

# The Neurobiology of Substance and Behavioral Addictions

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## ABSTRACT

Behavioral addictions, such as pathological gambling, kleptomania, pyromania, compulsive buying, and compulsive sexual behavior, represent significant public health concerns and are associated with high rates of psychiatric comorbidity and mortality. Although research into the biology of these behaviors is still in the early stages, recent advances in the understanding of motivation, reward, and addiction have provided insight into the possible pathophysiology of these disorders. Biochemical, functional neuroimaging, genetic studies, and treatment research have suggested a strong neurobiological link between behavioral addictions and substance use disorders. Given the substantial co-occurrence of these groups of disorders, improved understanding of their relationship has important implications not only for further understanding the neurobiology of both categories of disorders but also for improving prevention and treatment strategies.

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### Needs Assessment

Over the last decade, the volume of research on behavioral addictions has grown significantly, particularly in the neurobiology of these disorders, their relationship to substance addictions, and effective treatment interventions. This article provides the most up-to-date knowledge regarding the pathophysiology and treatment of these behaviors.

### Learning Objectives

At the end of this activity, the participant should be able to:

- Understand the clinical characteristics of behavioral addictions.
- Understand the shared neuropathophysiology of behavioral and substance addictions.
- Discuss the available treatments for behavioral addictions.

**Target Audience:** Neurologists and psychiatrists

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This activity has been peer-reviewed and approved by Eric Hollander, MD, chair at the Mount Sinai School of Medicine. Review date: November 13, 2006. Dr. Hollander does not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

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## INTRODUCTION

Several disorders, particularly those formally categorized in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision* as impulse-control disorders not elsewhere classified, have been described as "behavioral" addictions.<sup>1</sup> Impulse-control disorders include pathological gambling, kleptomania, intermittent explosive disorder, trichotillomania, and pyromania, and diagnostic criteria for compulsive computer use, compulsive sexual behavior, and compulsive buying have been proposed.<sup>2</sup> Although there exists some controversy regarding the most precise categorization of these disorders, mounting evidence<sup>3-5</sup> supports phenomenological, genetic, and neurobiological links between behavioral and substance addictions. As such, an understanding of the biological similarities between these disorders offers the potential to guide prevention and treatment efforts for addictions in general.

Multiple lines of evidence support a relationship between behavioral and substance addictions. For example, behavioral and substance addictions share common core clinical features: 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; and a hedonic quality during the performance of the problematic behavior.<sup>3</sup> In addition, evidence suggests that impulse-control disorders often share other common features with substance use disorders, including aspects of tolerance, withdrawal, repeated unsuccessful attempts to cut back or stop, and impairment in major areas of life functioning.<sup>4</sup> Phenomenological data<sup>6</sup> further support a relationship between behavioral and substance addictions (eg, high rates of pathological gambling and substance use disorders have been reported during adolescence and young adulthood) and the telescoping phenomenon (reflecting the rapid rate of progression from initial to problematic behavioral engagement in women compared with men) initially described for alcoholism has been applied to pathological gambling.<sup>7</sup>

Consistent with the notion that impulse-control disorders share possible genetic or neurobiological links to substance use disorders, studies have demonstrated the high comorbidity of pathological gambling with substance use disorders, with rates of nicotine dependence approaching 70%,<sup>8</sup>

alcohol abuse or dependence in the range of 50% to 75%<sup>9,10</sup> and other drug use problems nearing 40%.<sup>11</sup> Additionally, individuals with substance use disorders are up to 10-fold more likely to have pathological gambling.<sup>12</sup> Similarly, studies have also found high rates of substance use disorders among individuals with kleptomania (23% to 50%)<sup>13,14</sup> and compulsive buying (30% to 46%).<sup>14,15</sup>

## NEUROBIOLOGY OF ADDICTIONS

### Serotonin

Biochemical similarities involving serotonin (5-HT) systems have been observed in disorders linked by impaired impulse control. Studies of platelet monoamine oxidase B activity, considered a possible peripheral marker of 5-HT function, have found decreased levels in both individuals with pathological gambling and substance use disorders.<sup>16</sup> Low levels of the 5-HT metabolite 5-hydroxyindole acetic acid has been found in the cerebrospinal fluid of individuals with pathological gambling and those with alcohol use disorders.<sup>17</sup> Pharmacologic challenge studies that measure hormonal response after administration of serotonergic drugs also provide evidence for serotonergic dysfunction in both impulse-control disorders and substance use disorders. Meta-chlorophenylpiperazine, a metabolite of trazodone that acts as a partial agonist and has high affinity for 5-HT receptors (especially the 5-HT<sub>2C</sub> subtype, which has been implicated in aspects of mood, anxiety behavior, and neuroendocrine function) generated a euphoric response in individuals with pathological gambling, one similar to that reported in individuals with alcohol use disorders and different from that reported by healthy control subjects.<sup>18</sup> Impulse control disorder behaviors may be conceptualized as an imbalance between an overstimulated drive state, an impairment in inhibition or reward processing, or a combination of these factors. 5-HT's dysfunction in impulse-control disorders may reflect the impairment in frontal inhibition which prevents individuals from controlling their desires.

### Dopamine

Dopaminergic systems influencing rewarding and reinforcing behaviors have been implicated in both substance and behavioral addictions.<sup>19,20</sup> Alterations in dopaminergic pathways have been proposed as underlying the seeking of rewards

(gambling, drugs) that trigger the release of dopamine and produce feelings of pleasure.<sup>21</sup> Central to addiction is the dopaminergic mesolimbic pathway linking the ventral tegmental area to the nucleus accumbens or ventral striatum.<sup>22</sup> Dopaminergic activity within the nucleus accumbens has been a focus for developmental models of motivational circuitry underlying pathological gambling and substance use disorders in adolescence.<sup>5,23</sup> "Reward deficiency syndrome", a hypothesized hypo-dopaminergic state involving multiple genes and environmental stimuli that puts an individual at high risk for multiple addictive, impulsive, and compulsive behaviors, is one proposed mechanism of addiction.<sup>21</sup>

A common process implicated in drug priming is the release of dopamine in the nucleus accumbens.<sup>19</sup> Similarly, gambling has been shown to produce priming-like effects in problem gamblers.<sup>24</sup> Additionally, drugs with similar mechanisms of action can "cross-prime" for reinstatement of other drugs within that class (ie, amphetamine for cocaine).<sup>25</sup> Consistent with this cross-priming effect in substance use disorders, a recent study<sup>25</sup> found that amphetamine increased motivation for gambling in gamblers that could be predicted by the reported severity of gambling problems. Taken together, these findings lend further evidence for the involvement of dopaminergic and/or other aminergic pathways in the pathophysiology of both pathological gambling and substance use disorders. Thus, alterations in dopamine functioning may reflect an exaggerated craving or urge state, wherein the reward from the impulse-control disorder behavior takes priority over an understanding of consequences from the behavior.

### **Endogenous Opioids**

The  $\mu$ -opioid system is believed to underlie urge regulation through the processing of reward, pleasure and pain, at least, in part, via modulation of dopamine neurons in mesolimbic pathway through  $\gamma$ -aminobutyric acid inter-neurons. Alcohol reward is mediated by endogenous opioids and influenced by genetic factors influencing opioid function.<sup>26</sup> Individuals with a genetic predisposition to alcohol use disorders demonstrate enhanced  $\beta$ -endorphin release and euphoria after alcohol administration.<sup>26</sup> Opioidergic involvement in both behavioral and substance addictions is further substantiated by clinical studies demonstrating the efficacy of the opioid antagonists

naltrexone and nalmefene in the treatment of impulse-control disorders<sup>27-29</sup> and substance use disorders.<sup>30,31</sup> Individuals with altered opioidergic systems may feel a more intense euphoria after engaging in rewarding behaviors and, thus, have greater difficulty controlling desires to continue the addictive behavior.

### **Stress and Stress Hormones**

Cortisol changes have been related to impulse-control disorders. A study of male and female Kimberley aborigines whose urine was collected during a 2-day period just after receiving their wages (after which the community regularly partakes in gambling or the observation thereof) showed significantly higher rates of cortisol and epinephrine excretion than separate volunteers whose urine was collected several days later.<sup>32</sup> These data support the possibility of stress pathway involvement in gambling or that gambling invokes the stress pathway but should be interpreted cautiously.

A study of 21 men with pathological gambling<sup>33</sup> found no evidence of cortisol responsivity on a dexamethasone-suppression test. Additionally, no differences were found in cerebrospinal fluid levels of corticotropin-releasing hormone and corticotropin between men with pathological gambling and healthy volunteers.<sup>34</sup> Meyer and colleagues<sup>35</sup> measured salivary cortisol and heart rate in 19 volunteers recruited from casinos during blackjack versus card play without monetary stakes. They found statistically significant elevations in both measures during the blackjack compared to the control condition. In a counter-balanced crossover study of 29 male volunteers recruited from casinos, the same investigators<sup>36</sup> noted statistically significant increases in heart rate and cortisol levels during blackjack gambling compared with a control card-playing condition. These findings contrast with those from a similarly designed study of 15 problem gamblers by the same investigators.<sup>37</sup> Further study should examine the extent to which differences in these findings are attributable to specific group differences (eg, genetic constitutions or environmental exposures influencing stress responsiveness), insufficient power, or other explanations.

### **Neuroimaging**

Although there have been few neuroimaging studies of impulse-control disorders, the existing evidence suggests similarities between behavioral

and substance addictions. The ventromedial prefrontal cortex (vmPFC) has been implicated as a critical component of decision-making circuitry in risk-reward assessment in addiction.<sup>5</sup> Decreased activation has been noted in vmPFC in pathological gambling subjects during presentation of gambling cues,<sup>38</sup> performance of the Stroop Color-Word Interference Task,<sup>39</sup> and simulated gambling.<sup>40</sup> In the latter study, vmPFC activation in the pathological gambling subjects correlated inversely with gambling severity, providing further evidence of a role of vmPFC dysfunction in pathological gambling. Abnormal function of the vmPFC has also been demonstrated in association with substance use disorders and is considered important in the disadvantageous decision-making (involving short-term gains vs long-term losses) central to addiction.<sup>41,42</sup>

Consistent with the hypo-frontality of addictions, cocaine dependent subjects have demonstrate compromised white matter microstructure in inferior frontal regions.<sup>43</sup> Similar white matter microstructural findings have been demonstrated in individuals with kleptomania.<sup>44</sup>

Brain imaging data also suggest that the mesocorticolimbic dopamine system is involved in both substance and behavioral addictions. In a simulated gambling task,<sup>40</sup> pathological gambling subjects were distinguished from healthy control subjects by demonstrating diminished ventral striatal activation, and activation of this region-correlated inversely with gambling severity amongst the pathological gambling subjects. A study of gambling urges and cocaine cravings in pathological gambling and cocaine dependence<sup>5</sup> similarly implicated the ventral striatum, with diminished activation distinguishing addicted (pathological gambling or cocaine dependent) from control subjects during viewing of gambling or drug videotapes, respectively.

In a study of unmedicated subjects with pathological gambling, Hollander and colleagues<sup>45</sup> measured relative metabolic rate using <sup>18</sup>F-deoxyglucose in positron emission tomography to compare computer blackjack for monetary rewards versus points only. They noted significantly higher relative metabolic rates in the primary visual cortex, cingulate gyrus, putamen, and prefrontal cortex in the monetary condition compared with points only, suggesting heightened sensory and limbic activation with increased valence/risk. Other imaging studies have implicated brain regions that are involved

in attentional processing as distinguishing pathological gambling and control subjects when viewing gambling-related material.<sup>46</sup> Together, these findings suggest a complex network of brain regions are activated during gambling and related behaviors, and that activity within certain aspects of these regions differentiates pathological gambling from control subjects.

### **Decision-Making and Neurocognition**

The Iowa Gambling Task<sup>42</sup> was developed as a tool to investigate decision-making, particularly that involving risk-reward assessment. Like subjects with substance use disorders, those with pathological gambling display impaired performance on the Iowa Gambling Task.<sup>42,47</sup> Compared with non-addicted subjects, those with pathological gambling or substance use disorders preferentially choose smaller immediate monetary rewards over larger delayed ones (termed "delayed discounting" of rewards).<sup>48</sup> Herein, the rapid temporal discounting of rewards was exacerbated by concurrent substance use disorders in individuals with pathological gambling. Taken together, these findings lend further evidence for the role of frontal cortical regions and the mesocorticolimbic system in pathological gambling and strengthen arguments regarding commonality in brain regions with other addictions.

Individuals with pathological gambling demonstrate poor performance on measures of higher-order attention,<sup>49</sup> consistent with findings of high rates of comorbid attention-deficit/hyperactivity disorder.<sup>50</sup> Furthermore, pathological gamblers have demonstrated slower reactions than occasional gamblers to irrelevant external light stimuli while gambling, suggestive of a greater narrowing of attention while gambling.<sup>51</sup>

Studies<sup>52</sup> have demonstrated that individuals with pathological gambling may have a broad range of executive functioning deficits. The Stroop task has been used to assess neurocognition in individuals with impulse-control disorders. The Stroop task assesses cognitive control involving attention and the ability to inhibit a pre-potent response (reading) when presented with a cognitive conflict (mismatched color-word pair). Studies using the Stroop task have found that pathological gamblers are significantly slower and less accurate than healthy subjects.<sup>53</sup> Individuals with kleptomania, however, have not demonstrated deficits on the Stroop task,<sup>54</sup> although other tests of executive

functioning (the Wisconsin Card Sorting Test) have shown impairment in those kleptomania patients with severe symptoms.<sup>54</sup> The extent to which seemingly discrepant findings represent methodological differences (eg, differences in tasks or sample sizes), subject group differences related to specific impulse-control disorders, or heterogeneities within impulse-control disorders warrants additional investigation.

### **Genetic Vulnerability**

Family studies consistently have demonstrated that pathological gambling subjects have elevated rates of first-degree relatives with substance use disorders<sup>55</sup> and these findings suggest a shared genetic vulnerability between pathological gambling and other addictions. Twin studies in men from the Vietnam Era Twin Registry demonstrated that 12% of the genetic and 8% of the nonshared environmental risk for pathological gambling overlapped with those for alcohol dependence.<sup>55</sup> These findings suggest that both familial factors and shared genetic vulnerability may account for a portion of the risk for pathological gambling. A more recent investigation,<sup>56</sup> however, found that shared genetic contributions for pathological gambling were not limited to externalizing disorders but included major depression. Interestingly, the shared genetic contribution to pathological gambling and major depression was as large as or more substantial than those for alcohol dependence, highlighting the need for additional research into the specific biological mechanisms underlying this association.

Investigations into specific genes relating to the norepinephrine, 5-HT, and dopamine neurotransmitter systems contribution in pathological gambling have been performed. As the dopamine (D)<sub>2A1</sub> allele of the D<sub>2</sub> receptor has been implicated in compulsive/addictive behavior, such as drug abuse, compulsive eating, and smoking, Diskins and Hodgins<sup>51</sup> found in 171 non-Latino whites with pathological gambling, 51% carried the D<sub>2A1</sub> allele compared with 26% of controls.<sup>57</sup> Frequency of homozygosity of the dopamine *Dde 1* allele of the D<sub>1</sub> receptor have also been found to be elevated compared to controls in pathological gambling, tobacco smokers and Tourette syndrome probands.<sup>58</sup> Finally, allelic variants of the *DRD4* gene, containing five to eight copies of an incorporated 48 base pair nucleotide repeat, have been associated with pathological gambling.<sup>59-60</sup>

### **TREATMENT**

Although pharmacologic treatment of impulse-control disorders is at an early stage, several important factors appear to be emerging. Similar to results seen in studies of substance use disorders,<sup>61</sup> selective serotonin reuptake inhibitors (SSRIs) have shown mixed results in impulse-control disorders with some studies, but not others, demonstrating a benefit distinct from placebo.<sup>62</sup> As with substance use disorders, studies using opioid antagonists, such as naltrexone or nalmefene, have demonstrated efficacy in double-blind trials for pathological gambling<sup>27,29</sup> and an open-label study for kleptomania.<sup>28</sup> The efficacy of opioid antagonists in the treatment of impulse-control disorders may be due to the opioidergic modulation of mesolimbic dopamine circuitry,<sup>27</sup> though direct investigation of the precise mechanism of action is needed.

Patterned after Alcoholics Anonymous, 12-step self-help groups, such as Gamblers Anonymous, seem to be the mainstay of treatment for impulse-control disorders. These groups, however, suffer from high dropout rates, and there are little controlled data to support their efficacy. Several therapist-driven techniques (cognitive-behavioral therapy, motivational interviewing, relapse prevention), largely modeled on treatments for substance use disorders, have demonstrated efficacy in a few controlled studies.<sup>48</sup>

Improved treatment strategies for impulse-control disorders should be informed by a neurobiological understanding of the pathophysiology of impulse-control disorders. It is possible that polymorphisms of the gene encoding the  $\mu$ -opioid receptor may predict treatment response to opioid antagonists in impulse-control disorders as has been found in studies of alcoholism.<sup>63</sup> Serotonergic medications may effectively target abnormal serotonergic function in individuals with impulse-control disorders. As an improved understanding emerges of the neurobiological differences existing in individuals with impulse-control disorders, it is important to investigate the potential of these findings in advancing prevention and treatment strategies.

As empirically validated treatments emerge and their mechanisms of action become more completely understood, clinicians must treat individuals in the here and now. Existing data, consistent with clinical experience, suggest that specific groups of individuals with impulse-control disorders respond preferentially to specific treatment

interventions. One clinical guidepost that can be used to inform treatment selection involves the presence or absence of co-occurring disorders,<sup>64</sup> and treatment algorithms for pathological gambling based on co-occurring disorders have been proposed.<sup>65</sup> For example, individuals with cycling mood disorders may not respond well to SSRIs<sup>66</sup> but rather to a mood stabilizer such as lithium.<sup>67</sup> Alternatively, SSRIs may be particularly helpful for individuals with co-occurring affective disorders.<sup>68</sup> Individuals with a substance use disorder (eg, alcohol dependence) or strong gambling urges may respond preferentially to a  $\mu$ -opioid antagonist.<sup>65</sup> Additional areas of co-occurring symptomatology (eg, attention-deficit/hyperactivity disorder) have been investigated to date less systematically but could offer additional information to guide treatment selection.<sup>69</sup>

Taken together, emerging data suggest that co-occurring disorders seem to be the rule rather than the exception for pathological gambling,<sup>8</sup> might be used to guide to pharmacotherapy selection. Further research is needed to support these initial findings and to develop more structured, empirically validated algorithms to assist clinicians.

## CONCLUSION

Biochemical, functional neuroimaging, genetic studies, and treatment research have all suggested a strong neurobiological link between pathological gambling and substance use disorders. Given the substantial co-occurrence of these disorders, an improved understanding of their relationship has important implications not only for understanding further the neurobiology of both categories of disorders but also for improving prevention and treatment strategies. The vast majority of research in behavioral addictions has focused on pathological gambling. The extent to which other impulse-control disorders represent behavioral addictions is presently unclear and may vary from one impulse-control disorder to another. For example, among individuals with obsessive-compulsive disorder, impulse-control disorders clustered into several groups, including a "reward-based" one, that may best align with behavioral addictions.<sup>70</sup> Moreover, data linking specific impulse-control disorders (eg, trichotillomania) to obsessive-compulsive disorder or alternatively to addictions exist. These data suggest that impulse-control disorders represent a heterogeneous group of disorders as a class, and that additional heterogeneity exists within individual impulse-control disorders that

might influence their classification, prevention, and treatment. Additional investigation is needed to better understand impulse-control disorders and their relationship to other psychiatric disorders, including substance use disorders, with the ultimate goal of using this information to advance prevention and treatment strategies for individuals suffering from these disorders. **CNS**

## REFERENCES

- Holden C. 'Behavioral' addictions: do they exist? *Science*. 2001;294:980-982.
- Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, text revision. Washington, DC: American Psychiatric Association; 2000.
- Grant JE, Potenza MN. Pathological gambling and other behavioral addictions. In: Frances RJ, Miller SI, Mack AH, eds. *Clinical Textbook of Addictive Disorders*. 3rd ed. New York: Guilford Press; 2005:303-320.
- Blanco C, Moreyra P, Nunes EV, Saiz-Ruiz J, Ibanez A. Pathological gambling: addiction or compulsion? *Semin Clin Neuropsychiatry*. 2001;6:167-176.
- Potenza MN. Should addictive disorders include non-substance-related conditions? *Addiction*. 2006;101(suppl 1):142-151.
- Chambers RA, Potenza MN. Neurodevelopment, impulsivity, and adolescent gambling. *J Gambl Stud*. 2003;19:53-84.
- Potenza MN, Kosten TR, Rounsaville BJ. Pathological gambling. *JAMA*. 2001;286:141-144.
- Crockford DN, el-Guebaly N. Psychiatric comorbidity in pathological gambling: a critical review. *Can J Psychiatry*. 1998;43:43-50.
- Petry NM, Stinson FS, Grant BF. Comorbidity of DSM-IV pathological gambling and other psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2005;66:564-574.
- McCormick RA, Russo AM, Ramirez LF, Taber JJ. Affective disorders among pathological gamblers seeking treatment. *Am J Psychiatry*. 1984;141:215-218.
- Cunningham-Williams RM, Cottler LB, Compton III WM, Spitznagel EL. Taking chances: Problem gamblers and mental health disorders—results from the St. Louis Epidemiologic Catchment Area study. *Am J Pub Health*. 1998;88:1093-1096.
- Spunt B, Lesieur H, Hunt D, Cahill L. Gambling among methadone patients. *Int J Addict*. 1995;30:929-962.
- Grant JE, Kim SW. Clinical characteristics and associated psychopathology of 22 patients with kleptomania. *Compr Psychiatry*. 2002;43:378-384.
- McElroy SL, Pope HG, Hudson JI, Keck PE, White KL. Kleptomania: a report of 20 cases. *Am J Psychiatry*. 1991;148:652-657.
- Christenson GA, Faber RJ, de Zwaan M, et al. Compulsive buying: descriptive characteristics and psychiatric comorbidity. *J Clin Psychiatry*. 1994;55:5-11.
- Schlosser S, Black DW, Repertinger S, Freet D. Compulsive buying: demography, phenomenology, and comorbidity in 46 subjects. *Gen Hosp Psychiatry*. 1994;16:205-212.
- Potenza MN. The neurobiology of pathological gambling. *Semin Clin Neuropsychiatry*. 2001;6:217-226.
- Benkelfat C, Murphy DL, Hill JL, George DT, Nutt D, Linnoila M. Ethanol-like properties of the serotonergic partial agonist m-chlorophenylpiperazine in chronic alcoholic patients. *Arch Gen Psychiatry*. 1991;48:383.
- Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry*. 2005;162:1403-1413.
- Bergh C, Eklund T, Sodersten P, Nordin C. Altered dopamine function in pathological gambling. *Psychol Med*. 1997;27:473-475.
- Blum K, Cull JG, Braverman ER, Comings DE. Reward deficiency syndrome. *Am Scientist*. 1996;84:132-145.
- Nestler E, Aghajanian GK. Molecular and cellular basis of addiction. *Science*. 1997;278:58-62.
- Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *Am J Psychiatry*. 2003;160:1041-1052.
- Loba P, Stewart SH, Klein RM, Blackburn JR. Manipulations of the features of standard video lottery terminal (VLT) games: effects in pathological and non-pathological gamblers. *J Gambl Stud*. 2001;17:297-320.
- Zack M, Poulos CX. Amphetamine primes motivation to gamble and gambling-related semantic networks in problem gamblers. *Neuropsychopharmacol*. 2004;29:195-207.
- Dackis C, O'Brien C. Neurobiology of addiction: treatment and public policy ramifications. *Nat Neurosci*. 2005;8:1431-1436.
- Grant JE, Potenza MN, Hollander E, et al. A multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. *Am J Psychiatry*. 2006;163:303-312.
- Grant JE, Kim SW. An open label study of naltrexone in the treatment of kleptomania. *J Clin Psychiatry*. 2002;63:349-356.

29. Kim SW, Grant JE, Adson D, Shin YC. Double-blind naltrexone and placebo comparison study in the treatment of pathological gambling. *Biol Psychiatry*. 2001;49:914-921.
30. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry*. 1992;49:876-880.
31. Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry*. 1999;56:719-724.
32. Schmitt LH, Harrison GA, Spargo RM. Variation in epinephrine and cortisol excretion rates associated with behavior in an Australian Aboriginal community. *Am J Phys Anthropol*. 1998;106:249-253.
33. Ramirez LF, McCormick RA, Lowy MT. Plasma cortisol and depression in pathological gamblers. *Br J Psychiatry*. 1988;153:684-686.
34. Roy A, Adinoff B, Roehrich L, et al. Pathological gambling. A psychobiological study. *Arch Gen Psychiatry*. 1988;45:369-373.
35. Meyer G, Hauffa BP, Schedlowski M, Pawlak C, Stadler MA, Exton MS. Casino gambling increases heart rate and salivary cortisol in regular gamblers. *Biol Psychiatry*. 2000;48:948-953.
36. Krueger THC, Schedlowski M, Meyer G. Cortisol and heart rate measures during casino gambling in relation to impulsivity. *Neuropsychobiology*. 2005;52:206-211.
37. Meyer G, Schwertfeger J, Exton MS, et al. Neuroendocrine response to casino gambling in problem gamblers. *Psychoneuroendocrinology*. 2004;29:1272-1280.
38. Potenza MN, Steinberg MA, Skudlarski P, et al. Gambling urges in pathological gambling: a functional magnetic resonance imaging study. *Arch Gen Psychiatry*. 2003;60:828-836.
39. Potenza MN, Leung HC, Blumberg HP, et al. An fMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers. *Am J Psychiatry*. 2003;160:1990-1994.
40. Reuter J, Raedler T, Rose M, Hand I, Glascher J, Buchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nat Neurosci*. 2005;8:147-148.
41. London ED, Ernst M, Grant S, Bonson K, Weinstein A. Orbitofrontal cortex and human drug abuse: functional imaging. *Cereb Cortex*. 2000;10:334-342.
42. Bechara A. Risky business: emotion, decision-making, and addiction. *J Gambli Stud*. 2003;19:23-51.
43. Lim KO, Choi SJ, Pomara N, Wolkin A, Rotrosen JP. Reduced frontal white matter integrity in cocaine dependence: a controlled diffusion tensor imaging study. *Biol Psychiatry*. 2002;51:890-895.
44. Grant JE, Correia S, Brennan-Krohn T. White matter integrity in kleptomania: a pilot study. *Psychiatry Res Neuroimaging*. 2006;147:233-237. Epub 2006 Sep 7.
45. Hollander E, Pallanti S, Baldini Rossi N, Sood E, Baker BR, Buchsbaum MS. Imaging monetary reward in pathological gamblers. *World J Biol Psychiatry*. 2005;6:113-120.
46. Crockford DN, Goodyear B, Edwards J, Quickfall J, el-Guebaly N. Cue-induced brain activity in pathological gamblers. *Biol Psychiatry*. 2005;58:787-795.
47. Cavedini P, Riboldi G, Keller R, D'Annunzi A, Bellodi L. Frontal lobe dysfunction in pathological gambling patients. *Biol Psychiatry*. 2002;51:334-341.
48. Petry NM. *Pathological Gambling: Etiology, Comorbidity, and Treatment*. Washington, DC: American Psychological Association; 2005.
49. Ruge L, Melamed L. Neuropsychological assessment of attention problems in pathological gamblers. *J Nerv Ment Dis*. 1993;181:107-112.
50. Specker SM, Carlson GA, Christenson GA, Marcotte M. Impulse control disorders and attention deficit disorder in pathological gamblers. *Ann Clin Psychiatry*. 1995;7:175-179.
51. Diskin KM, Hodgins DC. Narrowing of attention and dissociation in pathological video lottery gamblers. *J Gambli Stud*. 2000;16:461-467.
52. Goudriaan AE, Oosterlaan J, de Beurs E, van den Brink W. Neurocognitive functions in pathological gambling: a comparison with alcohol dependence, Tourette syndrome and normal controls. *Addiction*. 2006;101:534-547.
53. Kertzman S, Lowengrub K, Aizer A, Ben Nahum Z, Kotler M, Dannon PN. Stroop performance in pathological gamblers. *Psychiatry Res*. 2006;142:1-10.
54. Grant JE, Odlaug BL, Wozniak JR. Neuropsychological functioning in kleptomania. *Behav Res Ther*. 2006 Sep 26; [Epub ahead of print].
55. Shah KR, Potenza MN, Eisen SA. Biological basis for pathological gambling. In Grant JE, Potenza MN, eds. *Pathological Gambling: A Clinical Guide to Treatment*. Washington DC: American Psychiatric Publishing, Inc; 2004:127-142.
56. Potenza MN, Xian H, Shah K, Scherrer JF, Eisen SA. Shared genetic contributions to pathological gambling and major depression in men. *Arch Gen Psychiatry*. 2005;62:1015-1021.
57. Comings DE, Rosenthal RJ, Lesieur HR, et al. A study of the dopamine D2 receptor gene in pathological gambling. *Pharmacogenetics*. 1996;6:223-234.
58. Comings DE, Gade R, Wu S, et al. Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. *Mol Psychiatry*. 1997;2:44-56.
59. Comings DE, Gonzalez N, Wu S, et al. Studies of the 48 bp repeat polymorphism of the DRD4 gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse. *Am J Med Genet*. 1999;88:358-368.
60. Perez de Castro I, Ibanez A, Torres P, Saiz-Ruiz J, Fernandez-Piqueras J. Genetic association study between pathological gambling and a functional DNA polymorphism at the D4 receptor gene. *Pharmacogenetics*. 1997;7:345-348.
61. O'Brien CP, McKay J. Pharmacological treatments for substance use disorders. In: Nathan PE, Gorman JM, eds. *A Guide to Treatments that Work*. 2nd ed. New York, NY: Oxford University Press; 2002:125-156.
62. Grant JE, Potenza MN. Impulse control disorders: clinical characteristics and pharmacological management. *Ann Clin Psychiatry*. 2004;16:27-34.
63. Oslin DW, Berrettini W, Kranzler HR, et al. A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology*. 2003;28:1546-1552.
64. Potenza MN. Impulse control disorders and co-occurring disorders: dual diagnosis considerations. *Journal of Dual Diagnosis*. In press.
65. Hollander E, Kaplan A, Pallanti S. Pharmacological treatments. In: Grant JE, Potenza MN. *Pathological Gambling: A Clinical Guide to Treatment*. Washington DC: American Psychiatric Publishing, Inc. 2004:189-206.
66. Hollander E, DeCaria CM, Finkell JN, Begaz T, Wong CM, Cartwright C. A randomized double-blind fluvoxamine/placebo crossover trial in pathological gambling. *Biol Psychiatry*. 2000;47:813-817.
67. Hollander E, Pallanti S, Allen A, Sood E, Baldini Rossi N. Does sustained-release lithium reduce impulsive gambling and affective instability versus placebo in pathological gamblers with bipolar spectrum disorders? *Am J Psychiatry*. 2005;162:137-145.
68. Grant JE, Potenza MN. Escitalopram in the treatment of pathological gambling with co-occurring anxiety: An open-label study with double-blind discontinuation. *Int Clin Psychopharmacol*. 2006;21:203-209.
69. Black DW. An open-label trial of bupropion in the treatment of pathologic gambling. *J Clin Psychopharmacol*. 2004;24:108-110.
70. Stein DJ, Lochner C. Obsessive compulsive spectrum disorders: a multidimensional approach. *Psychiatr Clin N Am*. 2006;29:343-351.