Precision Medicine in Addiction: A Bright Future?

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1

Disclosure

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

2

Content

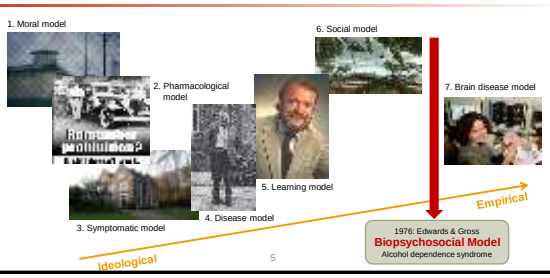
- History of the concept of Addiction
- Addiction (also) a treatable brain disease
- Neurobiological and Psychological Treatments
- Improving efficacy
- Conclusions and recommendations

3

History Concept of Addiction

4

History of the concept of alcoholism



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Addiction – a brain disease

- Genetic vulnerability 50–70%
- Biological risk factors low alcohol response
- Brain abnormalities cue-reactivity (VS; OFC), impulsivity (ACC)
- Effective neurobiological interventions
- Effective neurobiological preventions

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Addiction a Treatable Brain Disease

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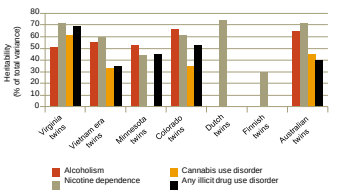
Heritability estimates

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



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

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

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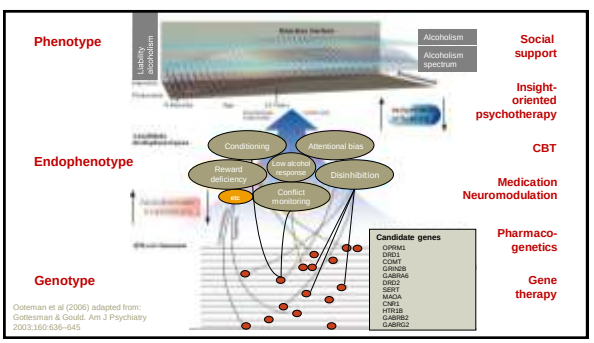


9

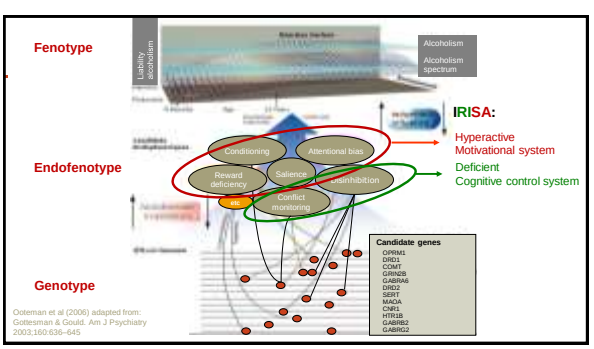
Neurobiology of addiction

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

Naive
Experimenting moderate use
Binging
Abuse
Dependence (craving)
Addiction (compulsive use)

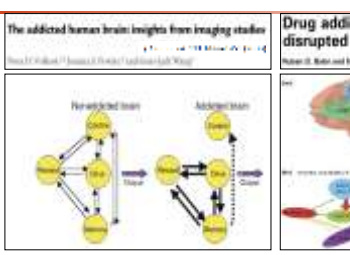
10

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



11

Brain Structures and Functions in Addiction



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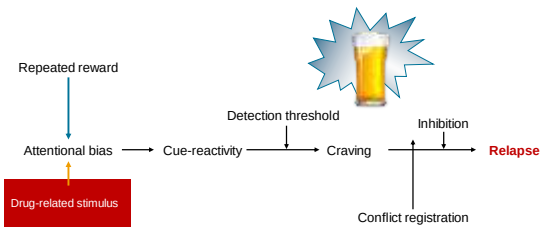
Reward → attentional bias → cue-reactivity → craving - deficient cognitive control - → relapse



13

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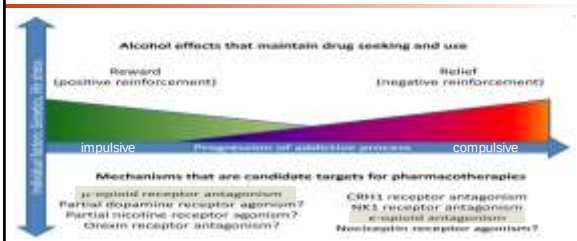
Binging
Abuse
Dependence (craving)
Addiction (compulsive use)

14

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

14

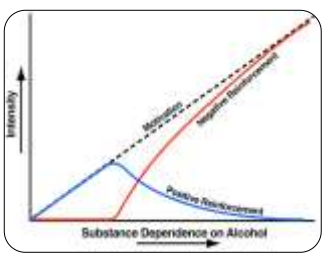
From reward to relief and from impulsive to compulsive



Adapted from Heilig et al., 2010

15

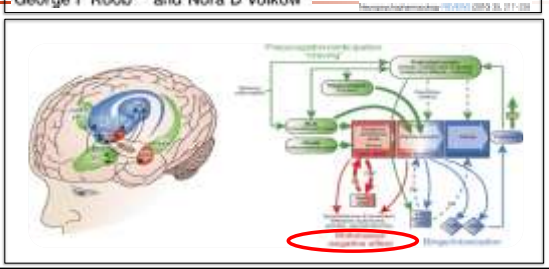
Dark side of addiction: addiction and stress



16

Neurocircuitry of Addiction

George F Koob*,[1] and Nora D Volkow[2]



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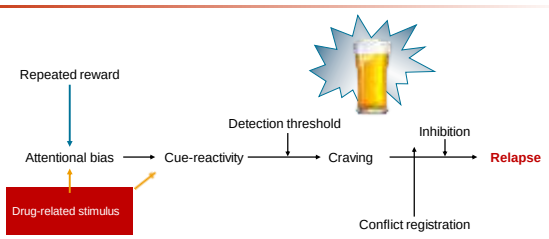
Reward → attentional bias → cue-reactivity → craving - deficient cognitive control - → relapse



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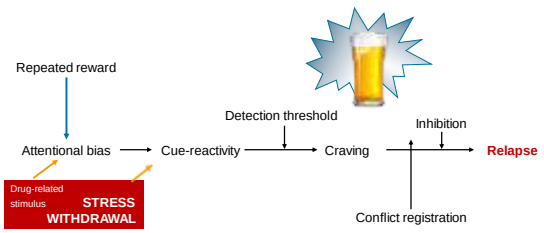
Reward → attentional bias → cue-reactivity → craving - deficient cognitive control - → relapse

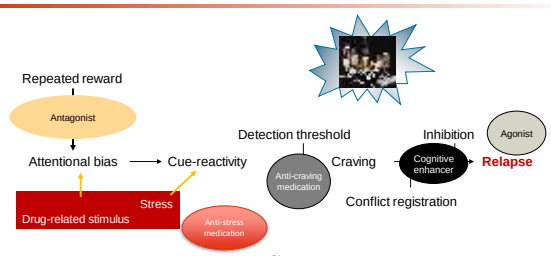


19

Conceptual Treatment Models
Pharmacological Tx

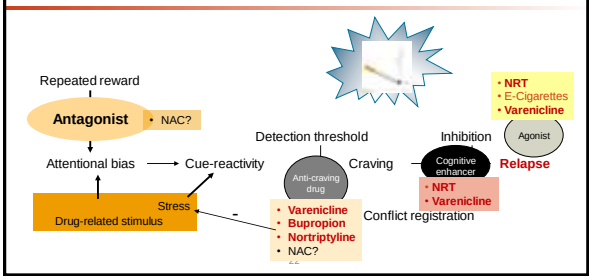
20

Model for Pharmacotherapy of Addiction



21

Pharmacotherapy of Nicotine Dependence



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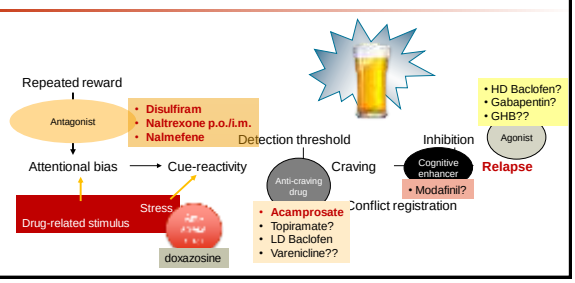
Pharmacotherapy Alcohol Use Disorder



23

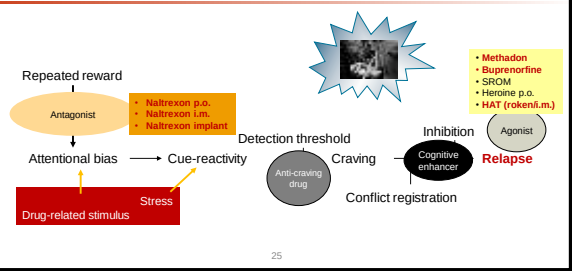
Effective Pharmacotherapy Alcohol Dependence

Treatment Goal	1st Choice	2nd Choice	3rd Choice
Abstinence	Acamprosate (NNT=11) Naltrexon?? (NNT=20)	Disulfiram (NNT=25; NS)*	LD Baclofen?? Gabapentin? (GHB??)
Reduced Drinking	Naltrexon# (NNT=11)	Topiramaat?	Modafinil?? Varenicline?? HD Baclofen?? Doxasozine??

* no supervision
# off-label

24

Pharmacotherapy of Opioid Use Disorder



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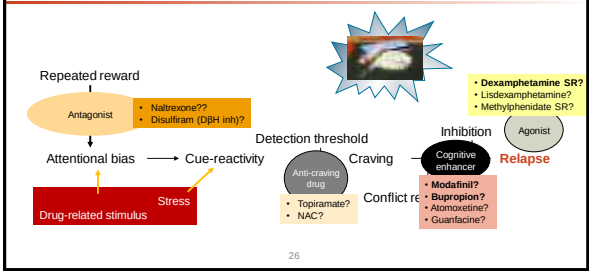
25

Pharmacotherapy of Cocaine Use Disorder



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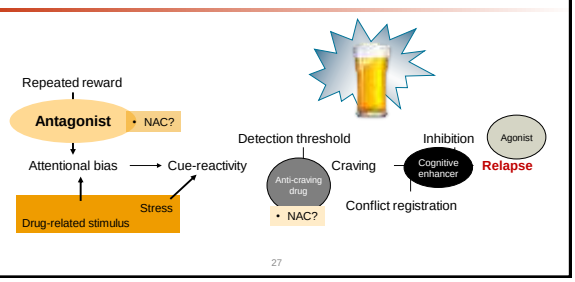
26

Pharmacotherapy of Cannabis Dependence



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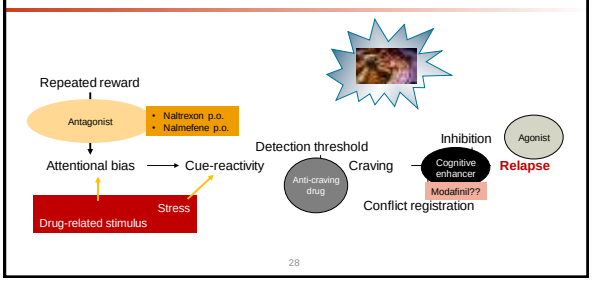
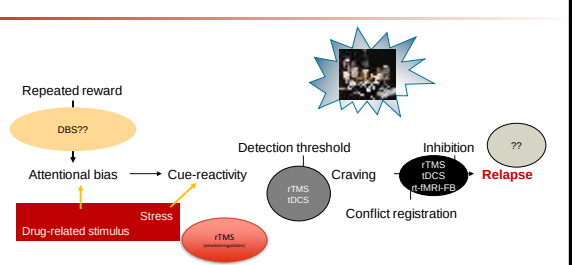
Pharmacotherapy of Gambling Disorder



28

28

Model for Neuromodulation in Addiction



29

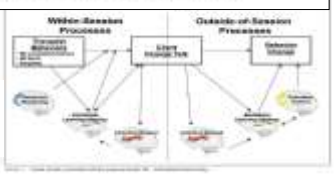
29

Conceptual Treatment Models
Psychological Treatment

30

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

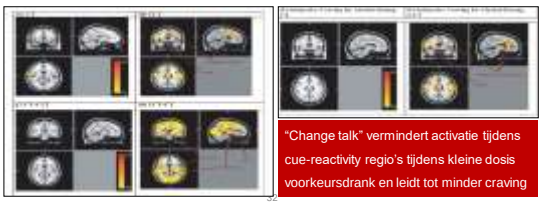
JSAD, 2011



31

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

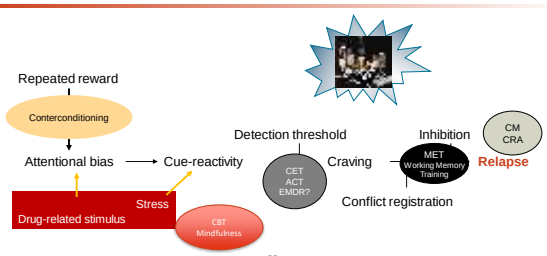
ACER, 2011



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

32

Model for Psychotherapy of Addiction



33

33

Conclusion about Available Interventions

- Many pharmacological interventions for alcohol, nicotine and opioid dependence
- Very few pharmacological interventions for stimulant and cannabis dependence
- Very few pharmacological interventions for PG
- Many psychological interventions for all addictions
- Maybe some neuromodulaltion opportunities in the future
- **BUT**
- How effective are these interventions?

34

34

Effectiveness of Addiction Tx

35

Effectiveness of Addiction Tx Medication

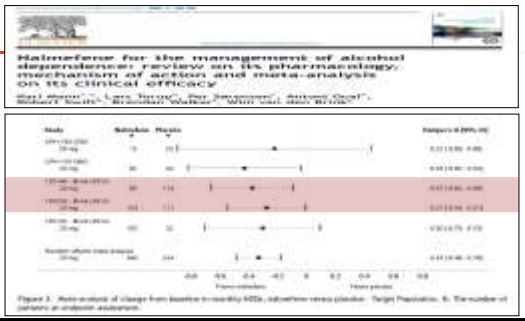
36

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

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

Results
Acamprosate: Abstinence RD=9% → **NNT=11**
Heavy drinking RD=5% → **NNT=20**
Naltrexone: Abstinence RD=1% (ns)
Heavy drinking RD=9% → **NNT=11**
In direct comparison no difference between acamprosate and naltrexone

37



38

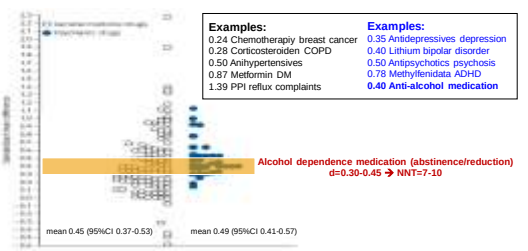
Comparing Effect-Sizes of Alcohol Medications

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

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

39

Effectiveness compared to general medicine

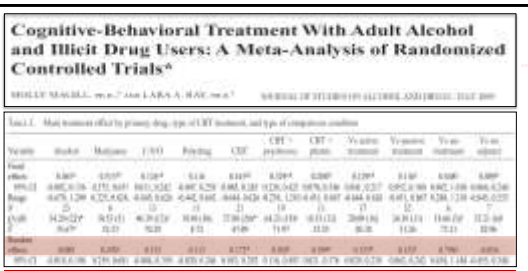


Leucht et al., British Journal of Psychiatry (2012) 200, 97–106.

40

Effectiveness of Addiction Tx Psychotherapy

41



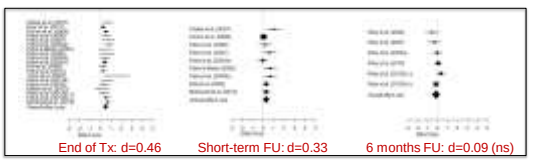
Meta-analysis: 53 RCTs and mean of 18 sessions of CBT:
Effect of CBT generally significant but small (overall g=0.17; range g=0.09-0.47)
Best results in cannabis and in combination with psychosocial support

42

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

Addiction 2014

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

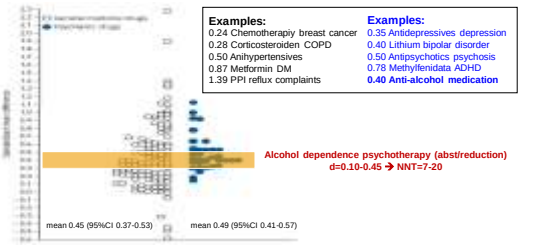


End of Tx: d=0.46 Short-term FU: d=0.33 6 months FU: d=0.09 (ns)

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

43

Effectiveness compared to general medicine



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

44

Conclusion Effectiveness Interventions

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

45

45

Improving Treatment Effectiveness

46

How can we do better?

Possible solutions

- Improve compliance: psychotherapy, long-acting formulations
- Combine pharmacotherapy with psychotherapy
- Combine different medications: polypharmacy
- New medications: based on basic science, "repurposing"
- **Patient-treatment matching: precision/personalized medicine**
  *** phenotype, endophenotype, genotype, tx process**
- New treatment modalities, e.g. neuromodulation

47

47

Different types of matching variables

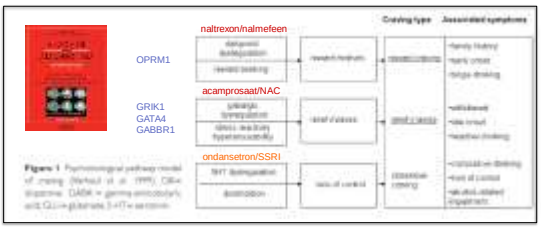
Characteristic	Phenotype	Endophenotype	Genotype
Stability	Low-Moderate	Low-High	High
Feasibility	High	Low	High
Price	Low	High	Moderate → Low
Biological process	Distant	Close	Close
Psychological process	Close	Distant	Distant

48

A THREE-PATHWAY PSYCHOBIOLOGICAL MODEL OF CRAVING FOR ALCOHOL

1999

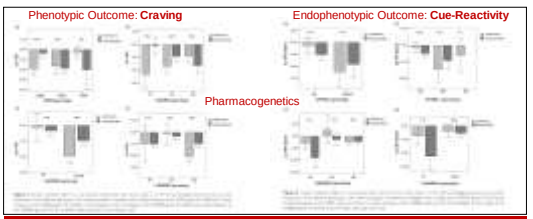
ROEL VERHEUL*, WIM VAN DEN BRINK and PETER GEERLINGS



49

Predicting the effect of naltrexone and acamprosate in alcohol-dependent patients using genetic indicators

2009



Just a start, but too naive and too small, but now we have much more →

50

Precision/Personalized Medicine
Pharmacotherapy
Alcohol Dependence
Phenotype

51

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

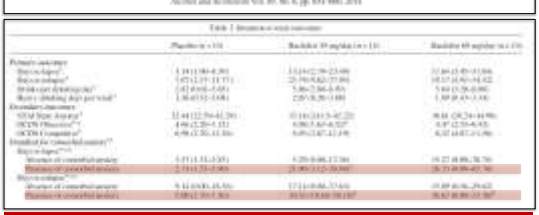
2005

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

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

52

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



Small study with strong interaction effect and significant effects of baclofen only in the subgroup with a life-time anxiety disorder (see later).

53

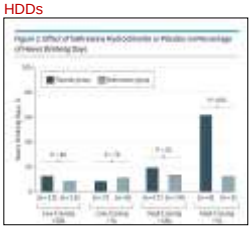
Association of the Sweet-Liking Phenotype and Craving for Alcohol With the Response to Naltrexone Treatment in Alcohol Dependence
A Randomized Clinical Trial

JAMA Psychiatry, 2016

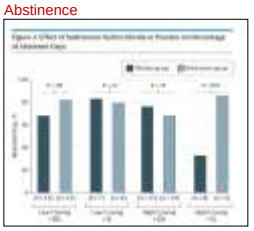
54

Sweet (dis)liking and NTX-effect on HDDs en abstinence

HDDs



Abstinence



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

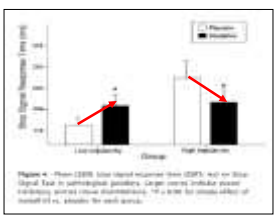
55

Precision/Personalized Medicine
Pharmacotherapy
Alcohol Dependence
Endophenotype

56

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

2009



In PG:

Low baseline impulsivity → modafinil results in more impulsivity and craving

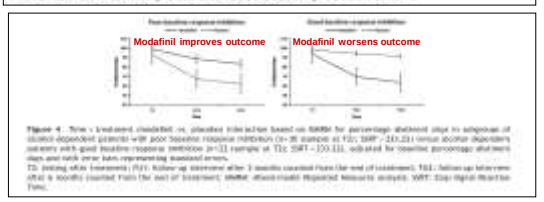
High baseline impulsivity → modafinil results in less impulsivity and craving

57

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

2012

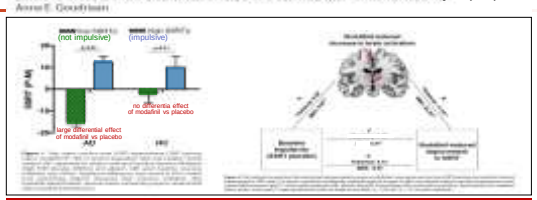
Leen Joos[a,b,*], Anna E. Goudriaan[b,c], Lianne Schmaal[b], Erik Fransen[d], Wim van den Brink[b], Bernard G.C. Sabbe[a], Geert Dom[a,e]



58

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

Biological Psychiatry, 2013

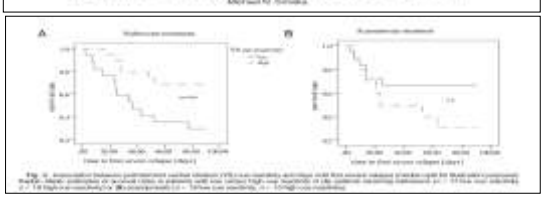


Among impulsive alcohol dependent patients, modafinil causes reduction of motor-impulsivity via increased activity of thalmus en SMA (areas involved in stop of actions that were started)

59

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

2014

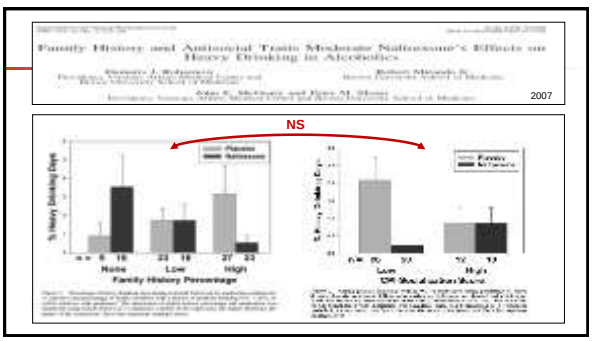


Patients with high pre-Tx VS activity during visual cues-exposure do better with NTX

60

Precision/Personalized Medicine
Pharmacotherapy
Alcohol Dependence
Genotype

61



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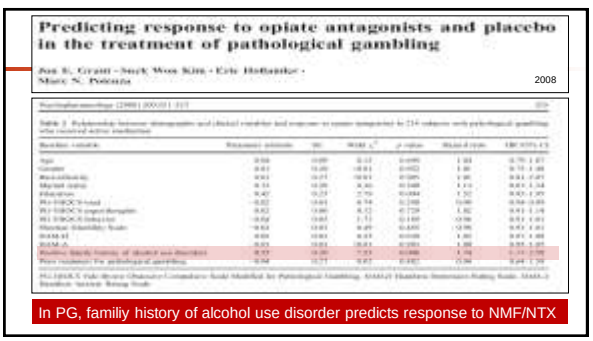
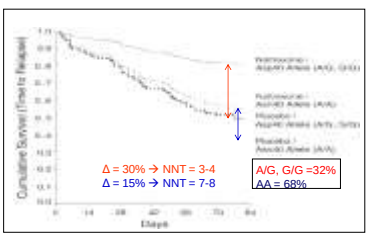


In PG, familiy history of alcohol use disorder predicts response to NMF/NTX

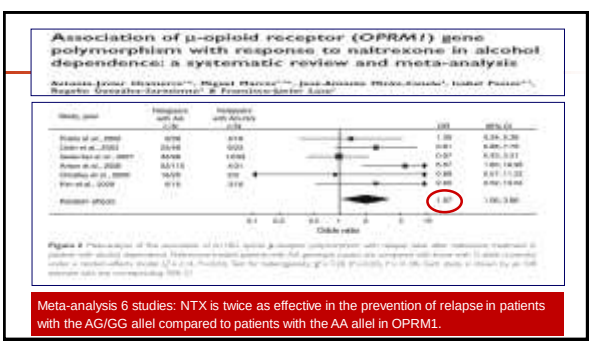
63

Candidate Genes: Naltrexone and OPRM1



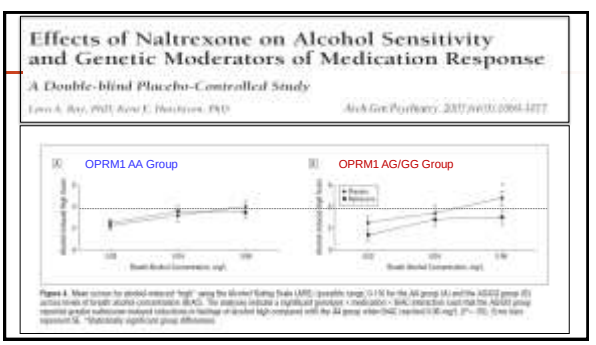
Oslin et al. 2003	+
McGeary et al. 2006	+
Anton et al. 2008	+
Kim et al. 2008	+
Ooteman et al. 2009	+
Gerlernter et al. 2007	-
Tidey et al. 2008	-
Oroszi et al., 2009	+
Coller et al., 2011	-
ETC.	

64



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

65



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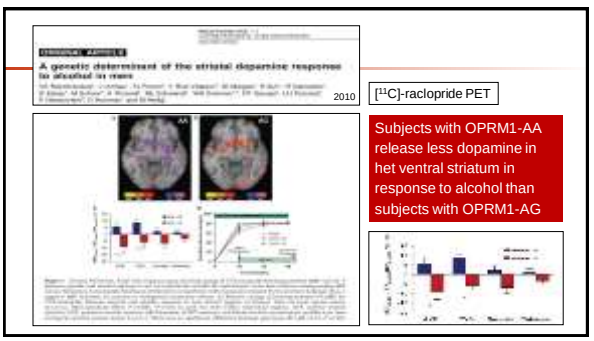

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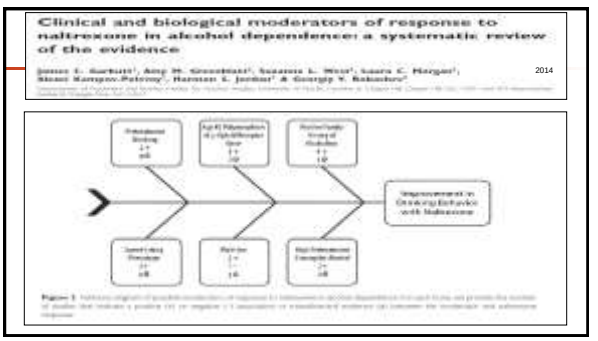

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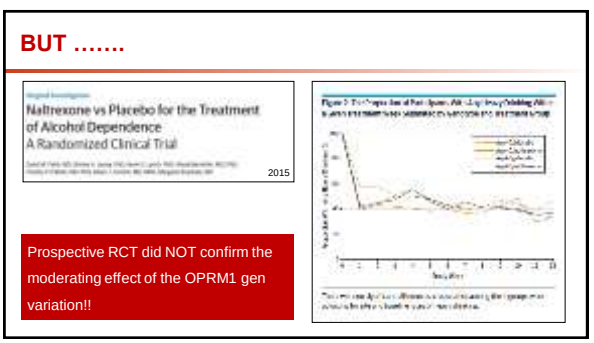

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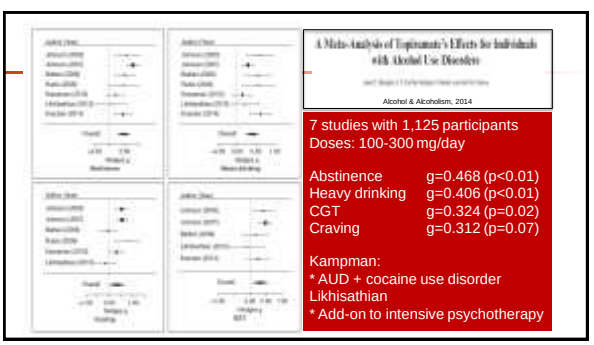


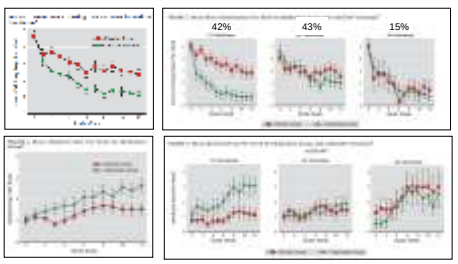
71

72

Candidate Genes: Topiramate (200mg) and GRK1

HDDs per week

Abstinence days/week

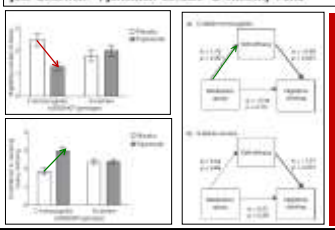


73

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

Addiction Biology 2014

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



Only CC group shows effect of topiramate on night time drinking

Only CC group shows effect of topiramate on self-efficacy

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

Explanation?
Pharmacotherapy=Psychotherapy?

74

Baclofen and GABA-B receptor subunit 1 gene

Article Title: **Moderation of baclofen response by a GABAB receptor polymorphism: Results from the BacALD study**
Authors: Kirsten C Morley; Natasha Luquin; Andrew Baillie; Isabel Fraser; Ronald J Trent; Glenys Dore; Nghi Phung; Paul S Haber
Author Affiliations: University of Sydney

Abstract:
Background: Baclofen has been shown to reduce alcohol consumption in alcohol-dependent individuals, but there is marked heterogeneity in response. The present study evaluated whether the response to baclofen is moderated by a single nucleotide polymorphism (rs29220) in the GABAB receptor subunit 1 gene (GABBR1).
Methods: Alcohol dependent patients were treated for 12 weeks with 30 mg/day of baclofen, 75 mg baclofen or placebo. Predefined primary outcomes included survival time to lapse (any drinking) and relapse (> 5 drinks per day in men and > 4 in women), and the composite outcomes of drinks per drinking day, number of heavy drinking days, and percentage days abstinent.
Results: We observed significant medication x genotype interaction effect for time to relapse (OR: 3.40, 95% CI:1.01-11.46) and a near significant interaction effect for time to lapse (OR: 3.29, 95% CI:0.98-11.06). Patients with the CC genotype demonstrated increased percentage days abstinent and a greater time to relapse following baclofen treatment (80% vs 36%; 50.55 days vs 9.71 days), while those with the G- genotype showed no medication differences (5.7% vs 59%; 27.21 days vs 28.88 days). Patients with the CC genotype reported significantly less dizziness than the G- carriers (24% vs 0% for CC and G- respectively, P < 0.01).
Conclusion: Our study is the first demonstration that the GABBR1 rs29220 polymorphism is associated with response to baclofen in the treatment of alcohol dependence which may have important implications for treatment selection.

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

75

Genome-wide Association Study of Alcohol Dependence

GWAS

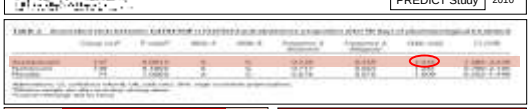
2009

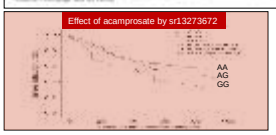
GATA binding Protein 4 = transcription factor regulating the transciption of Atrial Natriuretic Peptide (ANP) and involved in neuroendocrine stress response

76

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

PREDICT Study 2010





Jorde et al.
Genetic variation in the atrial natriuretic peptide transcription factor GATA4 modulates amygdala responsiveness in alcohol dependence.
Biological Psychiatry, 2014, 75, 790-797

77

Personalized or Precision Pharmacotherapy

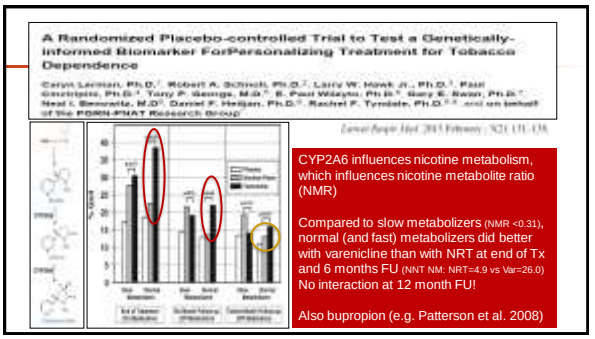
Treatment Goal	1st Choice	2nd Choice	3rd Choice
Abstinence	**Acamprosaat** (anxiety, withdrawal, GATA4) **Naltrexon??** (ASPD, SL+, FH+, OPRM1)	**Disulfiram** (partner)	Baclofen (anxiety, GABBR1) Gabapentin (sleep problems) (GHB??)
Reduced Drinking	**Naltrexon#** (ASPD, SL+, FH+, OPRM1) **Nalmefene**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

off-label

78

Precision/Personalized Medicine
Pharmacotherapy
Nicotine Dependence
Phenotype

79



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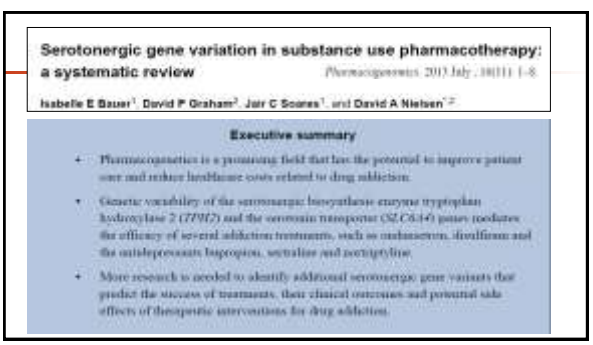
Precision/Personalized Medicine
Pharmacotherapy
Nicotine Dependence
Genotype

81

82



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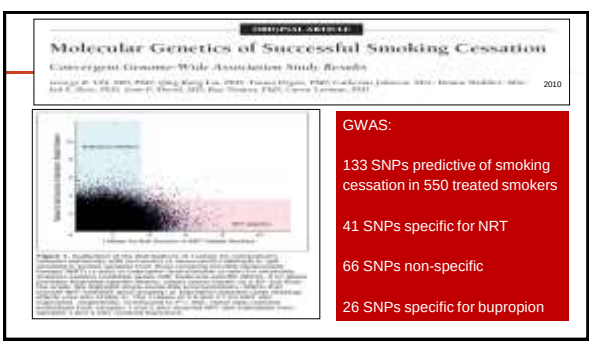


84

Precision/Personalized Medicine
Pharmacotherapy
Stimulant and Opioid Dependence
Genotype

85

A review of pharmacogenetic studies of substance-related disorders*

Drug Alcohol Depend. 2013 July 1; 132: 1–14.

Jermaine D. Jones[1,*] and Sandra D. Comer[1]

Results—Findings from these studies provide preliminary evidence of clinically relevant pharmacogenetic effects. However, independent replication of these findings has been sparse.

Conclusions—Although this growing body of literature has produced conflicting results, improved statistical controls may help to clarify the findings. Additionally, the use of empirically derived sub-phenotypes (i.e., which serve to differentiate distinct groups of affected individuals) may also help to identify genetic mediators of pharmacologic response in relation to SRDs. The identification of genetic mediators can inform clinical care both by identifying risk factors for SRDs and predicting adverse events and therapeutic outcomes associated with specific pharmacotherapies.

86

86

Precision/Personalized Medicine
Specific Psychotherapy
Alcohol Dependence

87

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

PROJECT MATCH RESEARCH GROUP*

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

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

88

UK Alcohol Treatment Trial: client–treatment matching effects

UKATT Research Team*

2007

*(opposite direction)

*(opposite direction)

UK Alcohol treatment trial (UKATT): N=742 with 2 interventions (MET, SBNT)
130 interactions: 13 matching variables, 5 outcomes, and 2 assessment points
* Of these 130 interactions 4 p<0.10 and 2 p<0.05* (none for both assessments)
* Conclusion: Observed interactions most likely chance findings!

89

Cannabis Dependence: CBT of MDFT?

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

2011

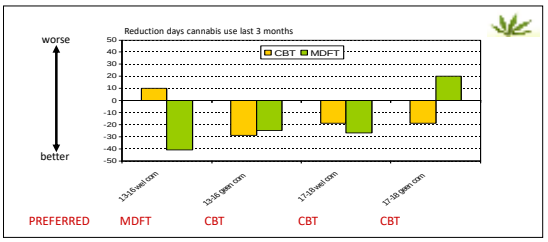
Overall CBT just as effective as MDFT in treatment adolescents with cannabis dependence

2012

90

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

2012



91

Working alliance and outcome in youth addiction and MH Tx

Van Benthem et al., in preparation

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

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

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

92

Conclusions

93

Conclusions

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

94

Thank You

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95