#### Using Science to Improve the Treatment of Gambling Addiction

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#### **Disclosure Information**

I have the following financial relationships to disclose: No conflicts with respect to this presentation My research is supported by NIAAA, AFSP, and the **TLC** Foundation Grant/Research support from: Takeda Pharmaceuticals I will discuss <u>off-label use</u> and/or investigational use in my presentation as there are no FDA-approved medications for gambling addictions.



# Impulse Control Disorders/Behavioral Addictions?

- Gambling
- Stealing
- Sexual behavior
- Shopping
- Fire-setting
- Internet use
- Overeating

Common Core Qualities of Behavioral Addictions

Repetitive or compulsive engagement in a behavior despite adverse consequences

Diminished control over the problematic behavior

Appetitive urge or craving state prior to engagement in the problematic behavior

Hedonic quality during the performance of the problematic behavior.

# Common Core Qualities of Behavioral Addictions

- Tolerance
- Withdrawal
- Impairment in major areas of life functioning
- > Telescoping

# Developmental Biology

- Gambling addiction generally start in young adulthood.
- Environmental and genetic influences vulnerability to and expression of gambling addiction
- Changes in brain structure and function during adolescence might influence the motivation to engage in risk-taking behaviors.



Notice: Judgment is last to develop!



**Balance** 

#### **Youth Problem Behaviors**



#### Family/Genetic Factors

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

Additionally, 64% of the co-occurrence between gambling and alcoholism - attributable to genes that simultaneously influence both disorders.

#### Role of Trauma

Neglectful parenting style

Addictive behaviors - more likely to report histories of

- physical neglect
- emotional abuse
- Sexual abuse

# Neurobiology



### Neurochemistry of Behavioral Dyscontrol



#### Glutamate

Levels of glutamate within the nucleus accumbens mediate reward-seeking behavior

Restoring extracellular glutamate concentration in the nucleus accumbens seems to decrease cravings. 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

### Biochemistry – Opioid System

The endogenous opioid system influences the experiencing of pleasure.

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

Addictions have been associated with elevated blood levels of the endogenous opioid βendorphin. Neurocognition in Behavioral Addictions

Executive function deficits are greater in those with behavioral addictions than in control subjects, including:

Planning

- Cognitive flexibility
- Inhibition



#### 7/27/2018



#### Impulsivity as an Endophenotype

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

### Cognition: Early Symptom?

### **Treatment Implications**



SiPRESS



"Betcha I recover before you do."

#### Treatment

• Pharmacotherapy

No medication FDA-approved for gambling or sex

 Cognitive-Behavioral Therapy (CBT) Length of treatment unknown; brief interventions have shown benefit; Multiple versions of CBT have shown benefit;

Yau YH, Potenza MN. Gambling disorder and other behavioral addictions: recognition and treatment. Harv Rev Psychiatry. 2015 Mar-Apr;23(2):134-46.

#### Pharmacotherapies

Several medications do not appear to offer any benefits over placebo:

Bupropion Atypical antipsychotics Acamprosate Baclofen

Grant JE, Schreiber LR, Odlaug BL. Phenomenology and treatment of behavioural addictions. Can J Psychiatry. 2013 May;58(5):252-9

#### Pharmacotherapies (cont'd)

- The following medications may offer some benefits for behavioral addictions
- Serotonin reuptake inhibitors
- Opiate antagonists
- N-acetyl cysteine (NAC)

Grant JE, Schreiber LR, Odlaug BL. Phenomenology and treatment of behavioural addictions. Can J Psychiatry. 2013 May;58(5):252-9



#### 7/27/2018

#### 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

# N-Acetyl Cysteine (Cont)



Grant JG, et al., N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. Biol Psychiatry. 2007 Sep 15;62(6):652-7

# N-Acetyl Cysteine (Cont)

#### RESULTS

- N=16 (59.3%) met responder criteria
- Mean effective dose: 1476.9 (±311.3) mg/d



Grant JG, et al., N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. Biol Psychiatry. 2007 Sep 15;62(6):652-7

# **Psychosocial Treatments**

- Motivational enhancement
- Individual and Group Cognitive behavioral therapy
  - social skills, assertiveness, anger management; cognitive restructuring
- Imaginal exposure
- Brief interventions

Grant JE, Schreiber LR, Odlaug BL. Phenomenology and treatment of behavioural addictions. Can J Psychiatry. 2013 May;58(5):252-9

# Psychosocial Treatments (Cont)

#### **Brief Interventions**

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

Workbooks include CBT and motivational enhancement techniques.

CBT workbook, a workbook plus a telephone motivational enhancement.

Petry NM, Ginley MK, Rash CJ. A systematic review of treatments for problem gambling. Psychol Addict Behav. 2017 Dec;31(8):951-961

#### **Motivation to Quit Behavioral Addictions**

1) <u>Positive</u> aspects of impulsive behavior (what are the positive things behavioral addiction gives me?)	2) <u>Negative</u> aspects of quitting (what do I lose if I stop behavioral addiction?)
3) What are the <u>negative</u> consequences of behavioral addiction (current and future?)	4) What are the <u>advantages</u> of quitting behavioral addiction (what do I have to gain?)



# Psychosocial Treatments (Cont)

#### Imaginal Exposure

Client and therapist develop an imaginal exposure script that includes all the relevant internal and external triggers that relate to the behavioral addiction



Grant JE, et al., Imaginal desensitisation plus motivational interviewing for pathological gambling: randomised controlled trial. Br J Psychiatry. 2009 Sep;195(3):266-7.

# **Clinical Subtyping**

Comorbidity? Neurocognition? Genetics? Imaging?

### Comorbidity – Means What?

- addictions cause the other disorder?
- Other disorder causes addiction?
- addiction one branch of a tree?
  - Co-occurrence by chance?
- Common stress, genetics, trauma cause?

#### Bipolar Spectrum Gamblers PG-YBOCS Total Score Over Time



Hollander et al, 2002

# Heterogeneous Profiles?



# 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:  $23.4 (\pm 8.1) \text{ mg/d}$ 

 Table. Changes on outcome measures

	Visit 1 n=29	Visit 6 n=28	p-value
PG-YBOCS total score	21.8	8.9	<.001
Responder, <i>n</i> (%)	n/a	18 (62.1)	<.001
Dollars lost per week	743	309	<.001
Hours gambled per week	10.4	4.0	<.001

# Open-Label Study of Memantine in Gambling Disorder

#### RESULTS

#### Table. Performance on cognitive tasks

 Cognitive flexibility improved from baseline to endpoint

 GD subjects were comparable to healthy controls at study endpoint

	Baseline v Endpoint		Baseline v Controls		Endpoint v Controls	
	т	P- value	т	P- value	т	P- value
IDED total errors	2.20	0.037	2.09	0.041	1.06	0.294

 Pharmacological modulation of the glutamate system may reduce gambling, and may do so by improving neurocognitive function related to cognitive flexibility.

# **Open-Label Study of Tolcapone in Gambling: Genotyping**

#### RESULTS

val/val COMT polymorphism was associated with significantly greater improvement from tolcapone compared to met/met **Figure.** Change in PG-YBOCS from baseline to end of treatment in different COMT Gambling Disorder subjects



Tolcapone and genotype appear to have interactive effects on dopaminerelated executive functioning, with tolcapone enhancing Val-COMT subjects but either not improving or impairing Met-COMT subjects

### Relapse Rate by Genotype



Days

#### Conclusions

Gambling addiction is common and associated with significant morbidity and mortality

Neurobiology is being worked out and allows for more targeted subtyping of individuals and their treatment

#### **QUESTIONS?**



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