Disclosures

- Consultant to Shire, INSYS, RiverMend Health, Jazz Pharmaceuticals, Opiant/Lakelight Therapeutics
- Research Grants from National Center for Responsible Gaming
- Research Gift from Mohegan Sun
- Consultant to Gambling and Legal Entities on Issues Related to Impulse Control Disorders

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Co-Occurring Disorders

- 96% of Individuals with PG Have One or More Co-occurring Psychiatric Disorder and 64% Have 3 or More (Kessler et al, 2008)

- In Most People with PG (74%), a Co-occurring Disorder Preceded the Onset and Predicted the Persistence of PG (Kessler et al, 2008)

- Co-occurring Disorders May Provide Guidance as to Which Treatments Might be Most Effective

- Subsyndromal Levels of Gambling Associated with Harms, Raising Questions Regarding Diagnostic Thresholding (Weinstock et al, 2018)
<table>
<thead>
<tr>
<th>Disorder</th>
<th>LR Gam Vs Non/LF Gam</th>
<th>AR Gam Vs Non/LF Gam</th>
<th>PP Gam Vs Non/LF Gam</th>
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<tbody>
<tr>
<td>Major Dep</td>
<td>1.02</td>
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<td>1.25</td>
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<tr>
<td>Dysthymia</td>
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<td>3.10</td>
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<td>2.11*</td>
<td>3.02*</td>
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<td>Hypomania</td>
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<td>2.23***</td>
<td>5.37***</td>
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*=p<0.05; **=p<0.01; ***=p<0.001

Source: Desai and Potenza, 2008
## PG Severity & Axis I Disorders in Women

<table>
<thead>
<tr>
<th>Disorder</th>
<th>LR Gam Vs Non/LF Gam</th>
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<td>1.59***</td>
<td>2.59***</td>
<td>3.41***</td>
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<td>4.44**</td>
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*=p<0.05; **=p<0.01; ***=p<0.001

Source: Desai and Potenza, 2008
<table>
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<th>Disorder</th>
<th>Fem Vs M LR Gam</th>
<th>Fem Vs M AR Gam</th>
<th>Fem Vs M PP Gam</th>
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<td>Hypomania</td>
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<td>0.97</td>
<td>0.42</td>
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<td>1.85</td>
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<td>Nicotine Dep</td>
<td>0.99</td>
<td>1.59**</td>
<td>1.12</td>
</tr>
<tr>
<td>Drug Ab/Dep</td>
<td>1.15</td>
<td>1.82</td>
<td>2.22</td>
</tr>
</tbody>
</table>

*=p<0.05; **=p<0.01; ***=p<0.001

Source: Desai and Potenza, 2008
Rates of Major Depression By Gambling Severity and Gender

- Men
- Women

Gambling Severity
- Non-Gambling/Low Frequency
- Low-Risk
- At-Risk
- Problem/Pathological

Percentage
- 0
- 5
- 10
- 15
- 20
- 25
- 30
- 35

Desai and Potenza, 2008
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Rec Gam Vs Non Gam</th>
<th>Prob Gam Vs Non Gam</th>
</tr>
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<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>
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<tr>
<td>Schizophrenia</td>
<td>0.6 (0.2, 1.8)</td>
<td>3.5 (1.3, 9.7)*</td>
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<tr>
<td>Phobias</td>
<td>1.2 (0.9, 1.7)</td>
<td>2.3 (1.2, 4.3)*</td>
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<td>Somatization</td>
<td>1.7 (1.1, 2.8)*</td>
<td>3.0 (1.6, 5.8)*</td>
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<tr>
<td>Antisocial PD</td>
<td>2.3 (1.6, 3.4)*</td>
<td>6.1 (3.2, 11.6)*</td>
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<td>Alcohol Use</td>
<td>1.9 (1.3, 2.7)*</td>
<td>7.2 (2.3, 23.0)*</td>
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<tr>
<td>Alcohol Abuse/Dep</td>
<td>1.9 (1.6, 2.4)*</td>
<td>3.3 (1.9, 5.6)*</td>
</tr>
<tr>
<td>Nicotine Use</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
Schizophrenia and Schizoaffective Disorder and PG

- Approximately 10% of Individuals with Schizophrenia or Schizoaffective Disorder Have PG and Approximately 20% Have Gambling Problems (Desai and Potenza, 2009)
- Chasing Losses Among this Group was Associated with Alcohol and Drug Problems, a Family History of Gambling Problems and Greater Gambling Involvement (Yakovenko et al., 2018)
- PPG Was Associated with Polysubstance Use in this Sample and with Impulsivity Among Males (Fortgang et al., 2018)
Impulsivity and Problem-Gambling Severity By Gender in SCZ

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Fortgang et al., 2018
How Much Do Genetic Factors Underlie GD and Co-Occurring Disorders?

- Many Conditions Including Gambling Disorder (GD) Aggregate within Families
- Greater Likelihoods of Conditions in Individuals with Affected Family Members May Reflect Either Environmental or Genetic Factors or Both
- Twin Studies Offer the Opportunity to Estimate the Degree to Which Specific Conditions (and Their Co-Occurrences) May Reflect Environmental or Genetic Contributions (Shah et al., 2005)
Summary of VET-R Findings

- Greater Genetic Contributions to More Stringently Thresholded Levels of Problem/Pathological Gambling in Men (Eisen et al, 1998)

- Co-occurrences Between (P)PG and Major Depression, Generalized Anxiety Disorder, Stimulant Abuse/Dependence and Appear Linked to Predominantly Genetic Factors (Potenza et al, 2005; Giddens et al, 2011; Xian et al, 2014)

- Co-occurrences Between (P)PG and Panic Disorder, Alcohol Dependence, Nicotine Dependence and Cannabis Use Disorders Appear Linked to Both Environmental and Genetic Factors (Slutske et al, 2000, 2013; Giddens et al, 2011; Xian et al, 2014)
How Can We Use Our Knowledge Regarding Treatment of Co-occurring Disorders?

• Shared Genetic (and Thus Other Biological) Contributions Between GD and Other Psychiatric Disorders Suggests That Treatments for Other Disorders Might Be Helpful in Treating GD

• Such an Approach Might Be Particularly Effective if We Take Co-Occurring Disorders into Account When Testing and Developing Treatment Algorithms

• Such an Approach May Have Applicability to Both Pharmacological and Behavioral Therapies (Although be Cautious – See Project MATCH Results)
Proposed Pharmacotherapy Algorithm for PG

Individual with PG

Less Willing to Consider Drug Treatment
→ Consider N-Acetyl Cysteine

More Willing to Consider Drug Treatment
→ Co-Occurring Psychiatric Condition?
  → No
  → Consider Naltrexone
  → Yes
  → Substance Use Disorder or Positive FH of Alcoholism?
    → No
    → Mood or Anxiety Disorder?
      → Yes
      → Consider Naltrexone
      → No
      → Bipolar or Bipolar-Spectrum Disorder?
        → Yes
        → Consider Lithium or Other Mood Stabilizer
        → No
        → Consider SRI

FH – Family History
SRI – Serotonin Reuptake Inhibitor
GD, Alcohol & Co-Occurring Disorders

- In a US Veterans with AD and Another Co-Occurring Non-GD Disorder (N=174), 6.3% Met PG Criteria and 25.9% Had One or More Criteria (Grant et al., 2017)

- In a RCT of Disulfiram (DSF) and Naltrexone, DSF was Associated with Less Alcohol Abstinence in the Group with Problem Gambling Features (PGF+)

- PGF+ Was Associated with Less Improvement in: Drinking Days Per Week; and Psychiatric Domains (Overall BSI and Domains of Anxiety, Phobic Anxiety, Somatization, Paranoid Ideation and Interpersonal Sensitivity)

- Suggests Need for Active GD Screening

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Behavioral Therapies

• Behavioral Therapies (Including Cognitive Behavioral Therapy (CBT), Imaginal Desensitization, and Motivational Interviewing) Appear Efficacious in the Treatment of PG

• Several Forms of CBT for PG Exist Either Based on Approaches Used in Drug Addictions (Petry, 2005) or Focusing on Irrational Cognitions (Ladouceur and LaChance, 2006)

• Imaginal Desensitization May Involve Generating and Listening to Audio Cassettes (Grant et al, 2011)

• GA Also Appears Beneficial (Reviewed in Brewer and Potenza, 2008; Yip and Potenza, 2014)
Behavioral Therapies

• Many Early Studies of Pharmacological Therapy to Behavioral Therapy Have Not Demonstrated Substantial Additional Benefit, Although Existing Studies Are Small and Limited (Yip and Potenza, 2014)

• N-acetyl Cysteine Superior to Placebo with Respect to Diminishing Smoking and Improving Follow-Up Gambling Treatment Outcome in Individuals with PG and ND Receiving IDMI for PG (Grant et al., 2014)

• Topiramate in Conjunction with Psychotherapy Found Superior to Placebo (de Brito et al, 2017)

• Additional Research is Needed to Examine the Extent to Which Specific Therapies May Work Synergistically (and If So, for Whom)
WHO-Related Workgroups

- Meetings Have Focused on Internet Use Behaviors and Behavioral Addictions
Gambling Disorder – ICD-11

• “Gambling disorder is manifested by a persistent or recurrent gambling behavior that is characterized by an impaired control over gambling, increasing priority given to gambling over other activities to the extent that gambling takes precedence over other interests and daily activities and continuation of gambling despite the occurrence of negative consequences. The behavior pattern is of sufficient severity to result in significant impairment in personal, family, social, educational, occupational or other important areas of functioning. These features and the underlying pattern of gambling are normally evident over a period of at least 12 months in order for a diagnosis to be assigned, although the required duration may be shortened if all diagnostic requirements are met and symptoms are severe.”
Hazardous Addictive Behaviors in ICD-11

- The ICD Considers Conditions and Behaviors Relating to World Public Health
- Subsyndromal Behaviors Relating to Gambling and Gaming May Be Particularly Important to Consider Given the Relatively Small Number of Individuals with Disorders as Compared to the Larger Numbers of People Gambling and Gaming (Shaffer and Korn, 2002)
- Akin to Harmful Alcohol Use in ICD-10, Hazardous Gambling or Betting and Hazardous Gaming Included in ICD-11 (“Factors Influencing Health Status or Contact with Health Services”)
Hazardous Gambling or Betting

“Hazardous gambling or betting refers to a pattern of gambling and betting that appreciably increases the risk of harmful physical or mental health consequences to the individual or to others around the individual. The increased risk may be from the frequency of gambling or betting, from the amount of time spent on these activities or the context of gambling and betting, from the neglect of other activities and priorities, from risky behaviors associated with gambling or betting or its context, from the adverse consequences of gambling and betting, or from the combination of these. Hazardous gambling and betting has not yet reached the level of having caused harm to physical or mental health of the user or others around the user. The pattern of gambling and betting often persists in spite of awareness of increased risk of harm to the individual or to others.”

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Conclusions & Future Directions

- Gambling Disorder Frequently Co-Occurs with Many Other Psychiatric Disorders
- Relationships Extend to Subsyndromal Levels
- Gambling/Gaming/Sports Boundaries are Blurring
- WHO Instruments For Use in Identifying Hazardous and Disordered Gaming and Gambling Are Being Developed for Worldwide Use
- Use of These Instruments in Multiple Settings May Help Optimize Policy, Prevention, Treatment and Responsible Gambling Efforts in Rapidly Changing Digital-Technology Environments
Acknowledgments

Women & Addictions
Carolyn Mazure
Rani Desai
Paul Maciejewski

Div Substance Abuse
Bruce Rounsaville
Kathleen Carroll
Suchitra Krishnan-Sarin
Stephanie O’Malley
Elaine Lavelle
Dana Cavallo
Ran Wu

Imaging
Todd Constable
Godfrey Pearlson
Rajita Sinha
Bruce Wexler
Robert Fulbright
Cheryl Lacadie
Patrick Worhunsky
Jiansong Xu
Judson Brewer
Hedy Kober
Elise DeVito
Michael Stevens
Alex Neumeister

Genetics
Joel Gelernter
Seth Eisen
Hong Xian
Jeff Scherrer
Justine Giddens

RCTs
Jon Grant
SW Kim
Shane Kraus
Ismene Petrakis

Gambling Center
Of Excellence
Iris Balodis
Corey Pilver
Sarah Yip
Igor Yakovenko
Scott Bullock
Rebecca Fortgang
Monica Solorzano
Ardeshir Rahman
Yvonne Yau
And Many Others!

Translational
Jane Taylor
R. A. Chambers

CT Partnerships
Marvin Steinberg & CCPG
Jeremy Wampler & PGS

NIH (NIDA, NIAAA, ORWH) VA CCPG WHR DMHAS NCRG Moh Sun