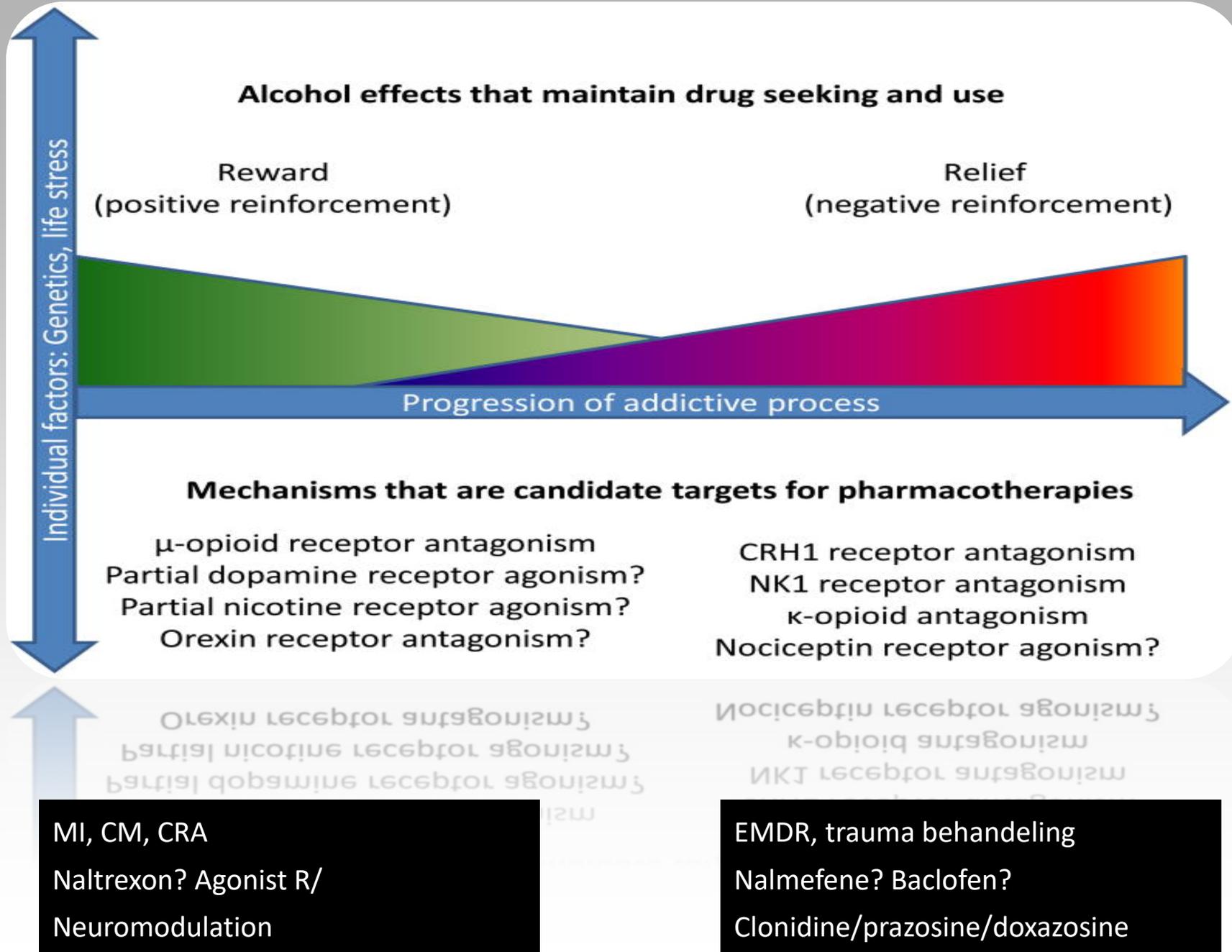
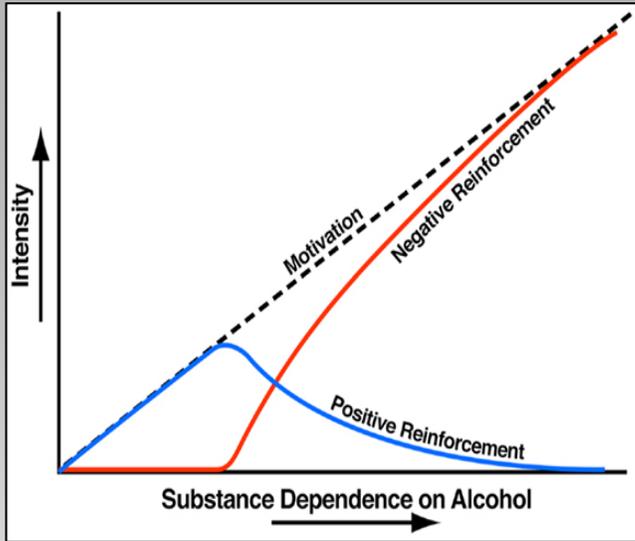


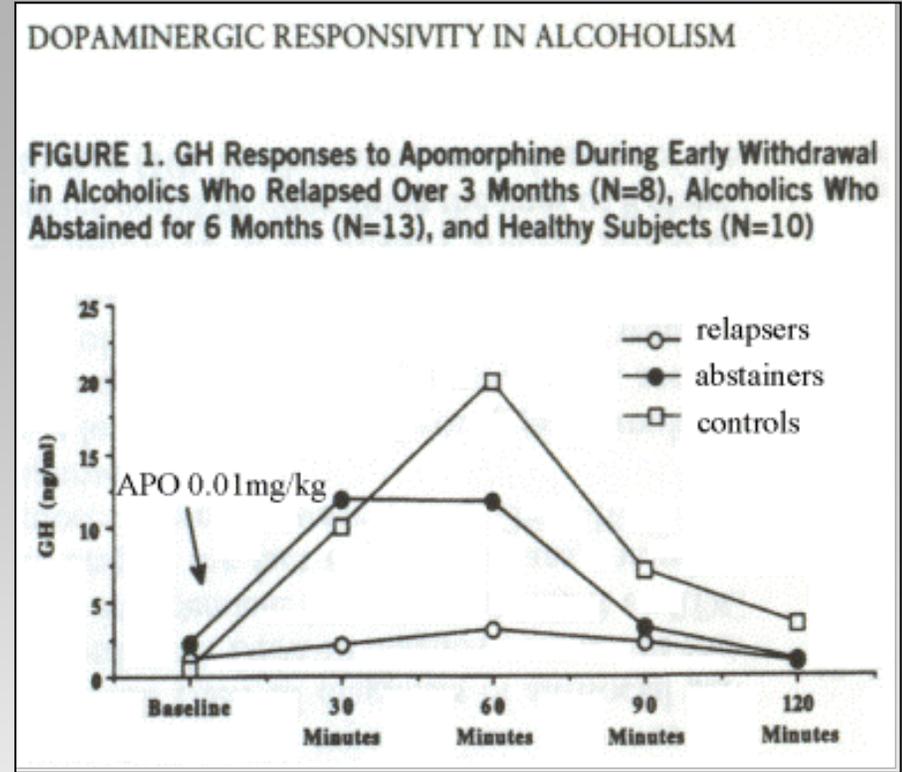
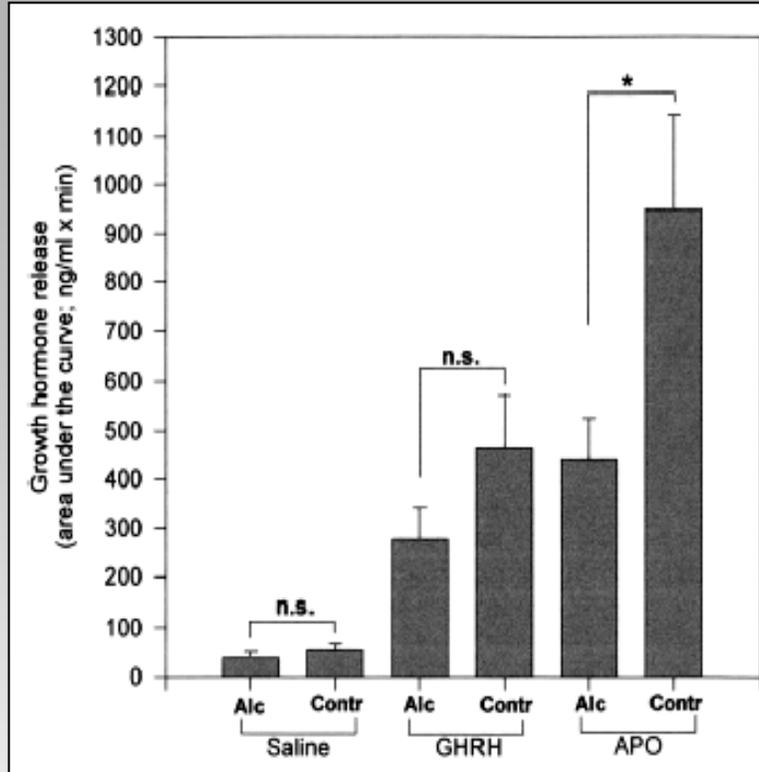
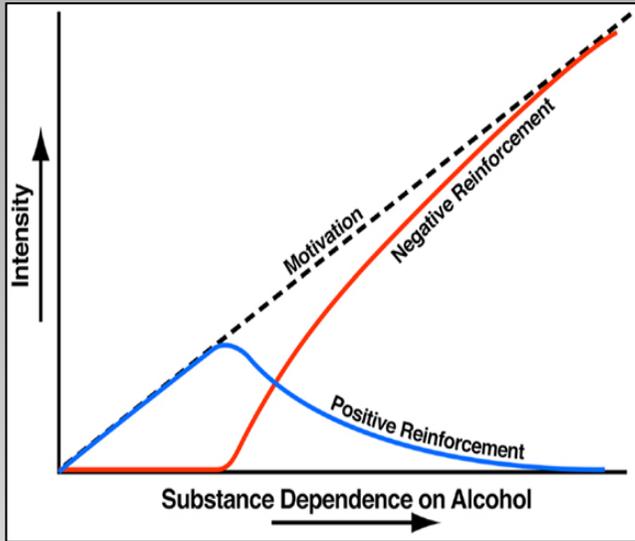
Substance addicted vs controls

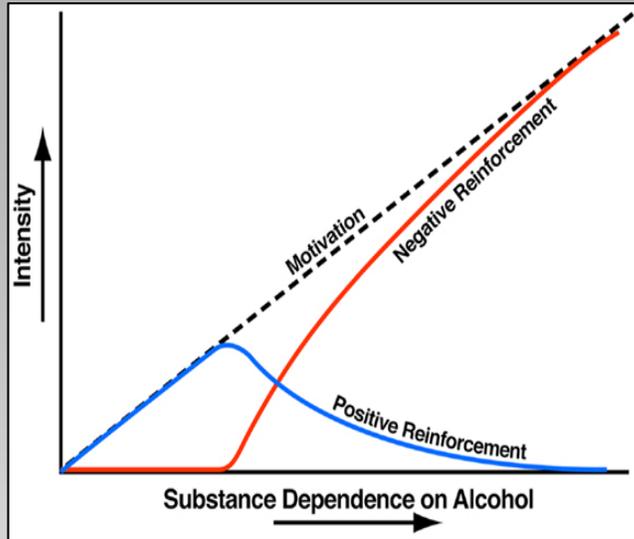


Gambling addicted vs controls









Stageren Verslaving

-Stagering: impulsiviteit – compulsiviteit

-Anamnese (craving), biomarkers, testen?

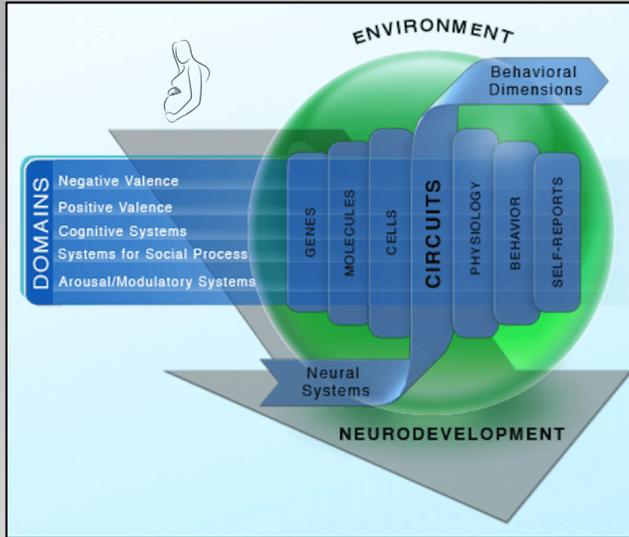
-consequenties:

psychotherapie vb CM vs EMDR?

farmacotherapie vb Naltrexon vs Nalmefene

behandel doelen & intensiteit

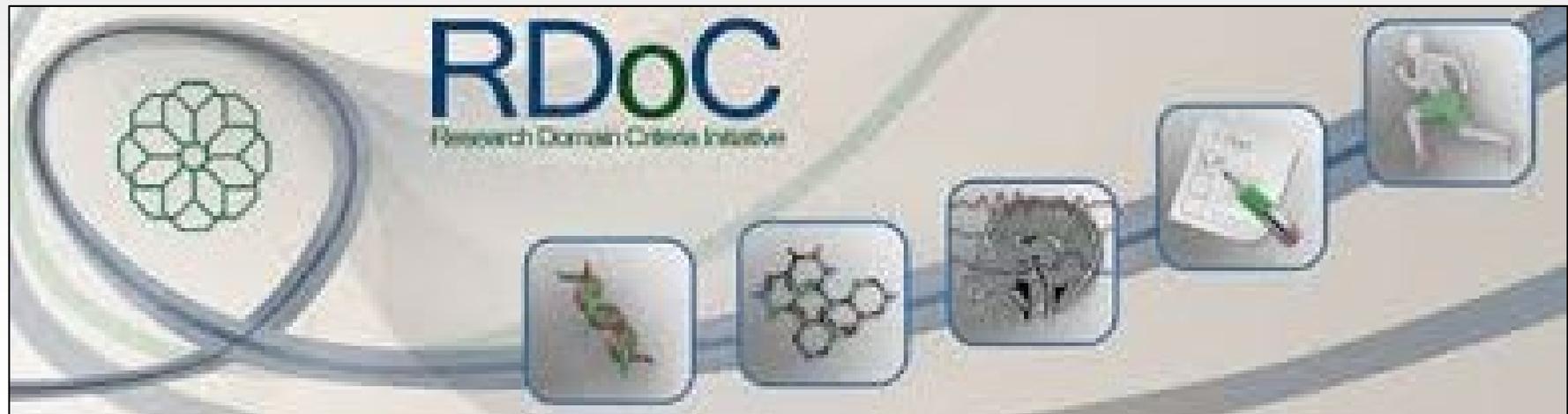


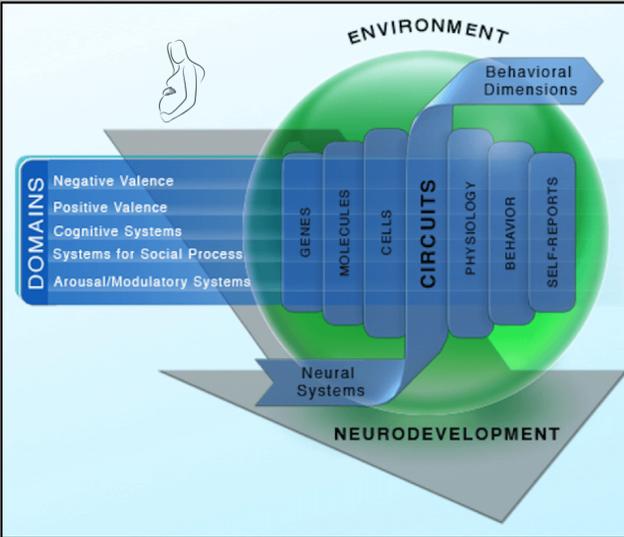


RDoC

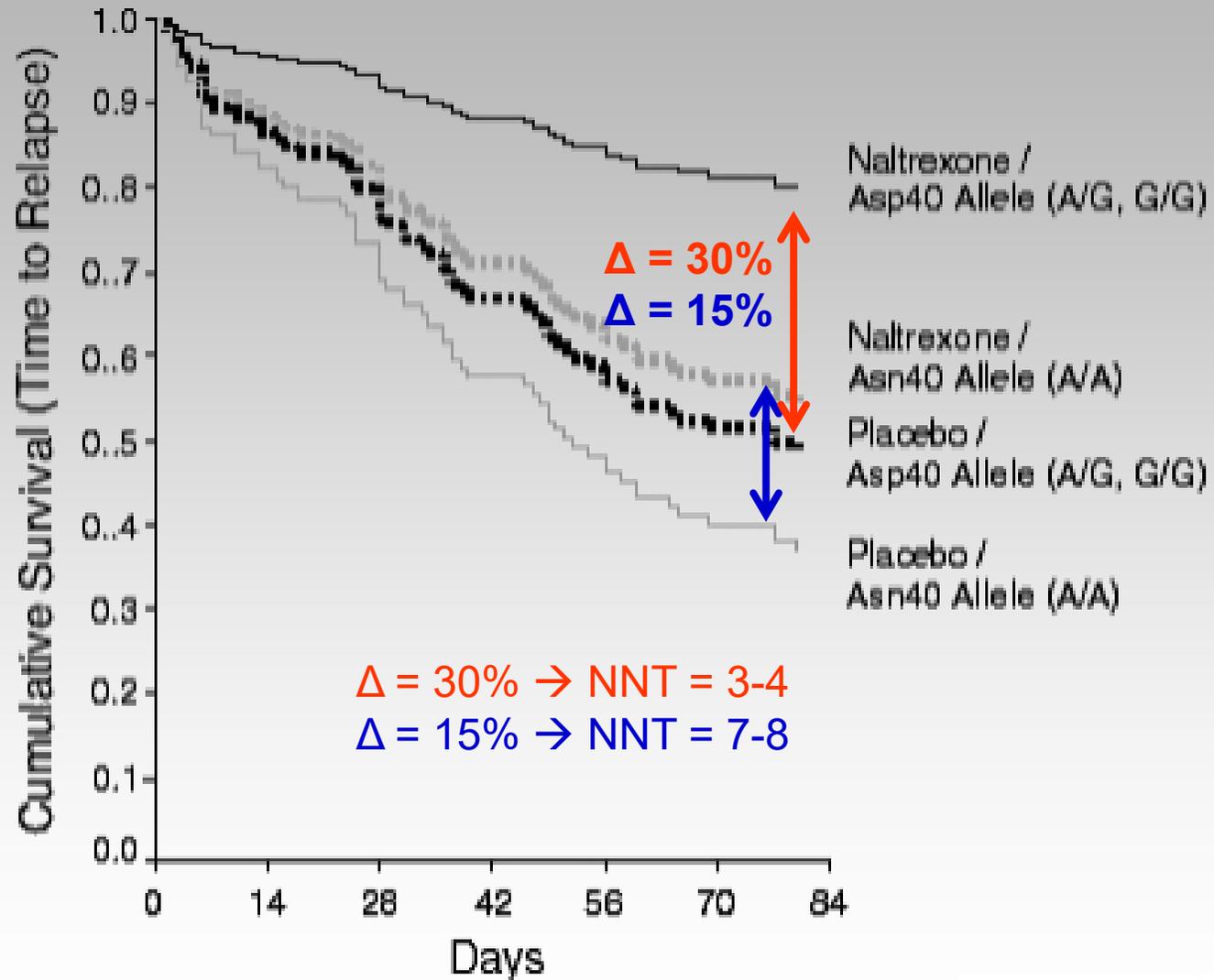
- Transdiagnostisch
- Moleculair tot vragenlijst
- Continuüm model

NEGATIVE VALENCE	POSITIVE VALENCE	COGNITIVE	SOCIAL	AROUSAL & REGULATION
<p>Acute Threat "Fear"</p> <p>Potential Threat "Anxiety"</p> <p>Sustained Threat</p> <p>Loss</p> <p>Frustrative Non-Reward</p>	<p>Approach Motivation</p> <ul style="list-style-type: none"> - Reward Valuation - Effort Valuation - Expectancy - Action Selection <p>Initial Responsiveness to Reward</p> <p>Sustained Responsiveness to Reward</p> <p>Reward Learning</p> <p>Habit</p>	<p>Attention</p> <p>Perception</p> <ul style="list-style-type: none"> - Visual - Auditory - Olfactory <p>Declarative Memory</p> <p>Language Behaviour</p> <p>Cognitive Control</p> <ul style="list-style-type: none"> - Goal Selection, Updating, Representation & Maintenance - Response Selection - Inhibition - Performance Monitoring <p>Working Memory</p> <ul style="list-style-type: none"> - Active Maintenance - Flexible Updating - Limited Capacity - Interference Control 	<p>Affiliation & Attachment</p> <p>Social Communication</p> <ul style="list-style-type: none"> - Reception of Facial Communication - Production of Facial Communication - Reception of Non-Facial Communication - Production of Non-Facial Communication <p>Perception & Self</p> <ul style="list-style-type: none"> - Agency - Self-Knowledge <p>Perception & Others</p> <ul style="list-style-type: none"> - Animacy Perception - Action Perception - Understanding of Mental States 	<p>Arousal</p> <p>Circadian Rhythms</p> <p>Sleep & Wakefulness</p>

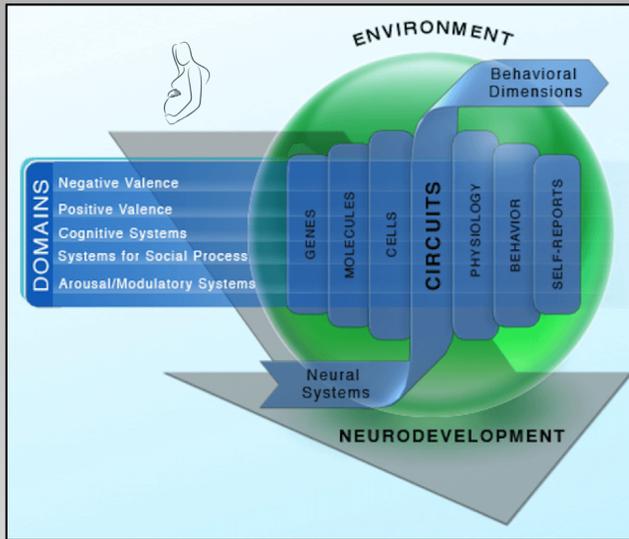




Farmacogenetica en alcohol: Naltrexon

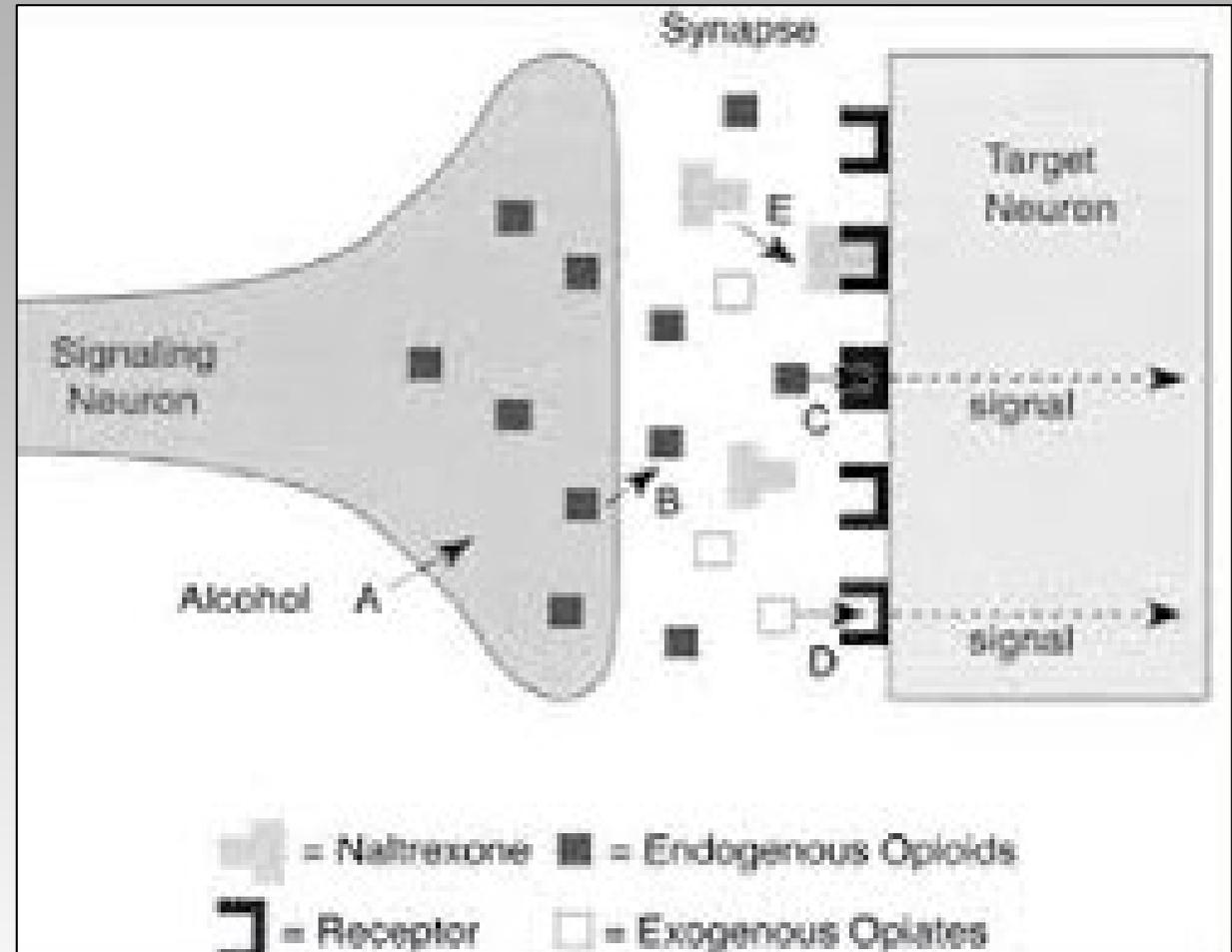


(Oslin et al. Neuropsychopharmacology, 2003)

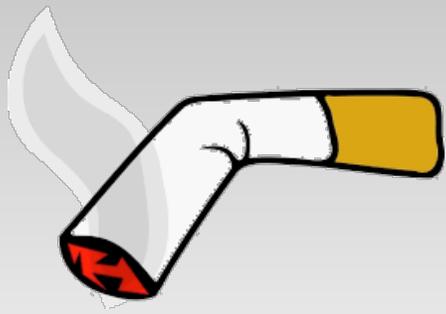
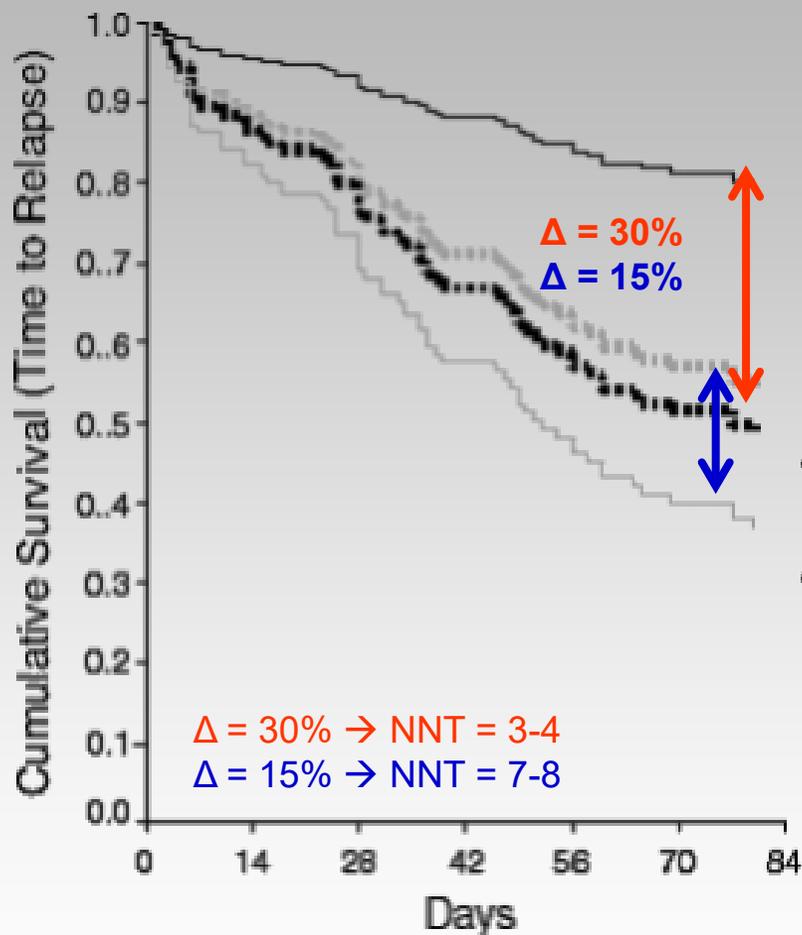


Cost-Effectiveness Analysis of Genotype-Guided Treatment Allocation in Patients with Alcohol Use Disorders Using Naltrexone or Acamprosate, Using a Modeling Approach

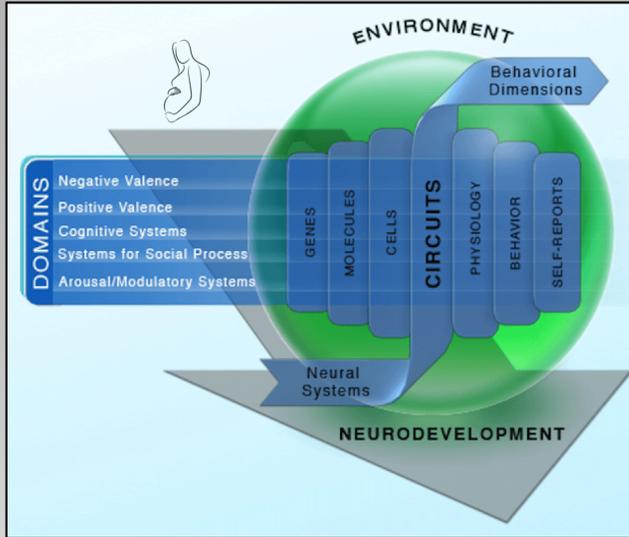
Reinier L. Sluiter^a Wietske Kievit^a Gert Jan van der Wilt^b Aart H. Schene^c
 Martina Teichert^d Marieke J.H. Coenen^e Arnt Schellekens^f



Farmacogenetica

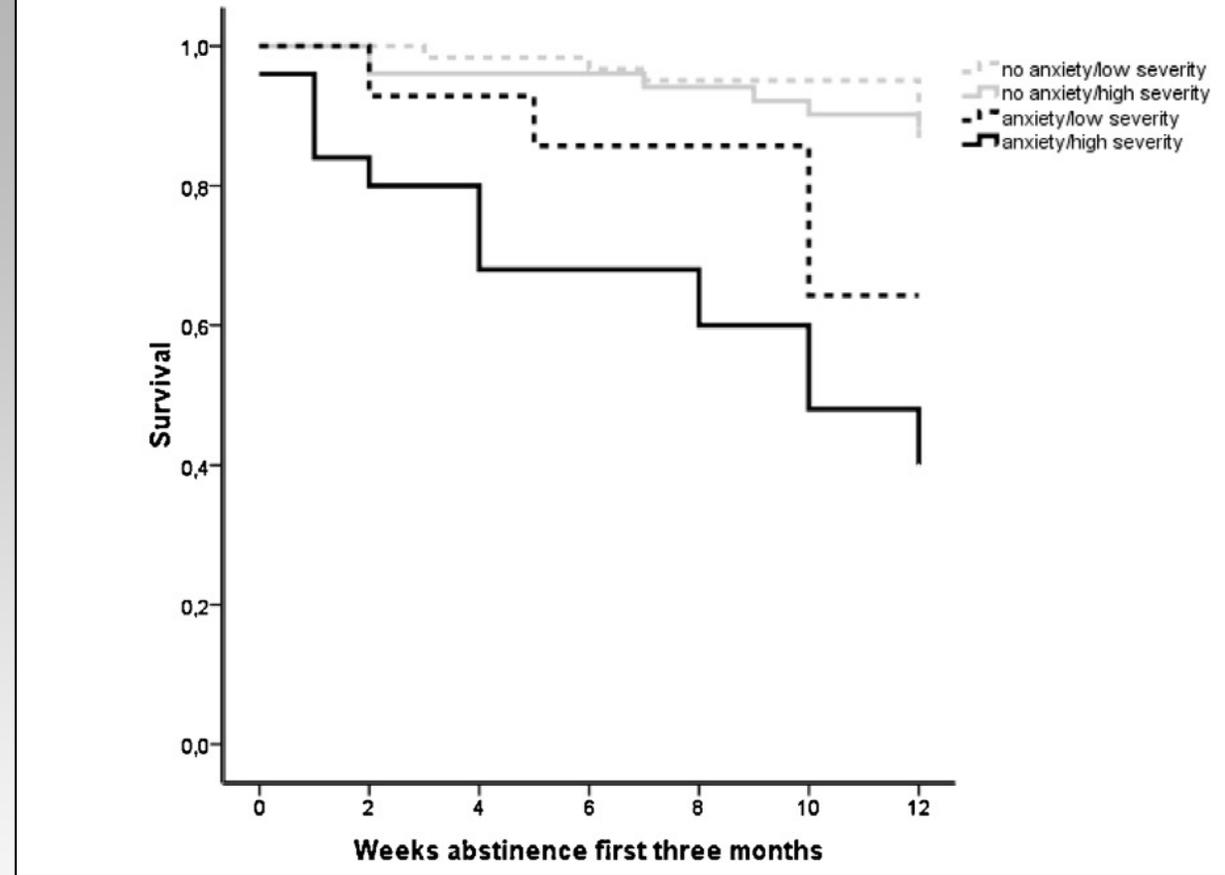


(Oslin et al. Neuropsychopharmacology, 2003)

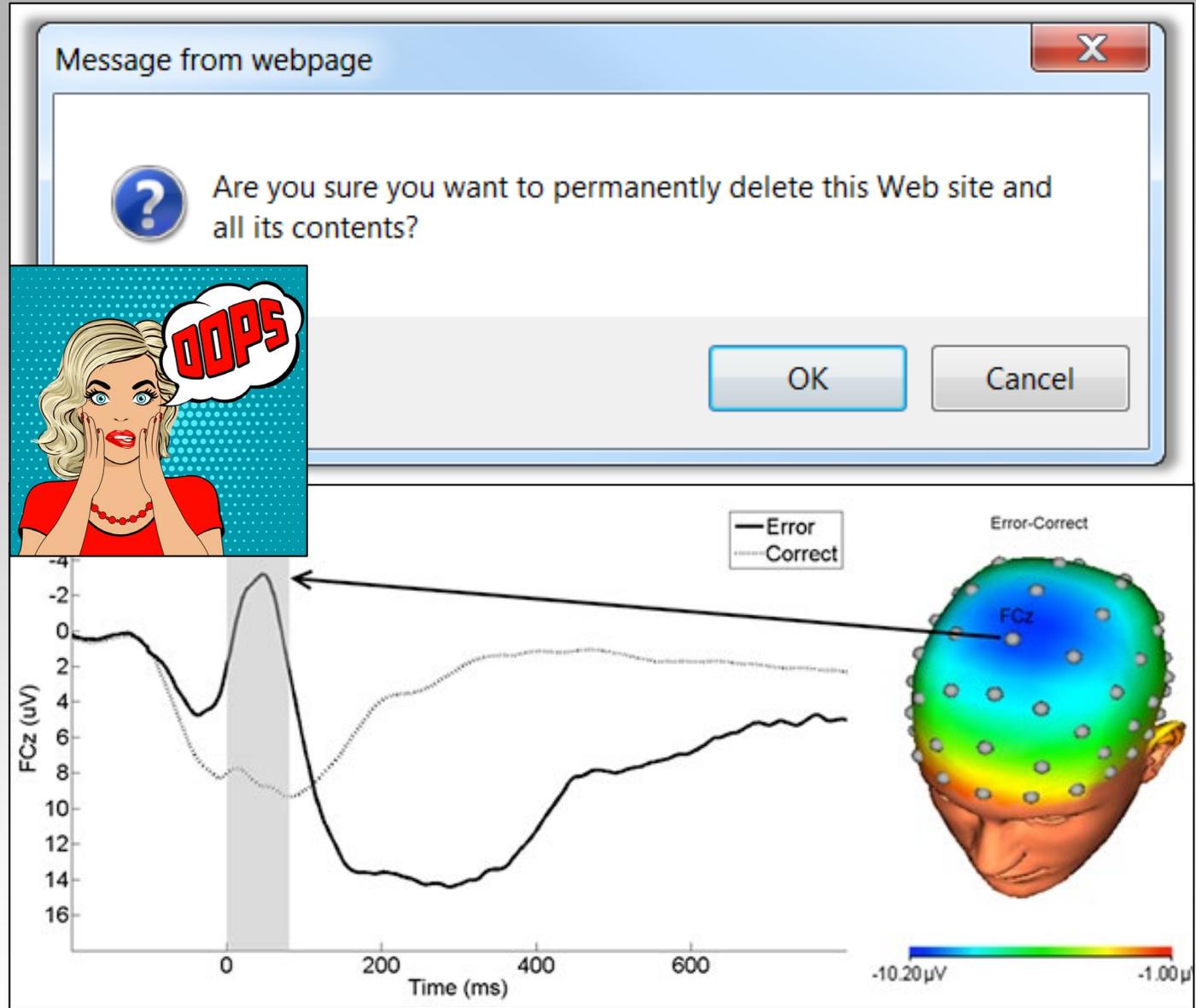
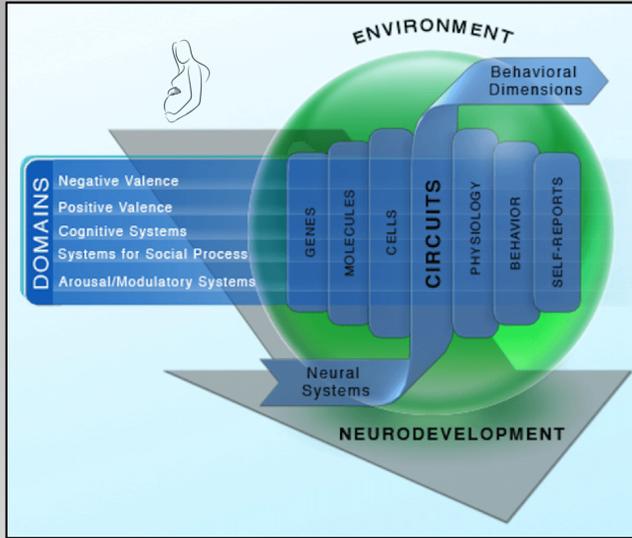


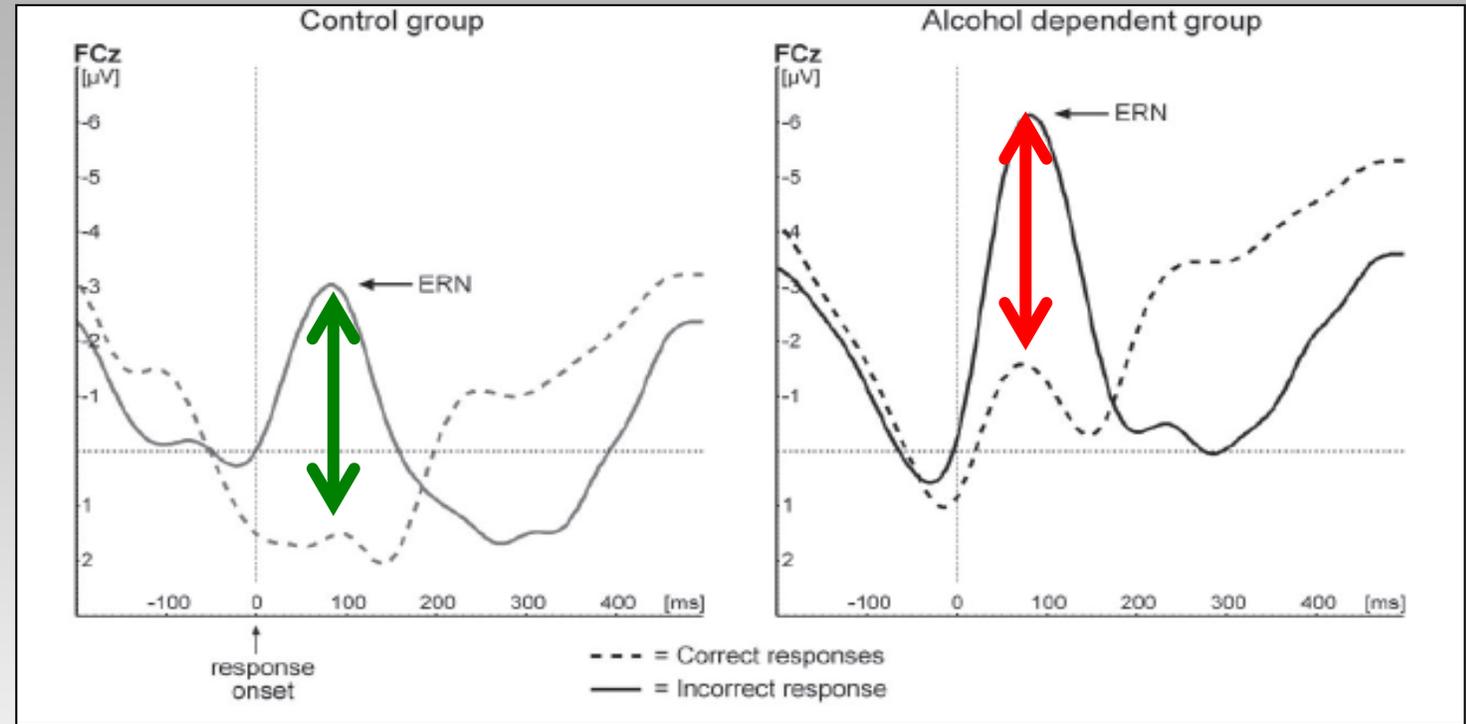
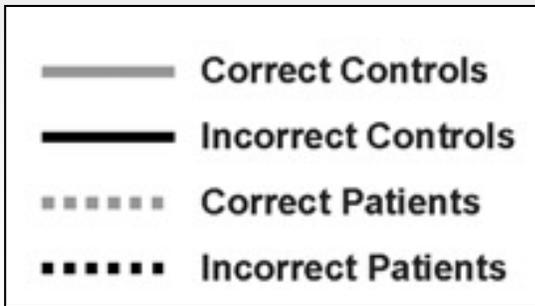
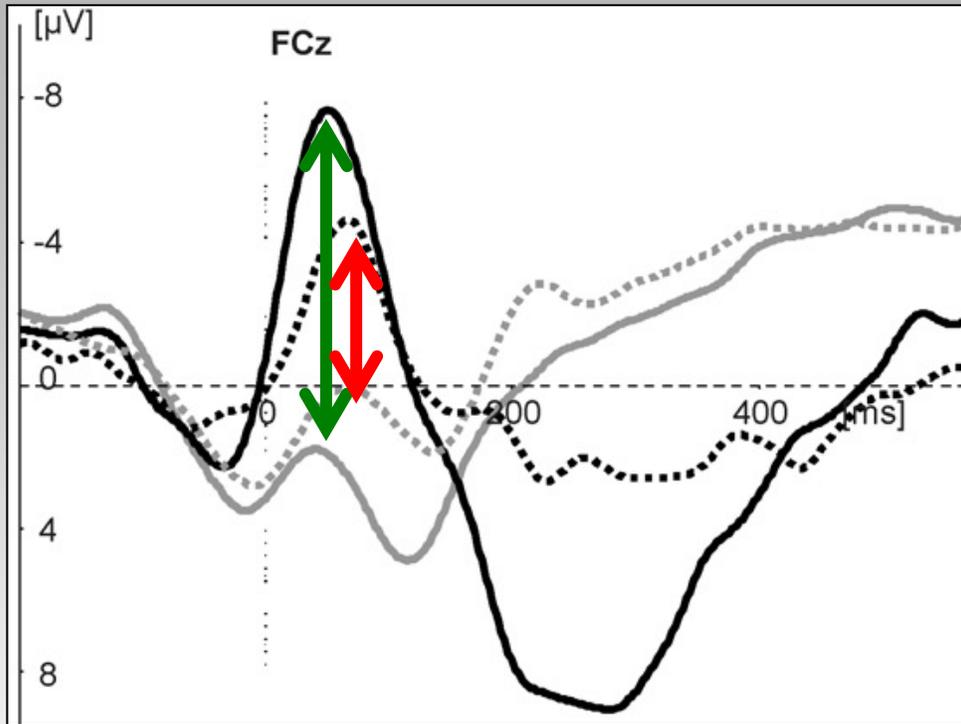
Angststoornissen:
 -30-50%
 -Hoge & snelle terugval

a) Early relapse (i.e. within 1-3 months after detoxification)



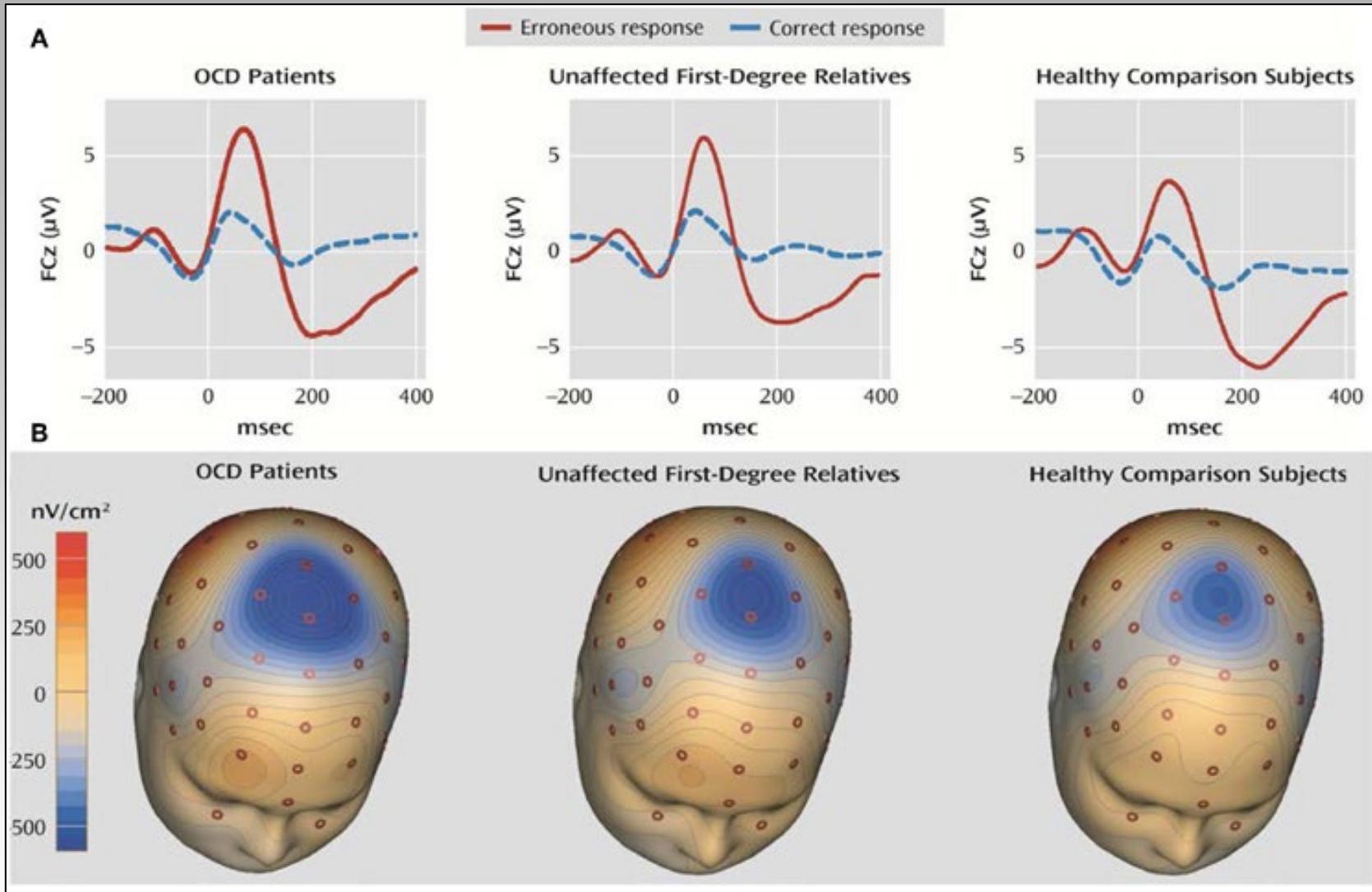
(Schellekens et al. Eur Psychiatry 2015)





(Franken et al. Biological Psychology 2007)

(Schellekens et al. Addiction 2011)



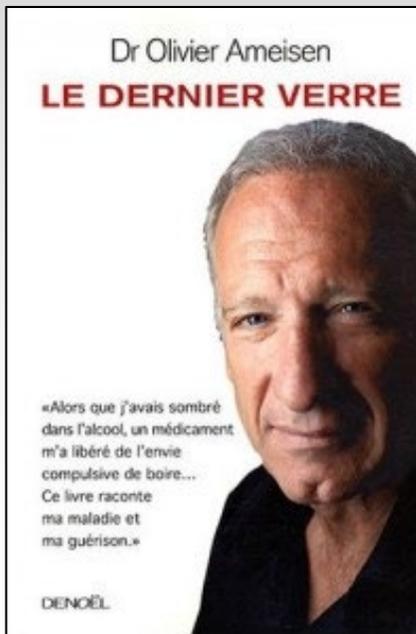
EMDR?
Baclofen?
SSRI?

Meta-analyse baclofen & alcohol

Efficacy, tolerability, and safety of low-dose and high-dose

**baclofen in the treatment of alcohol dependence:
A systematic review and meta-analysis**

Mimi Pierce, Arjen Sutterland, Esther Beraha, Kirsten Morley,
Wim van den Brink



Meta-analyse baclofen & alcohol

-13 RCTs baclofen vs placebo

-Lage dosering (<60mg): n=7; Hoge dosering (>60mg): n=4; LD en HD: n=2

-Uitkomsten

* TTL = Time To Lapse (n=8; N=852)

* PDA = Percent Days Abstinence (n=7; N=457)

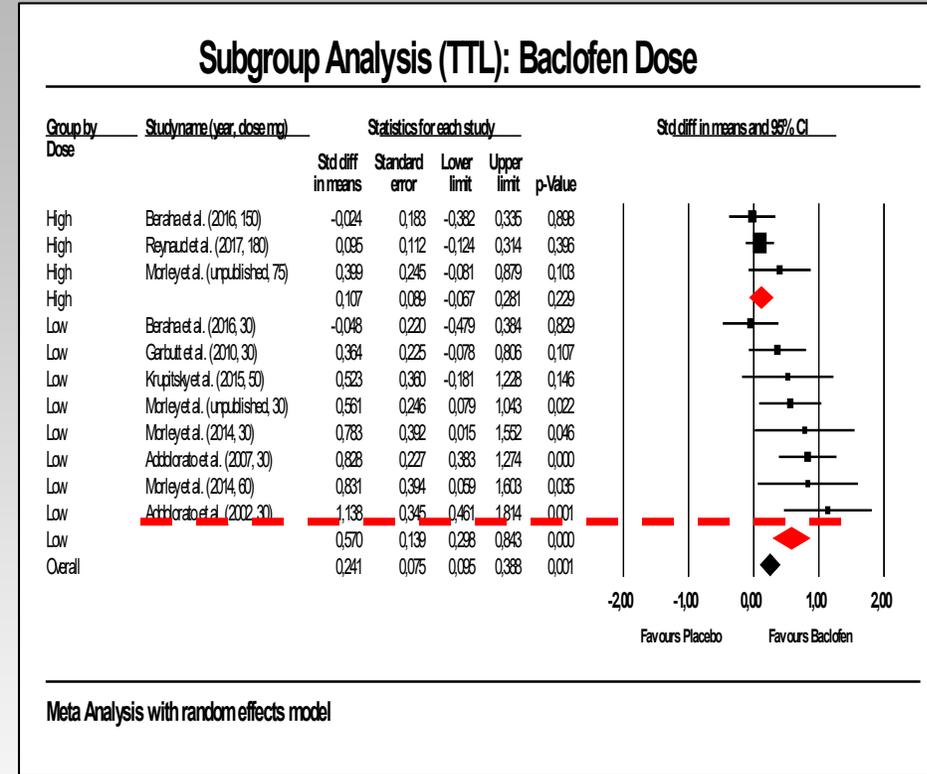
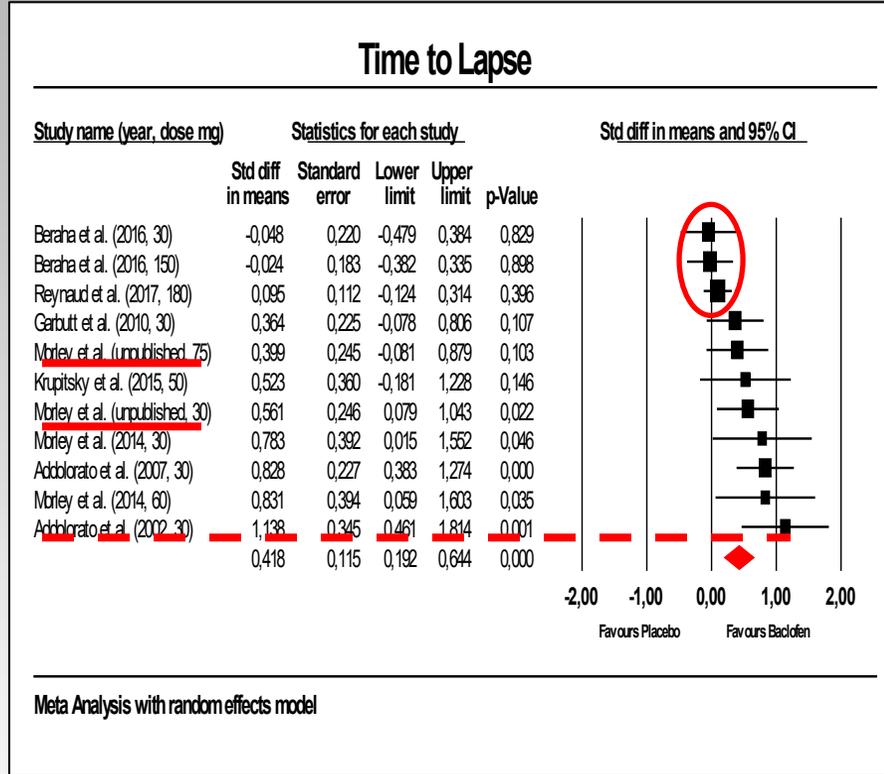
* PAE = Percent Abstinent at Endpoint (m=8; N=1244)

-Statistiek

* Random effect model met evaluatie over hele studieperiode

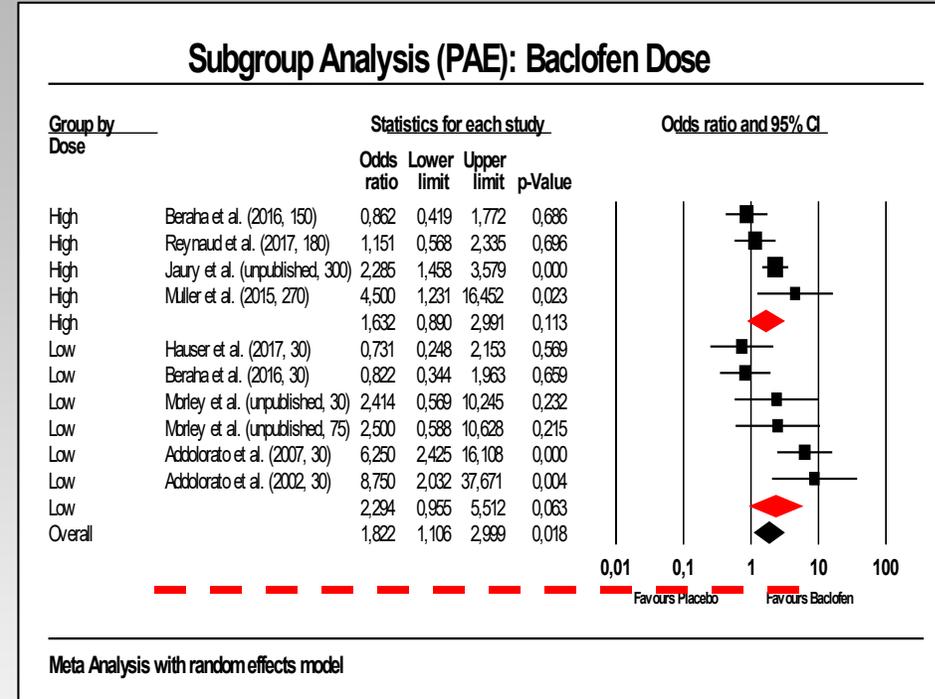
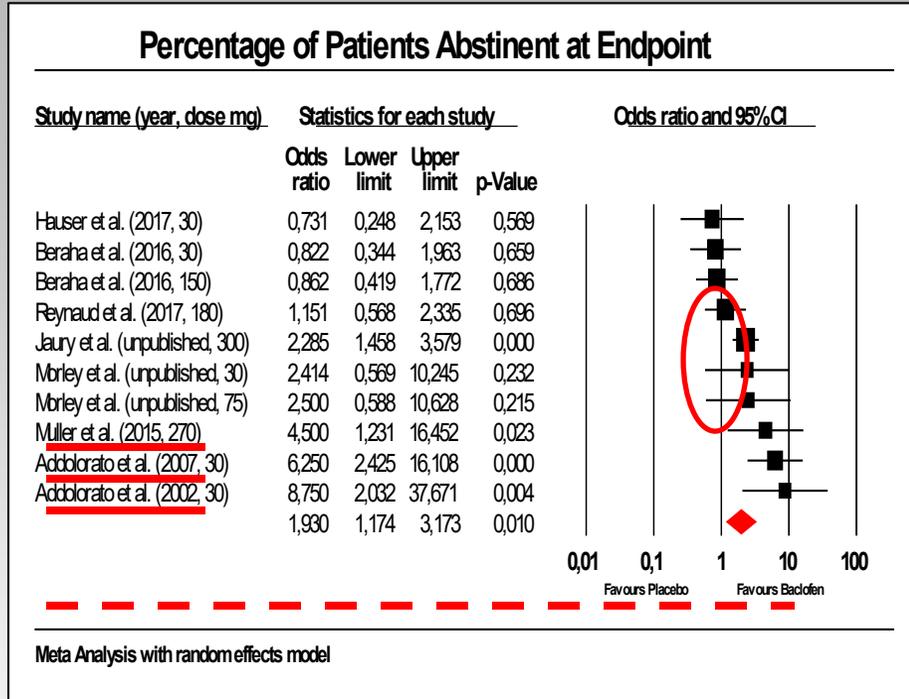
* Stratificatie voor dosis; meta-regressie voor alcoholgebruik bij intake

Effect op TTL (vooral lage dosis)



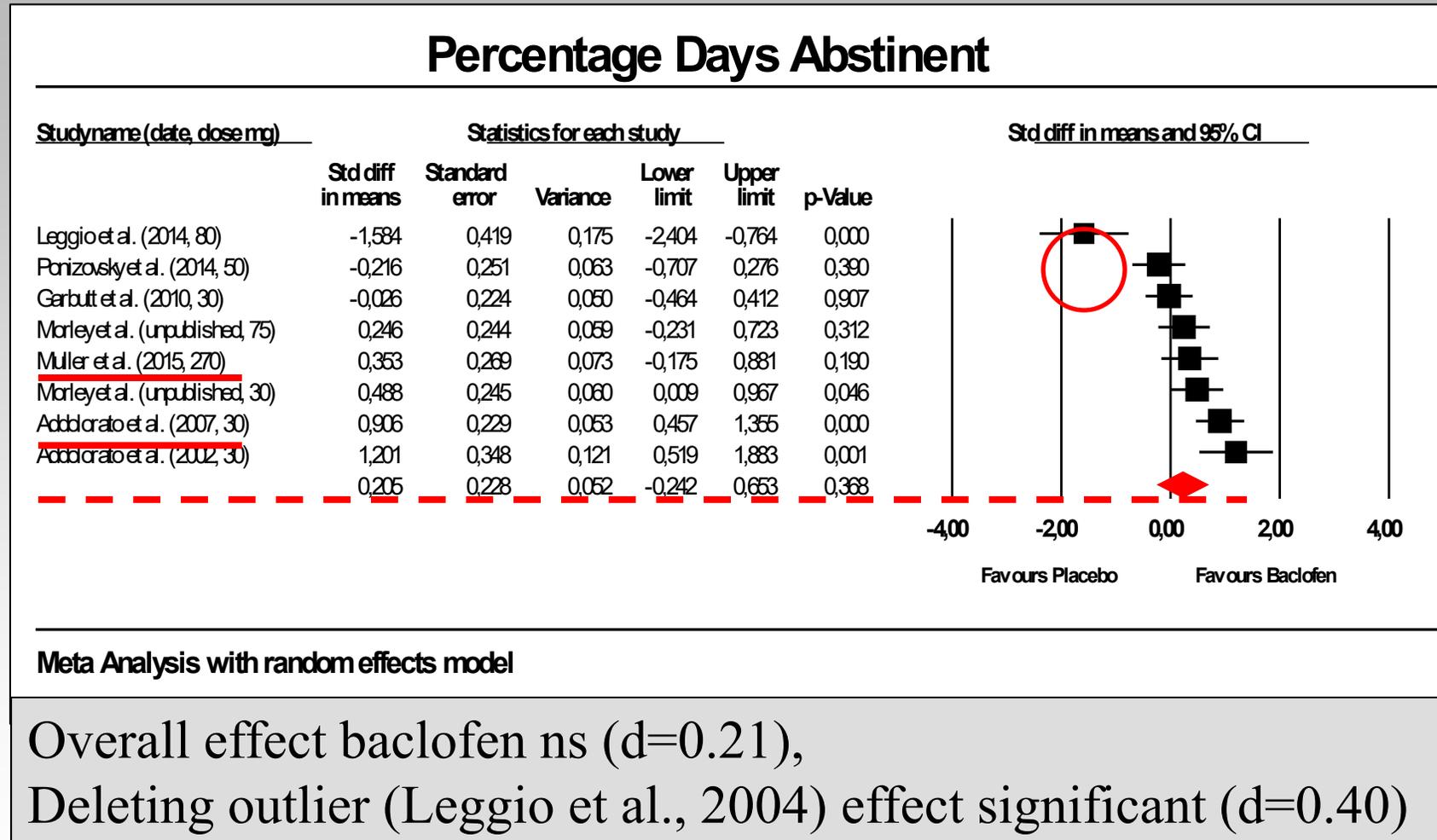
Overall significant effect baclofen (d=.42)
 HD effect ns (d=.11);
 LD effect significant (d=.57)

Effect op PAE (vooral lage dosis)



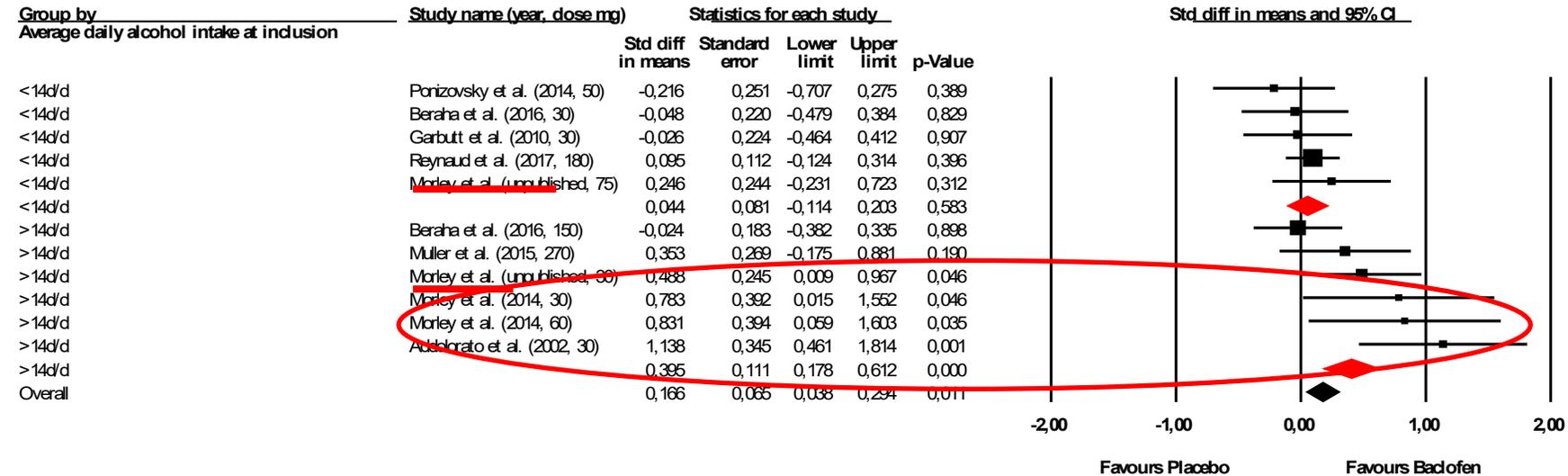
Overall significant effect of baclofen (OR=1.93)
 HD effect ns (OR=1.63);
 LD effect significant (OR=2.29)

Geen effect PDA



Effect vooral bij heavy drinkers

Subgroup Analysis: Average Daily Alcohol Intake at Inclusion

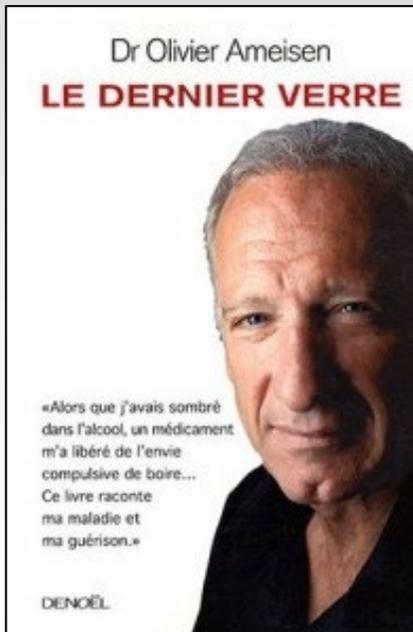


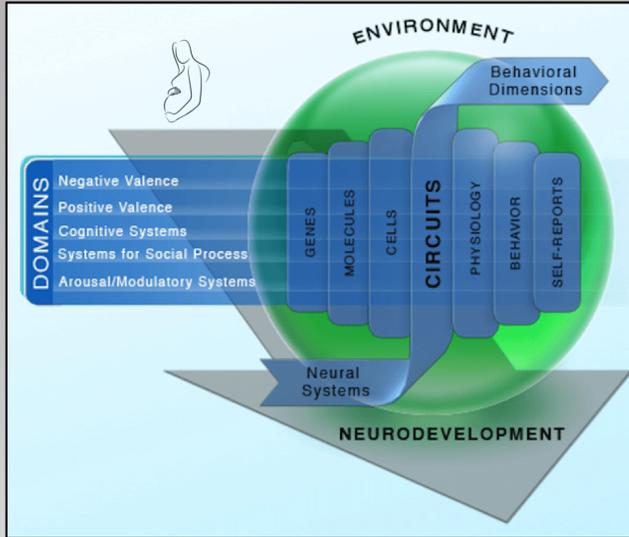
Meta Analysis with random effects model

Significant effect baclofen only in studies >14 U/day at baseline
(d=0.04 (ns) vs. d=0.40)

Baclofen en stress related disorders?

- Discussie baclofen ongoing: heterogeniteit!
- Suggestie dat baclofen vooral zou werken bij comorbide depressie comorbide angst
- Dier studie laat effect zien van baclofen op stress conditioned place preference cortisol response
- Baclofen vooral substitutie en geen anti-craving





Profileren van Verslaving

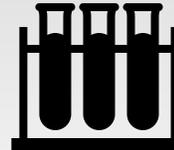
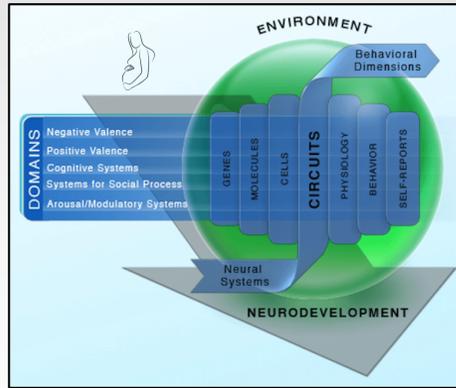
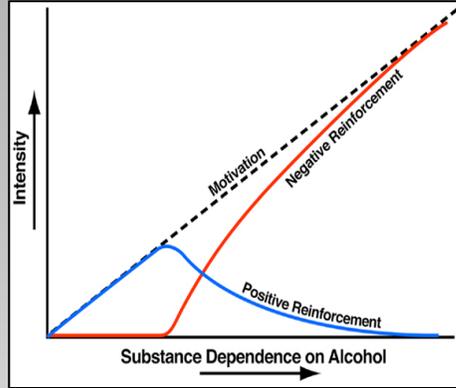
-Profiling: verschillende mechanismen
 Verslaving: fam Hx, age of onset
 Co-morbiditeit, psychologische factoren

-Anamnese (craving), biomarkers, testen?

-Consequenties:

psychotherapie vb CM vs EMDR?

farmacotherapie vb Naltrexon en baclofen



Conclusies



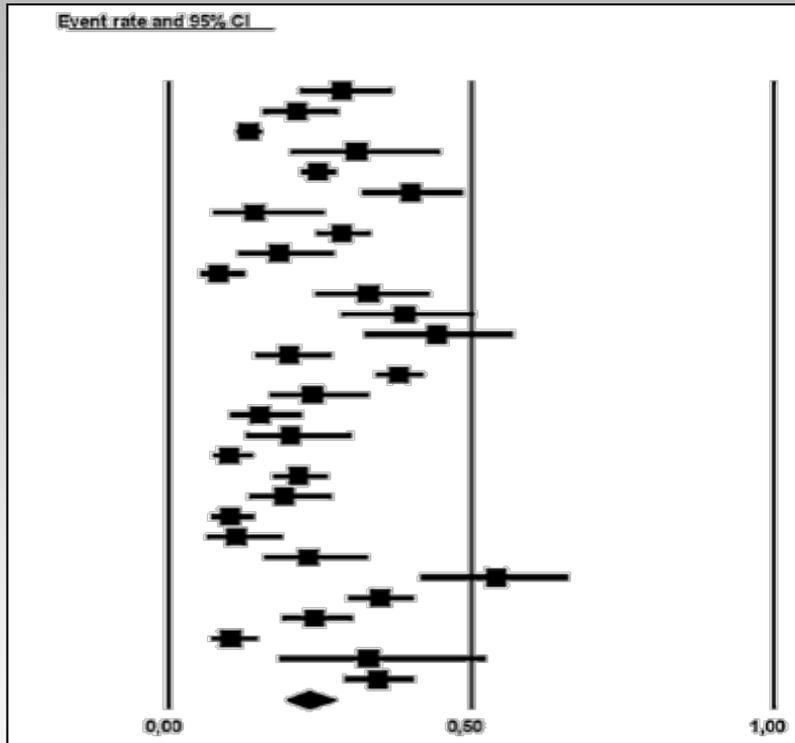
- Verslaving is heterogene aandoening (bij uitstek)
- Gepersonaliseerde benadering
 - Biomarkers
 - Psychomarkers
 - Sociomarkers
- Farmacotherapie, psychotherapie, sociaal-maatschappelijk, behandeldoelen

Op zoek naar de graal...!

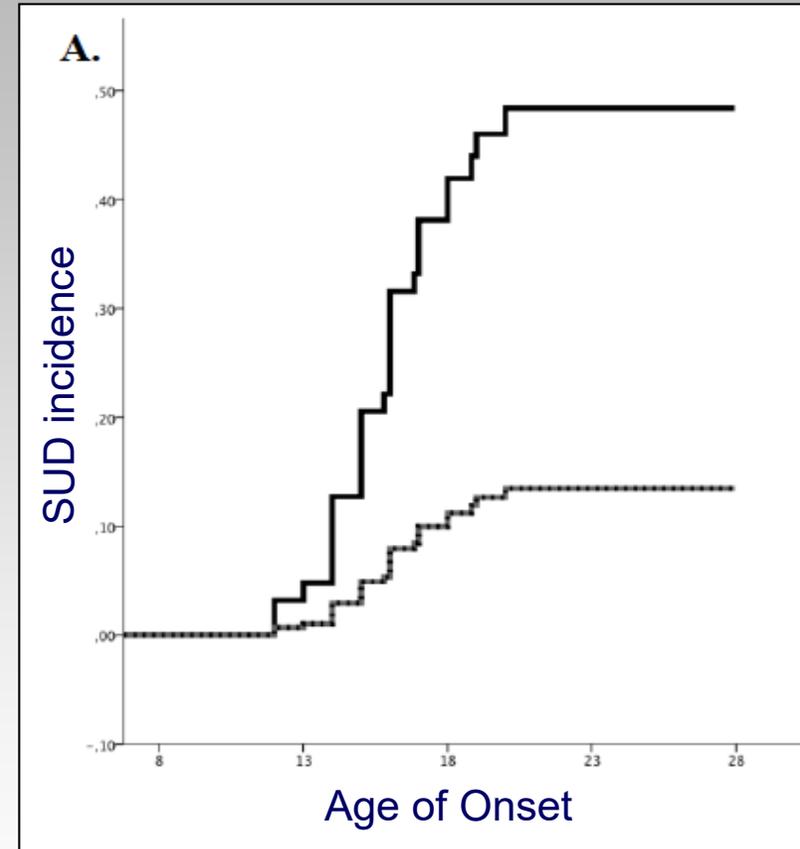
Arnt Schellekens
Psychiater Radboudumc, PI Donders Institute
Wetenschappelijk Directeur NISPA



Epidemiology



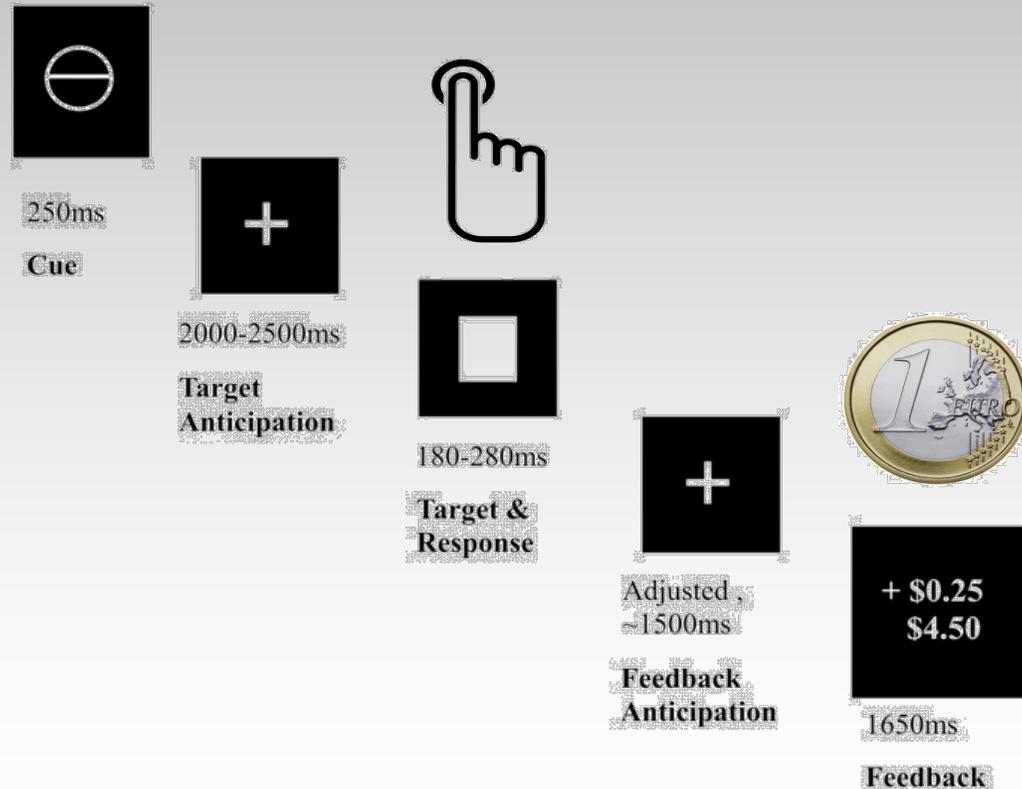
± 25
%



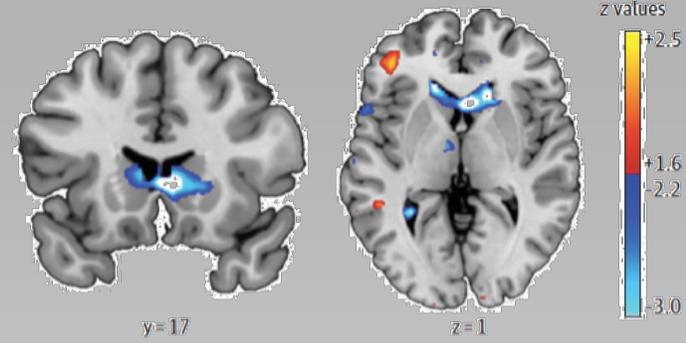
Disruption of Reward Processing in Addiction

An Image-Based Meta-analysis of Functional Magnetic Resonance Imaging Studies

Maartje Luijten, PhD; Arnt F. Schellekens, MD, PhD; Simone Kühn, PhD; Marise W. J. Machielse, MD, PhD; Guillaume Sescousse, PhD



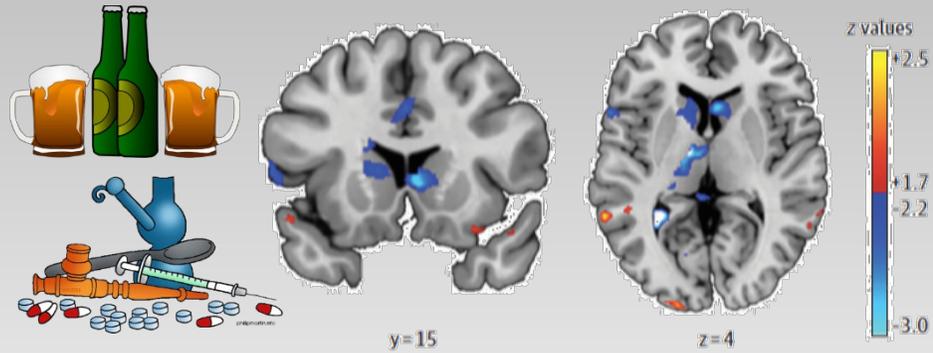
All addicted vs controls



y=17

z=1

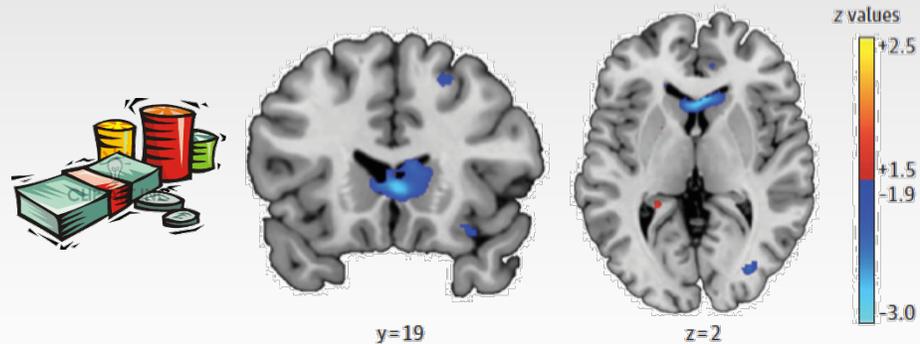
Substance addicted vs controls



y=15

z=4

Gambling addicted vs controls

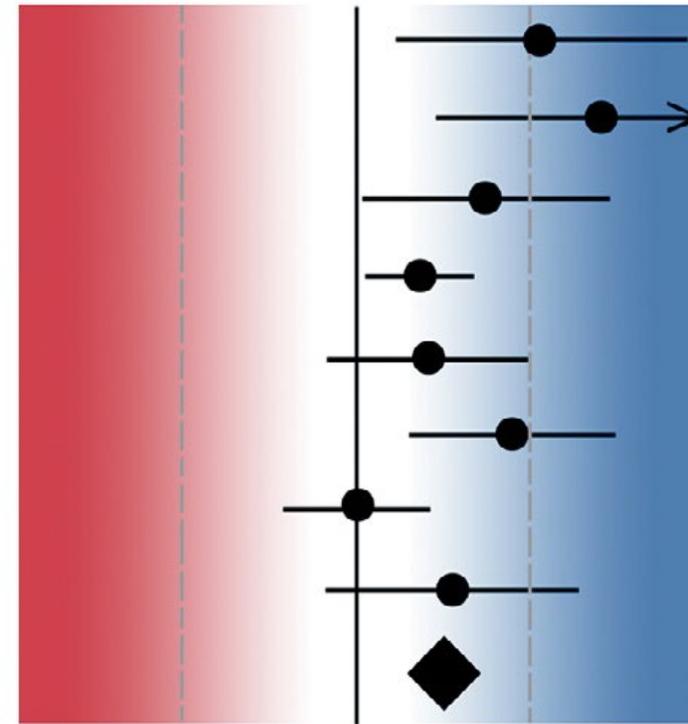


y=19

z=2

Std diff in means and 90% CI

-2.0 0.0 2.0

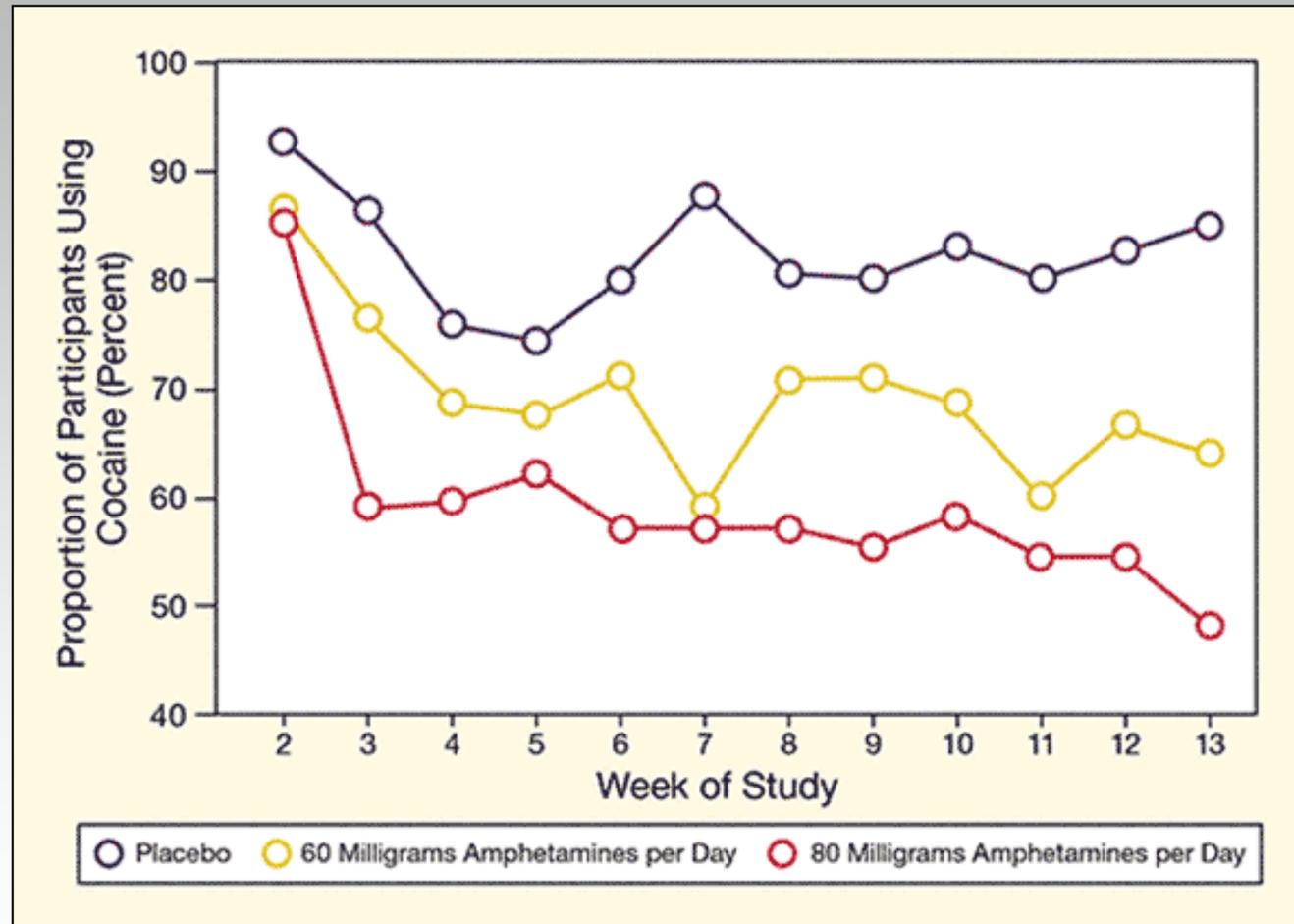


“HYPER”

“HYPO”

VS-Responsiveness
ADHD vs. Healthy

Clinical Case



Study	Sample size	Medication and maximum dose	SUD type	Duration (weeks)
Schubiner et al. (2002) ²⁴	48	Methylphenidate IR 3 × 30 mg	Cocaine	12
Carpentier et al. (2005) ²⁵	25	Methylphenidate IR 3 × 15 mg	Various ^c	8
Levin et al. (2006) ²⁶	98	Methylphenidate SR 2 × 20–40 mg Bupropion 400 mg	Opioid	12
Levin et al. (2007) ²⁹	106	Methylphenidate SR 40 + 20 mg	Cocaine	14
Konstenius et al. (2010) ³⁰	24	Methylphenidate (OROS) 72 mg	Amphetamine	12
Winhusen et al. (2010) ³⁴	255	Methylphenidate (OROS) 72 mg	Nicotine	11
Riggs et al. (2011) ³¹	308	Methylphenidate (OROS) 72 mg	Various ^c	16
Konstenius et al. (2014) ³⁰	54	Methylphenidate (OROS) 180 mg	Amphetamine	24
Levin et al. (2015) ³⁸	126	Amphetamine (MAS) 60 or 80 mg	Cocaine	13
Kollins et al. (2014) ³⁹	32	Lisdexamfetamine 70 mg	Nicotine	4
Wilens et al. (2008) ⁴⁰	147	Atomoxetine 25–100 mg	Alcohol	12
Thurstone et al. (2010) ⁴¹	70	Atomoxetine 25–100 mg	Various ^c	12
McRae-Clark et al. (2010) ⁴²	38	Atomoxetine 100 mg	Marijuana	12
Riggs et al. (2004) ⁴⁵	69	Penolide 75–112.5 mg	Various ^c	12

Effect on ADHD ^b	Effect on SUD ^b
+	0
0	Not evaluated
0	0
0	0(+)
0	0
++	0
0(+)	0(+)
+	+
++	++
++	0
++	0(+)
0	0
+	0
+	0

Measure	CBT/Integrated			Cohen's d (baseline to post-treatment) within treatment group)
	Baseline mean (SD)	Post-treatment mean (SD)	Follow-up mean (SD)	
<i>Primary outcome</i> ARS total score	N = 60 35.65 (9.30)	N = 48 28.09 (9.01)	N = 39 28.47 (8.37)	.83
<i>Secondary outcomes</i> TLFB (days of excessive use in prior week)	N = 60 1.47 (3.64)	N = 48 0.28 (0.70)	N = 39 0.51 (1.04)	.45

Measure	CBT/SUD			Cohen's d (baseline to post-treatment) within treatment group)	P values Post treatment (between treatment groups)
	Baseline mean (SD)	Post-treatment mean (SD)	Follow-up mean (SD)		
<i>Primary outcome</i> ARS total score	N = 59 36.78 (10.98)	N = 46 31.54 (11.39)	N = 39 31.29 (10.37)	.47	.030
<i>Secondary outcomes</i> TLFB (days of excessive use in prior week)	N = 59 2.06 (5.30)	N = 46 0.40 (0.95)	N = 39 0.60 (1.24)	.44	.453

International Consensus Statement on Screening, Diagnosis and Treatment of Substance Use Disorder Patients with Comorbid Attention Deficit/Hyperactivity Disorder

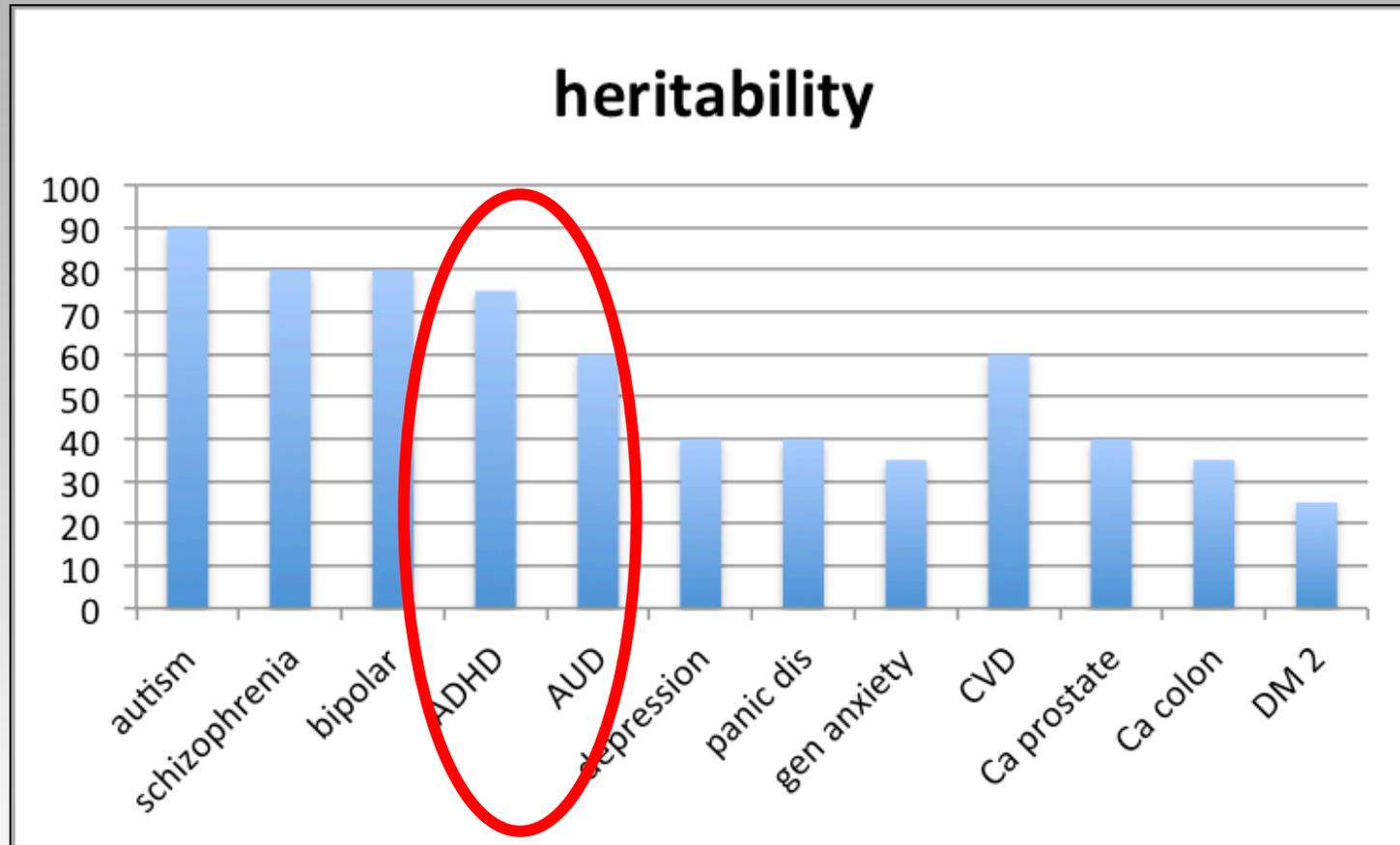
Cleo L. Crunelle^{a,b} Wim van den Brink^c Franz Moggi^d
Maija Konstenius^e Johan Franck^e Frances R. Levin^f Geurt van de Glind^g
Zsolt Demetrovics^h Corné Coetzeeⁱ Mathias Luderer^j Arnt Schellekens^k
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International Consensus Statement on Screening, Diagnosis and Treatment of Substance Use Disorder Patients with Comorbid Attention Deficit/Hyperactivity Disorder

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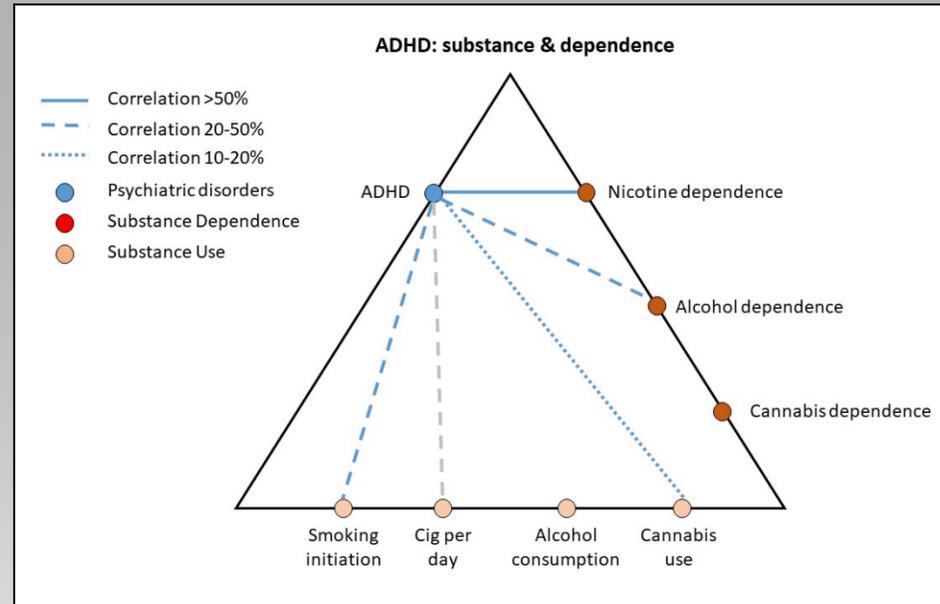
- **Early onset SU(D)**
- **More severe course**
- **Treatment resistance**
- **Poor QoL**
- **Increased co-morbidity**

- **Early diagnosis**
- **Non-Stimulant treatment**
- **Robust Dose stimulants**
- **Non-pharmacological treatment**



Relating addiction and psychiatric disorders

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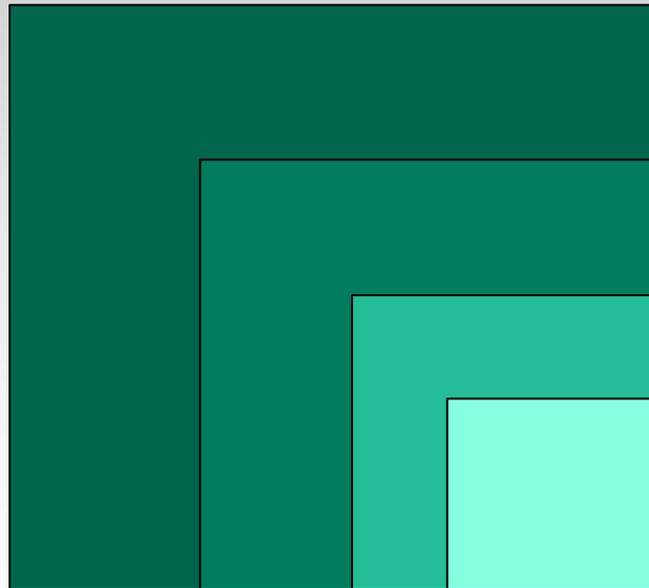
		ADHD	MDD	Schizophrenia	Bipolar disorder	Autism spectrum	Anorexia Nervosa
	N	20,183/ 35,191	59,851/ 113,154	36,989/ 54,065	20,129/ 27,969	18,381/ 27,969	3,495/ 10,982
Nicotine dependence	38,602	.53 (.07) 1.85×10^{-13}	.42 (.06) 3.6×10^{-11}	.18 (.05) 1.1×10^{-3}	.13 (.06) 2.17×10^{-2}	.08 (.10) 4.43×10^{-1}	.02 (.06) 7.2×10^{-1}
Alcohol Dependence [§]	141,958	.44 (.10) 4.21×10^{-6}	.57 (.16) 3.00×10^{-4}	.36 (.05) 3.24×10^{-11}	.19 (.10) 4.76×10^{21}	-.08 (.13) 5.47×10^{-1}	.03 (.13) 8.08×10^{-1}
Smoking initiation [#]	74,035	.37 (.08) 3.14×10^{-6}	.33 (.05) 3.10×10^{-11}	.11 (.04) 6.5×10^{-3}	.13 (.05) 6.8×10^{-3}	.06 (.08) 4.54×10^{-1}	-.05 (.08) 6.01×10^{-1}
Cigarettes per day [#]	38,181	.38 (.11) 5.00×10^{-4}	.12 (.08) 1.60×10^{-1}	.12 (.05) 3.20×10^{-2}	.21 (.07) 6.1×10^{-3}	-.03 (.11) 8.21×10^{-1}	-.14 (.14) 3.18×10^{-1}
Lifetime cannabis use [*]	53,179/ 131,586	.16 (.04) 1.50×10^{-4}	.21 (.08) 5.99×10^{-3}	.24 (.03) 5.81×10^{-15}	.29 (.06) 7.06×10^{-8}	.23 (.06) 9.03×10^{-5}	.11 (.06) 8.01×10^{-2}

Clinical Case

- ♂ 25 yrs
- *Reason: detoxification phenibut (35g/day)*
 - *Anxiolytic (1.5g/day)*
- *Psychiatric Hx:*
 - *SUD: GHB & cocaine*
 - *OCD & suspicion ADHD*
- *Family Hx:*
 - *SUD: alcohol*
 - *OCD & ADHD*

Clinical Case

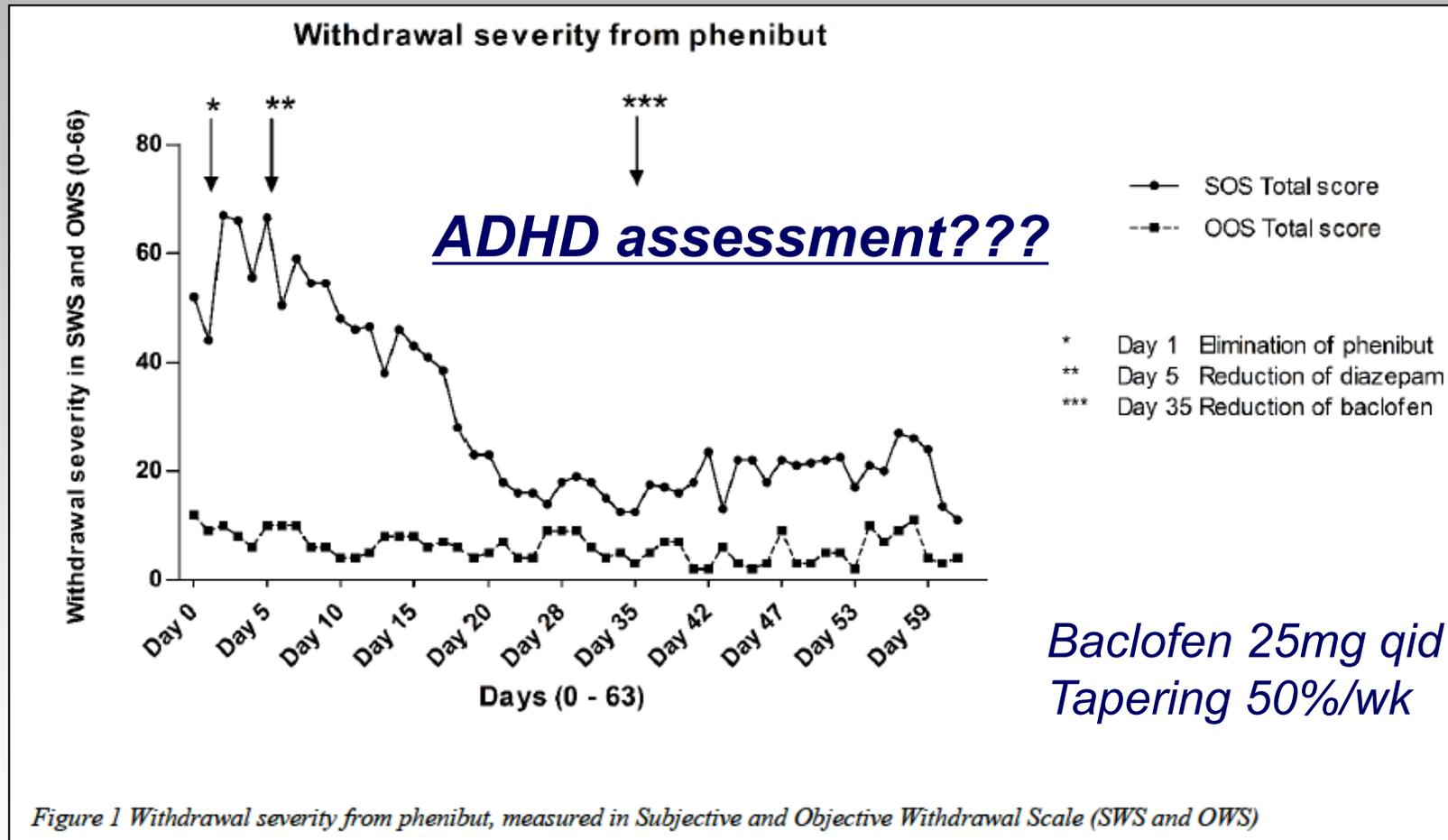
Number of comorbid conditions ^a	No comorbid disorder n (%)	One comorbid disorder n (%)	Two comorbid disorders n (%)	Three comorbid disorders ^c n (%)	Four comorbid disorders ^c n (%)
In patients without ADHD (n= 1037)	653 (63.0)	272 (26.2)	82 (7.9)	26 (2.5)	4 (0.4)
In patients with ADHD (n= 168)	42 (25.0)	68 (40.5)	39 (23.2)	10 (6.0)	9 (5.4)



SUD: $\eta=1,5$
ADHD+SUD: $\eta=3,3$

50% rule of comorbidity

Clinical Case



Clinical Case

- *Screeners*

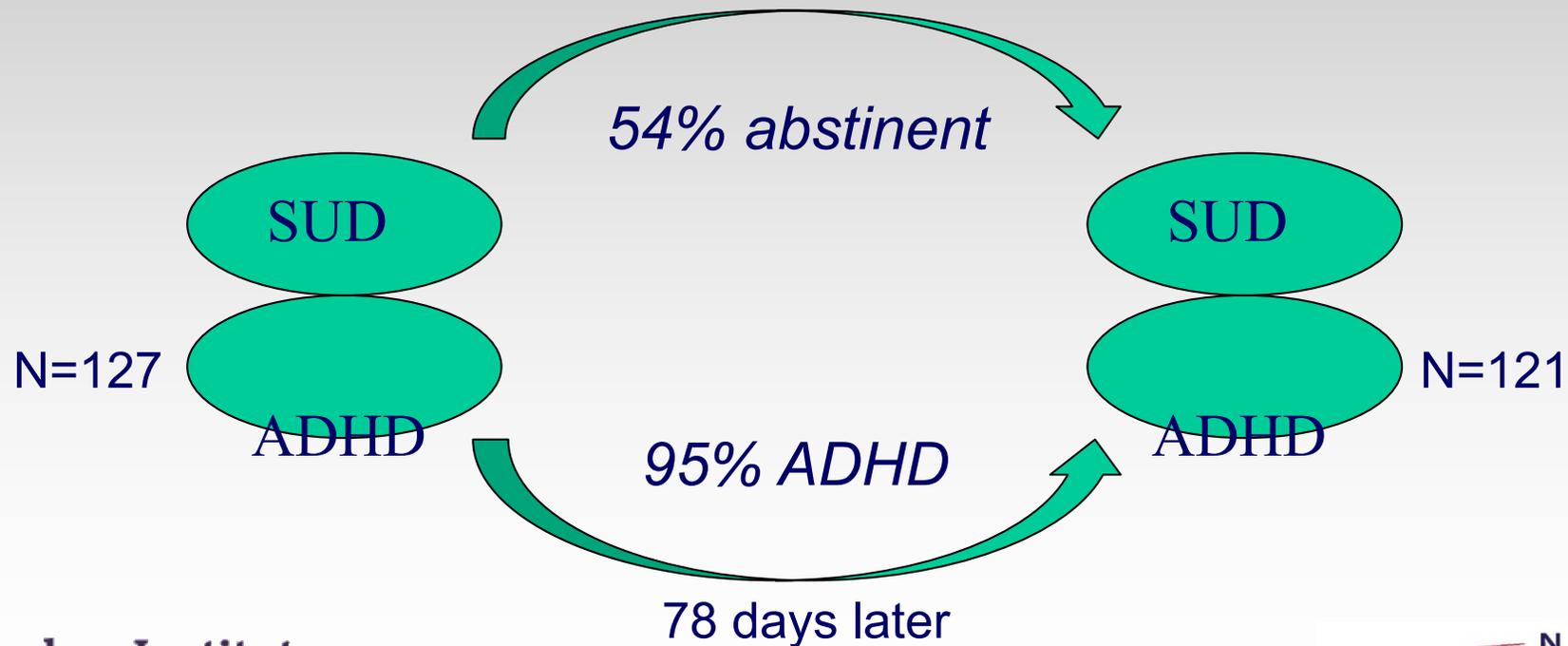
Table 1. Tools for screening ADHD in individuals with comorbid SUD

ADHD screening tool	ASRS-SV	WURS	CAARS	ADSA
Number of items	6	61	26*	54
Time to fill in	<2 min	<15 min	<8 min	<12 min
Considered in populations with SUD (yes/no)	Yes	Yes	Yes	Yes
Sensitivity, range	67–100% ^{a-f}	80–93% ^{e, f}	94% ^f	58–71% ^g
Specificity, range	66–82% ^{a-f}	60–70% ^{e, f}	86% ^f	94–82% ^g
Sensitivity if combined	+WURS: 57–92% ^{e, f} +CAARS: 67% ^f	+ASRS: 57–92% ^{e, f}	+ASRS: 67% ^f +WURS: 87% ^f	
Specificity if combined	+WURS: 91% ^f +CAARS: 92% ^f	+ASRS: 91% ^f	+ASRS: 92% ^f +WURS: 90% ^f	

- *Consider lower cut-off (ASRS: 11; CAARS: 60)*

Clinical Case

- *Structured Interviews*
 - *Conner's Adult ADHD Diagnostic Interview (CAADID)*
 - *Diagnostic InterView for ADHD in adults (DIVA)*
 - *Psychiatric Research Interview Subst/Ment dis (PRISM)*



Clinical Case

- *Collatoral Information (parents. school reports, etc)*
 - *Current/childhood Sx*
 - *Family Hx*
 - *School & Occupation*
 - *Social function*
 - *Physical exam*

- *Continuous proces over time*
 - *Check severe withdrawal*
 - *Check severe intoxication*

Clinical Case

Treatment

Consider adequate medical treatment of both ADHD and SUD.

Always consider a combination of psychotherapy and pharmacotherapy.

Integrate the ADHD and other psychiatric comorbidity treatment with SUD treatment as soon as possible.

Psychotherapy, preferentially targeting the combination of ADHD and SUD, should be considered.

Long-acting methylphenidate, extended-release amphetamines, and atomoxetine are effective in the treatment of comorbid ADHD and SUD, and up-titration to higher dosages may be considered in some patients. The abuse potential is limited with long-acting agents.

Caution and careful clinical management is needed to prevent abuse and diversion of prescribed stimulants.

Clinical Case

- *R/*
 - *Less effective in comorbid SUD*
 - *Bupropion: contradictory findings*
 - *Methylphenidate: contradictory findings*
 - *High dose stimulants: potentially positive*
 - *Methylphenidate up to 180mg*
 - *Mixed Amphetamine (ER) up to 80mg*
 - *Pemoline: potentially positive*
 - *Atomoxetine: potentially positive*
- *Diversion: >adolescents, irregular visits, short acting, etc*

Clinical Case

- *Psychotherapy*
 - *CBT (consider integrated SUD-ADHD CBT)*
 - *Dialectic Behavioral Therapy*
 - *Individual Coaching*
 - *Skills training*
 - *Mindfulness*

- *Evidence is limited!*