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Pharmacological treatments in pathological gambling

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Pathological gambling (PG) is a relatively common and often disabling psychiatric condition characterized by intrusive urges to engage in deleterious gambling behaviour. Although common and financially devastating to individuals and families, there currently exist no formally approved pharmacotherapeutic interventions for this disorder. This review seeks to examine the history of medication treatments for PG. A systematic review of the 18 double-blind, placebo-controlled pharmacotherapy studies conducted for the treatment of pathological gambling was conducted. Study outcome and the mean dose of medication administered was documented in an effort to determine a preferred medication choice in this population. A variety of medication classes have been examined in the treatment of PG with varying results. Antidepressants, atypical antipsychotics and mood stabilizers have demonstrated mixed results in controlled clinical trials. Although limited information is available, opioid antagonists and glutamatergic agents have demonstrated efficacious outcomes, especially for individuals with PG suffering from intense urges to engage in the behaviour. Given that several studies have demonstrated their efficacy in treating the symptoms associated with PG, opioid antagonists should be considered the first line treatment for PG at this time. Most published studies, however, have employed relatively small sample sizes, are of limited duration and involve possibly non-representative clinical groups (e.g. those without co-occurring psychiatric disorders). Response measures have varied across studies. Heterogeneity of PG treatment samples may also complicate identification of effective treatments. Identification of factors related to treatment response will help inform future studies and advance treatment strategies for PG.

Introduction

Pathological gambling (PG) is a psychiatric disorder characterized by persistent and recurrent maladaptive patterns of gambling behaviour [1]. Although the majority of individuals participate in gambling as a social activity, individuals who develop PG become over involved in terms of time invested and money wagered, and continue to gamble despite the significantly negative impact on their personal, social and financial well-being [2].

Individuals with PG suffer significant impairment in their ability to function socially and occupationally. Work-related problems such as absenteeism, poor performance and job loss are common [3]. PG is also frequently associated with marital problems and diminished intimacy and trust within the family [4]. Financial difficulties often exacerbate the personal and family problems [4]. PG is also associated with greater health problems (for example, cardiac problems and liver disease) and an increased use of medical services [5, 6].

Both epidemiological and clinical research demonstrates that PG is highly comorbid with other psychiatric conditions. Data from the National Epidemiologic Survey of Alcohol and Related Conditions showed that pathological gamblers are more likely to have a mood disorder, bipolar disorder, generalized anxiety disorder, post-traumatic stress disorder, a substance use disorder or an alcohol use disorder [7].

With the functional impairment and health problems that individuals with PG experience, it is not surprising that they also report poor quality of life. In two studies systematically evaluating quality of life, individuals with PG reported significantly poorer life satisfaction compared with general, non-clinical adult samples [8, 9]. Among pathological gamblers, attempted or completed suicide is not uncommon [10].

The purpose of this article is to review the double-blind, placebo-controlled trials of various pharmacological agents used for pathological gambling [for a comprehensive review of open-label studies, please see (11, 12)]. We utilized search engines, including Medline, PubMed and professional library resources to obtain information on the double-blind, placebo-controlled trials conducted for PG over the past approximately 10 years. The pharmacological trials identified and reviewed in this article include antidepressants, opioid antagonists, mood stabilizers, atypical antipsychotics, glutamateric agents or atypical stimulants for treating PG. Please see Table 1 for a summary of double-blind, placebo-controlled pharmacotherapy trials for PG.

Pharmacotherapy

Despite the personal and social impact of gambling addiction, no medication has yet received regulatory approval in any jurisdiction as a treatment for PG. There have been, however, 18 double-blind, placebo-controlled trials of various pharmacological agents (antidepressants, opioid antagonists, glutamatergic agents, mood stabilizers) for the treatment of PG, and many of these studies suggest that certain medication therapies may be beneficial in treating this disorder.

Antidepressants were one of the first medications used to treat PG based the phenomenological association between PG and compulsivity [13], findings of serotonergic dysfunction within PG [14–16], the possible utility of clomipramine to treat PG [17] and use of fluvoxamine to treat compulsive buying, a so-called obsessive-compulsive spectrum disorder [18]. Later research focused on the commonalities between clinical symptoms of PG and substance use disorders, such as lack of control, increasing tolerance and continued engagement in a behaviour despite negative consequences [1] and the similar neurological pathways for PG and substance addictions, leading to the exploration of opiate antagonists as a treatment option [19, 20]. More recent research has highlighted the existence of PG subtypes [21, 22] and other issues relevant to PG, such as comorbidity [23] and family psychiatric history [24, 25], prompting the examination of mood stabilizers, atypical antipsychotics, glutamateric agents and atypical antipsychotics as efficacious PG pharmacotherapy.

Antidepressants

A variety of antidepressant medications have been studied for the treatment of PG, but controlled clinical trials have demonstrated mixed results. Two studies examining paroxetine have been conducted. The first 8 week study demonstrated significantly greater improvement for those pathological gamblers assigned to paroxetine compared with placebo (61% of subjects on paroxetine showed improvement *vs.* only 23% on placebo) [26]. A 16 week, multicentre study of paroxetine, however, failed to find a statistically significant difference between active drug and placebo, perhaps in part due to the high placebo response rate (48% to placebo, 59% to active drug) [27].

Fluvoxamine has also demonstrated mixed results in two placebo-controlled, double-blind studies, with one 16 week, crossover study supporting its efficacy at an average dose of 207 mg day^{-1} [28] and a second 6 month parallel-arm study with high rates of drop-out finding no significant difference in response to active or placebo drug [29]. A recent case report using functional magnetic resonance imaging (fMRI) to understand the effects of fluvoxamine in PG, however, may demonstrate the possible use of neuroimaging biomarkers to elucidate better who will or will not respond to a selective serotonin re-uptake inhibitor (SSRI) [30] or other pharmacotherapeutic intervention.

In a double-blind, 6 month, placebo-controlled trial using sertraline, a mean dosage of 95 mg day^{-1} demonstrated no statistical advantage over placebo in a group of 60 pathological gamblers [31].

In the only double-blind, placebo-controlled study using a non-SSRI antidepressant, researchers found that bupropion failed to separate from placebo after 12 weeks in 39 subjects with PG. When subjects with at last one post-randomization visit were assessed, nearly 36% of bupropion subjects and 47% of placebo subjects were classified as responders [32].

Opioid antagonists

Given their ability to modulate dopaminergic transmission in the mesolimbic pathway, opioid receptor antagonists have been investigated in the treatment of pathological gambling [20]. An initial double-blind study suggested the efficacy of naltrexone, a Food and Drug Administration (FDA)-approved treatment for alcohol dependence, in reducing the intensity of urges to gamble, gambling thoughts and gambling behaviour [19]. In an 11 week, double-blind, placebo-controlled study of 45 PG subjects, significant improvement was seen in 75% of naltrexone subjects (mean dose 188 mg day^{-1}) compared with 24% of placebo subjects. In particular, individuals reporting higher intensity gambling urges responded preferentially to treatment [19].

Findings from the initial naltrexone study were replicated in a larger, longer study of 77 subjects randomized to either naltrexone or placebo over an 18 week period. Subjects assigned to naltrexone had significantly greater reductions in gambling urges and gambling behaviour compared with subjects on placebo. Subjects assigned to naltrexone also had greater improvement in psychosocial functioning. By study endpoint, 39.7% of those on naltrex-

Table 1

Double-blind, placebo-controlled pharmacotherapy trials for pathological gambling

Reference	Medication	Design/duration	Subjects	Mean daily dose (±SD)	Strengths; weaknesses	Outcome
Antidepressants						
Kim *et al.* [26]	Paroxetine	Parallel design 8 weeks with 1 week placebo lead-in	53 enrolled; 41 completers	51.7 ± 13.1 mg	Only one subject dropped out due to an adverse event; excluded Axis I disorders and atypical gender distribution of PG	Paroxetine group significantly improved compared with placebo
Grant *et al.* [27]	Paroxetine	Parallel design 16 weeks	76 enrolled; 45 completers	50 ± 8.3 mg	Multisite study; significant baseline differences between treatment groups and exclusion of Axis I disorders	Paroxetine and placebo groups with comparable improvement
Hollander *et al.* [28]	Fluvoxamine	Crossover 16 weeks with a 1 week placebo lead-in	15 enrolled; 10 completers	195 ± 50 mg	First randomized trial of fluvoxamine; excluded drug or alcohol abuse and high early placebo effect	Fluvoxamine superior to placebo
Blanco *et al.* [29]	Fluvoxamine	Parallel design 6 months	32 enrolled; 13 completers	200 mg	6 month study duration; small sample size	Fluvoxamine not statistically significant from placebo
Sáiz-Ruiz *et al.* [31]	Sertraline	Parallel design 6 months	60 enrolled; 44 completers	95 mg	6 month study duration; high placebo response rate	Similar improvement in both groups
Black *et al.* [32]	Bupropion	Parallel design 12 weeks	39 enrolled; 22 completers	324 mg	Only trial of a non-SSRI antidepressant; small sample size	No difference between groups on any measure
Opioid antagonists						
Kim *et al.* [19]	Naltrexone	Parallel design 12 weeks with 1 week placebo lead-in	89 enrolled; 45 completers	188 ± 96 mg	First systematic investigation of naltrexone; atypical gender distribution of PG	Naltrexone group improved significantly compared with placebo
Grant *et al.* [33]	Naltrexone	Parallel design 18 weeks	77 enrolled; 49 completers	Fixed dose (50 mg, 100 mg, 150 mg)	Longest PG trial investigating naltrexone; excluded bipolar disorder and substance use disorders	Naltrexone group improved significantly compared with placebo
Toneatto *et al.* [34]	Naltrexone	11 weeks with cognitive behavioural therapy (CBT)	52 enrolled; 38 completers	100 ± 59 mg	Sample included co-current alcohol use disorder; no control group and small sample size	Naltrexone plus CBT and placebo plus CBT both improved
Grant *et al.* [35]	Nalmefene	Parallel design 16 weeks	207 enrolled; 73 completers	Fixed dose study (25 mg, 50 mg, 100 mg)	Large sample size; excluded bipolar disorder and substance use disorders	Nalmefene 25 mg and 50 mg significantly improved compared with placebo
Grant *et al.* [36]	Nalmefene	Parallel design 16 weeks with 1 week placebo lead-in	233 enrolled; 126 completers	Fixed dose study (20 mg, 40 mg)	Large sample size; current Axis I disorders and individuals seeking psychotherapy were excluded	intention-to-treat nalmefene no different from placebo. *Post hoc* analyses: 40 mg nalmefene significant improvement on primary measure.
Mood stabilizers						
Hollander *et al.* [39]	Lithium carbonate	Parallel design 10 weeks	40 bipolar-spectrum patients enrolled; 29 completers	1,170 ± 221 mg	Included bipolar spectrum disorders; sample may not generalize to all individuals with PG	Lithium group significantly improved compared with placebo
Berlin *et al.* [42]	Topiramate	Parallel design 14 weeks	42 enrolled		Only double-blind study of topiramate; small sample size	No significant treatment effect of topiramate
Atypical antipsychotics						
McElroy *et al.* [43]	Olanzapine (Zyprexa)	Parallel design 12 weeks	42 enrolled; 25 completers	8.9 ± 5.2 mg	First study to examine olanzapine; did not use a validated instrument to diagnose PG	No differences between groups on any measure
Fong *et al.* [44]	Olanzapine (Zyprexa)	Parallel design 7 weeks	23 enrolled; 21 completers	2.5 mg day^{-1}–10 mg day^{-1}	Explored treatment based on game played; high placebo response rate	No differences between groups on any measure
Other agents						
Grant *et al.* [48]	N-acetyl cysteine	8 week open-label followed by 6 week double-blind discontinuation	27 enrolled in open-label; 13 randomized to double-blind; 13 completed double-blind phase	1476.9 ± 311.3 mg	Only trial to investigate NAC; small sample size	83.3% of those assigned to N-acetyl cysteine were still responders at end of the double-blind phase, compared with 28.6% assigned to placebo.
Zack & Poulos [49]	Modafinil	Two sessions, double-blind, counter-balanced	10 high impulsivity and 10 low impulsivity	200 mg	Only study to examine modafinil; excluded major depressive disorder and attention deficit hyperactivity disorder	Decreased motivation to gamble and risky decision-making in high impulsivity gamblers

one were able to abstain from all gambling for at least 1 month, whereas only 10.5% on placebo attained complete abstinence for the same time period [33].

In another double-blind, placebo-controlled study, 52 PG subjects with co-occurring alcohol use disorder were all provided seven sessions of cognitive behavioural therapy. Although both groups responded, there were no significant differences between the naltrexone and placebo groups. This study, however, provided both groups with an effective cognitive behavioural intervention, failed to include a no-treatment group, and used a mean dose of naltrexone lower than previously reported as beneficial [34].

Another opioid antagonist, nalmefene, has also shown promise in the treatment of PG. In a large, multicentre trial using a double-blind, placebo-controlled, flexible dose design, 207 subjects were assigned to receive either nalmefene at varying doses or placebo. At the end of the 16 week study, 59% of those assigned to nalmefene showed significant reductions in gambling urges, thoughts and behaviour compared with only 34% on placebo [35].

A second multicentre nalmefene study was performed with 233 participants using nalmefene (20 or 40 mg) or placebo. In analyses performed using an intention-to-treat population, nalmefene failed to show statistically significant differences from placebo on primary and secondary outcomes. *Post hoc* analyses of only participants who received a full titration of the medication for at least 1 week, however, demonstrated that nalmefene 40 mg day^{-1} resulted in significantly greater reductions in the primary outcome measure. These findings suggest that medication dosing may be an important consideration in achieving symptom control [36].

Given that two double-blind, placebo-controlled studies of naltrexone and two multicentre double-blind, placebo-controlled trials of nalmefene suggest the efficacy of opioid antagonists in reducing the intensity of urges to gamble, gambling thoughts and gambling behaviour, this class of medication should be considered a first line treatment for PG. A prospective 6 month follow-up study found that a majority of individuals who respond to naltrexone maintain the response after medication discontinuation [37]. Furthermore, pooled analyses of those who responded to opioid antagonists demonstrated significant reduction in gambling urges, particularly among participants with a positive family history of alcohol dependence [38].

Mood stabilizers

Sustained-release lithium carbonate was used in a 10 week, double-blind, placebo-controlled study of 40 subjects with bipolar spectrum disorders and PG. Lithium (mean concentration 0.87 mEq l^{-1}) reduced the thoughts and urges associated with PG. No significant differences between groups, however, were found in the episodes of gambling per week, time spent per gambling episode or the amount of money lost [39]. Follow-up research from the same investigators using FDG-PET imaging suggests that lithium may preferentially target gamblers with increased glucose metabolic rates in the orbitofrontal and medial frontal cortices [40].

Although a randomized, blinded-rater study of topiramate compared with fluvoxamine demonstrated a 60% PG remission rate for the topiramate group [41], a 14 week, double-blind, placebo-controlled trial of topiramate in 42 subjects failed to show any significant treatment effect for topiramate on the primary or secondary outcome measures [42].

Atypical antipsychotics

Two studies have examined the use of olanzapine in the treatment of PG. In a 12 week, double-blind, placebo-controlled trial of 42 subjects with PG, olanzapine (mean dose 8.9 $\pm$ 5.2 mg) and placebo demonstrated similar reductions in gambling behaviour and gambling urges [43]. Similarly, Fong and colleagues [44] tested 21 PG subjects in a 7 week, double-blind, placebo-controlled trial and found similar reductions in cravings to gamble and gambling behaviour in both the olanzapine and placebo groups.

Other agents

Because improving glutamatergic tone in the nucleus accumbens has been implicated in reducing the reward-seeking behaviour in substance addictions [45–47], N-acetyl cysteine (NAC), a glutamate modulating agent, was administered to 27 PG subjects over an 8 week period with responders randomized to receive an additional 6 week double-blind trial of NAC or placebo. 59% of subjects in the open-label phase experienced significant reductions in PG symptoms and were classified as responders. At the end of the double-blind phase, 83% of those assigned to receive NAC were still classified as responders compared with only 28.6% of those assigned to placebo [48].

A non-treatment trial examined the effects of an atypical stimulant, modafinil, on pathological gamblers classified according to impulsivity [49]. Modafinil's behavioural effects are thought to stem in part from effects on norepinephrine and possibly dopaminergic transmission [50]. Gamblers with high impulsivity showed decreased motivation to gamble and risky decision-making, whereas those with low impulsivity showed increased responses [49].

A study examining memantine, an N-methyl D-aspartate receptor antagonist that appears to reduce glutamate excitability, found that the medication

improved cognitive flexibility simultaneously with improvement in gambling behaviour [51]. These studies reflect a potential direction for pharmacological research in PG, which would involve examining the relative efficacy of different drug classes in individuals with differences in cognitive presentation.

Conclusions

Research on the pharmacological treatment of PG appears promising, particularly in the case of opioid antagonists. The heterogeneity of PG treatment samples, however, may complicate the identification of effective treatments. As such, researchers and clinicians should be aware of the limitations of our treatment knowledge. Most published studies have employed relatively small sample sizes, are of limited duration and involve possibly non-representative clinical groups (e.g. those without co-occurring psychiatric disorders). Future research should ensure adequate power through the inclusion of larger sample sizes of individuals with PG who take the study drug for a longer duration of time and are longitudinally assessed over several years. Further, an effort should be made to ensure population-representative samples and a greater effort to include minority groups in clinical trial samples. In addition, response measures have varied across studies. The use of clinician-administered diagnostic scales for PG should be encouraged as should measures that adequately assess urges to engage in the behaviour as these have been shown to impact on treatment efficacy in PG [38]. At present, issues such as the duration of treatment cannot be sufficiently addressed with the available data. Identification of factors related to treatment response will help inform future studies and advance treatment strategies for PG.

Competing Interests

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