Using Science to Improve the Treatment of Gambling Addiction

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Disclosure Information

I have the following **financial** relationships to disclose:

No conflicts with respect to this presentation

My research is supported by NIAAA, AFSP, and the TLC Foundation

Grant/Research support from: Takeda Pharmaceuticals

I will discuss *off-label use* and/or investigational use in my presentation as there are no FDA-approved medications for gambling addictions.
Impulse Control Disorders/Behavioral Addictions?

- Gambling
- Stealing
- Sexual behavior
- Shopping
- Fire-setting
- Internet use
- Overeating
Common Core Qualities of Behavioral Addictions

- Repetitive or compulsive engagement in a behavior despite adverse consequences.
- Diminished control over the problematic behavior.
- Appetitive urge or craving state prior to engagement in the problematic behavior.
- Hedonic quality during the performance of the problematic behavior.
Common Core Qualities of Behavioral Addictions

- Tolerance
- Withdrawal
- Impairment in major areas of life functioning
- Telescoping
Gambling addiction generally start in young adulthood.

Environmental and genetic influences - vulnerability to and expression of gambling addiction

Changes in brain structure and function during adolescence might influence the motivation to engage in risk-taking behaviors.
Motivation

Emotion

Judgment

Cerebellum

Prefrontal Cortex

Amygdala

Nucleus Accumbens

Physical coordination

Notice: Judgment is last to develop!
Age 24

Balance

- Judgment
- Emotion
- Motivation

Physical coordination, sensory processing
Youth Problem Behaviors

- delinquency
- sexual behavior
- smoking
- gambling
- drug use
- male

Problem Behaviors
Family/Genetic Factors

- Male twin study - 12 to 20% of the genetic variation in risk for gambling, and 3 – 8% of the nonshared environmental variation in the risk for gambling, accounted for by risk for alcoholism.

- Additionally, 64% of the co-occurrence between gambling and alcoholism - attributable to genes that simultaneously influence both disorders.
Role of Trauma

- Neglectful parenting style

- Addictive behaviors - more likely to report histories of
  - physical neglect
  - emotional abuse
  - Sexual abuse
Neurobiology
Neurochemistry of Behavioral Dyscontrol

GLUTAMATE
SEROTONIN
DOPAMINE

Impulsivity

GLUTAMATE
DOPAMINE
Glutamate

- Levels of glutamate within the nucleus accumbens mediate reward-seeking behavior.
- Restoring extracellular glutamate concentration in the nucleus accumbens seems to decrease cravings.
Role of Dopamine

- Dopamine release into the nucleus accumbens - translates motivated drive into action - a “go” signal

- Dopamine release associated with rewards and reinforcing

- Dopamine release - maximal when reward is most uncertain
Biochemistry – Opioid System

- The endogenous opioid system influences the experiencing of pleasure.

- Opioids modulate mesolimbic dopamine pathways via disinhibition of γ-aminobutyric acid input in the ventral tegmental area.

- Addictions have been associated with elevated blood levels of the endogenous opioid β-endorphin.
Neurocognition in Behavioral Addictions

- Executive function deficits are greater in those with behavioral addictions than in control subjects, including:
  - Planning
  - Cognitive flexibility
  - Inhibition
Expressed behavior

Cognition

Brain abnormalities

Etiology

Genetic ↔ Environmental
Inhibitory Control - Familial
Impulsivity as an Endophenotype

- Impulsivity Across Psychiatric Groups
  - Substance use disorders
  - Behavioral addictions
  - ADHD
  - Bipolar disorder
  - Personality disorders
  - Suicidality
Cognition: Early Symptom?
Treatment Implications
GAMBLERS ANONYMOUS

"Betcha I recover before you do."
Treatment

- Pharmacotherapy
  No medication FDA-approved for gambling or sex

- Cognitive-Behavioral Therapy (CBT)
  Length of treatment unknown; brief interventions have shown benefit;
  Multiple versions of CBT have shown benefit;

Pharmacotherapies

Several medications do not appear to offer any benefits over placebo:

- Bupropion
- Atypical antipsychotics
- Acamprosate
- Baclofen
Pharmacotherapies (cont’d)

• The following medications may offer some benefits for behavioral addictions

• Serotonin reuptake inhibitors

• Opiate antagonists

• N-acetyl cysteine (NAC)

Figure 1. Baseline and Terminal Visit Gambling Symptom Ratings
(Carry Forward Paired t-test)

- Baseline Visit (N=17)
- Terminal Visit (N=17)

Symptom Severity Measure

Urge Strength\(^a\)
Urge Frequency\(^b\)
Thought Frequency\(^c\)
Subjective Distress\(^d\)

\(^a\) 0=None, 2=Mild, 4=Moderate, 6=Severe, 8=Extreme. Significantly different (t=14.28, p<0.05)*.

\(^b\) 0=None, 1=Once a day, 3=Three times a day, 5=Five times a day, 6=More than five times a day. Significantly different (t=7.29, p<0.05)*.

\(^c\) 0=None, 1=Once a day, 3=Three times a day, 5=Five times a day, 6=More than five times a day. Significantly different (t=5.25, p<0.05)*.

\(^d\) 0=None, 2=Mild, 4=Moderate, 6=Severe, 8=Extreme. Significantly different (t=8.68, p<0.05)*.

* Bonferroni corrected
Glutamate and N-Acetyl Cysteine (NAC)

NAC:
- An amino acid and antioxidant
- Lacks significant side effects
- Potentially modulates brain glutamate transmission

Glutamate levels within the nucleus accumbens mediate reward-seeking behavior.
**RESULTS**

- N=16 (59.3%) met responder criteria
- Mean effective dose: 1476.9 (±311.3) mg/d
Psychosocial Treatments

• Motivational enhancement

• Individual and Group Cognitive behavioral therapy
  – social skills, assertiveness, anger management; cognitive restructuring

• Imaginal exposure

• Brief interventions

Psychosocial Treatments (Cont)

Brief Interventions

Single-session interventions, workbooks, bibliotherapy, or motivational interviewing.

Workbooks include CBT and motivational enhancement techniques.

CBT workbook, a workbook plus a telephone motivational enhancement.
## Motivation to Quit Behavioral Addictions

<table>
<thead>
<tr>
<th>1) <strong>Positive</strong> aspects of impulsive behavior (what are the positive things behavioral addiction gives me?)</th>
<th>2) <strong>Negative</strong> aspects of quitting (what do I lose if I stop behavioral addiction?)</th>
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<tr>
<td>3) What are the <strong>negative</strong> consequences of behavioral addiction (current and future?)</td>
<td>4) What are the <strong>advantages</strong> of quitting behavioral addiction (what do I have to gain?)</td>
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Thoughts/Feelings

Antecedent (Triggers)

- Particular people
- Environment
- Feelings
e.g., urges, argument with spouse, boredom, anxiety

Behavior

- Gambling/alternate behavior
e.g., I drove by the bar, next think I knew it was last call
- Abstinence
e.g., I thought about the effect it would have on my family, and took a different route home

Consequence

- Positive
e.g., I gambled and I forgot about that argument with my wife
- Negative
e.g., the next day, I felt like I’m a failure.
Imaginal Exposure

Client and therapist develop an imaginal exposure script that includes all the relevant internal and external triggers that relate to the behavioral addiction.
Clinical Subtyping

Comorbidity?
Neurocognition?
Genetics?
Imaging?
Comorbidity – Means What?

- Addictions cause the other disorder?
- Other disorder causes addiction?
- Addiction one branch of a tree?
- Co-occurrence by chance?
- Common stress, genetics, trauma cause?
Bipolar Spectrum Gamblers
PG-YBOCS Total Score Over Time

* p<.05

Hollander et al, 2002
Heterogeneous Profiles?
RESULTS

• N=28 (96.6%) completed study
• N=18 (62.1%) met responder criteria
• Mean effective dose: 23.4 (± 8.1) mg/d

Table. Changes on outcome measures

<table>
<thead>
<tr>
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<th>Visit 1 n=29</th>
<th>Visit 6 n=28</th>
<th>p-value</th>
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<tbody>
<tr>
<td>PG-YBOCS total score</td>
<td>21.8</td>
<td>8.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Responder, n (%)</td>
<td>n/a</td>
<td>18 (62.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dollars lost per week</td>
<td>743</td>
<td>309</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hours gambled per week</td>
<td>10.4</td>
<td>4.0</td>
<td>&lt;.001</td>
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</table>
Open-Label Study of Memantine in Gambling Disorder

**RESULTS**

- Cognitive flexibility improved from baseline to endpoint
- GD subjects were comparable to healthy controls at study endpoint
- Pharmacological modulation of the glutamate system may reduce gambling, and may do so by improving neurocognitive function related to cognitive flexibility.

**Table. Performance on cognitive tasks**

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<th>Baseline v Endpoint</th>
<th>Baseline v Controls</th>
<th>Endpoint v Controls</th>
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<tr>
<td></td>
<td>T</td>
<td>P-value</td>
<td>T</td>
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<tr>
<td><strong>ided total errors</strong></td>
<td>2.20</td>
<td><strong>0.037</strong></td>
<td>2.09</td>
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</table>
RESULTS

- **val/val** COMT polymorphism was associated with significantly greater improvement from tolcapone compared to **met/met**

Tolcapone and genotype appear to have interactive effects on dopamine-related executive functioning, with tolcapone enhancing Val-COMT subjects but either not improving or impairing Met-COMT subjects.
Relapse Rate by Genotype

Proportion Nonrelapsed vs Days

- Naltrexone / Asp40 Allele (A/G, G/G)
- Naltrexone Asn40 Allele (A/A)
- Placebo / Asp40 Allele (A/G, G/G)
- Placebo / Asn40 Allele (A/Al)
Conclusions

- Gambling addiction is common and associated with significant morbidity and mortality.
- Neurobiology is being worked out and allows for more targeted subtyping of individuals and their treatment.
QUESTIONS?

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