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The IDPH Office of Problem Gambling Prevention and Treatment

**Medication Assisted Therapy (MAT) Research for Pathological Gambling**

Presented by:

Jon Grant, JD, MD, MPH
March 12, 2015
12N – 1:30 pm, Central Time Zone

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## How to participate today:

There are several ways we will ask you to participate during the presentation:

- **Question and Answer box**: type your question or comment in this box.
- **Polling Questions:** by clicking on the answer(s) in the polling box.

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## Session Goals:

- **develop an understanding about the possible use of medications in treating individuals with gambling problems**
- **be aware of how medication and psychotherapy can work together to improve outcomes.**

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## Agenda for this webinar

- 12:00-12:05 – Introduction
- 12:05-1:15 – Training Session
- 1:15 – 1:30 – Question and Answer
- 1:30 pm – end of session – Please complete survey at the end of this webinar

## About the presenter:

Jon Grant, JD, MD, MPH, Professor, Dept. of Psychiatry and Behavioral Neuroscience. Jon Grant's research focuses on the neurobiology and treatment of impulse control disorders (e.g., gambling, stealing, shopping, sex), obsessive compulsive disorder, and drug addictions. He is an editorial board member of nine scientific journals, director of a Center of Excellence in Gambling Research supported by the National Center for Responsible Gaming, and editor in chief of the Journal of Gambling Studies. Grant is the author of nine books on impulse control disorders and over 250 peer-reviewed scientific articles, including publications in the Lancet, American Journal of Psychiatry, and Archives of General Psychiatry. He received his MD from Brown University and a JD from Cornell University Law School. He also obtained an MA in English literature from the University of Chicago and an MPH from Harvard University. He earned his BA from the University of Michigan. Grant is a member of the American College of Neuropsychopharmacology.

## Disclosure Information

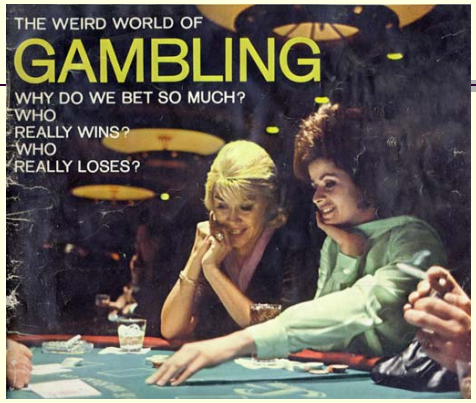
**Financial** relationships:

My research is supported by NIDA and the NCRG (Center of Excellence)

Grant/Research support from: Forest Pharmaceuticals and Roche Pharmaceuticals

I will discuss off-label and/or investigational use: opiate antagonists, NMDA antagonists, COMT inhibitors, and glutamate agents.

Collaborators: Suck Won Kim and Brian Odlaug (UMN), Samuel Chamberlain (Cambridge), Marc Potenza (Yale), Dan Stein (South Africa)




Source: Look Magazine, March, 1963

## Gambling Disorder

Persistent and recurrent maladaptive gambling behavior:

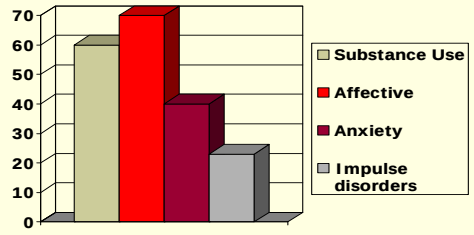
| | |
|---|---|
| Preoccupation | Lying |
| Tolerance | **Illegal acts** |
| Inability to control | Impairment |
| Withdrawal | Relying on others |
| Escape | Chasing losses |

## Public Health Significance

**Gambling is Associated with High Rates of:**

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

## Co-Occurring Disorders in Gambling Disorder




## 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).

## Neural Systems and Addiction

~~**Mesocorticolimbic Dopamine System ("Overactive Motor")**~~

**Ventral Tegmental Area, Nucleus Accumbens**

**Frontal Serotonin Systems ("Bad Brakes")**

**Frontal/Prefrontal Cortical Function**

**Role for Neurotransmitter Systems Modulating DA, 5HT Function**

- **GABA, Glutamate, Opioids, ...**

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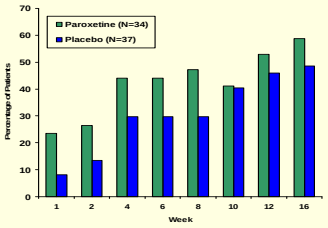
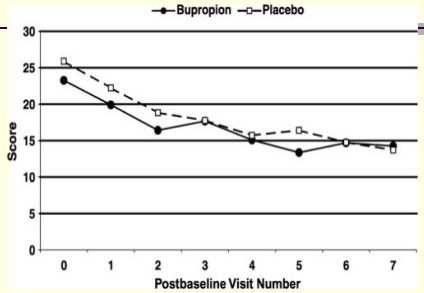
## Polling Question 1

## Treatment Implications

**CGI-I Score of 1 or 2 During Treatment with Paroxetine or Placebo**



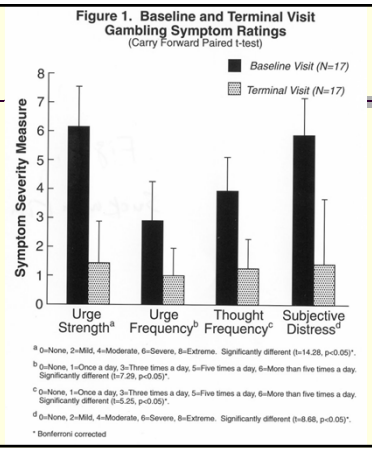

59% response rate in the paroxetine group
49% rate in the placebo group
45 completers (Grant et al. 2003)



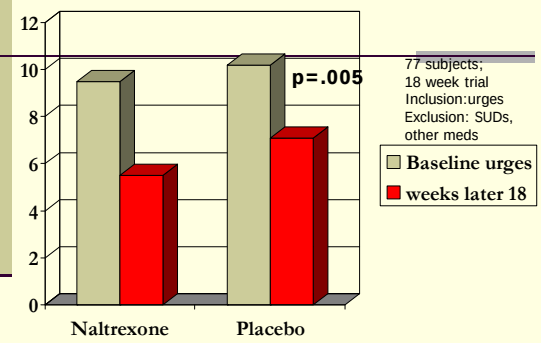

## Polling Question 2

## Opioid Antagonists

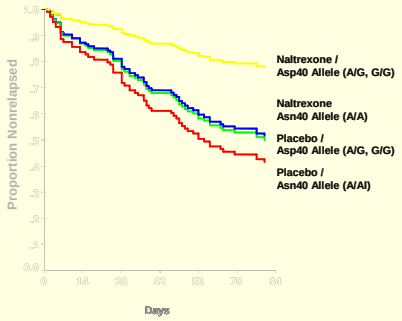
- The mu-opioid system:
  - underlies urge regulation through the processing of reward, pleasure and pain, at least in part via modulation of dopamine neurons in mesolimbic pathway through GABA interneurons.





## Relapse Rate by Genotype




## Analysis of Maximum Likelihood Estimates (N=282)

| Variable | Parameter Estimate | Standard Error | Chi-Square | Pr>ChiSq | Hazard Ratio |
|---|---|---|---|---|---|
| | | | | | |
| **FH-AUD** | 0.55 | 0.24 | 7.53 | **0.006** | 1.74 |

Baseline urges were significantly associated with response to higher doses of opiate antagonists (i.e. nalmefene 50mg or 100mg or naltrexone 100mg or 150mg).

## Polling Question 3

## 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

TABLE 1. Data for the Cue-Reactivity Procedure: Motivational and General Measures[a]

| | N-Acetylcysteine | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | Cocaine | | Neutral | | Cocaine | | Neutral | |
| Motivational Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| N-Acetylcysteine | | | | | | | | |
| Craving | 5.81 | 4.29 | 1.32 | 2.41 | 7.25 | 5.27 | 1.09 | 2.34 |
| Desire to use | 6.19[b] | 4.41 | 1.01 | 1.66 | 8.32 | 5.13 | 1.79 | 3.09 |
| Interest | 7.85[b] | 5.28 | 2.81 | 2.61 | 9.65 | 6.03 | 3.30 | 3.49 |
| Time viewed (seconds) | 3.92[b] | 1.70 | 2.86 | 1.40 | 4.86 | 2.27 | 2.58 | 1.33 |

[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 ($p<0.05$).

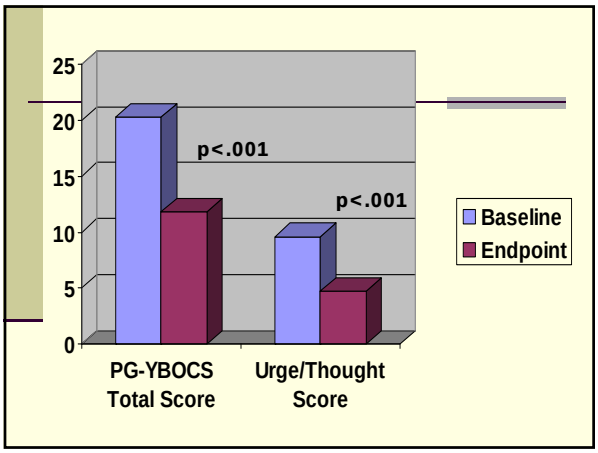
## Open-Label NAC for Gambling

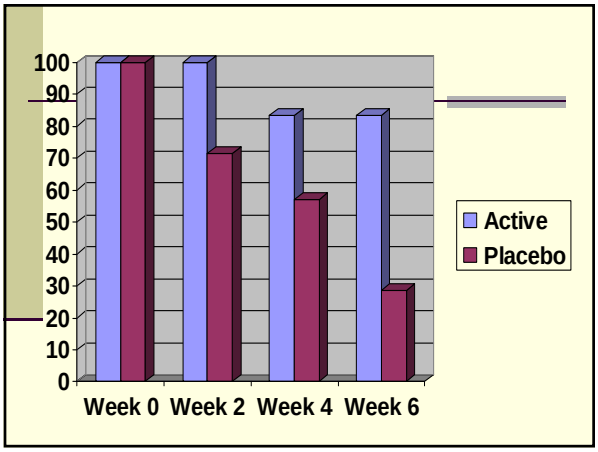
NAC 1800 mg/d, 8 weeks

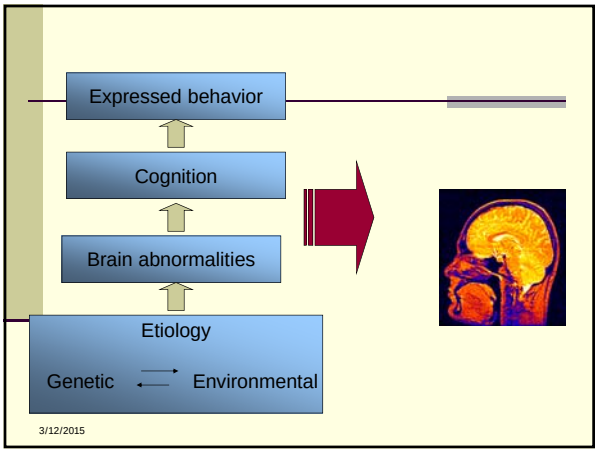
27 men and women aged 18 to 75 with a primary diagnosis of pathological gambling

Required to have moderate cravings to gamble

Grant et al., Biol Psychiatry. 2007;62(6):652-7


25
20
15
10
5
0
p<.001
p<.001
Baseline
Endpoint
PG-YBOCS Total Score
Urge/Thought Score


100
90
80
70
60
50
40
30
20
10
0
Active
Placebo
Week 0
Week 2
Week 4
Week 6


Expressed behavior
Cognition
Brain abnormalities
Etiology
Genetic
Environmental
3/12/2015

## Neurocognition in Gamblers

- Executive function deficits are greater in gamblers than in control subjects, including:
  - Planning
  - Cognitive flexibility
  - Inhibition

## Comparing No-Risk with Low-Risk Recreational Gamblers

| | No Risk (n=53) | Low Risk (n=40) | *p* |
|---|---|---|---|
| CGT Overall proportion bet | 0.49 ± 0.14 | 0.54 ± 0.13 | 0.093 |
| CGT Quality of decision making | 0.97 ± 0.04 | 0.94 ± 0.08 | 0.024* |
| CGT Risk adjustment | 2.18 ± 1.33 | 1.55 ± 0.86 | 0.011* |

## Motivation to Quit Gambling

| 1) Positive aspects of gambling (what are the positive things gambling gives me?) | 2) Negative aspects of quitting (what do I lose if I stop gambling?) |
|---|---|
| | |
| | |
| | |
| | |
| | |
| 3) What are the negative consequences of gambling (current and future?) | 4) What are the advantages of quitting gambling (what do I have to gain?) |
| | |

## Polling Question 4

## Impulsivity

**"… a multitude of behaviours or responses that are poorly conceived, premature, inappropriate, and that frequently result in unwanted or deleterious outcomes."**

## Impulsivity as Target

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

# Open-Label Study of Memantine in Gambling Disorder

- Memantine antagonizes NMDA (N-methyl D-aspartate) receptors, a type of glutamate receptors
- Impulsive decision-making may be dependent on neural regions within the prefrontal cortex that are under probable glutamatergic control.

**Open-Label study of Memantine in GD**

- n=29 subjects, mean age 50 years, 62% female
- Primary diagnosis of gambling disorder
- 10-weeks
- Dose titration from 10mg/d to 30mg/d
- All subjects underwent neurocognitive testing (pre/post)

Grant et al. Psychopharmacology (Berl) 2010 Dec;212(4):603-12

# 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 (±8.1) mg/d

**Table.** Changes on outcome measures across visits

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

Grant et al. Psychopharmacology (Berl) 2010 Dec;212(4):603-12

# Open-Label Study of Memantine in Gambling Disorder

**RESULTS**

- Cognitive flexibility improved from baseline to endpoint
- GD subjects were comparable to healthy controls at study endpoint

**Table.** Performance on **cognitive tasks** in subjects vs controls

| | **Baseline v Endpoint** | | **Baseline v Controls** | | **Endpoint v Controls** | |
|---|---|---|---|---|---|---|
| | **T** | **P-value** | **T** | **P-value** | **T** | **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 in PG, and may do so by improving neurocognitive function related to cognitive flexibility.

Grant et al. Psychopharmacology (Berl) 2010 Dec;212(4):603-12

## COMT Inhibitors: Open-Label Study of Tolcapone in Gambling Disorder

- Lower dopamine levels in the prefrontal cortex are thought to contribute to deficits in cognitive processing
- Suboptimal prefrontal cortex dopamine levels may mean that irrelevant sensory information is not filtered out of processing and cannot focus more on salient features of the environment

**Open-Label study of Tolcapone in GD**

- n=24 subjects, mean age 48.9 years, 58.3% female
- 8-weeks open-label
- Dose titration from 100mg/d to 100mg/tid
- Genotyping, neurocognitive testing, and fMRI done

## Open-Label Study of Tolcapone in Gambling: Primary Outcome Variables

**RESULTS**

- N=22 (91.7%) completed the study
- Side effects were mild/moderate; no liver toxicity found

**Table.** Primary measure (PG-YBOCS) across visits and percentage of responders

| | Visit 1 (n=24) | Visit 2 (n=24) | Visit 3 (n=23) | Visit 4 (n=22) | Visit 5 (n=22) | p-value |
|---|---|---|---|---|---|---|
| **PG-YBOCS total score** | 23.63 | 16.42 | 15.46 | 10.88 | 10.50 | <0.001 |
| **Responders, *n* [%]** | -- | 6 [25] | 7 [29.2] | 14 [58.3] | 15 [62.5] | 0.001 |

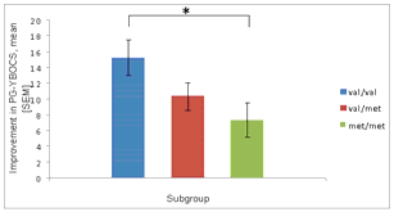
Grant et al. Eur Neuropsychopharmacol. 2013 Nov;23(11):1587-96

## 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**

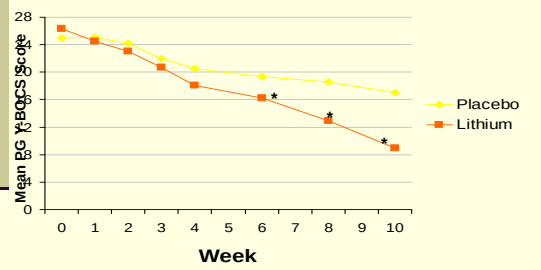
**Figure.** Change in PG-YBOCS from baseline to end of treatment in different COMT Gambling Disorder subjects




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

Grant et al. Eur Neuropsychopharmacol. 2013 Nov;23(11):1587-96

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




* p<.05

Hollander et al, 2002

## Gambling Subtypes May Suggest Treatment Directions for Individual Patients

- Problems with urges/cravings
- Problems with hypofrontality
- Comorbidity
- Using genetics and neuroimaging to refine subtypes further

## Other potential medications

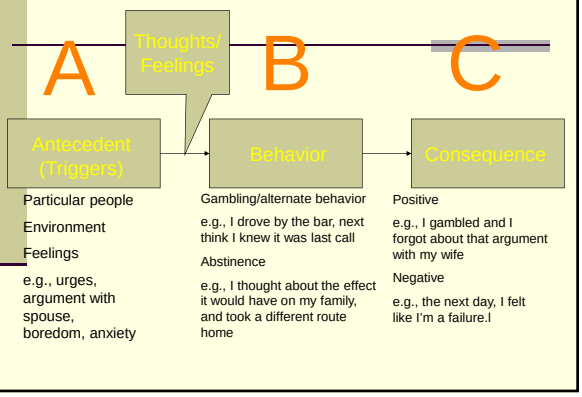
- Topiramate
- Acamprosate
- Baclofen
- Isradipine
- Antabuse

## Psychosocial Interventions

- 12-step self-help approaches
- Motivational enhancement
- Cognitive behavioral therapies
- Interventions often rely on a relapse prevention model that encourages abstinence by identifying patterns of abuse, avoiding or coping with high risk situations, and making lifestyle changes that reinforce healthier behaviors.

## Psychosocial Treatments

- 18 controlled studies
- Cognitive Behavioral Therapy
- Sessions 1 to 16
- Increased awareness of irrational cognitions, and cognitive restructuring.
- Identification of gambling triggers and the development of non-gambling sources to compete with the reinforcers associated with gambling.



## 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 intervention, or a wait-list.

## Groups

Group CBT – 3 studies

- Cognitive restructuring
- Coping skills and identification of high-risk situations.
- Imaginary exposure with response prevention.
- Financial limit setting and activity scheduling of leisure activities.
- Problem-solving training
- Relapse prevention

## Imaginal Exposure

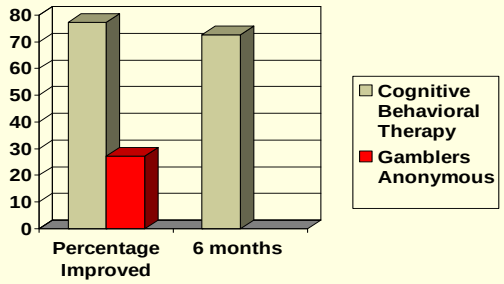
Client and Therapist develop an imaginal exposure script that includes all the relevant internal and external triggers that relate to your gambling

Urges or cravings can be activated using exposure to triggering events via imaginal exposure exercises.

## Script for PG:

*"It's Friday and I have been looking forward to gambling all week. As I am thinking about gambling right now, my urge = 75. Work has been quite stressful and it will feel good to escape for a while and have some fun at the casino. I am bringing $200 and I have to leave the casino when that is gone, maybe 2-3 hours. I hope the money can last a little while so I don't have to leave so soon. I notice my heart flutter slightly, have butterflies in my stomach, and I can hardly wait to get there. I am hoping my favorite machine is available and the traffic on the way to the casino is not too bad.*

## Motivational Interviewing Plus Imaginal Desensitization




## Conclusions

- Disordered gambling is treatable.
- Emerging data suggest that CBT and opioid antagonists are most effective treatments.
- Individualizing treatment is the new focus.

## Question and Answer

We will now take time to answer any questions that have been submitted.

## Final Questions and Answers

We will now take time to answer any final questions.

Thank you for attending!

**Please complete the survey following the end of this broadcast.**

*Upcoming Trainings:*

Parkinson's/RLS Medication Affecting Increase in Problem Gambling, A Gambling Webinar Session

*Wednesday, April 8, 2015, 12:00-1:30 pm*

For more information on these trainings go to www.trainingresources.org.