Evidence-Based Treatment Approaches for Gambling Disorder

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Disclosure Information

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I will discuss off-label and/or investigational use: opiate antagonists, NMDA antagonists, COMT inhibitors, and glutamate agents.
THE WEIRD WORLD OF GAMBLING

WHY DO WE BET SO MUCH?
WHO REALLY WINS?
WHO REALLY LOSES?

Source: Look Magazine, March, 1963
Gambling Disorder

Persistent and recurrent maladaptive gambling behavior:

- Preoccupation
- Tolerance
- Inability to control
- Withdrawal
- Escape
- Lying
- Illegal acts
- Impairment
- Relying on others
- Chasing losses
Public Health Significance

Gambling is Associated with High Rates of:

- Divorce
- Poor General Health
- Mental Health Problems
- Job Loss and Lost Wages
- Bankruptcy, Arrest and Incarceration
Co-Occurring Disorders in Gambling Disorder

- Substance Use
- Affective
- Anxiety
- Impulse disorders
Treatment Implications
GAMBLERS ANONYMOUS

"Betcha I recover before you do."
CIG-I Score of 1 or 2 During Treatment with Paroxetine or Placebo

59% response rate in the paroxetine group
49% rate in the placebo group
45 completers (Grant et al. 2003)
Opioid Antagonists

- The mu-opioid system:
  - underlies urge regulation through the processing of reward, pleasure and pain, at least in part via modulation of dopamine neurons in mesolimbic pathway through GABA interneurons.
Figure 1. Baseline and Terminal Visit
Gambling Symptom Ratings
(Carry Forward Paired t-test)

<table>
<thead>
<tr>
<th>Symptom Severity Measure</th>
<th>Baseline Visit (N=17)</th>
<th>Terminal Visit (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urge Strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0= None, 2=Mild, 4=Moderate, 6=Severe, 8=Extreme. Significantly different (t=14.28, p&lt;0.05)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urge Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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&lt;0.05)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thought Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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&lt;0.05)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective Distress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0= None, 2=Mild, 4=Moderate, 6=Severe, 8=Extreme. Significantly different (t=8.68, p&lt;0.05)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Bonferroni corrected
Naltrexone
Placebo
Baseline urges
weeks later
p=.005
77 subjects;
18 week trial
Inclusion: urges
Exclusion: SUDs,
other meds

Baseline urges
weeks later 18
### Analysis of Maximum Likelihood Estimates (N=282)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr&gt;ChiSq</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH-AUD</td>
<td>0.55</td>
<td>0.24</td>
<td>7.53</td>
<td>0.006</td>
<td>1.74</td>
</tr>
</tbody>
</table>

Baseline urges were significantly associated with response to higher doses of opiate antagonists (i.e. nalmefene 50mg or 100mg or naltrexone 100mg or 150mg).
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
### TABLE 1. Data for the Cue-Reactivity Procedure: Motivational and General Measures

<table>
<thead>
<tr>
<th>Motivational Measure</th>
<th>N-Acetylcysteine</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N-Acetylcysteine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cocaine</td>
<td>Mean</td>
<td>SD</td>
<td>Neutral</td>
</tr>
<tr>
<td>Craving</td>
<td>5.81</td>
<td>4.29</td>
<td>1.32</td>
<td>2.41</td>
</tr>
<tr>
<td>Desire to use</td>
<td>6.19&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.41</td>
<td>1.01</td>
<td>1.66</td>
</tr>
<tr>
<td>Interest</td>
<td>7.85&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.28</td>
<td>2.81</td>
<td>2.61</td>
</tr>
<tr>
<td>Time viewed (seconds)</td>
<td>3.92&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.70</td>
<td>2.86</td>
<td>1.40</td>
</tr>
</tbody>
</table>

|                      |  | Placebo |  |  |  |
|                      | Cocaine | Mean | SD | Neutral | Mean | SD |
|                      |  |  |  |  |  |  |
|                      |  |  |  |  |  |  |

<sup>a</sup> Means represent raw unadjusted means (i.e., not estimated marginal means) and standard deviations collected during the procedure.

<sup>b</sup> Data for cocaine slides within N-acetylcytsteine condition significantly less than cocaine slides within placebo condition (p<0.05).
Open-Label NAC for Gambling

NAC 1800 mg/d, 8 weeks

27 men and women aged 18 to 75 with a primary diagnosis of pathological gambling

Required to have moderate cravings to gamble

Grant et al., Biol Psychiatry. 2007;62(6):652-7
The chart illustrates the comparison between baseline and endpoint scores for PG-YBOCS Total Score and Urge/Thought Score. The scores show a significant decrease, indicated by a p-value of <.001 for both categories.
Expressed behavior

Cognition

Brain abnormalities

Etiology

Genetic ↔ Environmental
Neurocognition in Gamblers

- Executive function deficits are greater in gamblers than in control subjects, including:
  - Planning
  - Cognitive flexibility
  - Inhibition
## Comparing No-Risk with Low-Risk Recreational Gamblers

<table>
<thead>
<tr>
<th></th>
<th>No Risk (n=53)</th>
<th>Low Risk (n=40)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGT Overall proportion bet</td>
<td>0.49 ± 0.14</td>
<td>0.54 ± 0.13</td>
<td>0.093</td>
</tr>
<tr>
<td>CGT Quality of decision making</td>
<td>0.97 ± 0.04</td>
<td>0.94 ± 0.08</td>
<td>0.024*</td>
</tr>
<tr>
<td>CGT Risk adjustment</td>
<td>2.18 ± 1.33</td>
<td>1.55 ± 0.86</td>
<td>0.011*</td>
</tr>
</tbody>
</table>
Hypofrontality: reduced baseline activity of prefrontal cortex, orbitofrontal cortex, and anterior cingulate

Results in individuals reporting “being driven by irresistible inner forces to gamble,” and having “no ability to stop” themselves
Impulsivity

“… a multitude of behaviours or responses that are poorly conceived, premature, inappropriate, and that frequently result in unwanted or deleterious outcomes.”
Impulsivity as an Endophenotype

- Impulsivity Across Psychiatric Groups
  - Substance use disorders
  - Behavioral addictions
  - ADHD
  - Bipolar disorder
  - Personality disorders
  - Suicidality
Impulsivity is Complex

- Modafinil (200 mg)

- In H-I subjects, the drug decreased desire to gamble, salience of Gambling words, disinhibition and risky decision-making.

- In L-I subjects, modafinil increased scores on these indices.
Open-Label Study of Memantine in Gambling Disorder

- Memantine antagonizes NMDA (N-methyl D-aspartate) receptors, a type of glutamate receptors

Open-Label study of Memantine in GD
- n=29 subjects, mean age 50 years, 62% female
- Primary diagnosis of gambling disorder
- 10-weeks
- Dose titration from 10mg/d to 30mg/d
- All subjects underwent neurocognitive testing (pre/post)

Grant et al. Psychopharmacology (Berl) 2010 Dec;212(4):603-12
Open-Label Study of Memantine in Gambling Disorder

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

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th>Visit 6</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG-YBOCS total score</td>
<td>21.8</td>
<td>8.9</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>
</tr>
</tbody>
</table>

Grant et al. Psychopharmacology (Berl) 2010 Dec;212(4):603-12
Open-Label Study of Memantine in Gambling Disorder

RESULTS

- Cognitive flexibility improved from baseline to endpoint

<table>
<thead>
<tr>
<th></th>
<th>Baseline v Endpoint</th>
<th>Endpoint v Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDED total errors</strong></td>
<td><strong>T</strong></td>
<td><strong>P-value</strong></td>
</tr>
<tr>
<td></td>
<td>2.20</td>
<td><strong>0.037</strong></td>
</tr>
</tbody>
</table>

Grant et al. Psychopharmacology (Berl) 2010 Dec;212(4):603-12
COMT Inhibitors: Open-Label Study of Tolcapone in Gambling Disorder

- Lower dopamine levels in the prefrontal cortex are thought to contribute to deficits in cognitive processing

Open-Label study of Tolcapone in GD
- n=24 subjects, mean age 48.9 yrs.
- 58.3% female
- 8-weeks open-label
- Dose titration from 100mg/d to 100mg/tid
Open-Label Study of Tolcapone in Gambling: Primary Outcome Variables

RESULTS

• N=22 (91.7%) completed the study
• No liver toxicity found

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th>Visit 5</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG-YBOCS total score</td>
<td>23.63</td>
<td>10.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Responders, n [%]</td>
<td>--</td>
<td>15 [62.5]</td>
<td>0.001</td>
</tr>
</tbody>
</table>
RESULTS

• **val/val** COMT polymorphism was associated with significantly greater improvement.

- [Graph showing improvement in PG-YBOCS, mean [SEM] for different subgroups: val/val, val/met, met/met.]

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Bipolar Spectrum Gamblers
PG-YBOCS Total Score Over Time

Hollander et al, 2002

* p<.05
Gambling Subtypes May Suggest Treatment Directions for Individual Patients

- Problems with urges/cravings
- Problems with hypofrontality
- Comorbidity
- Using genetics and neuroimaging to refine subtypes further
Psychosocial Interventions

- 12-step self-help approaches
- Motivational enhancement
- Cognitive behavioral therapies
Brief Interventions

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

- Workbooks include CBT and motivational enhancement techniques.
Groups

- Cognitive restructuring
- Coping skills/identification of high-risk situations.
- Imaginary exposure with response prevention.
- Financial limit setting and activity scheduling of leisure activities.
- Problem-solving training
- Relapse prevention
Imaginal Exposure

“It’s Friday and I have been looking forward to gambling all week. As I am thinking about gambling right now, my urge = 75. Work has been quite stressful and it will feel good to escape for a while and have some fun at the casino. I am bringing $200 and I have to leave the casino when that is gone, maybe 2-3 hours. I hope the money can last a little while so I don’t have to leave so soon. I notice my heart flutter slightly, have butterflies in my stomach, and I can hardly wait to get there. I am hoping my favorite machine is available and the traffic on the way to the casino is not too bad.
Motivational Interviewing Plus Imaginal Desensitization

Percentage Improved

Cognitive Behavioral Therapy
Gamblers Anonymous

6 months
Conclusions

• Disordered gambling is treatable.

• Emerging data suggest that CBT and opioid antagonists are most effective treatments.

• Individualizing treatment is the new focus.
QUESTIONS?