


Pharmacological Treatment of Pathological Gambling

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Disclosure Information

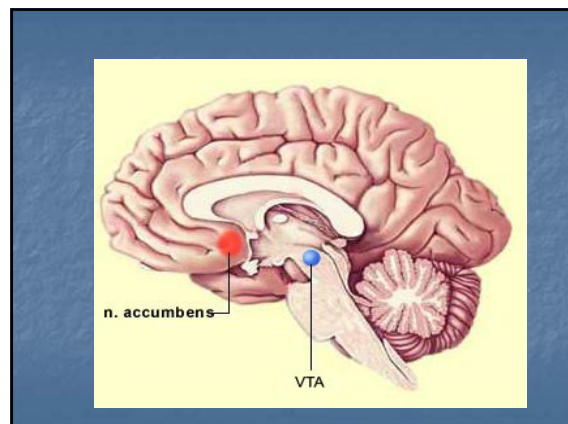
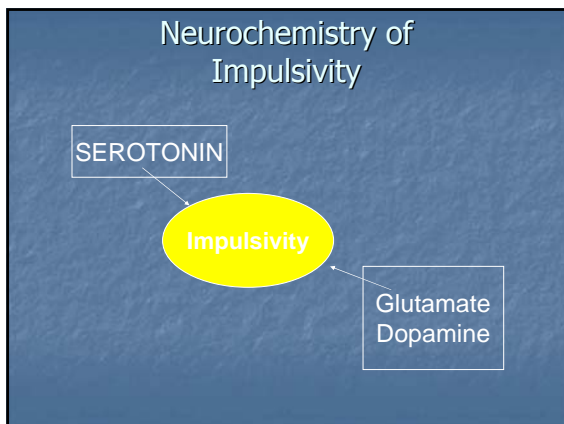
- I have the following financial relationships to disclose:
 - Grant/Research support from: Forest Pharmaceuticals, GlaxoSmithKline
- I will discuss the following off-label use and/or investigational use in my presentation:
 - All medications used to treat impulse disorders are off-label and include - SSRIs, lithium, antiepileptics, opioid antagonists, stimulants, antipsychotics, calcium channel blockers, muscle relaxants, antiemetics

Core Features of Impulse Control Disorders

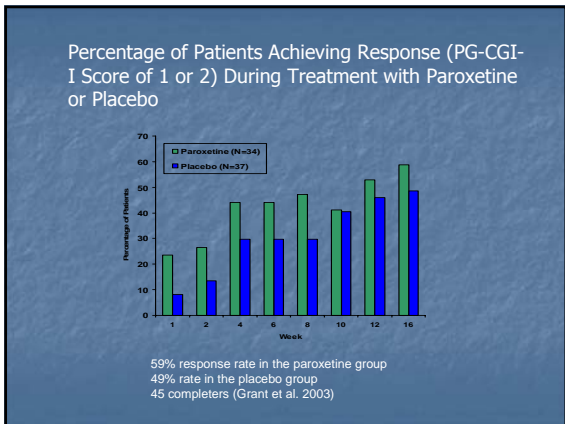
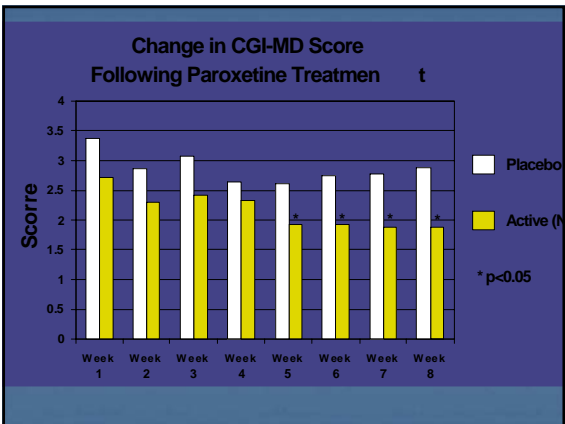
- Repetitive or compulsive engagement in a behavior despite adverse consequences
- Diminished control over the problematic behavior
- An appetitive urge or craving state prior to engagement in the problematic behavior
- A hedonic quality during the performance of the problematic behavior.

Common Core Qualities of Behavioral Addictions

- Tolerance
- Withdrawal
- Repeated unsuccessful attempts to cut back or stop
- Impairment in major areas of life functioning



Pathological Gambling Treatment

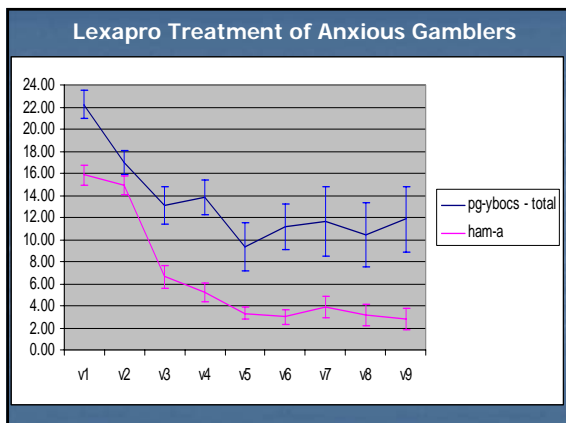


Clinical Subtyping

Within Gambling – Motivating Drive, Comorbidity, Family History

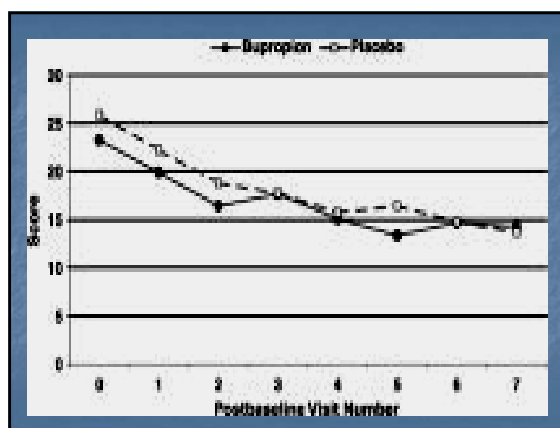
Within individuals at various time points

- ### Anxiety/Depressive/Obsessionality
- SRI medications
 - Anxiolytics
 - CBT

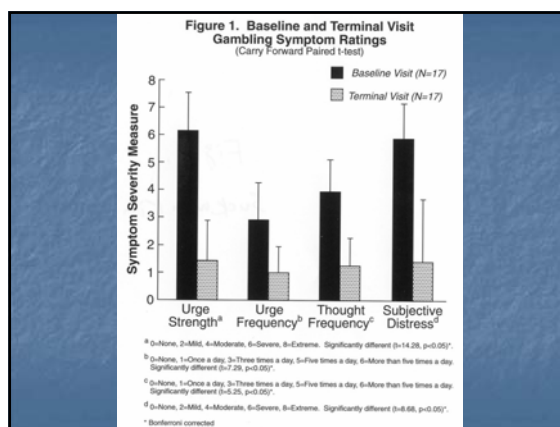


- ### Pleasure/Urges
- Relapse prevention techniques
 - Naltrexone
 - Acamprosate
 - Baclofen
 - Isradipine
 - Ondansetron

- ### 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

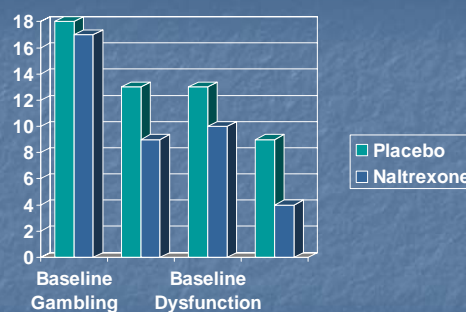


- ### Opioid Antagonists
- The mu-opioid system:
 - underlies urge regulation through the processing of reward, pleasure and pain, at least in part via modulation of dopamine neurons in mesolimbic pathway through GABA interneurons.
 - linked to physiological responses during Pachinko.



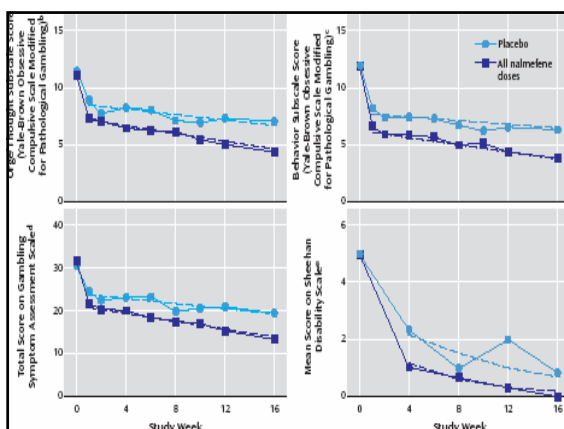
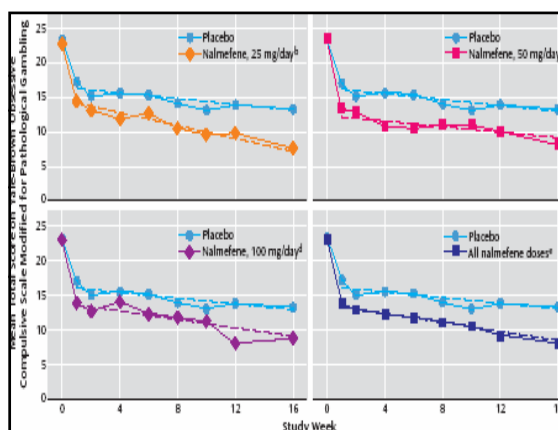
18-Week Naltrexone Study

- 77 subjects
- 3 doses of naltrexone – 50, 100, 150mg
- Depression, anxiety and other disorders allowed
- Required to have urges of at least moderate intensity

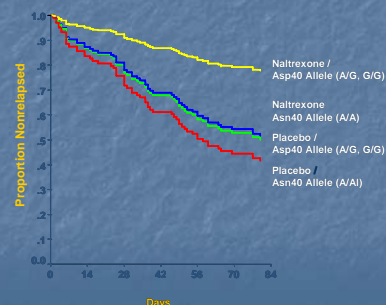


Nalmefene

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



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) (parameter estimate = 1.77; SE= 0.84; Wald χ^2 =4.41; p= .036; HR= 5.86; HR 95% CI=1.12-30.6

- ### 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

- Repeated behaviors associated with reward produce persistent neuroplasticity in extracellular glutamate levels in the nucleus accumbens
- NAC is converted to cystine, a substrate for the glutamate/cystine antiporter.
- This antiporter allows for the uptake of cystine causing the reverse transport of glutamate into the extracellular space

- Stimulates inhibitory metabotropic glutamate receptors, and thereby reducing synaptic release of glutamate and dopamine.
- Restores extracellular glutamate concentration in the nucleus accumbens
- Appears to block reinstatement of compulsive behaviors and decrease cravings.

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

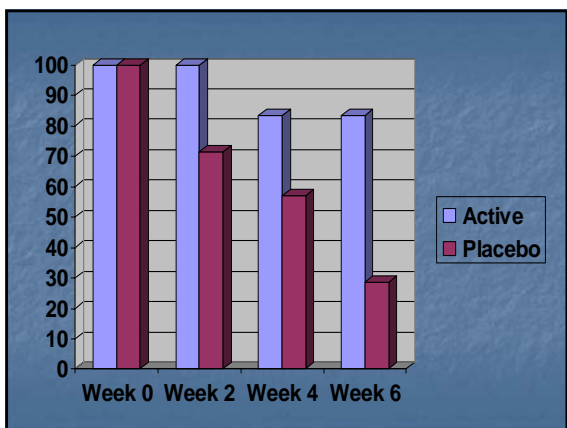
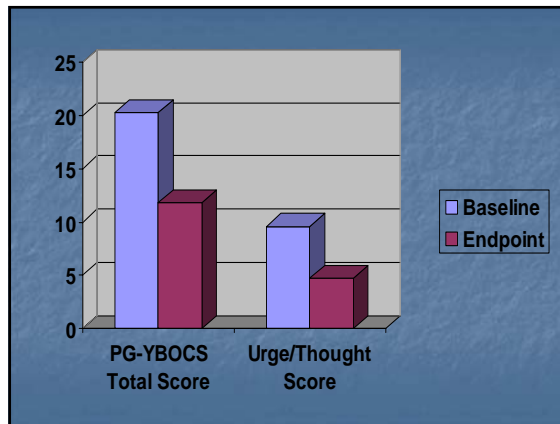
Motivational Measure	N-Acetylcysteine				Placebo			
	Cocaine		Neutral		Cocaine		Neutral	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<i>N-Acetylcysteine</i>								
Craving	5.81	4.29	1.32	2.41	7.25	5.27	1.09	2.34
Desire to use	6.19 ^b	4.47	1.61	1.66	8.32	5.13	1.79	3.09
Interest	7.63 ^b	5.28	2.81	2.61	9.65	6.03	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 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

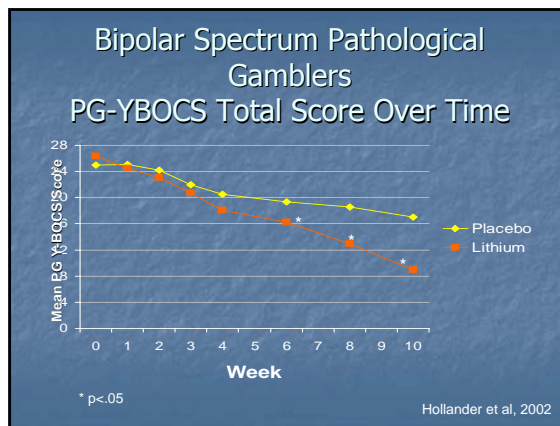
6B / Boswell, Grant and Slutske
Day 2 – August 14, 2008

- 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



- ### Impulsivity
- Attentional – consider stimulants
 - Impulsive – anti-epileptics or lithium

- Lithium carbonate SR
 - Double-blind study
 - Bipolar spectrum disorders
 - 29 completers
 - 83% responders
 - mean dose 1170mg/day



Other potential medications

- Topiramate
- Acamprosate
- Baclofen
- Isradipine
- Antabuse

Conclusions

- Pathological Gambling is a common disorder
- Frequently co-occurs with other disorders
- Result in significant distress as well as social and functional impairment.
- Emerging data suggest subtyping may result in improved response to pharmacological and psychotherapeutic interventions.