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Pathological Gambling: Biological and Clinical Considerations

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Abstract

Pathological gambling (PG) is categorized as an impulse control disorder (ICD). Phenomenological, neurobiological and pharmacological data suggest similarities in the pathophysiologies of substance use disorders (SUDs) and PG. Both behavioral and pharmacological approaches, including those that have been empirically validated for SUDs, have shown promise in the treatment of PG. Findings from biological studies of PG are reviewed, and treatment approaches based on controlled studies are summarized.

Keywords

pathological gambling (PG); impulse control disorders (ICDs); substance use disorders (SUDs)

Introduction

Pathological gambling (PG) is classified in the Diagnostic and Statistic Manual-IV (DSM-IV) as an Impulse Control Disorder (ICD; American Psychiatric Association, 1994). Recent epidemiological investigations estimate the prevalence of lifetime PG in the USA as ranging from 0.4% to 1.5% within the adult population (Hoffmann, 1999; James, 1999; Petry et al., 2005). PG is associated with other psychiatric disorders, including substance use disorders (SUDs), medical disorders, and negative measures of functioning (Desai et al. 2007; Petry et al. 2005; National Research Council, 1999). PG and SUDs share similar clinical characteristics as reflected in the DSM-IV diagnostic criteria for the disorders (American Psychiatric Association, 1994). Given these similarities, the efficacy of established treatments for SUDs has been explored for the treatment of PG.

First included in the DSM-III in 1980 (American Psychiatric Association Committee, 1980), PG has been relatively understudied as compared to other disorders with similar clinical characteristics, such as SUDs. Relatively few biological investigations have probed its etiology and few controlled studies have assessed the efficacies of treatment modalities for PG.

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Nonetheless, considerable progress in these areas has been made over the past decade. Here, findings from neurobiological, pharmacotherapy and behavioral treatment studies of PG are reviewed. Where relevant, comparable neurobiological findings from research of SUDs are additionally included, though are not systematically reviewed.

Neurochemistry

Serotonin (5-HT)

The neurotransmitter serotonin (5-HT) has been implicated in control over motivated behaviors. Abnormalities in 5-HT function have been reported in individuals with PG (DeCaria et al. 1998; Pallanti et al. 2006). For example, a blunted prolactin response following administration of intravenous clomipramine (CMI), a tricyclic antidepressant that inhibits reuptake of 5-HT and norepinephrine (NE), has been reported in PG (Moreno et al. 1991; DeCaria et al. 1998). Studies of alcohol dependence (AD) have reported similarly blunted prolactin responses following administration of both direct and indirect 5-HT agonists (i.e. sumatriptan and fenfluramine; reviewed in Ratsma et al. 2002). Men with PG have been reported to display an augmented prolactin response to metachlorophenylpiperzaine (m-CPP), a metabolite of trazodone and partial 5-HT receptor agonist with affinity for 5-HT1 and 5-HT2 receptors (Moreno et al. 1991). Behaviorally, m-CPP administration in individuals with PG is associated with a “buzz” or “high” (DeCaria et al. 1998; Pallanti et al. 2006) that is typically not reported by healthy control comparison subjects who tend to report an aversive response. Differential neuroendocrine responses to m-CPP have been found to correlate with indices of PG severity, such as the Yale-Brown Obsessive-Compulsive Scale Modified for Pathological Gambling (PG-YBOCS; Pallanti et al. 2006). Behavioral and neuroendocrine responses to m-CPP similar to those observed in PG subjects have been reported in individuals with impulsive tendencies or other ICDs (Potenza and Hollander, 2002), suggesting abnormal 5-HT regulation in PG and other impulsive disorders and behaviors.

Abnormalities in cerebrospinal fluid (CSF) levels of 5-HT and its metabolites have been reported in individuals with impaired impulse control (Nordin and Eklundh, 1999; Nordin and Sjodin, 2006). However, findings have varied across studies. Decreased CSF levels of the 5-HT metabolite 5-hydroxyindole acetic acid (5-HIAA) have been reported in men with PG (Nordin and Eklundh, 1999). In contrast, enhanced CSF levels of 5-HIAA and decreased CSF levels of tryptophan and 5-HT have also been reported in individuals with PG (Nordin and Sjodin, 2006). Reduced platelet levels of monoamine oxidase (MAOA), an enzyme involved in the metabolism of 5-HT, have been reported in individuals with PG (DeCaria et al. 1998). Decreased CSF levels of 5-HIAA have been associated with other impulsive behaviors including AD (Fils-Aime et al., 1996; reviewed in Ratsma et al., 2002), violence, suicidality and aggression (Cardinal, 2006). Decreased CSF 5-HIAA levels among AD criminal offenders classified as impulsive, when compared to those not classified as impulsive, have also been reported (reviewed in Ratsma et al., 2002).

Molecular genetic studies have probed serotonergic gene variants in relationship to PG. Polymorphisms in genes coding for the serotonin transporter [*5HTTLPR*] have been reported to be linked to PG in a sex-specific manner (Perez de Castro et al. 1999; Ibanez et al. 2003). Polymorphisms in genes coding for monoamine oxidases (MAOs) [*MAO-A* (intron I), *MAO-A* (promoter), *MAO-B* (intron II)] have also been associated with PG in some preliminary studies (Perez de Castro et al. 1999). Findings from these molecular genetic studies require replication and further verification due to small sample sizes, incomplete subject characterization and other methodological considerations (Ibanez et al. 2003), particularly as molecular genetic studies in PG have not consistently been replicated (see Dopamine (DA) section below). Together, the molecular genetic and other biological studies suggest

serotonergic involvement in PG, although further research is required to determine a precise role for 5-HT in the pathophysiology of PG.

Dopamine (DA)

Dopamine (DA) has been implicated in reinforcing and rewarding behaviors, and although DA has been long been associated with these processes in drug addiction, its role in PG is less clear. Elevated measures of DA have been observed in recreational and problem gamblers during casino gambling and while playing Pachinko, a game involving elements of pinball and slot machines (Shinohara et al. 1999; Meyer et al. 2004). Bergh and colleagues (1997) have reported decreases in CSF levels of DA and increases in DA metabolites (i.e. homovanillic acid (HVA) and 3,4-dihydroxphenylacetic acid (DHP)) in individuals with PG (Bergh et al. 1997). However, these differences did not remain significant after correcting for CSF flow-rate (Nordin and Eklundh, 1999). More recently, increases in CSF HVA levels and 5-HIAA have been reported in individuals with PG (Nordin and Sjodin, 2006), contrary to previous investigations of CSF 5-HT metabolite concentration levels (Bergh et al. 1997). These findings suggest a need for further research of CSF concentration levels in PG using larger sample sizes and correcting for potentially confounding factors, such as flow-rate.

The influences of drugs with dopaminergic properties on gambling-related thoughts and behaviors have been investigated in individuals with gambling problems (Zack and Poulos, 2004; Zack and Poulos, 2007). In a study of ten individuals with gambling problems, eight with drinking problems, six with both and twelve with neither, subjects were administered either placebo or 30 mg oral D-amphetamine (AMPH), a drug with pro-dopaminergic properties, prior to completing a modified reading task containing words associated with gambling, alcohol, positive or negative affect and neutral words (Zack and Poulos, 2004). In comparison to placebo sessions, participants in both gambling groups had significantly faster reading times for gambling-associated words and significant reductions in reading speed for neutral words. Participants in the problem gambling groups additionally reported significant increases in motivation to gamble during AMPH sessions in comparison to placebo sessions, and severity of problem gambling was associated with AMPH-related positive subjective responses and motivation to gamble. More recently, Zack and Poulos (2007) compared the influence of 3 mg oral haloperidol, a D2-like receptor antagonist, on performance of a slot-machine task and the previously described reading task (Zack and Poulos, 2004) in a sample of 20 individuals with PG and 18 healthy control participants. In both PG and non-PG groups, haloperidol was associated with gambling-related increases in blood pressure. In comparison to controls, haloperidol administration among PG participants was associated with self-reported rewarding responses to gambling, post-gambling motivation for gambling, and facilitation of gambling-related stimuli on the reading task (Zack and Poulos, 2007). As haloperidol antagonizes DA D2-like receptors (the family to which striatally enriched DA D2 and D3 receptors belong), the findings suggest that acutely blocking D2-like receptors in PG subjects enhances gambling motivations and behaviors. These data may in part explain why drugs that antagonize D2-like receptors (e.g., olanzapine) have not shown success in clinical trials (Fong et al. 2008; McElroy et al. 2008).

PG and other ICDs have been observed in individuals with Parkinson's disease (PD), a disorder involving the degradation of DA neurons, particularly within the nigrostriatal pathway (Potenza et al. 2007). Multiple factors have been associated with ICDs in PD including use of DA agonists and/or levo-dopa or doses thereof, age or early age at PD onset, marital status, and personal or familial history of impulsivity or disorders characterized by impaired impulse control (Weintraub et al. 2006; Potenza et al. 2007; Weintraub et al. 2008). As such, ICDs in PD may reflect the underlying pathophysiology of PD, treatment of PD, some combination of PD's pathophysiology and its treatment, or other factors. The findings from Zack and Poulos

(2007) specifically raise questions regarding the etiology of PG in individuals being treated with prodopaminergic drugs for PD; i.e., whether there may be specific aspects of the pathophysiology of PD that might contribute to the occurrence of PG and possibly other ICDs in PD. Further research is required to understand the factors underlying ICDs in PD and how to best manage these disorders clinically (Potenza et al. 2007).

Molecular genetic studies have identified polymorphisms in genes coding for DA-related proteins in individuals with PG. Polymorphisms in genes coding for DA D1 (*DRD1* Ddel), DA D2 (*DRD2* Taq I A) and DA D4 (*DRD4* (exon III)) receptors have been reported in individuals with PG (Comings, 1998). Similar distributions of allelic variants have been reported in SUD populations; e.g., variations in the *DRD2* gene have been reported in relation to alcohol abuse and dependence (Kreek et al. 2005; Comings, 1998). However, findings from a large, more recent, well-designed investigation suggest that the relationship between the DA D2 receptor gene variant and alcoholism may be explained by allelic variations in the ankyrin repeat and kinase domain containing 1 (ANKK1) gene, a gene in linkage disequilibrium with that coding for the DA D2 receptor (Dick et al. 2007). Furthermore, an investigation of DA receptor gene variants using a discordant sibling pair design failed to identify *DRD2*-related differences (da Silva Lobo et al. 2007). As such, additional research is needed to clarify a role for genetic factors related to DA in the pathophysiology of PG.

Norepinephrine (NE)

Norepinephrine (NE) systems have been implicated in drug relapse, reward and sensitization (reviewed in Weinshenker & Schroeder, 2007). NE systems have also been hypothesized to mediate aspects of attention, arousal and sensation-seeking in PG (Potenza and Hollander, 2002). Support for a role for NE in PG comes from multiple studies involving predominantly male subjects. High levels of NE and NE metabolites have been observed in CSF and urine samples of PG as compared to control subjects (Roy et al. 1988), and measures of extraversion have been found to correlate with NE measures (Roy et al. 1989). A separate study also found high levels of the NE metabolite 3-methoxy-4-hydroxyphenyl glycol (MHPG) in the CSF of individuals with PG (Bergh et al. 1997). However, this elevation was not observed when controlling for CSF flow rate (Nordin and Eklundh, 1999). Although NE and/or related biological measures have been found to rise in non-PG subjects when gambling (Shinohara et al. 1999; Meyer et al. 2004), larger increases have been reported in PG subjects (Meyer et al. 2004). However, gambling-related motivations have been found to correlate positively with norepinephrine levels among both PG and non-PG gamblers (Meyer et al. 2004). As AMPH influences NE as well as DA systems, it is possible that AMPH-related increases in gambling priming and motivation may relate to NE function (Zack and Poulos, 2004). More research is needed to investigate in PG the function of NE and related systems (e.g., those underlying stress responsiveness; Potenza et al. 2002).

Research suggests a similarly complex relationship between NE and AD. Decreases in NE CSF levels have been reported among individuals with AD, and post-mortem studies have reported reductions in locus coeruleus NE neurons in AD (reviewed in Ratsma et al. 2002). Recent research suggests that disulfiram, the efficacy of which in treating AD is well-established, indirectly inhibits NE via inhibition of DA ß-hydroxylase, and preliminary research suggests potential treatment efficacy for CD (reviewed in Weinshenker & Schroeder, 2007). To our knowledge there have been no studies of disulfiram treatment for PG.

Other Neurotransmitter Systems

Multiple other neurotransmitter systems have been hypothesized to be involved in the pathophysiology of PG. Given a role in hedonic states, the opioid system has been hypothesized to underlie pleasures and urges in PG (Potenza and Hollander, 2002). Glutamate, the most

abundant excitatory neurotransmitter in the central nervous system, has been implicated in drug addiction (Kalivas and Volkow, 2005). Arguably the strongest support for involvement of these neurotransmitters in PG comes from clinical trials investigating drugs that influence these systems, as described later in this article.

Neural Systems

Data from functional magnetic resonance imaging (fMRI) studies of PG have helped to identify brain regions and neural systems contributing to PG. In an fMRI study of motivational and emotional states in men with and without PG, those with PG reported stronger gambling urges and showed relatively reduced activation of frontal cortical, basal ganglionic and thalamic brain regions while viewing gambling tapes during the period prior to the onset of subjective motivational or emotional response (Potenza et al. 2003b). Similar between-group differences were not observed during comparable periods of viewing happy or sad videotapes (Potenza et al. 2003b). These findings differ from those reported among OCD subjects during cue exposure, with OCD subjects displaying relatively increased activation of these cortical and sub-cortical regions (Breiter and Rausch, 1996). In the gambling videotape experiment (Potenza et al. 2003b), PG subjects and healthy control subjects differed significantly during presentation of the most robust gambling stimuli, with PG subjects demonstrating relatively diminished activation of the ventromedial prefrontal cortex (vmPFC), a brain region implicated in risk-reward decision-making and impulsive behaviors and disorders (Bechara, 2003; Brewer and Potenza, 2008).

Other neuroimaging studies additionally suggest vmPFC involvement in PG. Potenza and colleagues (2003) observed diminished blood oxygen level dependent (BOLD) signal change in the vmPFC following presentation of incongruent stimuli during the Stroop color word task in men with PG as compared to those without. A between-group activation difference in a similar region of vmPFC during the same Stroop task has been reported in individuals with bipolar disorder as compared to control participants (Blumberg et al. 2003). These data suggest that similar neural substrates may underlie impaired cognitive control in both disorders.

Tanabe and colleagues (2007) found that individuals with SUDs with or without co-occurring PG displayed less vmPFC activation than did control subjects during performance of the Iowa Gambling Task (Tanabe et al. 2007). In a separate study, PG subjects as compared to controls, showed less activation of the vmPFC during simulated gambling, and BOLD signal change in the vmPFC correlated inversely with gambling severity among individuals with PG (Reuter et al. 2005). Together, these studies consistently implicate relatively diminished activation of the vmPFC in the pathophysiology of PG.

Striatal and PFC regions contribute to processing of rewards. Activation of the ventral striatum has been observed during anticipatory phases of processing and vmPFC activation during consummatory or receipt phases (Knutson, 2003). The ventral PFC-striatal circuitry has been implicated in the selection of smaller, immediate reward whereas the selection of larger delayed reward involves more dorsal cortical networks (McClure, 2004). Hollander and colleagues (2005) found that blackjack gambling for money, in comparison to playing for points, was associated with greater corticostriatal activation among individuals with PG. The extent to which this finding is unique to PG is unclear as the study lacked a non-PG control comparison group. Relatively diminished striatal activation has been observed in PG as compared to control comparison subjects during simulated gambling (Reuter et al. 2005). This finding is consistent with findings of diminished ventral striatal activation during anticipatory phases of reward processing among individuals with addictions or those who might be considered “at-risk” for addictions: individuals with alcohol dependence (Wrase et al. 2007) or cocaine dependence (Pearlson et al. 2007); adolescents (Bjork, 2004); and individuals with a family history of

alcoholism (Hommer et al. 2004). Relatively diminished activation of the ventral striatum was also observed in PG as compared to non-PG subjects viewing gambling tapes, and this activation overlapped with one showing relatively diminished activation in cocaine dependent subjects as compared to control subjects viewing cocaine tapes (Potenza, 2008). Together, these findings suggest a significant involvement of ventral cortico-striatal circuits in PG, and that the involvement is similar to that observed in SUDs. The improved understanding of these neurobiological features of PG may facilitate identification of effective treatments for PG.

Pharmacological Treatments of PG

Multiple psychotropic medications have been examined in a hypothesis-driven manner in the treatment of PG. For example, the efficacies of pharmacotherapies for certain SUDs (e.g. naltrexone in the treatments of alcohol and opiate dependence) are empirically validated and reflected in FDA approvals for these indications. Given the neurobiological similarities between PG and SUDs and the proposed mechanisms of action of specific agents, it has been proposed that specific pharmacotherapies (e.g., opioid antagonists that modulate mesolimbic circuitry function) may be helpful in treating PG. Findings from pharmacotherapy studies, particularly double-blind, placebo-controlled randomized controlled trials (RCTs), are reviewed below.

Serotonin Reuptake Inhibitors

Based on findings of serotonergic dysregulation in individuals with PG (Nordin and Eklundh, 1999; Nordin and Sjodin, 2006), clinical trials have investigated serotonergic medications in the treatment of PG. Hollander and colleagues (2000) conducted a randomized, double-blind, crossover comparison study of fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), versus placebo for the treatment of PG in fifteen individuals. Following a one-week placebo lead-in phase, participants were randomized to receive either fluvoxamine or placebo. After eight weeks, participants receiving placebo were switched to fluvoxamine treatment, and vice versa, for an additional eight-week period. Whereas both placebo and fluvoxamine treatments were associated with significant improvements in PG-Clinical Global Impression (CGI) scores during the initial 8-week treatment phase, fluvoxamine, but not placebo, was associated with continued significant improvements in PG symptoms during the second eight-week crossover treatment phase, resulting in a statistically significant between-treatment difference. This and subsequent studies (Grant et al. 2003) have identified a significant placebo response in PG, highlighting the importance of placebo control conditions in understanding the influences of medications in the treatment of PG.

Kim and colleagues (2002) examined the efficacy and tolerability of the SSRI paroxetine in an eight-week, randomized, double-blind, placebo-controlled, parallel-arm trial. Following a one-week placebo lead-in, participants were administered at flexible dosing placebo or active paroxetine at 20–60 mg/day. Among participants who completed the study (n = 45), paroxetine (in comparison to placebo) was associated with significant improvements in CGI and Gambling Symptom Assessment Scale (G-SAS) scores.

Grant and colleagues (2003) conducted a sixteen-week, multi-center, randomized, placebo-controlled study of flexibly-dosed paroxetine at 10–60 mg/day for the treatment of PG in a sample of 76 individuals. Following a one-week placebo lead-in, participants with a reduction in PG-YBOCS scores ≤ 30% were randomized to receive either paroxetine or placebo. Significant improvement as measured using the CGI was seen with both the active drug and placebo. The proportions of responders did not differ significantly between the active medication and placebo groups with positive clinical response observed in 59% vs. 48% in the two arms, respectively. A 24-week, double-blind, flexible-dosing, placebo-controlled study of sertraline treatment in a sample of 66 individuals with PG also found significant overall

improvements across groups but no significant differences between placebo and active medication groups (Saiz-Ruiz et al. 2005).

Grant and Potenza (2006) examined the efficacy and tolerability of escitalopram in thirteen individuals with PG and co-occurring anxiety disorders in a twelve-week, open-label trial with double-blind discontinuation. During open-label treatment, significant decreases in PG-YBOCS scores and improvements in measures of daily functioning and gambling and anxiety symptoms were reported. Following double-blind discontinuation, randomization to placebo was associated with resumption of gambling and anxiety symptomatology, whereas randomization to active drug was associated with sustained improvement in both gambling and anxiety domains.

Together, these data show variability in study findings and suggest some short-term efficacy of SSRIs in the treatment of PG. In particular, SSRIs may be helpful for subgroups of individuals; e.g., those with co-occurring anxiety disorders. These findings are largely consistent with trials of SSRIs for AD, which have reported similar placebo effects and additionally suggest particular efficacy of SSRI treatment for subgroups of individuals; e.g., individuals with co-occurring depression or dysthymia (reviewed in Johnson, 2004).

Opioid Antagonists

Opioid receptor antagonists have been tested in the treatment PG due to their presumed mechanism of action involving indirect modulation of mesolimbic circuitry and their efficacy in the treatment of alcohol and opiate dependence (Kim, 1998; O'Brien, 2005). In a double-blind, placebo-controlled, twelve-week RCT, Kim and colleagues (2001) investigated the efficacy and tolerability of flexibly-dosed naltrexone in the treatment of PG. Forty-five of 83 patients completed the study. Of these, 75% receiving active drug improved as assessed by PG-CGI scores as compared to 24% of those receiving placebo, resulting in a statistically and clinically significant difference. In comparison to typical naltrexone dosage for alcohol and opiate dependence (i.e., 50 mg/day), significantly higher doses (average end-of-study dose = 188 mg/day; maximal dose = 250 mg/day) were used. Medication-associated liver function test abnormalities were reported in over 20% of naltrexone-treated subjects, consistent with the dose-dependent hepatotoxicity associated with naltrexone use.

More recently, Grant and colleagues (2008a) conducted an eighteen-week, double-blind, placebo-controlled RCT of naltrexone treatment for PG. Following a one-week placebo lead-in, participants non-responsive to placebo (n = 77) were randomized to receive placebo or naltrexone at 50 mg/day, 100 mg/day, or 150 mg/day. In comparison to placebo administration, naltrexone treatment at all three doses was associated with significant reductions in overall PG-YBOCS scores and both gambling urges and behaviors. The authors concluded that naltrexone given at dosages typically used in the treatments of alcohol or opiate dependence (50 mg/day) appeared sufficient and superior to placebo in the short-term treatment of PG. Naltrexone treatment was also well tolerated. In contrast to multiple prior studies, individuals with co-occurring disorders (e.g., major depressive disorder, anxiety disorders, eating disorders, and ICDs other than PG) were included, arguably increasing the generalizability of the findings to other clinical settings in which co-occurring disorders are frequently encountered.

Grant and colleagues (2006) compared nalmefene, an opioid antagonist lacking the dose-dependent hepatotoxicity profile of naltrexone, to placebo in a sixteen-week, randomized, double-blind, multi-center study of PG. Participants (n = 204) were randomized to receive placebo or nalmefene treatment at 25 mg/day, 50 mg/day or 100 mg/day. Nalmefene treatment, particularly at 25 mg/day, was associated with significant improvements in PG-YBOCS scores and other outcome measures in comparison to placebo. Medication-associated adverse events

(e.g. nausea, dizziness, insomnia) were reported less frequently among participants receiving the lowest dose of nalmefene (25 mg/day) as compared with other nalmefene doses. These data suggest that low dose nalmefene (25 mg/day, roughly equivalent to 50 mg/day of naltrexone) is well-tolerated and efficacious in the short-term treatment of PG, and additional research is required to assess the long-term efficacy and tolerability of nalmefene treatment for PG.

Using data from nalmefene (Grant et al. 2006) and naltrexone (Grant et al. 2008a) studies, Grant and colleagues (2008b) conducted stepwise logistic regression analyses to identify factors associated with positive treatment response (Grant et al. 2008b). A positive family history of alcoholism was the factor most robustly associated with a positive response to opioid antagonist treatment. In contrast, younger age was most strongly associated with a placebo response. The association between family history of alcoholism and opioid antagonist treatment response in PG subjects is not only reminiscent of findings from studies of treatment outcome for naltrexone in the treatment of alcohol dependence, but also suggests that there exist common genetic factors across diagnostic boundaries that influence treatment response and may be used to guide individualized selection of therapies (Slutske et al. 2000; Oslin et al. 2003).

Mood Stabilizers

Pallanti and colleagues (2002) conducted a fourteen-week, randomized, single-blind trial of lithium carbonate versus divalproex sodium (valproate) treatment for PG. Participants assigned to lithium treatment (n = 23) received initial doses of 600 mg/day which were titrated to 1200 mg/day based on individual tolerability (mean dose = 795.6 mg/day). Participants assigned to valproate treatment (n = 19) received initial doses of 600 mg/day, which were titrated to 1500 mg/day based on individual tolerability (mean dose = 873.7 mg/day). After fourteen weeks of treatment, both groups had significant improvements in PG-YBOCS scores when compared to baseline scores. There were no significant differences between the two treatment groups: 60.9% of patients receiving lithium and 68.4% of patients receiving valproate were considered responders based on CGI improvement scores. Although these data suggest that both lithium and valproate may be effective in short-term treatment of PG, the absence of a placebo control limits interpretation of the findings.

Hollander and colleagues (2005a) conducted a ten-week, double-blind, placebo-controlled RCT of sustained-release lithium carbonate in 40 outpatients with co-occurring PG and bipolar-spectrum disorder. Lithium as compared to placebo treatment was associated with greater reductions in gambling and manic symptomatology, and decreases in mania scores paralleled gambling score changes. Among patients who completed all 10 weeks of treatment, lithium treatment was associated with significantly greater improvements in CGI scores. These findings suggest that sustained-release lithium treatment may be efficacious in treating PG in individuals with co-occurring bipolar-spectrum disorder. Further research is needed to assess the efficacy of lithium for individuals with PG and without bipolar symptomatology.

Olanzapine, a drug with DA and 5-HT antagonism properties, has been investigated in the treatment of PG. Fong and colleagues (2008) conducted a seven-week, double-blind, placebo-controlled RCT of olanzapine in 21 individuals with PG whose preferred form of gambling was video poker. Whereas both treatment groups displayed significant reductions in gambling urges, there were no significant differences between placebo and active medication groups. McElroy and colleagues (2008) conducted a twelve-week, double-blind, placebo-controlled RCT of olanzapine in 42 outpatients with PG. Olanzapine treatment was associated with a higher drop-out rate, and there were no significant differences between placebo and active medication groups for any of the gambling variables assessed. These data suggest that olanzapine is not effective for the short-term treatment of PG.

Bupropion

Black and colleagues (2004) conducted an 8-week, open-label trial of bupropion, a drug with monoamine (DA, NE, 5-HT) reuptake inhibition and nicotinic receptor antagonism properties, in ten individuals with and without co-occurring Axis I disorders (two individuals with a history of SUDs, two individuals with a history of depression, one individual with attention deficit hyperactivity disorder (ADHD). Bupropion treatment was associated with significant improvements on PG-YBOCS, Sheehan Disability and ADHD checklist scales, although lack of a control condition limits the ability to attribute the changes to drug treatment. More recently, Black and colleagues (2007) conducted a parallel-group, double-blind, placebo-controlled, flexibly-dosed RCT of bupropion treatment for PG. Individuals with co-occurring disorders similar to those previously reported (Black, 2004) were included, and seven of the 39 participants met criteria for ADHD. Treatment groups (active drug and placebo) were balanced to control for the presence of co-occurring disorders. Following a two-week observational lead-in period, participants were randomized to receive either placebo or active bupropion. No significant differences in improvement on PG-YBOCS scores between active and placebo groups were observed, although both groups displayed improvement over time (Black et al. 2007). Together, these findings do not suggest a significant role for bupropion in the treatment of PG and highlight the importance of a placebo control group in clinical trials involving subjects with PG.

Glutamatergic Agents

N-acetyl-cysteine (NAC), an amino acid and glutamate modulating agent, has been found to block cocaine-induced reinstatement of drug-seeking in rats and reduce cue-induced craving in individuals with cocaine dependence (Kalivas and Volkow, 2005), and preliminary evidence suggests efficacy for NAC and other glutamatergic agents (e.g., riluzole) in treating PG, ICDs and impulsive behaviors, such as trichotillomania and self-injurious behaviors (Pittenger et al. 2005; Coric et al. 2007; Odlaug and Grant, 2007). Grant and colleagues (2007) conducted an eight-week, open-label, pilot-study with a double-blind discontinuation phase of NAC treatment for PG in a group of 27 individuals with PG with and without other Axis I disorders (thirteen subjects met criteria for alcohol use disorder or major depressive disorder; four met criteria for past-year major depressive disorder; eight met criteria for nicotine dependence). Five participants were concurrently using psychotropic medications including sertraline, fluoxetine, or venlafaxine. Among the 23 participants who completed the eight-week, open-label treatment phase, there were significant reductions in PG-YBOCS scores when compared to baseline. Among the thirteen participants who entered the double-blind discontinuation phase, a significantly greater percentage of participants assigned to the NAC treatment condition continued to meet responder criteria at study termination in comparison to participants receiving placebo (83.3% versus 28.6%). These findings suggest a role for glutamatergic therapies in the treatment of PG.

Summary

Several classes of agents (opioid antagonists like naltrexone and nalmefene, mood stabilizers like lithium, serotonin reuptake inhibitors like paroxetine or fluvoxamine, and glutamatergic modulators like NAC) appear promising in the short-term treatment of PG. Specific individuals, based on clinical characteristics like co-occurring disorders or family histories, may respond preferentially to specific treatments. Further research is required to assess the long-term utility of pharmacotherapies for PG and better identify specific factors related to treatment outcome.

Behavioral Therapies

Multiple non-pharmaceutical therapeutic interventions (e.g. psychoanalytic, interpersonal, behavioral, cognitive) have been investigated in PG. Findings from controlled RCTs are reviewed. Subtypes of psychosocial interventions reviewed are similar to those included in a recent meta-analysis of RCTs of psychosocial interventions for the treatment of SUDs; e.g. cognitive behavioral therapy (CBT), contingency management, relapse prevention and combined CBT/contingency management (Dutra et al., 2008). For further review of behavioral therapies for PG, see Brewer and Potenza (2008).

Aversion and Exposure Therapies

McConaghy and colleagues (1983) compared the efficacy of aversion therapy versus imaginal desensitization in twenty treatment-seeking individuals classified as compulsive gamblers. Following randomization, subjects were assessed and no significant differences between treatment groups were observed at one month. Imaginal desensitization was associated with significantly greater reductions in gambling urges and behaviors at one year, although both groups displayed significant reductions in sympotmatology.

McConaghy and colleagues (1991) compared imaginal desensitization, aversion therapy, imaginal relaxation, and brief and prolonged *in vivo* exposure in a retrospective follow-up study of 120 subjects who had previously received treatment. Among the 63 individuals who agreed to participate in the follow-up study, the average time since receipt of treatment ranged from two to nine years, with an average of 5.5 years. 79% of participants who had received imaginal desensitization therapy displayed either cessation or control of gambling behaviors. In comparison, 53% of participants who had received other behavioral therapies displayed cessation of gambling or control over gambling behaviors, suggesting potential superiority of imaginal desensitization treatment over other behavioral therapies for PG.

Echeburua and colleagues (1996) compared the efficacy of combined *in vivo* exposure, stimulus control and relapse prevention, cognitive restructuring, combined treatment and wait-list control in a group of 64 individuals with PG. At twelve-month follow-up, 69% of participants in the exposure, stimulus control and relapse prevention group were abstinent or displayed significant reductions in gambling behaviors. In comparison, only 38% or participants from the cognitive restructuring and combined treatment groups displayed significant reductions or abstinence.

Echeburua and colleagues (2000) compared the efficacy of stimulus control and exposure with response prevention therapies in a sample of 69 treatment-seeking slot-machine gamblers meeting DSM-IV criteria for PG. This study compared individual relapse prevention, group relapse prevention and no treatment. All subjects in initial stimulus control and exposure with response prevention discontinued gambling. At three months, both individual and group relapse prevention had a success rate of 91% compared with 61% in the control group, and these gains were largely maintained at twelve months.

Cognitive Therapies

Sylvain and colleagues (1997) compared the efficacy of cognitive behavioral therapy (CBT) versus wait-list control in a sample of 29 men with a DSM-III diagnosis of PG. Participants were randomly assigned to treatment or control conditions and were assessed at six- and twelve-month follow-up periods. Treatment was composed of four components: cognitive correction of incorrect perceptions related to gambling, problem-solving training, social skills training, and relapse prevention training. While more than a third of the participants discontinued treatment, significant improvements were seen in the treatment group versus the control group

on measures of gambling severity, gambling frequency, desire to gamble and perception of control over gambling. These changes were largely maintained at six and twelve months.

Ladouceur and colleagues (2001) investigated the efficacy of combined cognitive correction and relapse prevention in a sample of 66 individuals with PG randomly assigned to receive either treatment or wait-list control. In comparison to wait-list control, treatment was associated with significant reductions in gambling urges, frequency of gambling and perceived self-efficacy, and these gains were maintained at six and twelve months. In a separate study, Ladouceur and colleagues (2003) investigated the efficacy of cognitive control and relapse prevention training in a group setting. Fifty-six individuals with PG were randomized to treatment or wait-list control conditions. Consistent with previous findings (Ladouceur et al. 2001), active treatment as compared to the control condition was associated with significantly greater improvements in perceived self-efficacy and reductions in gambling urges and frequency. Eighty-eight percent of participants in the treatment group no longer met DSM-IV criteria for PG, whereas only 20% of the participants in the control group no longer met criteria. Results were largely maintained at six and twelve months. Additional data supporting the efficacy of CBT in the treatment of PG are described in the Gambler's Anonymous (GA) section below.

Hodgins and colleagues (2001) compared the efficacy of short-term self-help (CBT workbook) versus combined self-help and motivational enhancement therapy via telephone in a sample of 102 individuals with gambling problems who were randomized to one of the two active treatment conditions or a wait-list control. At one-month follow-up, participants receiving combined self-help and motivational enhancement therapy displayed significantly greater reductions in days of gambling, total money loss and expenditures on gambling days in comparison to both the self-help and wait-list control groups. At 12-month follow-up, all three groups had significant reductions in gambling variables. However, there were no significant between-group differences, suggesting that improvements may be attributable to natural recovery or other factors not assessed in this study.

Taken together, the data suggest that multiple behavioral therapies, including imaginal desensitization and CBT, may be helpful for individuals with PG. Many of these approaches have been assessed for longer durations than have been evaluated in the case of pharmacotherapies. Methodological limitations (e.g., lack of use of clinical DSM-based diagnoses) and differences across studies (e.g., with respect to outcome measures) indicate the need for additional research to allow for better comparisons of these approaches.

12-Step Therapy: Gambler's Anonymous (GA)

GA is considered the most frequently used intervention for PG (Petry, 2005), and GA meetings have become more widely available since their initiation in 1958 (National Research Council, 1999). In comparison to other therapies such as imaginal desensitization and CBT, relatively little research has investigated the efficacy of GA, perhaps due to the anonymity inherent in the program. Existing studies suggest that the majority of first-time attendees do not maintain regular GA attendance/involvement (Stewart and Brown, 1988).

Petry (2003) conducted a retrospective analysis of 342 individuals with PG seeking clinical care in the state of Connecticut to identify demographic or clinical characteristics associated with GA attendance. Fifty-four percent of the sample reported previously attending one or more GA meetings. In comparison to non-attendees, GA attendees had significantly higher SOGS scores, longer durations of gambling problems, greater interested in treatment, larger debts, lower composite drug scores and gambled on fewer days during the past month. GA attendance was also associated with current or previous marriage, higher income and older age.

Petry and colleagues (2006) compared the efficacy of GA versus CBT in a sample of 231 individuals with PG who were randomly assigned to one of three conditions: GA referral alone; GA referral and CBT workbook; GA referral and eight individual CBT sessions. Overall decreases in gambling behaviors were reported across all three treatment groups. In comparison to GA referral alone, both CBT and CBT workbook conditions were associated with significantly greater improvements during treatment, and these improvements were partially maintained at one-year follow-up. GA attendance adherence, CBT sessions completed and CBT workbook sessions completed were associated with gambling abstinence. These data suggest that combined CBT and GA attendance is effective in treating PG. Additional research is required to examine other combinations of treatment approaches; e.g., the influence of GA attendance on pharmacotherapy treatment outcomes.

Conclusion

PG is often experienced by individuals seeking care within mental health care or medical settings (Grant et al. 2005; Morasco et al. 2006; Ladd and Petry 2002; Pasternak and Fleming 1999; Potenza et al. 2002; Desai and Potenza in press). Identification of individuals with PG through active screening may help address gambling problems at earlier stages and lead to improved outcomes. Given the high rates of co-morbidity and the phenomenological and diagnostic similarities between PG and SUDs (American Psychiatric Association, 1994; Desai et al. 2007; Petry et al. 2005; National Research Council, 1999), several studies have focused on neurobiological systems previously implicated in SUDs (e.g. 5-HT, NE). Based on these similarities, established treatments for SUDs have also been explored as potential treatment strategies for PG (e.g. naltrexone).

Recent investigations into the biological underpinnings of PG have provided insight into the pathophysiology of the disorder, and this information has been used to guide the development and testing of improved treatment strategies for the disorder. When compared to findings from neurobiological studies of SUDs, multiple similarities exist. However, seemingly conflicting data from PG and SUD studies exist, and further research is required to identify the precise unique roles of specific neurotransmitters and neural systems in these disorders.

Existing findings suggest a beneficial effect of specific treatment interventions for PG, with both pharmacological and behavioral treatments displaying efficacy in controlled studies. As more empirically validated treatments for PG are identified, a challenge remains in understanding which individuals will respond best to specific treatments. Ongoing research investigating individual differences and the relationship between specific neural, genetic, environmental and clinical factors and treatment outcome should lead to clinically relevant advances in the treatment of PG.

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