Precision Medicine in Addiction: A Bright Future?

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Disclosure

<table>
<thead>
<tr>
<th>Interest</th>
<th>Name of organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grants</td>
<td>Alkermes</td>
</tr>
<tr>
<td>Honoraria</td>
<td>Lundbeck, Merck Serono, El Lilly, Indixier, Pfizer,</td>
</tr>
<tr>
<td>Advisory Board/Consultant</td>
<td>Lundbeck, Merck Serono, Indixier, Mundipharma, DB Pharma, Bioproject, Novartis, Kinnov Therapeutics, Opiant Pharmaceuticals</td>
</tr>
</tbody>
</table>

History Concept of Addiction

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

History of the concept of alcoholism

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

Heritability estimates

<table>
<thead>
<tr>
<th>Type of dependence</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>50–70%</td>
</tr>
<tr>
<td>Nicotine</td>
<td>50–75%</td>
</tr>
<tr>
<td>Cannabis</td>
<td>35–75%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>35–80%</td>
</tr>
<tr>
<td>Heroin</td>
<td>40–60%</td>
</tr>
</tbody>
</table>

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

Heritability estimates for alcohol dependence, nicotine dependence, cannabis and other illicit drug use disorders across samples of twins.
Reward → attentional bias → cue-reactivity → craving - deficient cognitive control - → relapse

**Neurobiology of addiction**

<table>
<thead>
<tr>
<th>Function</th>
<th>Brain Structures</th>
<th>Neurotransmitters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reward deficiency</td>
<td>Ventral tegmental area (VTA), Nucleus accumbens (NAc)</td>
<td>Endorphins (μ-receptors)</td>
</tr>
<tr>
<td>Sensitization</td>
<td>Striatum, GHT</td>
<td>Serotonin, Noradrenaline</td>
</tr>
<tr>
<td>Conditioned</td>
<td>Striatum, thalamus</td>
<td>Dopamine, Noradrenaline</td>
</tr>
<tr>
<td>Relapse</td>
<td>Striatum, thalamus, prefrontal cortex (PFC, ACC)</td>
<td>Dopamine, Noradrenaline</td>
</tr>
</tbody>
</table>

**Dark side of addiction: addiction and stress**

![Graph showing intensity vs. substance dependence on alcohol](image)

**From reward to relief and from impulsive to compulsive**

Adapted from Heilig et al., 2010
**Reward → attentional bias → cue-reactivity → craving - deficient cognitive control - → relapse**

Repeated reward
- Attentional bias
- Cue-reactivity
- Craving
- Deficient cognitive control
- Relapse

**Conceptual Treatment Models**

- **Pharmacological Tx**
- 

**Model for Pharmacotherapy of Addiction**

Repeated reward
- Antagonist
- Attentional bias
- Cue-reactivity
- Craving
- Relapse

**Pharmacotherapy of Nicotine Dependence**

Repeated reward
- Antagonist
- Attentional bias
- Cue-reactivity
- Craving
- Relapse

**Pharmacotherapy Alcohol Use Disorder**

Repeated reward
- Antagonist
- Attentional bias
- Cue-reactivity
- Craving
- Relapse

**Effective Pharmacotherapy Alcohol Dependence**

<table>
<thead>
<tr>
<th>Treatment Goal</th>
<th>1st Choice</th>
<th>2nd Choice</th>
<th>3rd Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinence</td>
<td>Acamprose (NNT=11)</td>
<td>Disulfiram (NNT=25; NS)</td>
<td>Disulfiram (NNT=25; NS)</td>
</tr>
<tr>
<td>Reduced Drinking</td>
<td>Naltrexone (NNT=11)</td>
<td>Topiramate</td>
<td>Modules?? Varenicline?? HD Baclofen?? Doxazosine??</td>
</tr>
</tbody>
</table>

* NNT = number needed to treat
* NS = not significant
* Off-label use

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4/23/2019
**Pharmacotherapy of Opioid Use Disorder**

Repeated reward → Stress → Drug-related stimulus → Antagonist

- Naltrexone p.o., Naltrexone i.m., Naltrexone implant

Attentional bias → Cue-reactivity → Detection threshold → Inhibition → Craving → Conflict registration → Relapse

**Pharmacotherapy of Cocaine Use Disorder**

Repeated reward → Stress → Drug-related stimulus → Antagonist

- Naltrexone p.o., Naltrexone i.m., Naltrexone implant

Attentional bias → Cue-reactivity → Detection threshold → Inhibition → Craving → Conflict registration → Relapse

**Pharmacotherapy of Cannabis Dependence**

Repeated reward → Stress → Drug-related stimulus → Antagonist

- NAC?

Attentional bias → Cue-reactivity → Detection threshold → Inhibition → Craving → Conflict registration → Relapse

**Pharmacotherapy of Gambling Disorder**

Repeated reward → Stress → Drug-related stimulus → Antagonist


Attentional bias → Cue-reactivity → Detection threshold → Inhibition → Craving → Conflict registration → Relapse

**Model for Neuromodulation in Addiction**

Repeated reward → Stress → Drug-related stimulus → Antagonist

DBS? rTMS tDCS rt-fMRI FB rTMS (emotion regulation)

Attentional bias → Cue-reactivity → Detection threshold → Inhibition → Craving → Conflict registration → Relapse

**Conceptual Treatment Models**

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

**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 neuromodulation opportunities in the future
- **BUT**
  - How effective are these interventions?
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

**Comparing Effect-Sizes of Alcohol Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect Size (Cohen's d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalmefene</td>
<td></td>
</tr>
<tr>
<td>ESENSE 1</td>
<td>0.37</td>
</tr>
<tr>
<td>ESENSE 2</td>
<td>0.27</td>
</tr>
<tr>
<td>Alcohol treatment</td>
<td>0.12 to 0.33</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>0.24 to 0.35</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>0.30 to 0.53</td>
</tr>
</tbody>
</table>

**Effectiveness compared to general medicine**

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

Mean 0.45 (95%CI 0.37-0.53)
Mean 0.49 (95%CI 0.41-0.57)

**Examples:**
- Chemotherapy breast cancer: d=0.35
- Antidepressants: d=0.30
- Corticosteroids COPD: d=0.50
- Anti-alcohol medication: d=0.60

**Effectiveness of Addiction Tx Psychotherapy**

Meta-analysis: 53 RCTs and mean of 18 sessions of CBT

Effect of CBT: generally significant but small (overall g=0.17; range g=0.09-0.47)
Best results in cannabis and in combination with psychosocial support
Prize-based contingency management for the treatment of substance abusers: a meta-analysis


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

CMA probably only more effective than CBT at the short by not the long term.

Effectiveness compared to general medicine

Examples:
- 0.24 Chemotherapy breast cancer
- 0.29 Corticosteroids COPD
- 0.67 Antidepressants, AD
- 0.38 Anti-alcohol medication

Mean 0.45 (95%CI 0.37–0.53)                 Mean 0.49 (95%CI 0.41–0.57)

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?

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

Different types of matching variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phenotype</th>
<th>Endophenotype</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stability</td>
<td>Low-Moderate</td>
<td>Low-High</td>
<td>High</td>
</tr>
<tr>
<td>Feasibility</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Price</td>
<td>Low</td>
<td>High</td>
<td>Moderate (\rightarrow) Low</td>
</tr>
<tr>
<td>Biological process</td>
<td>Distant</td>
<td>Close</td>
<td>Close</td>
</tr>
<tr>
<td>Psychological process</td>
<td>Close</td>
<td>Distant</td>
<td>Distant</td>
</tr>
</tbody>
</table>
A THREE-PATHWAY PSYCHOBIOLOGICAL MODEL OF CRAVING FOR ALCOHOL
ROEL VERHEUL*, WIM VAN DEN BRINK and PETER GEEKINGS

Phenotypic Outcome: Craving
Endophenotypic Outcome: Cue-Reactivity

Pharmacogenetics

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

Precision/Personalized Medicine
Pharmacotherapy
Alcohol Dependence
Phenotype

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

Baclofen for the Treatment of Alcohol Dependence and Possible Role of Comorbid Anxiety
K.C. Smith1, A. Büller1, S. Liang1, G. Ahlheim1, L. Logan1, and F.A. Haber1

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

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

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

Phenotypic characteristics (craving, anxiety) do predict course, but they do NOT predict treatment effect
Sweet (dis)liking and NTX-effect on HDDs en abstinence

HDDS

Abstinence

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

Precision/Personalized Medicine
Pharmacotherapy
Alcohol Dependence
Endophenotype

In PG:
Low baseline impulsivity → modafinil results in more impulsivity and craving
High baseline impulsivity → modafinil results in less impulsivity and craving

Effect of modafinil on impulsivity and relapse in alcohol dependent patients: A randomized, placebo-controlled trial
Leen Joris¹, Anna E. Goodmanc, Liangie Schmaufc, Erika Fransenb, Wim van den Brinka, Bernard G. C. Sibbela, Geert Dutteb

Patients with high pre-Tr VS activity during visual cues exposure do better with NTX
Predicting response to opiate antagonists and placebo in the treatment of pathological gambling


Candidate Genes: Naltrexone and OPRM1

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

Effects of Naltrexone on Alcohol Sensitivity and Genetic Moderators of Medication Response

A Double-blind Placebo-Controlled Study

Oprin et al. 2007 2008 2009 2010 2011 2012
Subjects with OPRM1 AA release less dopamine in the ventral striatum in response to alcohol than subjects with OPRM1 AG.

BUT ……

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

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

- 7 studies with 1,125 participants
- Doses: 100-300 mg/day
- Abstinence: g=0.468 (p<0.01)
- Heavy drinking: g=0.406 (p=0.03)
- CGT: g=0.324 (p=0.02)
- Craving: g=0.312 (p=0.07)

Kampman:
* AUD + cocaine use disorder
* Add on to intensive psychotherapy

Topiramate Treatment for Heavy Drinkers: Moderation by a GBR1 Polymorphism
Candidate Genes: Topiramate (200mg) and GRK1

HDDs per week

<table>
<thead>
<tr>
<th>Abstinence days/week</th>
<th>0%</th>
<th>60%</th>
<th>40%</th>
<th>20%</th>
<th>0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>75%</td>
<td>70%</td>
<td>25%</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Baclofen and GABA-B receptor subunit 1 gene

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

Personalized or Precision Pharmacotherapy

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<td>Acamprosate (anxiety, withdrawal, GATA4)</td>
<td>Disulfiram (psychosis)</td>
<td>Baclofen (anxiety, GABAB1)</td>
</tr>
<tr>
<td>Reduced Drinking</td>
<td>Naltrexone?? (ASPD, SL+, FH+, OPRM1)</td>
<td>Nalmefene (dysphoria??)</td>
<td>Gabapentin (deep pain) (GABAB3)</td>
</tr>
<tr>
<td></td>
<td>Naltrexone (ASPD, SL+, FH+, OPRM1)</td>
<td>Topiramate (GRK1, PTSD?)</td>
<td>Modafinil (impulsivity)</td>
</tr>
<tr>
<td></td>
<td>Nalmefene (dysphoria??)</td>
<td>Varenicline (smoking?)</td>
<td>Doxaxozine (FH+)</td>
</tr>
</tbody>
</table>
CYP2A6 influences nicotine metabolism, which influences nicotine metabolite ratio (NMR). Compared to slow metabolizers (NMR <0.31), normal and fast metabolizers did better with varenicline than with NRT at end of Tx and 6 months FU (p=0.007). No interaction at 12 month FU! Also bupropion (e.g., Patterson et al. 2008).

Genetic variants in the serotonin transporter influence efficacy of bupropion and nortriptyline in smoking cessation - 2012

GWAS: 133 SNPs predictive of smoking cessation in 550 treated smokers
41 SNPs specific for NRT
66 SNPs nonspecific
26 SNPs specific for bupropion
A review of pharmacogenetic studies of substance-related disorders*

Jeremy D. Jones and Sandra D. Comer

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 promising results, improved statistical control may help to clarify its 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 markers of pharmacologic response in relation to SEDs. The identification of potential moderators can inform clinical care both by identifying risk factors for SEDs and by predicting adverse events and therapeutic outcomes associated with specific pharmacotherapies.

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

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

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

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

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

Thank You
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