Problem Gambling

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Disclosure Information

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

- 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
THE WEIRD WORLD OF GAMBLING

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

Source: Look Magazine, March, 1963
Costs

Problem and Pathological Gambling Are Associated with High Rates of:

- Divorce
- Poor General Health, Mental Health Problems
- Job Loss and Lost Wages
- Bankruptcy, Arrest and Incarceration

Problem & Pathological Gambling Associated with Estimated Annual Societal Cost of $5 Billion
Core Features of PG

- 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 PG

- Tolerance
- Withdrawal
- Repeated unsuccessful attempts to cut back or stop
- Impairment in major areas of life functioning
<table>
<thead>
<tr>
<th>National Comorbidity Study</th>
<th>Past Year Rates (%) for All Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anorexia</strong></td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Schizophrenia / schizophreniform</strong></td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Panic Disorder</strong></td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Anti-social Personality</strong></td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Social Phobia</strong></td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Obsessive Compulsive</strong></td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Dysthymia</strong></td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Drug Use Disorder</strong></td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Cognitive Impairment</strong></td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Gambling addiction</strong></td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Major Depression</strong></td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Alcohol Use Disorder</strong></td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Any Phobia</strong></td>
<td>11.0</td>
</tr>
<tr>
<td><strong>Any Anxiety</strong></td>
<td>12.7</td>
</tr>
<tr>
<td><strong>Any NCS disorder</strong></td>
<td>28.0</td>
</tr>
</tbody>
</table>
Characteristics

- Age: usually begins in early adulthood
- Gender: 32% female, 68% male
- Males tend to start at an earlier age
- Telescoping phenomenon
- Mean time: 16 hours per week
- Amount Lost: 45% of gross annual income
- Triggers:
  - Advertisements, Boredom, Stress
Social/Personal Consequences

- Family dysfunction and domestic violence (spousal and child abuse)
- Alcohol and other drug problems
- Psychiatric conditions including major depression and anxiety disorders
- Suicidal thoughts and attempts
- Significant financial problems (bankruptcy, unemployment, poverty)
- Criminal behavior (theft, prostitution, homicide, fraud, embezzlement)
Relationship Between Gambling and Substance Use Disorders

- High Rates of Co-Occurrence
  - Population and Clinical Samples

- Similar Clinical Courses
  - High Rates in Adolescence, Lower Rates in Older Adults
  - “Telescoping” Pattern in Women

- Similar Clinical Characteristics
  - Tolerance, Withdrawal, Repeated Attempts to Cut Back or Quit
  - Appetitive Urge or Craving States

- Similar Biologies
  - Genetic Contributions, Neural Circuits
Family/Genetic Factors

- 52% of gamblers with first-degree relative with alcohol use disorder

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

- Additionally, 64% of the co-occurrence between PG and alcoholism appears to be attributable to genes that simultaneously influence both disorders.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Rec Gam Vs Non Gam</th>
<th>Prob Gam Vs Non Gam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depression</td>
<td>1.7 (1.1, 2.6)*</td>
<td>3.3 (1.6, 6.8)*</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>1.8 (1.0, 3.0)*</td>
<td>2.1 (0.8, 5.7)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0.6 (0.2, 1.8)</td>
<td>3.5 (1.3, 9.7)*</td>
</tr>
<tr>
<td>Phobias</td>
<td>1.2 (0.9, 1.7)</td>
<td>2.3 (1.2, 4.3)*</td>
</tr>
<tr>
<td>Somatization</td>
<td>1.7 (1.1, 2.8)*</td>
<td>3.0 (1.6, 5.8)*</td>
</tr>
<tr>
<td>Antisocial PD</td>
<td>2.3 (1.6, 3.4)*</td>
<td>6.1 (3.2, 11.6)*</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td>3.9 (2.4, 6.3)*</td>
<td>7.2 (2.3, 23.0)*</td>
</tr>
<tr>
<td>Alcohol Abuse/ Dep</td>
<td>1.9 (1.3, 2.7)*</td>
<td>3.3 (1.9, 5.6)*</td>
</tr>
<tr>
<td>Nicotine Use</td>
<td>1.9 (1.6, 2.4)*</td>
<td>2.6 (1.6, 4.4)*</td>
</tr>
<tr>
<td>Nicotine Dep</td>
<td>1.3 (1.0, 1.7)*</td>
<td>2.1 (1.1, 3.8)*</td>
</tr>
</tbody>
</table>

NS = Mania, Suicidality, OCD, Panic, GAD, Drug Use, Drug Abuse/ Dep

* = p<0.05
The Brain
High rates of co-occurrence of PG and SUDs start in young adulthood.

Environmental and genetic influences - vulnerability to and expression of addictive disorders

Changes in brain structure and function during adolescence might influence the motivation to engage in risk-taking behaviors like gambling.
Adolescents/Young Adults

- Gambling associated with higher rates of tobacco, alcohol and illegal drug use
- Association with tobacco and alcohol were same for women and men
- Associated with hyperactivity and anxiety
- Associated with unprotected sex in men and women
- Associated with disordered eating in men and women
## Estimates of Problem Gambling-Lifetime

*(National Research Council, 1999)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage Range</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>&lt;1 - 3%</td>
<td>1.5%</td>
</tr>
<tr>
<td>College</td>
<td>3 - 11%</td>
<td>5%</td>
</tr>
<tr>
<td>Adolescent</td>
<td>1 - 7%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

Estimates based on meta-analysis of surveys conducted 1988-1997 *(National Research Council, 1999)*. Problem gambling defined in most studies by the SOGS/SOGS-RA.
# Estimates of Problem Gambling—Past Year

(National Research Council, 1999)

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage</th>
<th></th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>&lt;1 - 2%</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Adolescent</td>
<td>1 - 9%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Adolescent-Drug Tx</td>
<td>9 - 13%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

Estimates based on meta-analysis of surveys conducted 1988-1997 (National Research Council, 1999). Problem gambling defined in most studies by the SOGS/SOGS-RA.
Youth Problem Gambling as a Component of Problem Behaviors

- Smoking
- Sexual behavior
- Delinquency
- Gambling
- Drug use
- Male
Biology
Motivational Neural Circuits

- Multiple brain structures underlying motivated behaviors.

- Motivated behavior involves integrating information regarding internal state (e.g., hunger, sexual desire, pain), environmental factors (e.g., resource or reproductive opportunities, the presence of danger), and personal experiences (e.g., recollections of events deemed similar in nature).
Neurochemistry of Impulsivity

- SEROTONIN
- Glutamate
- Dopamine

Impulsivity
### Roles for Neurotransmitters

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Role in Impulse Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (NE)</td>
<td>Arousal, Excitement</td>
</tr>
<tr>
<td>Serotonin (5HT)</td>
<td>Behavior</td>
</tr>
<tr>
<td></td>
<td>Initiation/Cessation</td>
</tr>
<tr>
<td>Dopamine (DA)</td>
<td>Reward, Reinforcement</td>
</tr>
<tr>
<td>Opioids</td>
<td>Pleasure, Urges</td>
</tr>
</tbody>
</table>
Serotonin & Impulse Control

- Low CSF 5-HIAA Associated w/ Impaired Impulse Control (Potenza and Hollander, 2002)

- Altered Biochemical and Behavioral Responses to m-CPP (5HT1R and 5HT2R Partial Agonist) (DeCaria et al, 1998)

- Blunted 5HT Response in vmPFC in Impulsive Aggression (Siever et al, 1999; New et al, 2002)
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, suggesting it plays a central role in guiding behavior during risk-taking situations.
Dopamine and ICDs in PD

- PG and Other ICDs Reported in Association with Parkinson’s Disease (Dodd et al, 2005)
- Association Linked to Dopamine Agonist Treatment (Weintraub & Potenza, 2006)
- Prior ICD and FH of EtOHism Associated with ICD Presence in PD (Weintraub et al, 2006; Voon et al, 2006)
- Need to Identify Neurobiological Factors Underlying Vulnerability to ICDs in PD
The endogenous opioid system influences the experiencing of pleasure.

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

Gambling or related behaviors have been associated with elevated blood levels of the endogenous opioid β-endorphin.
Pathological Gambling
Treatment
What Doesn’t Appear to Work?
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
Olanzapine/Zyprexa

- 2 double-blind studies
- Neither showed greater benefit than placebo
What Appears to Work Somewhat?
Change in CGI-MD Score Following Paroxetine Treatment

- **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)
Lexapro Treatment of Anxious Gamblers

![Graph showing Lexapro Treatment of Anxious Gamblers](image)

- **pg-ybocs - total**
- **ham-a**
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
### TABLE 1. Data for the Cue-Reactivity Procedure: Motivational and General Measures\(^a\)

<table>
<thead>
<tr>
<th>Motivational Measure</th>
<th>N-Acetylcysteine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cocaine</td>
<td>Mean</td>
</tr>
<tr>
<td>N-Acetylcysteine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craving</td>
<td>5.81</td>
<td>4.29</td>
</tr>
<tr>
<td>Desire to use</td>
<td>6.19(^b)</td>
<td>4.41</td>
</tr>
<tr>
<td>Interest</td>
<td>7.85(^b)</td>
<td>5.28</td>
</tr>
<tr>
<td>Time viewed (seconds)</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
PG-YBOCS Total Score

Urge/Thought Score
What Appears to Work Quite Well?
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)**

**Symptom Severity Measure**

- **Urge Strength**
- **Urge Frequency**
- **Thought Frequency**
- **Subjective Distress**

---

*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
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
Nalmefene

- 16 weeks
- Randomized
- 25mg, 50mg, 100mg, placebo
- 207 subjects
- 15 centers
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

Mean PG Y-BOCS Score over time for Placebo and Lithium groups.

- Placebo: Yellow diamonds
- Lithium: Red squares

* p<.05

Hollander et al, 2002
Clinical Subtyping

Within Gambling – Motivating Drive, Comorbidity, Family History

Within individuals at various time points
Anxiety/Depressive/Obsessionality

- SRI medications
- Anxiolytics
- CBT
Urge/Craving

- Opioid Antagonists
- Other Medications
- Therapies
Relapse Rate by Genotype

Proportion Nonrelapsed

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)
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
Impulsivity

- Attentional – consider stimulants
- Impulsive – anti-epileptics or lithium
Other potential medications

- Topiramate
- Ondansetron
- Acamprosate
- Memantine
- Baclofen
- Isradipine
- Antabuse
Psychotherapy

- Cognitive therapy
- Exposure and response prevention
- Stimulus control
- Covert sensitization
- Imaginal desensitization
- Family/couples therapy
Cognitive Behavioral Therapy

- Cognitive aspect includes psychoeducation, increased awareness of irrational cognitions, and cognitive restructuring.
- Behavioral techniques include identification of gambling triggers and the development of non-gambling sources to compete with the reinforcers associated with gambling.
- 9 published randomized trials of CBT for PG.
- Gamblers Anonymous and self-exclusion programs have been examined, but not in controlled studies.
Brief Interventions

- 29 subjects assigned to either workbook or to workbook plus a single in-depth interview.
- Both groups reported significant reductions in gambling at 6-months.
- A separate study assigned gamblers to a CBT workbook, a workbook plus a telephone motivational enhancement intervention, or a wait list.
- Abstinence at 6 months did not differ between groups although frequency of gambling and money lost were lower in the motivational intervention group.
Imaginal Desensitization

- Taught relaxation and then instructed to imagine experiencing and resisting triggers to gambling.
- Significant reduction in gambling behaviors in imaginal desensitization compared to traditional aversion therapy in 20 compulsive gamblers.
- 120 subjects randomly assigned to aversion therapy, imaginal desensitization, in vivo desensitization, or imaginal relaxation - subjects assigned to imaginal desensitization reported better outcomes at 1 month and up to 9 years later.
- No follow-up on approximately half of the subjects.
Motivational Interviewing Plus Imaginal Desensitization

Percentage Improved

6 months

Cognitive Behavioral Therapy
Gamblers Anonymous
Conclusions

- Pathological gambling appears to share neurobiology with addictions.
- Neurobiology of components of addictions allow for targets for pharmacotherapy.
- Emerging data suggest that medications for the pathophysiology, not a disorder, will be most effective.
- Medications should be used with psychotherapy for greater benefit.