Pharmacological Treatment of Pathological Gambling

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Disclosure Information

- I have the following financial relationships to disclose:
  - Grant/Research support from: Forest Pharmaceuticals, GlaxoSmithKline

- I will discuss the following off-label use and/or investigational use in my presentation:
  - All medications used to treat impulse disorders are off-label and include - SSRIs, lithium, antiepileptics, opioid antagonists, stimulants, antipsychotics, calcium channel blockers, muscle relaxants, antiemetics
Core Features of Impulse Control Disorders

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

- Tolerance
- Withdrawal
- Repeated unsuccessful attempts to cut back or stop
- Impairment in major areas of life functioning
Neurochemistry of Impulsivity

- SEROTONIN
- Glutamate
- Dopamine

Impulsivity
Pathological Gambling Treatment
Snapshots at jasonlove.com

GAMBLERS ANONYMOUS

"Betcha I recover before you do."
Change in CGI-MD Score Following Paroxetine Treatment

![Bar chart showing change in CGI-MD score over 8 weeks between Placebo and Active (N)]

- **Placebo**
- **Active (N)**

* p<0.05
Percentage of Patients Achieving Response (PG-CGI-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)
Clinical Subtyping

Within Gambling – Motivating Drive, Comorbidity, Family History

Within individuals at various time points
Anxiety/Depressive/Obsessionality

- SRI medications
- Anxiolytics
- CBT
Lexapro Treatment of Anxious Gamblers

![Graph showing the comparison of pg-ybocs - total and ham-a across different visits (v1 to v9). The graph indicates a decrease in pg-ybocs - total and an increase in ham-a over time.](graph.png)
Pleasure/Urge

- Relapse prevention techniques
- Naltrexone
- Acamprosate
- Baclofen
- Isradipine
- Ondansetron
Bupropion

- Works on dopamine
- Reduces urges to smoke in some people with nicotine dependence
- May also be beneficial for Attention Deficit Hyperactivity Disorder (ADHD)
- 12 week double-blind study – no difference from placebo
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.
  - linked to physiological responses during Pachinko.
Figure 1. Baseline and Terminal Visit Gambling Symptom Ratings
(Carry Forward Paired t-test)

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

<table>
<thead>
<tr>
<th>Symptom Severity Measure</th>
<th>Urge Strength</th>
<th>Urge Frequency</th>
<th>Thought Frequency</th>
<th>Subjective Distress</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Terminal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Urge Strength**
  - 0= None, 2=Mild, 4=Moderate, 6=Severe, 8=Extreme. Significantly different (t=14.28, p<0.05)*.

- **Urge Frequency**
  - 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)*.

- **Thought Frequency**
  - 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)*.

- **Subjective Distress**
  - 0= None, 2=Mild, 4=Moderate, 6=Severe, 8=Extreme. Significantly different (t=8.68, p<0.05)*.

* Bonferroni corrected
18-Week Naltrexone Study

- 77 subjects
- 3 doses of naltrexone – 50, 100, 150mg
- Depression, anxiety and other disorders allowed
- Required to have urges of at least moderate intensity
The graph shows the comparison of Placebo and Naltrexone in Baseline Gambling and Baseline Dysfunction. The Placebo group shows significantly higher scores in both categories compared to the Naltrexone group.

- **Baseline Gambling**:
  - Placebo: Scores range from 18 to 20.
  - Naltrexone: Scores range from 12 to 16.

- **Baseline Dysfunction**:
  - Placebo: Scores range from 18 to 22.
  - Naltrexone: Scores range from 6 to 10.
Nalmefene

- 16 weeks
- Randomized
- 25mg, 50mg, 100mg, placebo
- 207 subjects
- 15 centers
Relapse Rate by Genotype

- Naltrexone / Asp40 Allele (A/G, G/G)
- Naltrexone / Asn40 Allele (A/A)
- Placebo / Asp40 Allele (A/G, G/G)
- Placebo / Asn40 Allele (A/Al)
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) (parameter estimate = 1.77; SE= 0.84; Wald $\chi^2$ =4.41; p= .036; HR= 5.86; HR 95% CI=1.12-30.6
N-Acetyl Cysteine

- Amino acid and antioxidant
- Lack of significant side effects
- Levels of glutamate within the nucleus accumbens mediate reward-seeking behavior
- NAC potentially modulates brain glutamate transmission
Repeated behaviors associated with reward produce persistent neuroplasticity in extracellular glutamate levels in the nucleus accumbens.

NAC is converted to cystine, a substrate for the glutamate/cystine antiporter.

This antiporter allows for the uptake of cystine causing the reverse transport of glutamate into the extracellular space.
- Stimulates inhibitory metabotropic glutamate receptors, and thereby reducing synaptic release of glutamate and dopamine.

- Restores extracellular glutamate concentration in the nucleus accumbens.

- Appears to block reinstitution of compulsive behaviors and decrease cravings.
<table>
<thead>
<tr>
<th>Motivational Measure</th>
<th>N-Acetylcysteine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cocaine</td>
<td>Neutral</td>
</tr>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>N-Acetylcysteine</td>
<td>5.81</td>
<td>4.29</td>
</tr>
<tr>
<td>Craving</td>
<td>6.19(^b)</td>
<td>4.41</td>
</tr>
<tr>
<td>Desire to use</td>
<td>7.85(^b)</td>
<td>5.28</td>
</tr>
<tr>
<td>Interest</td>
<td>3.92(^b)</td>
<td>1.70</td>
</tr>
</tbody>
</table>

\(^a\) Means represent raw unadjusted means (i.e., not estimated marginal means) and standard deviations collected during the procedure.

\(^b\) Data for cocaine slides within N-acetylcysteine condition significantly less than cocaine slides within placebo condition (p<0.05).
Open-Label Study

- 27 men and women aged 18 to 75 with a primary diagnosis of pathological gambling
- Required to have a score of 16 or greater on the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS)
- Stable dose of other psychotropics
- 8 weeks
- **Dosing schedule:**
  - 600mg/day x 2 weeks
  - 1200mg/day x 2 weeks
  - 1800mg/day x 2 weeks

- Those who responded were randomized for 6 additional weeks to double-blind medication
The chart shows the comparison between baseline and endpoint scores for two categories: PG-YBOCS Total Score and Urge/Thought Score.

- **PG-YBOCS Total Score**: The baseline score is significantly higher than the endpoint score.
- **Urge/Thought Score**: The baseline score is notably higher than the endpoint score.

The chart indicates a substantial improvement from baseline to endpoint across both categories.
Impulsivity

- Attentional – consider stimulants

- Impulsive – anti-epileptics or lithium
- Lithium carbonate SR
- Double-blind study
- Bipolar spectrum disorders
- 29 completers
- 83% responders
- mean dose 1170mg/day
Bipolar Spectrum Pathological Gamblers
PG-YBOCS Total Score Over Time

Hollander et al, 2002

* p<.05
Other potential medications

- Topiramate
- Acamprosate
- Baclofen
- Isradipine
- Antabuse
Conclusions

- Pathological Gambling is a common disorder
- Frequently co-occurs with other disorders
- Result in significant distress as well as social and functional impairment.
- Emerging data suggest subtyping may result in improved response to pharmacological and psychotherapeutic interventions.