

Olanzapine in the Treatment of Pathological Gambling: A Negative Randomized Placebo-Controlled Trial

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Objective: Pathological gambling is associated with bipolar disorder and dopamine dysfunction. Olanzapine is a second-generation antipsychotic with mood-stabilizing properties and antagonistic activity at several dopamine receptors. The purpose of this study was to evaluate olanzapine in the treatment of pathological gambling.

Method: In this 12-week, single-center, randomized, double-blind, placebo-controlled, flexible-dose (2.5–15 mg/day) trial, 42 outpatients with pathological gambling by DSM-IV-TR criteria received olanzapine (N = 21) or placebo (N = 21). The primary outcome measure was the Pathological Gambling Adaptation of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS). The primary analysis of efficacy was a longitudinal analysis of the intent-to-treat sample, with treatment-by-time interaction as the effect measure. Subjects were enrolled from June 2, 2000, through November 28, 2005.

Results: Compared with placebo, olanzapine was associated with a similar rate of reduction in total scores on the PG-YBOCS scale, as well as in gambling episodes/week, hours gambled/week, and Clinical Global Impressions-Severity of Illness scale scores. The mean (SD) olanzapine daily dose at endpoint evaluation was 8.9 (5.2) mg/day. Eleven subjects (52%) receiving olanzapine and 6 (29%) receiving placebo discontinued prematurely; 3 subjects receiving olanzapine and 2 receiving placebo discontinued because of adverse events. Events causing olanzapine discontinuation were pneumonia, sedation, and hypomania.

Conclusion: Olanzapine was not superior to placebo in the short-term treatment of pathological gambling. It was also associated with a high discontinuation rate.

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Pathological gambling is classified in DSM-IV-TR as an impulse-control disorder not elsewhere classified, where it is defined as “persistent and recurrent maladaptive gambling behavior that disrupts personal, family, or vocational pursuits.”^{1(p671)} Substantial evidence indicates that pathological gambling is an important public health problem. Its lifetime prevalence in adults in the United States general population is estimated to be 1.6%,² and it is associated with psychiatric comorbidity, including suicide attempts, impaired quality of life, financial and legal problems, and disability.^{3–5}

A growing number of double-blind, placebo-controlled studies suggest pharmacotherapy may be helpful for some patients with pathological gambling.^{3–6} On the basis of the conceptualization that pathological gambling may be an obsessive-compulsive spectrum disorder, 6 such studies of SSRIs have been conducted to date.^{7–12} Three of these studies (N = 1, N = 15, and N = 45) found the SSRI superior to placebo in reducing gambling symptoms.^{7,8,10} The other 3 studies (N = 32, N = 76, and N = 60) failed to show separation between drug and placebo, but were limited by high placebo response rates.^{9,11,12} On the basis of evidence that pathological gambling may be related to addiction, studies were conducted that found that the opiate antagonists naltrexone (N = 83) and nalmefene (N = 207) were each shown superior to placebo in reducing gambling symptoms.^{13,14} On the basis of evidence that pathological gambling and bipolar disorder may be related,^{15,16} a controlled study of lithium in pathological gamblers with comorbid soft-spectrum bipolar disorders (N = 40) was conducted and found lithium was superior to placebo in reducing both gambling and manic symptoms.¹⁷

Several lines of evidence consistent with the latter study¹⁷ suggested to us that the second-generation antipsychotic olanzapine might be a useful treatment for pathological gambling. First, pathological gambling is strongly associated with bipolar disorder in clinical and community samples,¹⁵⁻¹⁹ and olanzapine has antimanic, antidepressant, and long-term mood-stabilizing effects in patients with bipolar disorder.²⁰⁻²² Second, drugs with mood-stabilizing properties, in addition to lithium, have been reported to reduce gambling symptoms in patients with pathological gambling, including those who do not have comorbid bipolar disorder. Haller and Hinterhuber²³ described a double-blind, placebo-controlled, 12-week crossover trial of carbamazepine in a man with a 16-year history of pathological gambling without bipolar disorder resistant to behavior therapy, psychoanalysis, Gamblers Anonymous, and benzodiazepines.²³ The patient's gambling stopped with carbamazepine but not with placebo and remained in remission for 30 months of continued carbamazepine treatment. Similarly, Pallanti et al.²⁴ conducted a single-blind, 14-week trial comparing valproate and lithium in 42 pathological gamblers and found that valproate performed as well as lithium in reducing gambling symptoms.²⁴

Another line of evidence suggesting to us that olanzapine might be beneficial for pathological gambling is that the drug has effects on several dopamine receptors,²⁵ and emerging research indicates that central dopamine dysfunction may play a role in the pathophysiology of pathological gambling.^{3-5,26-29} Thus, decreased concentrations of dopamine and increased concentrations of its metabolites have been found in the cerebrospinal fluid of pathological gamblers.²⁶ Allelic variants of the genes for the dopamine D₂, D₃, and D₄ receptors may be differentially distributed in persons with pathological gambling.²⁷ In addition, pathological gambling has been described in patients with Parkinson's disease receiving dopamine agonists.^{28,29}

We therefore conducted a single-center, randomized, parallel-group, placebo-controlled, flexible-dose study to assess the efficacy and safety of olanzapine during a 12-week course of treatment in 42 outpatients with pathological gambling. To rule out the possibility that olanzapine was treating pathological gambling secondary to mania, we excluded subjects with bipolar I disorder.¹ However, because mood disorders are common in persons with pathological gambling, gamblers with depressive and soft-spectrum bipolar disorders that were judged to be clinically manageable at study entry were included to increase the study's generalizability.

METHOD

Subjects

Study participants were outpatients at the University of Cincinnati Medical Center who were recruited by radio,

television, newspaper, and billboard advertisements requesting volunteers for a study of a medication for problematic gambling. Subjects were enrolled into the study if they were male or female aged 18 to 65 years, met DSM-IV-TR criteria for pathological gambling,¹ and had a South Oaks Gambling Screen³⁰ score of 5 or higher. They were randomly assigned to blinded study medication if they did not display greater than 50% improvement in their screening Pathological Gambling Adaptation of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS)³¹ scores after receiving 1 week of 1 tablet of single-blinded placebo (see Study Design).

Subjects were excluded from study participation if they met any of the following criteria: (1) ever had psychotic symptoms or met criteria for a psychotic disorder by DSM-IV-TR criteria; (2) had bipolar I disorder (bipolar II disorder and bipolar disorder not otherwise specified were allowed); (3) had a substance use disorder (by DSM-IV-TR criteria) within 1 month of study entry (except for a nicotine-related disorder); (4) had a personality disorder that could interfere with diagnostic assessment, treatment, or compliance (the presence of which was determined clinically during the screening process); (5) displayed clinically significant suicidality; (6) had begun any psychological treatment for pathological gambling within 3 months before study entry (with the exception of Gamblers Anonymous); (7) had a clinically unstable medical illness; (8) had clinically significant laboratory or electrocardiogram abnormalities; (9) received psychoactive medication (other than hypnotics, e.g., zolpidem as needed for insomnia) within 2 weeks of study medication initiation; or (10) had a history of hypersensitivity to olanzapine. Women were excluded if they were pregnant, lactating, or, if fertile, not practicing a form of medically accepted contraception.

The Institutional Review Board at the University of Cincinnati Medical Center approved the study protocol, and the study was conducted in compliance with the Declaration of Helsinki. All subjects signed approved written informed consent forms after the study procedures had been fully explained and before any study procedures were performed. Subjects were enrolled from June 2, 2000, through November 28, 2005.

Study Design

This was a 12-week, outpatient, randomized, double-blind, parallel-group, flexible-dose study conducted at the University of Cincinnati Medical Center. The trial consisted of 3 phases: a 1- to 4-week screening period, a 12-week double-blind treatment period, and a 1-week treatment discontinuation period. The screening period included a 1-week single-blind placebo run-in during which subjects had to display less than or equal to 50% improvement in their screening PG-YBOCS scores in order to be randomized. Subjects were evaluated at least

twice during the screening period; after 1, 2, 3, 4, 5, 6, 8, 10, and 12 weeks during the treatment period; and 1 week after study medication discontinuation.

The screening evaluation included an interview for demographic and clinical information and medical, psychiatric, and family histories; the South Oaks Gambling Screen³⁰ and an expanded version of the Structured Clinical Interview for DSM-IV-TR (SCID)³² to establish pathological gambling and comorbid Axis I diagnoses; the PG-YBOCS to help determine severity of pathological gambling; a physical examination; vital signs; height and weight; electrocardiogram; routine blood chemical and hematologic tests; and urinalysis. Of note, the structured interview for pathological gambling in our expanded SCID specifically asks subjects about all DSM-IV-TR criteria for pathological gambling, including all 10 of the A subcriteria. At this evaluation and each of the following visits, subjects were given take-home diaries in which to record their gambling behavior (number of gambling episodes, hours spent gambling, amount of money won and lost gambling, and types of gambling) on a daily basis. Once study medication was initiated, the number of tablets taken on a daily basis was also recorded in the diaries. Participation in Gamblers Anonymous, however, was not recorded.

At the last visit of the screening period (the baseline assessment), after the 1-week single-blind placebo washout, subjects continuing to meet inclusion criteria were enrolled in the treatment period and randomly assigned in a 1:1 ratio to therapy with olanzapine or placebo. At each visit following the baseline visit, subjects were assessed for gambling symptoms experienced since the last visit, other outcome measures, medication dose, medication compliance determined by tablet count, adverse events, use of nonstudy medications, vital signs, and weight.

All study medication was in identical 2.5-mg tablets supplied in numbered containers and dispensed to subjects according to a predetermined randomization schedule. Olanzapine was begun at 2.5 mg/day for the first 7 days. The dosage could then be increased, as tolerated, by 2.5 mg/day every 7 days to a maximum of 15 mg/day. Study medication could be reduced to a minimum of 2.5 mg daily because of bothersome side effects at any time during the 12-week treatment period. Subjects were instructed to take their entire daily dose of study medication in the evening. However, if they preferred, subjects could take half of the daily dose in the morning.

Outcome Measures

The primary outcome measure was the PG-YBOCS³¹ total score. Secondary outcome measures were weekly frequency of gambling episodes (determined from subjects' take-home diaries); total weekly hours spent gambling (also determined from the diaries); Clinical Global Impressions-Severity of Illness scale (CGI-S)³³ and CGI-

Improvement scale (CGI-I)³³ scores; Hamilton Rating Scale for Depression (HAM-D)³⁴ total scores; Young Mania Rating Scale (YMRS)³⁵ total scores; and the Global Assessment of Functioning scale (GAF)³² scores. Categorical responder criteria at treatment termination was defined 2 ways: (1) having a CGI-I pathological gambling scale score of 1 or 2, equaling "much" or "very much" improved; and (2) having a 35% or greater reduction in the PG-YBOCS total score compared with baseline.

Adverse events, clinical laboratory data, physical examination findings, and vital signs were assessed as safety measures. Adverse events were obtained through spontaneous patient reporting and by open-ended inquiring by investigators. Reportable adverse events were new symptoms or illnesses that occurred during the treatment phase and those that increased in severity compared with baseline.

Statistical Methods

Each treatment group's baseline characteristics were compared by using Fisher exact tests for categorical variables and independent-samples *t* tests for continuous variables.

The primary analysis of efficacy was a longitudinal analysis comparing the rate of change in PG-YBOCS scores during the treatment period between groups. The same analysis was applied to weekly gambling episodes, weekly hours spent gambling, and scores on the CGI-S, HAM-D, YMRS, and GAF scales. The difference in rate of change was estimated by random regression methods.^{36,37} A model for the mean of the outcome variable was used that included terms for treatment, time, and treatment-by-time interaction. Prior experience led us to expect that any observed improvement in either treatment group would be more rapid in the early part of the trial, and inspection of the data supported this assumption. To accommodate this behavior, time was modeled as a continuous variable, expressed as the square root of weeks since randomization. For the analyses of gambling episode frequency and hours spent gambling, the logarithmic transformation $\log([X/wk] + 1)$ was used to normalize the data and stabilize the variance. To simultaneously account for individual differences in initial level of the outcome, rate of change over time, and serial autocorrelation (i.e., the tendency for correlation among observations to decrease as a function of the amount of time between them), the SAS procedure MIXED was used (SAS Institute, Inc., Cary, N.C.), with random intercept and slope terms, and a first-order ante-dependence structure for the residual correlation matrix. The longitudinal analyses were intent-to-treat, using all available observations from all time points from all subjects who completed a baseline evaluation.

Several secondary analyses were also performed. Change scores from baseline to endpoint, using the last

observation carried forward, were computed for each measure (on the logarithmic scale for gambling episodes and hours spent gambling measures) and independent-samples *t* tests were used to compare these changes between the treatment groups. Categorical response to treatment (as defined above) was also analyzed for the intent-to-treat and completer groups, using the Cochran-Armitage exact trend test for 2-by-*k* ordered tables in SAS (PROC FREQ) (SAS Institute, Inc., Cary, N.C.).

For laboratory measures, including weight, the mean difference between endpoint and baseline measures was computed and then compared between treatment groups using the *t* test.

All statistical tests and confidence intervals were 2-sided, $\alpha = .05$.

RESULTS

Of 52 subjects screened, 10 were not randomized because they were lost to follow-up (*N* = 3), had bipolar I disorder (*N* = 2), had a suicide plan (*N* = 1), had unstable medical illness (*N* = 1), had a South Oaks Gambling Screen score less than 5 (*N* = 1), or displayed a greater than 50% decrease in their screening PG-YBOCS score with placebo washout (*N* = 2). Forty-two subjects met entry criteria and were randomly assigned to olanzapine (*N* = 21) or placebo (*N* = 21). Twenty-four subjects (57.1%) were women, 35 (83.3%) were Caucasian, and 7 (16.7%) were African American. Depressive disorders were the most common co-occurring psychiatric disorders, occurring in 27 subjects (64.3%) as lifetime diagnoses and currently in 6 subjects (14.3%). Eight subjects (19.0%) had lifetime soft-spectrum bipolar disorders. There were no significant differences between the treatment groups in demographic or clinical variables at baseline (Table 1).

Forty subjects (20 receiving olanzapine and 20 receiving placebo) had at least 1 post-randomization efficacy measure. Eleven subjects (52.4%) in the olanzapine group and 6 subjects (28.6%) in the placebo group did not complete all 12 weeks of treatment (Fisher exact *p* = .21). Although not statistically significant, the point estimate of risk for discontinuation from olanzapine treatment was nearly double that for placebo treatment. Five subjects withdrew from the study because of adverse events (olanzapine, *N* = 3; placebo, *N* = 2); 4 because of lack of efficacy (olanzapine, *N* = 3; placebo, *N* = 1); and 8 because of difficulties with protocol adherence (olanzapine, *N* = 5; placebo, *N* = 3). The latter specifically included patient choice (*N* = 2), lost to follow-up (*N* = 2), and beginning an exclusionary medication (*N* = 1) for the olanzapine group; and patient choice (*N* = 2) and lost to follow up (*N* = 1) for the placebo group. Subjects who discontinued olanzapine did not differ significantly from those who completed the 12-week trial on any baseline variable (data not presented). The remaining 25 subjects completed the

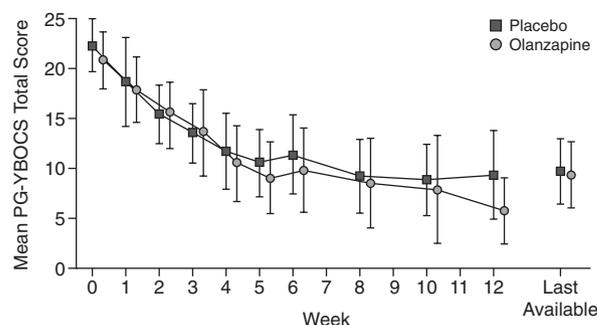
Table 1. Baseline Characteristics of 42 Subjects With Pathological Gambling Randomly Assigned to 12 Weeks of Double-Blind Treatment With Olanzapine or Placebo

Characteristic	Olanzapine Group (N = 21)	Placebo Group (N = 21)	p Value
Age, mean (SD), y	51.5 (11.2)	46.8 (8.2)	.14
Duration of pathological gambling, mean (SD), y	11.2 (10.2)	10.1 (9.7)	.73
Assessment scores, mean (SD)			
PG-YBOCS	20.9 (6.3)	22.4 (5.9)	.44
Obsessions	10.4 (3.7)	11.9 (2.9)	.17
Compulsions	10.5 (4.1)	10.5 (3.4)	.97
CGI-Severity of Illness scale	4.6 (0.7)	4.9 (0.7)	.25
Hamilton Rating Scale for Depression	6.2 (4.2)	6.6 (6.5)	.82
Young Mania Rating scale	2.3 (2.8)	2.0 (3.1)	.75
Global Assessment of Functioning scale	59.1 (8.1)	57.6 (6.4)	.53
Female, N (%)	13 (61.9)	11 (52.4)	.75
White, N (%)	20 (95.2)	15 (71.4)	.09
Lifetime comorbid diagnosis, N (%)			
Any mood disorder	12 (57.1)	15 (71.4)	.52
Depressive disorder ^a	9 (42.9)	8 (38.1)	1.00
Bipolar spectrum	2 (9.5)	6 (28.6)	.24
Due to a GMC	1 (4.8)	1 (4.8)	1.00
Any substance use disorder	8 (38.1)	6 (28.6)	.74
Any anxiety disorder	5 (23.8)	2 (9.5)	.41

^a*N* = 6 subjects with a current depressive disorder diagnosis; 3 received olanzapine and 3 received placebo.

Abbreviations: CGI = Clinical Global Impressions, GMC = general medical condition, PG-YBOCS = Pathological Gambling Adaptation of the Yale-Brown Obsessive Compulsive Scale.

Figure 1. Mean Pathological Gambling Adaptation of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS) Total Score Over 12 Weeks of Treatment in Subjects With Pathological Gambling Randomly Assigned to Olanzapine or Placebo^a



	0	1	2	3	4	5	6	7	8	9	10	11	12	Last Available
Placebo	21	20	20	19	19	19	17	16	15	15	15	15	15	21
Olanzapine	21	20	18	18	16	16	15	14	12	12	10	10	10	21

^aBars represent 95% confidence intervals.

12 weeks of treatment (10 receiving olanzapine and 15 receiving placebo).

The mean PG-YBOCS total score decreased similarly over the study period in both treatment groups (Figure 1). Furthermore, in the primary efficacy analysis using random regression, there were no differences in the rate of change between olanzapine or placebo for total scores on

Table 2. Mean Model-Based Differences Between Olanzapine Group (N = 21) and Placebo Group (N = 21) in Change From Baseline to Week 12 for 42 Subjects With Pathological Gambling Randomly Assigned to 12 Weeks of Double-Blind Treatment With Olanzapine or Placebo

Outcome Measure	Longitudinal Analysis ^a				Endpoint Analysis ^b			
	Estimate	95% CI	χ^2 (df = 1)	p Value	Estimate	95% CI	T (df = 38)	p Value
PG-YBOCS, total score	0.95	(-5.39 to 7.29)	0.09	.768	-0.85	(-6.26 to 4.56)	-0.32	.752
Obsession score	0.12	(-3.22 to 3.46)	0.00	.944	-0.95	(-3.85 to 1.95)	-0.66	.511
Compulsion score	0.95	(-2.60 to 4.50)	0.28	.599	0.10	(-2.89 to 3.09)	0.07	.946
CGI-Severity of Illness scale	-0.30	(-1.32 to 0.71)	0.34	.559	-0.25	(-1.22 to 0.72)	-0.52	.603
HAM-D	0.30	(-2.89 to 3.48)	0.03	.852	2.13	(-0.89 to 5.15)	1.41	.169
Young Mania Rating Scale	0.69	(-1.27 to 2.66)	0.49	.490	1.28	(-0.36 to 2.92)	1.57	.125
GAF	1.50	(-7.73 to 10.72)	0.10	.749	2.58	(-7.08 to 12.24)	0.54	.589
Hours gambled ^c	0.20	(-0.49 to 1.83)	0.52	.467	-0.02	(-0.36 to 0.30)	-0.12	.903
Times gambled ^d	0.15	(-0.39 to 1.18)	0.12	.726	0.07	(-0.31 to 0.46)	0.38	.710

^aEstimate is for mean (week 12 minus baseline) for olanzapine minus mean (week 12 minus baseline) for placebo. Test statistic is for the treatment-by-time interaction term, which represents the difference in rate of change between the olanzapine and placebo groups, with time modeled as square root of weeks since randomization. The estimate and its CI were obtained by multiplying the estimate and its CI by 12 weeks and squaring.

^bEstimate is for mean (week 12 minus baseline) for olanzapine minus mean (week 12 minus baseline) for placebo.

^cLog transformation ($\log[\text{hours gambled/week} + 1]$) was used for analysis; values in table are expressed in the original scale.

^dLog transformation ($\log[\text{times gambled/week} + 1]$) was used for analysis; values in table are expressed in the original scale.

Abbreviations: CGI = Clinical Global Impressions, GAF = Global Assessment of Functioning scale, HAM-D = Hamilton Rating Scale for Depression, PG-YBOCS = Pathological Gambling Adaptation of the Yale-Brown Obsessive Compulsive Scale.

the PG-YBOCS scale or on any of the secondary measures, including in gambling episodes/week, in hours spent gambling/week, or in CGI-S scores between the treatment groups (Table 2). There was also no difference in the rate of change in HAM-D, YMRS, or GAF scores between the treatment groups.

Similarly, in the secondary analysis of baseline-to-endpoint change scores, there were no significant differences between groups in the change in scores on the PG-YBOCS, CGI-S, HAM-D, YMRS, or GAF scale; in gambling episodes/week; or in hours spent gambling/week (Table 2).

In addition, there were no differences between treatment groups in either definition of categorical response in the intent-to-treat or completer analyses. The mean final CGI-I score at endpoint was rated much or very much improved in 14 olanzapine-treated subjects (66.7%) as compared with 15 placebo-treated subjects (71.4%) in the intent-to-treat population (Fisher exact $p = 1.0$) and 9 (90.0%) and 11 (73.3%), respectively, in the completer population (Fisher exact $p = .61$). Response, defined as 35% or greater reduction in PG-YBOCS total score, was obtained by 14 olanzapine-treated subjects (66.7%) and 14 placebo-treated subjects (66.7%) (Fisher exact $p = 1.0$) in the intent-to-treat population, and 8 (80.0%) and 11 (73.3%), respectively, in the completer population (Fisher exact $p = 1.0$).

The mean (SD) daily dose of olanzapine at endpoint evaluation for all 20 subjects was 8.9 (5.2) mg. The mean (SD) daily dose for the 10 subjects who completed the 12-week trial was 10.5 (5.0) mg. There were no gender-specific effects of treatment on any of the outcome measures (data not presented).

Adverse events occurring in at least 2 subjects receiving olanzapine are listed in Table 3. Although adverse

Table 3. Adverse Events Reported by 2 or More Subjects With Pathological Gambling Randomly Assigned to 12 Weeks of Double-Blind Treatment With Olanzapine or Placebo

Adverse Event	Olanzapine Group (N = 21)		Placebo Group (N = 21)	
	N	%	N	%
Somnolence	14	67	11	52
Increased appetite ^a	13	62	5	24
Dry mouth	5	24	6	29
Weight gain	4	19	1	5
Gastrointestinal virus	4	19	0	0
Headache	3	14	3	14
Depression	2	10	2	10
Edema	2	10	1	5
Nervousness	2	10	1	5
Paresthesias	2	10	1	5
Dizziness	2	10	0	0
Thinking abnormality	2	10	0	0
Joint stiffness	2	10	0	0
Increased eating behavior	2	10	0	0

^aDifference is significant, $p = .028$. There are no other significant differences between groups (all $p > .10$, Fisher exact test).

events appeared to be more common overall with olanzapine than with placebo, there was no statistically significant difference between treatment groups in the incidence of any particular adverse event except increased appetite. More subjects discontinued olanzapine (14.3%, $N = 3$) for adverse events than placebo (9.5%, $N = 2$), but this difference in incidence also was not statistically significant (Fisher exact $p = 1.0$). Adverse events causing discontinuation among olanzapine-treated subjects were development of pneumonia ($N = 1$), sedation ($N = 1$), and increased hypomania ($N = 1$). Adverse events causing discontinuation among placebo-treated subjects were abdominal pain with nausea and vomiting ($N = 1$) and worsening depression ($N = 1$).

There were no serious adverse events during the study. There were no changes in physical examination findings, vital signs, or clinical laboratory values suggestive of drug-related toxicity. However, subjects receiving olanzapine gained significantly more weight than those receiving placebo (mean [SD] = 5.98 [6.19] lb vs. 0.25 [3.37] lb, respectively; $p = .0015$).

DISCUSSION

In the primary longitudinal analysis of this randomized, double-blind trial in subjects with pathological gambling, olanzapine was comparable to placebo in rate of reduction of obsessive-compulsive features of gambling, gambling episode frequency, time spent gambling, and overall severity of illness. A secondary analysis, change from baseline to endpoint using last observation carried forward, yielded similar negative findings on all outcome variables. Taken together, these findings suggest that olanzapine is not efficacious for pathological gambling.

Several limitations of this study should be considered. First, the small sample size may have provided insufficient power to detect moderate treatment effects. Thus, it could be argued that the study design allowed for an unacceptably high probability of a type II error, rendering a nonsignificant result inconclusive (i.e., the study was a failed rather than a negative trial). However, the baseline-to-endpoint analysis of PG-YBOCS total scores, which found an effect size of -0.10 standard deviations (a nonsignificant advantage for placebo over olanzapine, $p = .75$) suggests this possibility is remote. The 95% confidence interval for this effect is -0.72 to 0.52 , which just barely includes the value 0.50 standard deviations. An effect size of 0.50 is conventionally considered to represent a "moderate" treatment effect.³⁸ In this study, such an effect is equivalent to a decrease of approximately 4 more PG-YBOCS points in the olanzapine group than in the placebo group. Given the current data, the probability of an olanzapine effect at least this large is less than 0.03 . Furthermore, it is possible to compute the predictive distribution for additional subjects, assuming optimistically that the true effect size is actually 0.50 standard deviations. This is one approach to futility monitoring (or interim power analysis), in which the probability that continuing a trial will eventually lead to a significant result is determined.³⁹ If data were obtained from an additional 40 subjects, the probability that the combined sample would produce a significant result is only 0.04 . In summary, the current data provide rather strong evidence that the effect of olanzapine is not of clinically meaningful magnitude (the probability of an effect size ≥ 0.50 is only 0.03), and even if this unlikely effect size is assumed to be true, doubling the size of the trial would have been very unlikely to produce a significant result in favor of olanzapine (the probability of future significance with $N = 80$ is only 0.04).

The high response to placebo observed in this and other pathological gambling pharmacotherapy studies^{9,11,12,40} deserves special comment. The placebo run-in period used in this study did not appear to reduce the placebo response.⁹ As noted by other authors regarding pharmacotherapy trials for pathological gambling⁴⁰ and impulse-control disorders in general,⁴¹⁻⁴³ the regular visits and monitoring of the impulsive behavior required by a clinical trial may be therapeutic in and of itself. Indeed, cognitive-behavioral therapy has been reported to be effective in pathological gambling and several other impulse-control disorders.⁴⁴⁻⁴⁶ Strategies suggested to manage such high placebo response rates have included abandonment of diaries for assessment of impulsive behaviors and use of double-blind, placebo-controlled treatment discontinuation trials.^{40,42}

It might also be argued that this study was negative because subjects without comorbid bipolar disorders were included. In other words, olanzapine may have been ineffective in the present study because subjects with bipolar I disorder were excluded and only 8 subjects (19%) had soft spectrum bipolar disorders. Indeed, several authorities have noted that comorbidity may be important in the pharmacotherapy of pathological gambling.^{17,18,47} Thus, pathological gambling might respond to olanzapine, and possibly other agents with mood-stabilizing and dopamine-receptor antagonistic properties, only when it co-occurs with a bipolar disorder or other conditions characterized by dopamine hyperactivity. For example, the only published reports of pathological gambling responding to a second-generation antipsychotic that we were able to locate are a patient with schizophrenia whose gambling responded to olanzapine⁴⁸ and a patient with Parkinson's disease whose dopamine agonist-induced gambling responded to risperidone.⁴⁹ These observations support suggestions that pathological gambling is a heterogeneous condition and that its subtyping may in part be determined by its co-occurring disorders.

Several other limitations, mostly regarding methodology, should be noted. One is that the structured interview used to diagnose pathological gambling, although based on DSM-IV criteria, was not a validated instrument. It could be argued that our interview was not sufficiently accurate and that some patients whose gambling was problematic, but not truly pathological, were subsequently enrolled in the trial, possibly contributing to the lack of differentiation between olanzapine and placebo. Use of recently developed validated interviews, such as the Structured Clinical Interview for Pathological Gambling,⁵⁰ might reduce the risk of this potential limitation in future studies. Another limitation of the present study is that attendance at Gamblers Anonymous meetings was not assessed. The negative findings could therefore be attributed to a higher rate of Gamblers Anonymous attendance in the placebo group compared with the olanzapine

group. Finally, categorical response was defined arbitrarily (in one way) as a 35% or greater decrease in PG-YBOCS score, and recent research suggests it might be best to define response of obsessive-compulsive spectrum disorders as a 30% or greater decrease.⁵¹ However, there is still considerable debate as to how to assess symptom change and response in clinical trials in pathological gambling.⁵² In addition, defining categorical response as a 30% or greater decrease in PG-YBOCS score did not change our study's results (data not shown).

In summary, in a 12-week trial in outpatients with pathological gambling, olanzapine was not found to be superior to placebo in reducing gambling symptoms, gambling frequency, or severity of illness. Also, it was associated with only fair tolerability and a relatively high treatment discontinuation rate.

Drug names: carbamazepine (Equetro, Carbatrol, and others), nalmefene (Revex), naltrexone (Vivitol, ReVia, and others), olanzapine (Zyprexa), zolpidem (Ambien and others).

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