Nefazodone Treatment of Pathological Gambling: A Prospective Open-Label Controlled Trial

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Background: Pathological gambling is a disabling and highly prevalent impulse-control disorder not otherwise specified (NOS). According to the hypothesis of abnormal serotonin function in the pathophysiology of poor impulse control and pathological gambling, we assessed the efficacy and tolerability of nefazodone, a 5-HT antagonist reported to be effective in other impulse-control disorders NOS, in the treatment of pathological gambling.

Method: Fourteen outpatients who met DSM-IV criteria for pathological gambling were enrolled in a prospective 8-week open-label oral nefazodone trial. Nefazodone was initiated at 50 mg/day and titrated upward to a maximum of 500 mg/day based on patient's response and side effects, with a minimum daily dose of 100 mg. Improvement in gambling was assessed via the pathological gambling modifications of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS), the Clinical Global Impressions-Improvement scale (PG-CGI-I), and self-rated gambling scales. Response was defined a priori as both a 25% reduction in PG-YBOCS score and a score of 1 (very much improved) or 2 (much improved) on the PG-CGI-I scale.

Results: Twelve subjects completed the study, and 2 subjects were early dropouts who did not receive the minimum required dose. Significant improvements were noted in all gambling outcome measures, as well as in depression and anxiety ratings (which did not significantly correlate with gambling reduction). Nine (75%) of 12 patients were rated as responders according to a priori criteria. Side effects (dry mouth and sedation) of moderate severity occurred in 4 subjects.

Conclusion: These preliminary results suggest that nefazodone may be effective in reducing symptoms of pathological gambling and is well tolerated.

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Pathological gambling is the most prevalent and disabling of the impulse-control disorders with a prevalence rate of 1.0% to 3.4% in the adult U.S. population,[1] and an increasing prevalence rate presumably related to the expansion of legalized gambling. In 1998, 86% of the general adult population was estimated to have gambled at some point in their lives, up from 68% in 1975.[2]

Results of pharmacologic challenge studies demonstrate a blunted prolactin response to clomipramine,[3] an enhanced prolactin response to meta-chlorophenylpiperazine (*m*-CPP), and an increased "high" response to *m*-CPP (E.H., manuscript submitted), consistent with presynaptic serotonin (5-HT) deficiency and postsynaptic 5-HT–receptor hypersensitivity in pathological gambling. According to these reports, the serotonergic system has been linked to the pathophysiology of pathological gambling.[4]

Currently, few controlled pharmacologic treatment studies of pathological gambling have been reported, although this is a recently developing area of research. In a single-blind, 8-week trial of the selective serotonin reuptake inhibitor (SSRI) fluvoxamine, Hollander et al.[5] reported improvement in 7 of 10 pathological gamblers. Two patients with comorbid cyclothymic disorder were noted to worsen on treatment with the SSRI. Hollander et al.[6] reported a superior effect of fluvoxamine (40.6% mean improvement on the pathological gambling modification of the Clinical Global Impressions scale [PG-CGI]) compared with placebo (16.6% PG-CGI mean improvement) in the second phase of a 16-week, double-blind crossover study. In the first phase, a high placebo response rate was noted, such that fluvoxamine did not differ from placebo. More recently, Zimmerman et al.[7] studied 15 patients with pathological gambling in a 12-week, open-label citalopram trial (mean dose = 34.7 mg/day). They reported a significant improvement on all gambling measures with 86.7% of the patients rated as responders on the clinician-rated PG-CGI-Improvement scale.

Nefazodone, a phenylpiperazine antidepressant, is primarily an antagonist at serotonin-2 (5-HT_2) receptors and has mixed noradrenergic/serotonergic reuptake inhibitor effects. Antagonism of 5-HT_2 receptors has been associated with the low rate of sexual side effects with nefazodone in comparison to SSRIs,[8] a profile that may be of interest in enhancing compliance in this impulsive

pathological gambling population. Nefazodone has recently been reported to be effective in another impulse-control disorder not otherwise specified (NOS), nonparaphilic compulsive sexual behavior, reducing the frequency of sexual obsessions and compulsions at a mean dosage of 200 mg/day.[9] We chose to study the safety and efficacy of nefazodone in pathological gambling, given evidence of 5-HT_2–receptor hypersensitivity in pathological gambling and efficacy of nefazodone in a related impulse-control disorder. We report the results of a preliminary 8-week prospective open-label controlled clinical trial in a sample of patients seeking treatment for pathological gambling.

METHOD

Fourteen outpatients with a DSM-IV diagnosis of pathological gambling and free of major medical illness were enrolled in an 8-week open-label trial of oral nefazodone. The study was approved by the Institutional Review Board of Mount Sinai School of Medicine, New York, N.Y. Subjects underwent a Structured Clinical Interview for DSM-IV (SCID)[10] to determine the diagnosis of pathological gambling, as well as comorbid Axis I disorders. Exclusion criteria included a diagnosis of current bipolar I disorder, schizophrenia, or other psychotic disorders or organic mental disorders, as well as women who were pregnant or nursing or of childbearing potential not using a medically acceptable method of birth control. In addition, patients at serious suicidal risk or who had displayed significant auto-aggressive behavior were excluded. After screening, subjects were seen at baseline and at the end of weeks 1, 2, 3, 4, 6, and 8, and clinician ratings and patient self-ratings and adverse events were recorded. A physical evaluation, electrocardiogram, and routine blood work were performed at baseline and endpoint.

Primary gambling efficacy measures included the pathological gambling modifications of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS)[11] and the Clinical Global Impressions-Improvement scale (PG-CGI-I).[12] At each visit, depressive symptoms were assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D)[13] and anxiety symptoms with the Hamilton Rating Scale for Anxiety (HAM-A).[14] In addition, gambling severity was assessed with the Pathological Gambling Behavioral Self-Report Scale (E.H., unpublished scale, 2002) and the Pathological Gambling 100-mm Visual Analog Craving Scale, a pathological gambling modification of the 5 self-rated 100-mm visual analog scales that have been used to evaluate the 5 key components of drug craving.[15] Safety data were collected at each visit by means of patients' spontaneous report of adverse events.

All subjects were free from other psychotropic medications for at least 4 weeks before entering the study. Open-label nefazodone was begun at 50 mg once daily at bedtime for the first 7 days and titrated to 100 mg once daily at bedtime or in divided doses for the next 7 days. Study medication was increased in increments of 100-mg doses per week to a maximum of 500 mg/day (at bedtime or in divided doses), based on the patient's response and side effects. All patients needed to achieve a minimum daily dose of 100 mg/day, and a constant dose was maintained during the last 4 weeks of the study. A priori response criteria were defined as both a 25% reduction in PG-YBOCS score and a score of 1 (very much improved) or 2 (much improved) on the PG-CGI-I scale.

Repeated measures multivariate analyses of variance (MANOVAs) were used to compare rating scale (PG-YBOCS, PG-CGI-I, HAM-D, HAM-A) score differences over time, while differences in self-reported gambling scales from baseline to endpoint were compared using paired t test with Bonferroni's correction. All statistical tests were 2-tailed.

RESULTS

Of the 14 enrolled subjects, 2 (14.3%) were married, 3 (21.4%) were divorced or separated, and 9 (64.3%) were single. Eight (57.1%) had a lifetime substance abuse/dependence history as revealed by SCID interview. Baseline demographic data, other comorbid conditions, and clinical characteristics of the enrolled patients are summarized in Table 1.

Two (14.3%) of the 14 enrolled subjects dropped out very early in the study; in each case withdrawal from the study was unrelated to treatment efficacy or tolerability. One dropped out after 4 days due to a domestic accident requiring hospitalization, and the other dropped out after 8 days due to obtaining new employment that required relocation. Both patients were taking 50 mg/day, below the minimum required dose of 100 mg/day, and were not included in the statistical analysis. The mean ± SD endpoint nefazodone dose was 345.83 ± 98.76 mg/day.

Figure 1A shows the mean PG-YBOCS scores over time, which significantly improved from baseline starting at week 2 and continuing throughout the 8-week trial. The total PG-YBOCS score ($F = 19.492$, $p \leq .001$), as well as scores of 2 PG-YBOCS subscales—thoughts/urges score ($F = 23.467$, $p \leq .001$) and behaviors score ($F = 14.226$, $p \leq .05$)—were significantly reduced with nefazodone treatment as compared with baseline. Significant improvement also occurred in PG-CGI-I scores (both patient- and clinician-rated) beginning at week 2 and continuing throughout the 8-week trial (patient PG-CGI-I: $F = 54.383$, $p \leq .001$; clinician PG-CGI-I: $F = 66.000$, $p \leq .001$) (Figure 1B). HAM-D ($F = 66.259$, $p \leq .001$) and HAM-A ($F = 29.642$, $p \leq .001$) scores significantly improved at endpoint as compared with baseline, and this improvement reached significance at week 2

Table 1. Baseline Demographic and Clinical Data (N = 14)[a]

Characteristic	Value
Age, mean ± SD, y	48.50 ± 8.33
Sex, male/female, N/N	10/4
Duration of pathological gambling, mean ± SD, y	20.00 ± 11.18
Marital status, N	
Single	9
Married	2
Separated	2
Divorced	1
Ethnicity, N	
White	6
Black	7
Hispanic	1
Education, N	
High school graduate	7
Some college	4
College graduate	3
Psychiatric familiarity, yes/no, N/N	5/9
Lifetime substance abuse/dependence (SCID), yes/no, N/N	8/6
Lifetime threshold psychiatric comorbidity (SCID), N[b]	
Panic disorder	2
Social phobia	2
Obsessive-compulsive disorder	1
Bipolar II disorder	3
Cyclothymia	2
Depressive episode	2
Binge-eating disorder	1
No. of DSM-IV pathological gambling criteria, mean ± SD[c]	7.93 ± 1.82
PG-YBOCS, mean ± SD	
Total	22.57 ± 6.69
Thoughts/Urges	11.29 ± 3.15
Behaviors	11.29 ± 3.93
CGI-S, mean ± SD	5.43 ± 0.94
HAM-D total, mean ± SD	10.64 ± 4.58
HAM-A total, mean ± SD	11.64 ± 6.81
GAF (SCID), mean ± SD	65.64 ± 11.17
Completers/dropouts, N/N	12/2

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, PG-YBOCS = pathological gambling modification of the Yale-Brown Obsessive Compulsive Scale.
[b]Patients may have more than 1 lifetime comorbid condition.
[c]Total number of criteria = 10 (5 or more indicate presence of pathological gambling).

and continued throughout the trial for both HAM-D and HAM-A scores (Figure 1C).

Table 2 summarizes baseline and endpoint scores on self-rated gambling scales during the nefazodone treatment study, and a summary of statistical results with Bonferroni's correction for multiple comparisons is provided. There was improvement on the Pathological Gambling Behavioral Self-Report Scale, with a significant reduction in the number of episodes per week ($t = 3.63$, $df = 11$, $p = .004$). Improvement on the Pathological Gambling 100-mm Visual Analog Craving Scale reached statistical significance on 2 of 5 items.

Table 3 describes the percentage of improvement and responder status of each individual patient. Overall, there was a mean ± SD percentage of improvement of 36.8% ± 23.4% on the PG-YBOCS total score, 34.1% ± 18.1% on the thoughts/urges subscale score, and 38.0% ± 33.1% on the behaviors subscale score. On the basis of the response criteria of both a 25% reduction in PG-YBOCS score and a PG-CGI-I (clinician-rated) score of 1 or 2, 9 (75%) of 12 patients were rated as responders in pathological gambling severity.

Of note, there was only a marginal relationship between percentage of improvement in pathological gambling scores on the PG-YBOCS and percentage of improvement in depression on HAM-D ($r = 0.425$, $p = .084$), and no significant relationship between percentage of improvement in gambling and percentage of improvement in anxiety on HAM-A ($r = 0.198$, $p = .269$).

No differences emerged in comparing male (N = 9) and female (N = 3) patients' responses on PG-YBOCS total score ($t = 0.356$, $df = 10$, $p = .729$) and subscale scores (thoughts/urges: $t = 0.223$, $df = 10$, $p = .828$; behaviors: $t = 0.419$, $df = 10$, $p = .684$), HAM-A ($t = 0.188$, $df = 10$, $p = .855$), and HAM-D ($t = 0.261$, $df = 10$, $p = .799$), although the sample sizes by gender are small.

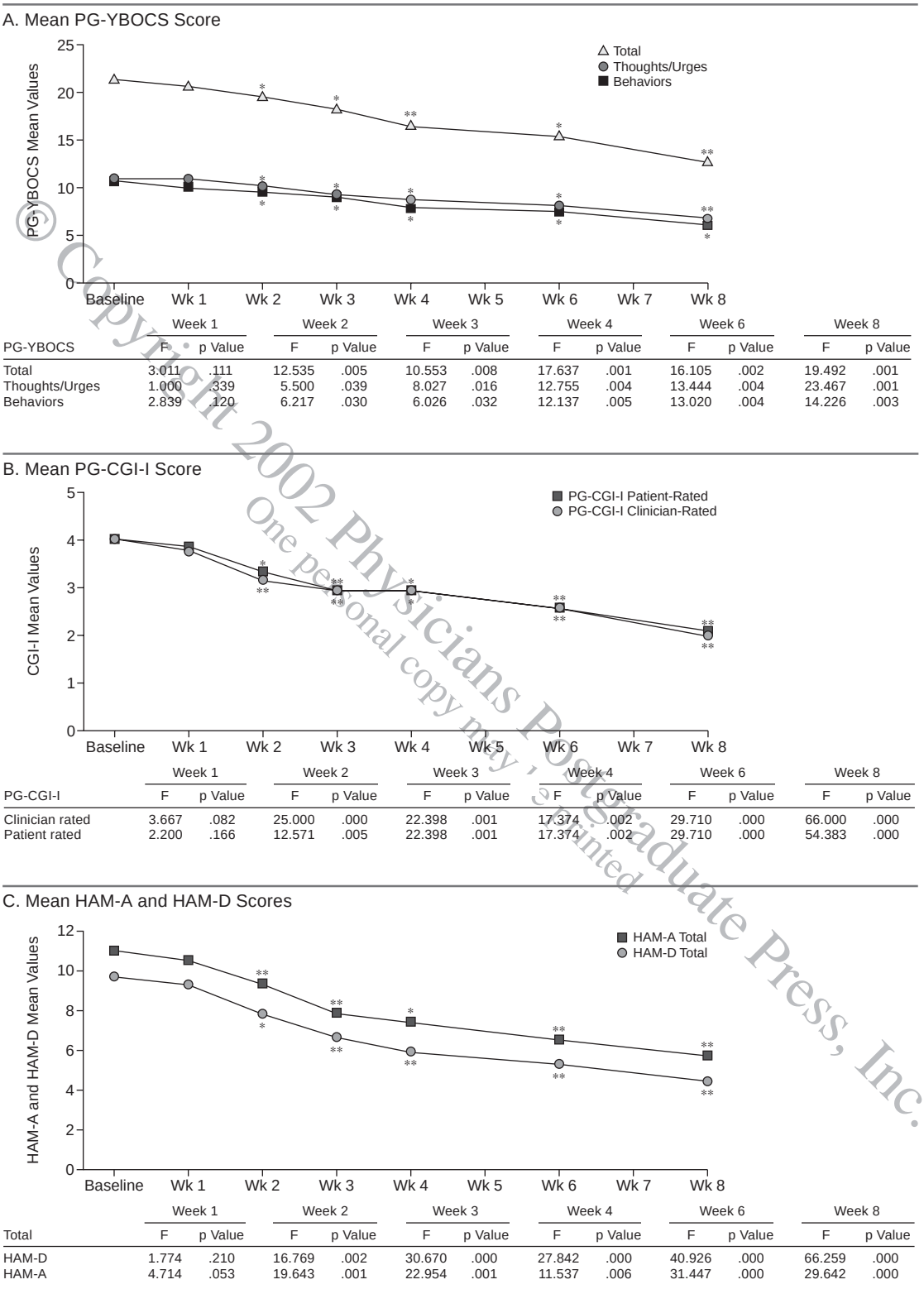
Side effects were recorded during the 8-week nefazodone treatment. Moderate dry mouth occurred in 3 subjects and moderate sedation, in 1 subject.

CONCLUSION

This open-label study provides encouraging preliminary data regarding the use of nefazodone in patients with pathological gambling. Nefazodone treatment was well tolerated; no patients dropped out due to side effects. Nine (75%) of 12 patients who remained on 8 weeks of nefazodone therapy were rated as responders on the basis of our a priori conservative criteria of both a PG-CGI-I score of 1 or 2 and a 25% reduction in PG-YBOCS score. There was significant improvement in the gambling outcome measures, with a 37% mean reduction in PG-YBOCS score, as well as reductions of 63% in episodes/week, 20% in amount of time gambled/week, and 62% in amount of money lost/week.

These preliminary results are consistent with and complement earlier studies of medications that influence the 5-HT system, such as the serotonin reuptake inhibitors fluvoxamine,[5,6] citalopram,[7] and clomipramine.[16] Nefazodone differs from SSRIs in having a primary antagonistic activity on the 5-HT_2–receptor, and prior studies have documented a significant correlation between platelet 5-HT_{2A} receptor binding and impulsive/aggressive behavior.[17] Meta-chlorophenylpiperazine (*m*-CPP) has potent binding to the 5-HT_2 receptor and weaker affinity for the 5-HT_{1A} and other subreceptors. Studies with 0.5-mg single-dose oral *m*-CPP in males with impulse-control disorders, including pedophilia and pathological gambling, have reported an increased sensation of "feeling dizzy," "strange," and, in pathological gambling, "high"

Figure 1. Score Over Time on Treatment With Nefazodone[a]



	Week 1		Week 2		Week 3		Week 4		Week 6		Week 8	
PG-YBOCS	F	p Value	F	p Value	F	p Value	F	p Value	F	p Value	F	p Value
Total	3.011	.111	12.535	.005	10.553	.008	17.637	.001	16.105	.002	19.492	.001
Thoughts/Urges	1.000	.339	5.500	.039	8.027	.016	12.755	.004	13.444	.004	23.467	.001
Behaviors	2.839	.120	6.217	.030	6.026	.032	12.137	.005	13.020	.004	14.226	.003

	Week 1		Week 2		Week 3		Week 4		Week 6		Week 8	
PG-CGI-I	F	p Value	F	p Value	F	p Value	F	p Value	F	p Value	F	p Value
Clinician rated	3.667	.082	25.000	.000	22.398	.001	17.374	.002	29.710	.000	66.000	.000
Patient rated	2.200	.166	12.571	.005	22.398	.001	17.374	.002	29.710	.000	54.383	.000

	Week 1		Week 2		Week 3		Week 4		Week 6		Week 8	
Total	F	p Value	F	p Value	F	p Value	F	p Value	F	p Value	F	p Value
HAM-D	1.774	.210	16.769	.002	30.670	.000	27.842	.000	40.926	.000	66.259	.000
HAM-A	4.714	.053	19.643	.001	22.954	.001	11.537	.006	31.447	.000	29.642	.000

[a]Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, PG-CGI-I = pathological gambling modification of the Clinical Global Impressions-Improvement scale (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change), PG-YBOCS = pathological gambling modification to the Yale-Brown Obsessive Compulsive Scale. Repeated measures multivariate analyses of variance comparisons with respect to baseline values.
*p ≤ .05. **p ≤ .001.

Table 2. Self-Rated Gambling Scale[a] Scores for 12 Completers With Pathological Gambling During an 8-Week Open-Label Nefazodone Trial

	Baseline		Endpoint		Percentage Improvement		Statistical Results[b]		
Scale	Mean	SD	Mean	SD	Mean[c]	SD	t	df	p Value
Pathological Gambling Behavioral Self-Report Scale									
US $ lost, wk	133.33	161.77	35.50	50.05	62.43	55.56	2.13	11	.057
No. episodes, wk	5.17	3.13	2.08	2.64	63.01	44.94	3.63	11	.004
Duration of episode, min	96.25	91.41	33.33	58.43	19.56	135.03	2.15	11	.054
Pathological Gambling 100-mm Visual Analog Craving Scale[d]									
I would like to gamble	69.92	25.29	48.50	37.60	36.57	36.01	2.93	11	.014
I intend to gamble in the near future	73.92	31.44	44.67	32.74	38.28	28.72	3.86	11	.003
Gambling will make me feel better	56.58	29.61	33.50	28.82	37.95	32.04	3.07	11	.011
Gambling will get rid of my discomfort	44.33	25.42	29.25	28.87	30.04	47.23	2.10	11	.059
I feel I can control my gambling	29.50	21.16	56.67	21.04	–835.34	2105.06	–3.57	11	.004

[a]E.H., unpublished scale, 2002.
[b]Paired t test for difference from baseline to final assessment point. According to Bonferroni's correction for multiple comparisons, statistical significance level at $p \leq .006$.
[c]Mean values represent the average of individual percentage of change values.
[d]0 mm = not at all; 100 mm = most ever.

Table 3. Individual Patient Percentage of Improvement and Responder Status[a]

	PG-YBOCS					
Patient	Thoughts/ Urges	Behaviors	Total	PG-CGI-I (clinician-rated)	HAM-D	HAM-A
1	28.57	50.00	40.00 R	2 R	50.00	85.71
2	30.77	33.33	32.14 R	3 NR	60.00	62.50
3	0.00	–40.00	–15.38 NR	2 R	41.18	45.45
4	18.18	9.09	13.64 NR	4 NR	50.00	42.86
5	16.67	54.55	41.18 R	2 R	66.67	80.00
6	60.00	50.00	54.84 R	2 R	66.67	66.67
7	64.29	93.75	80.00 R	1 R	60.00	50.00
8	37.50	28.57	33.33 R	2 R	35.71	36.84
9	38.46	33.33	36.00 R	2 R	36.36	12.50
10	27.27	22.22	25.00 R	2 R	33.33	30.00
11	44.44	66.67	53.33 R	1 R	50.00	25.00
12	42.86	54.55	48.00 R	1 R	100.00	100.00
Mean ± SD	34.08 ± 18.10	38.00 ± 33.12	36.84 ± 23.41	2.00 ± 0.85	54.16 ± 18.57	53.13 ± 26.40

[a]Criteria for improvement were a 25% reduction in PG-YBOCS score and a score of 1 (very much improved) or 2 (much improved) on the PG-CGI-I scale. Abbreviations: NR = nonresponder, R = responder, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, PG-CGI-I = pathological gambling modification to the Clinical Global Impressions-Improvement scale, PG-YBOCS = pathological gambling modification to the Yale-Brown Obsessive Compulsive Scale.

similar to that experienced during gambling activity (E.H., manuscript submitted). These findings further support an involvement of 5-HT_2 receptors—a receptor subtype antagonized by nefazodone—in pathological gambling.

The amelioration of gambling symptoms during treatment was expressed as a reduction on the PG-YBOCS scale, which assesses the specific domains of the disorder. Both the thoughts/urges (a measure of obsessionality about gambling) and behaviors subscale scores on the PG-YBOCS were significantly reduced at endpoint. Improvement in gambling was not related to improvement in depression and anxiety, although the relationship between this improvement and the mood and anxiety effects measured by the HAM-D and the HAM-A is difficult to interpret due to low baseline levels of mood and anxiety symptoms, which suggest secondary rather than primary mood and anxiety disorders.

Epidemiologic studies have demonstrated a higher prevalence of pathological gambling among males than females. Of interest, positron emission tomography with selective radiotracers in healthy subjects demonstrated significantly higher 5-HT_2–binding capacity in men than in women, especially in frontal and cingulate cortices.[18] This finding supports the hypothesis of a distinct liability for men and women for specific psychiatric disorders related to differences in brain receptors. Our study included 9 men and 3 women among the completers, numbers that are representative of the gender distribution of pathological gambling. While no gender differences in drug response were observed in our study, more studies of female gamblers are needed.

Nefazodone was well tolerated, and no subjects discontinued the treatment due to side effects. Previous reports on pathological gamblers demonstrated a worsening of symptomatology in some bipolar spectrum pathological

gambling patients that was associated with fluvoxamine treatment,[5] and there is evidence for both induction of mania[19–21] and improvement in dysphoric mania[22] with nefazodone. In our trial, no toxicity symptoms, exacerbation, or problematic side effects were seen, despite recent U.S. Food and Drug Administration warnings of hepatic failure/necrosis, thrombocytopenia, and hyponatremia with nefazodone treatment.

The open-label nature is the main limitation of this study, as early placebo response may be common in treatment studies of impulse-control disorders. Positive open-trial reports of fluvoxamine efficacy in compulsive shopping[23] and fluoxetine efficacy in trichotillomania[24] were subsequently not confirmed by controlled trials with fluvoxamine[25,26] and fluoxetine,[27] which were not more efficacious than placebo.

Sample recruitment also represents a potential limitation of the study. Patients were recruited through advertisements and were all motivated to seek treatment. The high motivation and acceptance of treatment in a tertiary care clinical setting in the subjects included in this study, as in all other pharmacologic treatment studies of pathological gambling, could potentially be a bias in influencing the low dropout rate. Current substance dependence was an exclusion criterion for entering the trial. Comorbid substance dependence with pathological gambling could potentially result in a lower response and higher discontinuation rate than found in our study. There was an absence of any psychotherapeutic or social support interventions during the trial, making the setting unusual for patients who are often involved in self-help support groups. Future pharmacologic treatment studies should investigate the impact of such psychosocial supports on outcome.

The length of the trial represents a further potential study limitation. The importance of an "addiction memory" in relapse occurrence and maintenance of learned addictive behavior has been recently proposed.[28] Follow-up studies of nefazodone treatment in pathological gambling of a longer duration could provide useful information on the course of gambling addiction and its response to this treatment. Finally, randomized, placebo-controlled, double-blind studies are needed to confirm these preliminary but promising findings on the efficacy and tolerability of nefazodone in the treatment of pathological gambling.

Drug names: citalopram (Celexa), clomipramine (Anafranil), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), nefazodone (Serzone).

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