Pathological Gambling: Co-Occurring Disorders and Psychopharmacology

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Alberta Gambling Research Conference - May, 2004
Presentation Overview

• Definitions
• Epidemiology
• Pharmacological Treatments
• Neurobiology
• Co-Occurring Disorders
• Conclusions and Future Directions
THE WEIRD WORLD OF GAMBLING

WHY DO WE BET SO MUCH?
WHO REALLY WINS?
WHO REALLY LOSES?
What is Gambling?

- Gambling is placing something of value at risk in hopes of achieving something of greater value (Potenza et al, *JAMA*, 2001)

- Perception influenced by the relative amounts of risk and reward

  - Mutual Funds vs. Day Trading
When Is Gambling a Problem?

- **Pathological Gambling (PG) (Level 3)**
  - Most Disordered Form of Gambling
  - DSM-IV-TR Disorder (Impulse Control D/O)
  - Analogous to “Substance Dependence”

- **Problem Gambling (Level 2)**
  - Widely Used But Not a DSM-IV-TR Disorder
  - Analogous to “Substance Abuse”

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## Lifetime Prevalence Estimates

<table>
<thead>
<tr>
<th>Group</th>
<th>Problem Gambling (L2)</th>
<th>Pathological Gambling (L3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>3.8% (2.9%-4.8%)</td>
<td>1.6% (1.3%-1.9%)</td>
</tr>
<tr>
<td>Youths</td>
<td>9.4% (7.6%-11.3%)</td>
<td>3.9% (2.3%-5.4%)</td>
</tr>
<tr>
<td>College Students</td>
<td>9.3% (4.4%-14.1%)</td>
<td>4.7% (3.4%-5.9%)</td>
</tr>
<tr>
<td>Adults in Treatment</td>
<td>15.0% (8.9-21.1%)</td>
<td>14.2% (10.7%-17.7%)</td>
</tr>
</tbody>
</table>

Source: Shaffer et al, 1997; Shaffer et al, 1999
## Past-Year Prevalence Estimates

<table>
<thead>
<tr>
<th>Group</th>
<th>Problem Gambling (L2)</th>
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<th>Source: Shaffer et al, 1997; Shaffer et al, 1999</th>
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</thead>
<tbody>
<tr>
<td>Adults</td>
<td>2.8% (1.9%-3.7%)</td>
<td>1.1% (0.9%-1.4%)</td>
<td></td>
</tr>
<tr>
<td>Youths</td>
<td>14.8% (9.0%-20.7%)</td>
<td>5.8% (3.2%-8.4%)</td>
<td></td>
</tr>
</tbody>
</table>
Gambling Impact and Behavior Study

- Problem/Pathological Gambling Associated with:
  - 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
Rational Approaches to the Treatment of PG

- Empirically-Validated Pharmacological Treatments (RCTs)
- Reliable and Valid Means for Assessment and Monitoring Treatment Response
- Underlying Biology (Targeting Psychopharmacological Strategies)
- Clinically-Relevant Subgroups
Empirically-Validated Treatments

- **Importance of Evidence-Based Treatments**
  - Use Generates Confidence That Effective and Safe Treatments Are Being Provided to Patients

- **When Is a Treatment Empirically Validated?**
  - Demonstrated Efficacy and Tolerability in RCTs
  - Replications
  - Effect Size
  - Duration of Treatment, Effect
Structured Trials

- Randomization
  - Minimize Systematic Bias
- Placebo-Control
  - Demonstrate Benefit Over Mock Treatment or “Sugar Pill”
- Double-Blind
  - Neither Investigator or Patient Knows Which Treatment (Active or Placebo) Is Being Received By the Patient
- Efficacy
  - How Effective Is the Treatment (Core Symptoms, Overall)
- Tolerability
  - What Adverse Effects are Associated with Treatment
Assessing Outcome

- Instruments Assessing Symptoms: Gambling-Related Thoughts and Behaviors
  - PG-YBOCS
  - G-SAS
  - ASI-PG
  - CGI-PG
  - TLFB-G

- Outcome Target
  - Abstinence vs. Diminished Symptoms
Assessing Outcome

- General Clinical Status
  - CGI (Clinical Global Improvement Scale)
- Other Symptoms
  - Concurrent or Discriminant Changes
    - Mood (BDI, HAM-D, CES-D)
    - Anxiety (HAM-A)
    - Substance (ASI, TLFB)
Assessing Outcome

- Adverse Effects
  - DOTES (Dosage Record of Treatment Emergent Symptoms)
- Compliance
  - Pill Count, MEMS Caps
- Analytical Methods
  - Intent to Treat vs. Completers
  - Missing Data (Last Observation Carried Forward vs. Non-Responder)
Psychopharmacology of PG

- No Drugs FDA-Approved for Treatment of PG
- Few Controlled Trials to Date
  - Open-Trials Confounded By Placebo Effect
  - Controlled Studies with >1 Subject Only Published Within Past Four Years
  - Most Controlled Studies Exclude Subjects with Co-Occurring Disorders, Limiting Generalizability
Psychopharmacology of PG

- Focus on Findings from Placebo-Controlled, Double-Blind, Randomized, Flexible-Dosing Trials
  - SSRIs (Fluvoxamine, Paroxetine)
  - Mu-Opioid Antagonists (Naltrexone)
  - Mood Stabilizers (Lithium)

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“It’s a new anti-depressant—instead of swallowing it, you throw it at anyone who appears to be having a good time.”
THALAMUS
AMYGDALA
HIPPOCAMPUS
PREFRONTAL CORTEX (PfC)
VENTRAL TEGMENAL AREA (VTA)
SUBSTANIA NIGRA
RAPHAE
STRIATUM
NUCLEUS ACCUMBENS (NAc)
Ventral Tegmental Area (VTA)
CAUDATE-PUTAMEN
HYPOTHALAMUS-SEPTUM
AMYGDALA
SECONDARY MOTIVATION CIRCUITRY

PRIMARY MOTIVATION CIRCUITRY

NEUROTRANSMISSION

GLUTAMATE ➔ DOPAMINE
GABA ➔ SEROTONIN

CORTICO-STRIATAL-THALAMO-CORTICAL PATHWAY

### Roles for Neurotransmitters

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

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Serotonin in ICDs and PG

• Low Levels of CSF 5-HIAA Associated with Impaired Impulse Control, PG (Nordin & Eklundh, 1999; Potenza and Hollander, 2002)

• In PG & ICD Subjects, Altered Biochemical and Behavioral Responses to m-CPP (5HT1R and 5HT2R Partial Agonist (DeCaria et al, 1998)

• Blunted 5HT Response in vmPFC in Impulsive Aggressive Subjects (Siever et al, 1999; New et al, 2002)
Decreased vmPFC Activity in Men with PG Viewing Final Part of Gambling Videotapes

Potenza et al, *Arch Gen Psychiatry*, 2003
Left vmPFC Implicated During Stroop Performance In ICDs


Bipolar - Cont (Blumberg et al, 2003, *Arch Gen Psychiatry*)
Fig. 5. Normal brain fitted with the five possible rods. The best rod is highlighted in solid white [except for (B), where it is shown in red]. The areas spared by the iron are highlighted in color: Broca, yellow; motor, red; somatosensory, green; Wernicke, blue. (A) Lateral view of the brain. Numbered black lines correspond to levels of the brain section shown in (C). (D and E) Medical view of left and right hemispheres, respectively, with the rod shown in white.
Double-Blind SSRI Studies

- Fluvoxamine (Blanco-Jerez et al, 2002; Hollander et al, 2000)
- Paroxetine (Kim et al, 2001; Grant et al, 2003)
- Mixed Findings with Regard to Efficacy and Tolerability
- Blanco-Jerez et al found high discontinuation rates at 6 months, complicating interpretation of findings
Fluvoxamine

- Placebo-Controlled, Double-Blind Crossover Study with 1-Week Single Blind Placebo Lead-In (Hollander et al, 2000)
- 15 Subjects Enrolled, 10 Completed (All Male)
- Seven of Ten Completers Determined to Be Responders By PG-CGI and PG-YBOCS Scores (Average EOS Dose of 195 (SD50) mg/day)
- Largest Difference Observed at EOS Timepoint, with Large Early Placebo Response

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Figure 1. Pathologic gambling Clinical Global Impression (PG-CGI) improvement scores in patients ($N = 10$) completing treatment with a placebo (phase I) followed by fluvoxamine (phase II; ——) or fluvoxamine (phase I) followed by a placebo (phase II; ———). Repeated-measures analysis of variance (RM-ANOVA): $F(1,8) = 14.8$, $p = .005$ (Drug Effect). RM-ANOVA: $F(1,8) = 6.0$, $p = .040$ (Phase Order $\times$ Drug Interaction). Post hoc ANOVA: phase I, $F(1,7) = 0.113$, $p = .747$; phase II, $F(1,7) = 12.45$, $p = .010$.

Figure 2. Pathologic gambling modification of the Yale–Brown Obsessive Compulsive Scale (PG-YBOCS) scores in patients ($N = 10$) completing treatment with a placebo (phase I) followed by fluvoxamine (phase II; ——) or fluvoxamine (phase I) followed by a placebo (phase II; ———). Repeated-measures analysis of variance (RM-ANOVA): $F(1,8) = 5.6$, $p = .046$ (Drug Effect). RM-ANOVA: $F(1,8) = 13.2$, $p = .007$ (Phase Order $\times$ Drug Interaction). Post hoc ANOVA: phase I, $F(1,7) = 0.268$, $p = .621$; phase II, $F(1,7) = 4.836$, $p = .064$. 

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Hollander et al, 2000
Paroxetine

- Double-Blind, Placebo-Controlled Trial of Eight-Week Duration w/ One-Week Single-Blind Placebo Lead-In (Kim et al, 2002)
- 41 Participants (20 Active, 21 Placebo) of 53 Enrolled
- EOS Active Dose of 52(SD13) mg/day
- Treatment w/Active Drug as Compared with Placebo Associated w/ Significantly Greater Clinical Improvement as Measured by Scores on the G-SAS, PT-G CI, and MD-CGI

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Change in CGI-MD Score Following Paroxetine Treatment

Week 1, 2, 3, 4, 5, 6, 7, 8

Placebo
Active (N)

* p<0.05

Kim et al, 2002
Paroxetine

- Initial Promising Results Led to First Multi-Center Treatment Trial for PG
- Results of Multi-Center Trial Largely Negative (Grant et al, 2003)
- Drug Treatment Associated with More Rapid Early Response
- Substantial, Sustained Placebo-Response
- Mixed Data Exist with Regard to Efficacy of SSRIs in the Treatment of PG

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Relationship Between PG and SUDs

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

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

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

• Similar Treatments
  - Self-Help, Cognitive Behavioral Therapy, Naltrexone
Clinical Relevance of PG and SUDs

- Group of Individuals with Co-Occurring PG and SUDs Experience More Severe Symptoms Than Those With SUDs Alone (Kaplan & Davis, 1997)
  - Increased Rates of Admission for Detoxification (Greater Than Two-Fold Rate)
  - Increased Rates of Admission for Psychiatric Stabilization (Greater Than 50% Increased Rate)
### Increased Suicidality in Individuals with Co-Occurring PG and SUDs

<table>
<thead>
<tr>
<th>Group</th>
<th>Passive Suicidal Thoughts (ST)</th>
<th>Active ST</th>
<th>Suicidal Attempts (Of Those w/ ST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtOH/Drug</td>
<td>50.3%</td>
<td>41.1%</td>
<td>28.8%</td>
</tr>
<tr>
<td>Gambling</td>
<td>55.4%</td>
<td>47.2%</td>
<td>18.0%</td>
</tr>
<tr>
<td>Both</td>
<td>75.0%</td>
<td>70.1%</td>
<td>41.3%</td>
</tr>
</tbody>
</table>

Source: Federman et al, 1998

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Alcohol Use and Gambling

Source: Push-tab Punchcard, ca 1950's
## Co-Occurring 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>Anti-Social 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

Source: Cunningham-Williams et al, 1998

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Genetics of PG, Alcoholism, AAB

- VET Registry Studies (6718 Twins) Suggest Familial Contributions to PG (Eisen et al, 1998)
- Shared Contributions Exist For the Development of PG and Alcohol Dependence (AD) (Slutske et al, 2000)
  - 12%-20% of Genetic Variation in the Risk for PG Accounted for by the Risk for AD
- Shared Genetic Contributions to PG, AD and Anti-social Behaviors (Slutske et al, 2001)
  - Common Link of Impulsiveness

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Naltrexone

• Mu-Opioid R Antagonist, FDA-Approved for AD

• Open-Label Case Reports, Series (Kim, 1998; Crockford & el-Guebaly, 1998; Kim & Grant, 2001)


• Placebo-Controlled, Randomized, Double-Blind, Parallel-Arm, Flexible Dosing Trial of Naltrexone (11 Week Duration After 1 Week Placebo Lead-In)
Naltrexone

- 83 Subjects Enrolled; 45 Subjects (25 Placebo, 20 Active Drug) Retained ≥2 Weeks at 100 mg/day
- EOS Active Drug Dose 188(SD96) mg/day
- Active Drug Found Superior To Placebo on Measures of CGI-PT, CGI-MD
- Greater Drug-Related Improvement in Subjects with High Initial Gambling Urge Measures
  - Similar to Naltrexone & Cravings in SUDs (e.g., EtOH Dependence)

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Naltrexone

- LFT Elevation in 20-25% of Subjects Receiving Naltrexone
  - Generally Observed in Combination w/ NSAID Use
  - High Rates of Dry Mouth, Nausea, Decreased Libido and Vivid Dreams Also Observed

- Relatively Frequent Observation of Adverse Effects and Black-Box Warning for Hepatotoxicity Suggest the Need for Caution and Careful Monitoring of Off-Label Use
Clinician Rated Clinical Global Impression (PG-CGI-MD)

Improvement

- Placebo
- Naltrexone

Week

0 1 2 3 4 5 6 7 8 9 10 11 12
Pathological Gambling (PG)

- Bipolar Spectrum
- Mood Disorders
- Personality Disorders
- Compulsive Sexual Behaviors
- Attention Deficit Hyperactivity
- Other Impulse Control Disorders
- Suicide
- Substance Use Disorders

Adapted From Potenza and Hollander, in press
Left vmPFC Implicated During Stroop Performance In ICDs

PG (Potenza et al, 2003, Am J Psychiatry)
Control (Potenza et al, 2003, Am J Psychiatry)
PG - Control (Potenza et al, 2003, Am J Psychiatry)
Bipolar - Cont (Blumberg et al, 2003, Arch Gen Psychiatry)

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Lithium

- Salt FDA-Approved for Tx of Bipolar Disorder
- Placebo-Controlled, Double-Blind, Parallel-Arm 10-Week Trial of Sustained-Release Lithium (Hollander et al, in press; presented 2001)
- 37 Bipolar-Spectrum Subjects Enrolled, 26 Completed (10 Lithium-Treated, 16 Placebo-Treated)
- Average EOS Dose of 1,170(SD221) mg/day (Therapeutic Blood Levels)

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Lithium

- Lithium-Treated Group Significantly Improved as Compared with Placebo-Treated Group on Measures of Gambling (PG-CGI, PG-YBOCS) and Mania (CARS-M)
  - 9/10 Lithium-Treated Subjects Categorized As Responders

- The Utility of Mood Stabilizers in the Treatment of PG without Co-occurring Bipolar-Spectrum Disorders Requires Examination
Treating Bipolar-spectrum PG: Lithium

PG-YBOCS Scores


*Lithium is not approved for the treatment of PG.*
Treating Bipolar-spectrum PG: Lithium Rating Scale for Mania


*Lithium is not approved for the treatment of PG.*
Summary

- Although No Drug Is FDA-Approved for Tx of PG, Safe and Effective Pharmacotherapies Are Emerging
  - Effective Classes Include SSRIs, Mu-Opioid Receptor Antagonists and Mood Stabilizers
  - Limitations Include
    - Small Samples, Short-Term Trial Durations
    - Frequent Exclusion of Dual-Diagnosed Subjects
    - Limited Geographic Sites
    - Variability in Findings

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Existing Challenges

- Translating Research Into Clinical Practice
- Defining Role for Pharmacotherapies
  - First-line or Adjunctive
  - Combination Behavioral & Pharmacological
- Matching Patients with Specific Treatments
  - Clinical Characteristics (Symptoms, Age, ...)
  - Co-Occurring Disorders
  - Genetic Factors, Brain Imaging Patterns
  - Environmental Exposures

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Conclusions

As More Safe and Effective Treatments Become Available, The Need for Early Identification Grows

- Screening, Awareness Strategies for Public, Clinicians

- Particularly Relevant for Health Care Providers in the Area of Addiction Given the High Rates of Co-Occurrence

- Helplines, Other Means of Transitioning into Treatment

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Frank & Ernest

IT'S ABOUT SELF-CONTROL.

"NO" THYSELF

Thaves 3-30
Do you really want to spend your golden years hooked up to a machine?

For most seniors, gambling is not a problem. But for others, it becomes a way to cope with the loss of loved ones, retirement or loneliness. Call for free, confidential help 1-800-346-6238 CT Problem Gambling Helpline.

Source: Connecticut Department of Mental Health and Addiction Services
PHARMACY Rx

Is the generic equivalent of this placebo ok?

www.comicspage.com

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Don’t gamble with patient medication safety!
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NIDA  APA  NIAAA  NARSAD  NIAAA  NCRG  Women’s Health Research at Yale
Fogarty Center  VA-MIRECC  Ortho McNeil  GlaxoSmithKline  Oy ContraL Forest