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A double-blind, placebo-controlled trial of olanzapine for the treatment of video poker pathological gamblers ☆

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Abstract

Emerging evidence suggests that dopaminergic and serotonergic functioning are altered in pathological gamblers; yet, there are no FDA-approved medications for pathological gambling and there have only been a limited number of clinical trials that have been conducted. Olanzapine was identified as a candidate medication for pathological gamblers because it modifies both dopaminergic and serotonergic function. Moreover, preliminary studies have shown that olanzapine effectively reduces impulsivity in other psychiatric disorders, a pharmacological target of interest for pathological gamblers. In this study, 21 pathological gamblers, whose primary gambling activity was video poker, were enrolled in a seven-week, double-blind, placebo-controlled trial. Outcome measures included self-reported urges for gambling, frequency of gambling behavior, and self-reported mood and anxiety levels. The results revealed that all study participants reported reduced levels of gambling urges, gambling behavior, and mood and anxiety symptoms. Olanzapine administration was not associated with an incremental effect versus placebo. While these findings suggest that olanzapine is not an efficacious treatment for video poker pathological gamblers, olanzapine may still be an effective treatment for a specific subset of pathological gamblers, including those with a co-occurring psychiatric disorder.
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1. Introduction

To date, there are no FDA-approved medications for the treatment of pathological gambling (PG). The process by which potential medications have been identified for this disorder is based on one of two approaches. The first approach is based on targeting symptoms of PG that overlap with other psychiatric disorders, such as bipolar affective disorder (BAD). For instance, both BAD and PG are characterized by mood instability, and impulsivity. Secondly, pathological gambling is seen at higher rates than expected in patients with bipolar disorder who were recruited from the research and community settings (McElroy et al., 1992; Kim et al., 2006). Thus, it has been hypothesized that medications that are approved for the treatment of BAD, such as mood stabilizers, might also effectively resolve similar symptoms in individuals with PG.

The results of this approach have yielded limited success. For example, case reports suggested that lithium and carbamazepine might be an efficacious treatment for pathological gamblers without co-occurring bipolar disorders (Moskowitz, 1980; Pallanti et al., 2002). Additionally, Pallanti completed the first controlled trial of a mood stabilizer in non-bipolar, pathological gamblers, comparing the efficacy of lithium versus valproate, and reported that both medications effectively reduced gambling urges and gambling frequency (Pallanti et al., 2002). More recently, Hollander completed a placebo-controlled trial of sustained lithium versus placebo in PG with co-occurring

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bipolar disorder and showed that lithium was superior to placebo with respect to the reduction of gambling urges and cravings (Hollander et al., 2005). To date, there have been no controlled clinical trials using other classes of mood stabilizers, namely atypical antipsychotics, in pathological gamblers with or without co-occurring bipolar disorder.

The second approach by which candidate medications are identified is by utilizing data from pre-clinical studies that examine the neurochemical alterations associated with PG. Medications that might reverse or resolve these alterations are then evaluated for efficacy. For example, PG is associated with changes in the levels of serotonin metabolites in the cerebrospinal fluid (Roy and Linnoila, 1989; Potenza, 2001; Goudriaan et al., 2004). Based on this finding, a number of trials using selective serotonin reuptake inhibitors (SSRIs) have been conducted, with varying degrees of success. (Zimmerman et al., 2002; Grant et al., 2003; Dannon et al., 2005).

Moreover, decreased concentrations of dopamine and increased levels of dopamine metabolites have been found in the cerebrospinal fluid of pathological gamblers, and are associated with the onset of PG (Roy et al., 1988; Shinohara, et al., 1999). In addition, allelic variants of the genes for dopamine D_2 receptors are differentially distributed among those with a family history of pathological gambling (Goudriaan et al., 2004). Finally, recent case studies in individuals with Parkinson's disease (PD) have shown that administration of dopamine agonists, which target the D_3 receptor, can trigger PG in previously asymptomatic individuals (Stocchi, 2005; Gallagher et al., 2007; O'Sullivan and Lees, 2007).

Although dopaminergic function has been implicated in PG, the role is much more complex than a simple matter of having "too much" or "too little". For instance, in a sample of pathological gamblers, Zack recently showed that administration of a dopamine antagonist, haloperidol, increased the rewarding effects of gambling and the desire to gamble (Zack and Poulos, 2007). They concluded that a dopamine *agonist* might be effective for pathological gamblers. In earlier work conducted by the same group, D-amphetamine was shown to increase the motivation and desire to gamble in problem gamblers (Zack and Poulos, 2004). Although seemingly contradictory, closer examination of these studies suggest that individuals with low levels of D2 receptors may be more susceptible to pharmacological manipulation, which may explain differential responses to rewards. There are no known reports of using amphetamines to treat pathological gamblers. In terms of dopamine antagonists, there are only a few published reports and no actual clinical trials, of pathological gambling responding to an atypical antipsychotic (Seedat et al., 2000; Potenza and Chambers, 2001).

Taken together, the evidence from these two approaches, suggest that a candidate medication targeting *both* dopaminergic and serotonergic functioning could ameliorate the symptoms of PG. Olanzapine, an atypical antipsychotic, demonstrates high affinity for both dopaminergic and serotonergic receptors (Bymaster et al., 1996). Moreover, olanzapine is FDA-approved for BAD and targets symptoms that are observed in both BAD and PG such as impulsivity (Bhana and Perry, 2001; Najt et al., 2007). Impulsivity is a complex concept and it can manifest in a number of different ways. Recently, Swann demonstrated that impulsivity appears differentially in depression versus manic states showing that motor impulsivity correlates with mania while non-planning impulsivity is associated with depression (Swann et al., 2007).

In addition to BAD, Olanzapine has shown preliminary efficacy in other disorders in which lack of impulse control is a key feature, such as trichotillomania, skin picking, and borderline personality disorder (Garnis-Jones et al., 2000; Stewart and Nejtek, 2003; Christensen, 2004; Shoja-Shafti, 2006). Each of these clinical conditions that responded to olanzapine, share phenomenological features with pathological gambling in that patients are unable to resist impulses and act without thinking about the consequences. Thus, given the available data regarding the efficacy of olanzapine, the current study was conducted to obtain data regarding the safety, tolerability, and potential efficacy of olanzapine for the treatment of pathological gambling.

2. Methods

2.1. Subjects

Recruitment began in September 1999 and enrollment was completed by March 2000. 23 participants were enrolled in the study and 21 completed the entire protocol ($n=12$ placebo and $n=9$ olanzapine, parallel groups design). Of those who did not meet study criteria, thirteen were not primarily video poker players, ten did not respond to attempts at contact following the initial phone call, five were eliminated because they were currently taking psychotropic medication, three were excluded due to medical problems, two were excluded for current major depression, one for exceeding the age limit of the study, one due to current substance abuse, one due to current legal constraints, and one did not meet criteria for pathological gambling.

Participants were recruited through advertisements and were paid for their participation. The diagnosis of PG was established using an administered, structured clinical interview for pathological gambling. Gambling patterns and behaviors were obtained through the South Oaks Gambling Screens (SOGS) and the Gambling Severity Index (Lesieur and Blume, 1987; Petry, 2003). Participants were included if they were between 18 and 65 years of age, reported that video poker was their primary game of choice, and had normal laboratory assessment and vital signs. Exclusion criteria included the need for immediate hospitalization, presence of suicidal ideation, diagnosis of a major Axis I disorder (e.g., schizophrenia, bipolar affective disorder, substance abuse or dependence), current prescription of psychotropic medications, or diagnosis of a medical disorder in which the administration of olanzapine was contraindicated. Only video poker pathological gamblers were recruited in order to recruit a homogenous sample. Past medication trials of pathological gambling have included subjects with a wide variety of preferred gambling types. In this study, there were no *a priori* data suggesting that video poker players would respond differentially to this medication.

2.2. Study design

Subjects were treatment-seeking pathological gamblers who were recruited through newspaper advertisements. The study was conducted using a double-blind, fixed dose design at the Trimeridian Gambling Center in Las Vegas, Nevada. This study was approved by the Institutional Review Board at the University of Nevada, Las Vegas. All participants gave informed consent after being fully informed about potential risks of participation. Subjects entering the trial were not involved in any other type of substance use disorder treatment.

Following enrollment in the study, subjects were randomly assigned to one of two study groups (placebo versus olanzapine). The dosing regimen of the olanzapine group was set at 2.5 mg for the first week, 5.0 mg for the second week, 7.5 mg for the third week, and 10.0 mg for weeks four to seven.

Study participants completed craving scales and gambling logs on a daily basis. They met with the study team on a weekly basis to complete self -report measures of mood and anxiety and to review the gambling logs for accuracy. No formalized therapy was provided. All subjects were encouraged to attend Gamblers Anonymous throughout the trial.

Study participants received the following compensation: $25 for the initial assessment, $5 per day for completing the gambling log and the craving scales, and $25 for each weekly visit. Moreover, study participants received a completion bonus that was equal to the sum of their initial and weekly payments.

2.3. Measures

The primary outcome measures for PG for this trial included craving and gambling behavior measures. For craving, the Brecksville Gambling Craving Scale (BGCS) and the Desire to Gamble Scale (DGS) were used. The BGCS and DGS are self-report instruments that assess intensity, duration and frequency of gambling urges and cravings and is modified from an instrument that measures cravings in substance use disorders (Halikas et al., 1991). Outcome measures for gambling behavior included the Clinical Global Impression for Pathological Gambling (CGI-PG) and a Gambling Behavior Diary which reported frequency, money spent and time spent on gambling. The CGI-PG rates illness severity and improvement and is modified from the Clinical Global Impression Scale (CGI) (Guy, 1976).

Secondary outcome measures to evaluate effects on general psychiatric health included the Brief Psychiatric Rating Scale (BPRS)(Rhoades and Overall, 1988), the Beck Depression Inventory (Lasa et al., 2000) the Hamilton Depression and Anxiety Rating Scales (HAM-A, HAM-D) (Dozois, 2003) and the Barratt Impulsiveness Scale (BIS) (Patton et al., 1995). Safety measures included assessments of adverse events at each study visit and monitoring for extrapyramidal side effects by the study team.

2.4. Statistical analysis

The statistical program used to analyze the data was SPSS (Release 12.0). The independent measure was group (placebo versus olanzapine). The primary outcome measures were changes in craving to gamble, changes in gambling behavior and changes in the mental health profile following the administration of olanzapine, as compared to placebo. Descriptive statistics for demographic data are presented for participants who completed the study ($n=21$).

The data were modeled using a mixed model, repeated measures approach. The between subject variable was study group (olanzapine versus placebo). The within-subjects, repeated measures included the study participants' response to the gambling measures and the mental health measures. Measures of gambling behavior were log transformed in order to ensure that the data were normally distributed.

A power analysis to detect differences between groups was not conducted because the purpose of this study was a preliminary one designed to detect any differences based on a small sample.

3. Results

3.1. Demographics and baseline gambling behaviors

Table 1 includes a review of the demographic data for subjects who completed the study ($n=21$). The placebo and the experimental groups did not differ at baseline with respect to demographic profile (e.g., age, education, gender, and ethnicity), response to measures of depression and anxiety, or gambling-related cravings (Table 1). Both groups were rated as moderate–severe pathological gamblers as based on SOGS and CGI-PG scores.

Table 1
Demographic indices and baseline measures of mental health status and gambling

Index	Controls ($n=12$) *M* (SD)	Treatment group ($n=9$) *M* (SD)	$p<.01$
Age	43.6 (9.0)	46.6 (12.5)	n.s.
Education	16.0 (2.5)	13.9 (2.8)	n.s.
Gender (male/female)	6/6	5/4	n.s.
Ethnicity	11 Caucasian; 1 African-American	8 Caucasian; 2 Pacific Islander; 1 Asian	n.s.
Beck Depression Inventory	6.9 (7.7)	6.5 (7.2)	n.s.
Hamilton Depression Scale	8.0 (6.3)	8.1 (6.9)	n.s.
Hamilton Anxiety Scale	6.9 (7.7)	6.5 (7.2)	n.s.
Brief Psychiatric Rating Scale	35.0 (12.3)	37.8 (12.8)	n.s.
Barratt Impulsivity Scale — Total	57.7 (17.6)	61.7 (20.9)	n.s.
South Oaks Gambling Scale (SOGS)	13.6 (2.5)	15.3 (3.0)	n.s.
Clinical Global Improvement Scale for Gambling (CGIS)	3.9 (0.8)	4.1 (1.1)	n.s.
Brecksville Gambling Craving Scale (BGCS)	16.0 (3.5)	18.8 (2.8)	n.s.
Gambling history (in years)	20.8 (12.6)	29.7 (13.1)	n.s.

3.2. Gambling craving and gambling behaviors over time

No interactions were observed between study group and change in gambling-related craving over time ($p>.05$). A reduction in gambling-related craving over time across both groups, measured using the Brecksville Gambling Craving Scale (BGCS), approached significance ($p<.08$). Another measure of craving for gambling, the Desire to Gamble (DES), was not sensitive to changes in gambling-related craving ($p>.05$). No differences were seen over gambling frequency, money spent and time spent gambling between both groups. There were, though, reductions in gambling behaviors across both groups, over time.

3.3. Mental health profile

No significant interactions were observed between study group and change in mental health profile over time. An interaction that approached significance was observed such that the placebo group reported a greater reduction in depressive symptoms over time relative to the study group, as indexed by the HAM-D ($p<.09$). There was no interaction or main effect of time or treatment observed for global measures of mental health, such as the BPRS ($p>.05$), levels of anxiety (HAM-A; $p>.05$), or the BDI ($p>.05$).

3.4. Adverse events

None of the participants who completed the study reported any serious adverse medical or psychiatric events. In terms of changes in weight, there were no significant differences between the olanzapine group (mean change in wt. = +0.5 lbs) compared to placebo group (mean change in weight = −1.0 lb). Two of the participants dropped out of the study following the onset of side effects, of sedation and fatigue, both of which are expected with olanzapine.

4. Discussion

These results revealed that the pathological gamblers enrolled in this study consistently reported reduced gambling urges, reduced gambling behavior, and improved mood state; however, treatment with olanzapine was not associated with significantly improved outcomes over placebo. Although pathological gamblers demonstrated reduced gambling behaviors after treatment, their overall improvement, in both groups, as measured by the clinician's global impression (CGI) was minimal and not statistically significant. Olanzapine was well-tolerated and there were no adverse events. The treatment retention was high and there were no notable extrapyramidal effects.

A high placebo response rate was observed in this study. Similar outcomes have been reported in other drug trials for pathological gambling (Hollander et al., 2000; Grant et al., 2006). One possible explanation for the high placebo rate is that certain subtypes of pathological gamblers may respond to brief psychosocial interventions. Although this study did not include a formal psychosocial treatment arm, participants met with a clinician on a weekly basis. It may be that meeting with a mental health professional may have contributed to this effect. Additionally, the lack of dedicated gambling treatment services may create a selection bias regarding the type of pathological gambler who seeks enrollment into research trials. Subjects who volunteer for research may be highly motivated to change their behavior and, in turn, might be more responsive to any perceived intervention.

Another explanation may be that the outcome measures were not sensitive or specific enough to detect the effects of olanzapine. This study utilized outcome instruments that have been used by clinicians that treat pathological gamblers along with tracking gambling behaviors. Outcome measures used in other pharmacological trials of pathological gamblers, such as the Pathological Gambling Yale-Brown Obsessive Compulsive Scale (PG-YBOCS), or the Gambling Symptom Assessment Scale (G-SAS) were not selected for use in this study because the study was completed before their use increased in clinical trials.

The current study does have several limitations. First, the sample size is modest, which limited the power of the study; yet a review of the data suggests that a meaningful effect would not have been observed with a larger sample. In addition, because the sample was comprised of only video poker players, this is not representative of all pathological gamblers who enter treatment (although the homogeneity of the sample may increase the reliability of the findings). Additionally, because this study excluded subjects with a co-occurring disorder, such as schizophrenia, bipolar disorder or active personality disorder, subjects might have been excluded who would have responded

Table 2
Comparison of the treatment group and controls on measures of mental health from week 1 to week 7

Index	Controls ($n=12$) M (SD)	Treatment group ($n=9$) M (SD)	$p<.01$
Barratt Impulsivity Scale — total			
Week 1	57.67 (17.58)	61.78 (20.19)	n.s.
Week 7	53.33 (17.35)	55.78 (13.63)	
Hamilton Depression Scale			
Week 1	5.17 (6.04)	3.89 (3.41)	n.s.
Week 7	3.50 (5.52)	4.11 (3.48)	
Hamilton Anxiety Scale			
Week 1	3.75 (5.07)	4.89 (4.73)	n.s.
Week 7	2.75 (3.02)	5.67 (3.74)	
Brief Psychiatric Rating Scale			
Week 1	21.42 (4.01)	25.33 (8.99)	n.s.
Week 7	21.17 (5.10)	24.67 (8.09)	
Clinical Global Impression Scale			
Week 1	4.00 (0.74)	4.11 (0.60)	n.s.
Week 7	3.67 (0.65)	3.33 (0.71)	
Pathological gambling craving scale			
Week 1	298.82 (78.33)	273.37 (79.05)	n.s.
Week 7	146.73 (74.84)	183.29 (77.62)	
Gambling behavior diary (days gambled per week)			
Week 1	4.17 (1.40)	4.11 (1.05)	n.s.
Week 7	2.50 (1.83)	2.44 (1.13)	
Gambling behavior diary (average money lost per day)			
Week 1	79.59 (81.56)	84.47 (72.73)	n.s.
Week 7	41.95 (49.94)	33.98 (41.44)	
Gambling behavior log (average time spent per day)			
Week 1	1.90 (0.72)	2.80 (1.45)	n.s.
Week 7	1.54 (1.68)	1.16 (1.10)	

positively to olanzapine. Recent work by Hollander has shown that pathological gamblers with bipolar disorder respond better to lithium as compared to placebo (Hollander et al., 2005).

Secondly, the subjects used daily, self-monitoring procedures to document their gambling behavior and urges. Behavior theory posits that daily self-monitoring of gambling may actually reduce that behavior (May et al., 2003). In turn, this could explain the negative findings, particularly if the reductions are larger in effect than the medication effects.

Thirdly, there may be a subset of pathological gamblers who would have responded differentially to medications based on neurobiology, impulsivity or perhaps based on gambling severity or type. As an example, impulsivity is a broad concept with multiple definitions and components. This group of PG were as impulsive as compared to healthy controls and may explain why there were no medication effects seen in this trial (Spinella, 2007).

Other limitations include elements seen in the study design. For instance, the length of the study was only seven weeks; it is possible that a longer trial would reveal differences between the treatment and the placebo groups. A seven-week trial duration was selected based on the usual amount of time it takes for olanzapine to demonstrate clinical improvement in BAD. Moreover, the dose, 10 mg, is well below the maximum safe dose and the usual dosages for BAD or for schizophrenia (20 mg). As a result, a higher dose may have yielded different results. Selection of drug is another possible limitation. Even though olanzapine in this study was ineffective, it may be that other atypical antipsychotics with a different pharmacological profile could be efficacious (Table 2).

Although this preliminary study does not provide support of efficacy for olanzapine in video poker pathological gamblers, future studies that examine its role with pathological gamblers with co-occurring bipolar disorder or other co-occurring impulse control disorders is warranted. An additional avenue to explore is the role of medication in impacting gambling urges and cravings. Furthermore, subtyping pathological gamblers through a predictor analysis (based on level of impulsivity or receptor genetics) might be a way of differentiating out the subsets of pathological gamblers that are likely to respond to this medication.

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