A Double-Blind Placebo-Controlled Study of the Efficacy and Safety of Paroxetine in the Treatment of Pathological Gambling

Suck Won Kim, M.D.; Jon E. Grant, M.D.; David E. Adson, M.D.; Young Chul Shin, M.D.; and Rocco Zaninelli, M.D.

Background: This randomized, double-blind, placebo-controlled study investigated the efficacy and tolerability of paroxetine in the treatment of pathological gambling.

Method: Patients fulfilling DSM-IV criteria for pathological gambling and scoring ≥ 5 on the South Oaks Gambling Screen were enrolled if no other Axis I disorder was present. A 1-week placebo run-in phase was followed by 8 weeks' treatment with paroxetine or placebo. The initial paroxetine dose of 20 mg/day could be increased after week 2 by 10 mg/week to a maximum of 60 mg/day. Changes in clinical status were assessed using the Gambling Symptom Assessment Scale (G-SAS) and the Clinical Global Impressions scale (CGI). Treatment-emergent symptoms were assessed weekly.

Results: Forty-five patients were included in an intent-to-treat analysis (N = 23 paroxetine, N = 22 placebo). Statistically significantly greater reductions in the total score of the G-SAS were observed in the paroxetine group compared with the placebo group at weeks 6 through 8 (p = .003, .003, and .042, respectively). Improvement on the CGI was also significantly greater in the paroxetine than in the placebo group at the same time-points (p = .033, .014, and .025, respectively). A significantly greater proportion of patients in the paroxetine group were responders at weeks 7 and 8 (p = .011 and .010, respectively).

Conclusion: The results of this trial indicate that paroxetine may be effective in the treatment of pathological gambling. There were no unexpected side effects from this treatment. However, additional studies with larger patient samples and a longer treatment phase are required to establish conclusively the efficacy and safety of paroxetine for this indication.

(J Clin Psychiatry 2002;63:501–507)

Received June 27, 2001; accepted Nov. 27, 2001. *From the Department of Psychiatry, University of Minnesota, Minneapolis (Drs. Kim, Grant, and Adson); the Department of Psychiatry, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea (Dr. Shin); and Neuroscience Clinical Development, GlaxoSmithKline, Collegeville, Pa. (Dr. Zaninelli).*

Financial support from GlaxoSmithKline Pharmaceuticals, Collegeville, Pa.

Corresponding author and reprints: Suck Won Kim, M.D., Department of Psychiatry, University of Minnesota Medical School, F256/2A West, 2450 Riverside Ave., Minneapolis, MN 55454-1495 (e-mail: kimxx003@umn.edu).

During the 1990s, changes in state and local legislation encouraged the development of all types of wagering (casino gambling, lotteries, Internet gambling). As a consequence, gambling and gambling-related problems are on the rise in the United States and Canada. A recent meta-analysis by Shaffer et al.[1] of 120 published studies indicates that the lifetime prevalence of serious gambling (meeting DSM criteria for pathological gambling) among adults is 1.6%. Among young persons less than 18 years of age, the prevalence is 3.9%, with past-year rates for adults and adolescents being 1.1% and 5.8%, respectively.[2] Pathological gamblers are prone to painful financial losses that often lead to bankruptcy, divorce, and/or criminal behavior.[3,4] Psychiatric disorders, including major depression and alcohol or substance abuse and dependence, may develop from or be exacerbated by pathological gambling. A study by Phillips et al.[5] indicates that the suicide rate in cities where gambling is legalized is 4 times higher than in cities without legal gambling.

Pathological gambling, the main feature of which is the irresistible urge to gamble, has been described phenomenologically as both an impulse-control disorder and an obsessive-compulsive spectrum disorder.[6,7] Biological findings implicating the serotonin neurotransmitter system lend credence to both descriptions. For example, a number of studies found that glucose metabolism in the orbital frontal cortex is inversely correlated to the levels of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid.[8–12] These findings suggest that decreased central nervous system serotonin function within this defined region engenders disinhibited behaviors and may thereby contribute to the development of impulse-

control disorders.[8–12] Aberrations in serotonin metabolism have also been implicated in the etiology of obsessive-compulsive disorder (OCD).[13] In support of these findings, the selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective in treating OCD[14] and may reduce impulsivity in patients in other impulse-control disorders such as kleptomania, skin picking, and compulsive buying.[15–17]

Against this theoretical background, a number of researchers have tested serotonergic agents as a treatment for pathological gambling. After an initial case report of the successful treatment of pathological gambling with the nonselective serotonin reuptake inhibitor clomipramine, Hollander and associates[18] went on to conduct 2 crossover studies with the SSRI fluvoxamine; the first single blind (N = 16),[19] the second double blind (N = 15).[20] In both studies, during the active-drug phase, patients exhibited reductions in the total score of the Yale-Brown Obsessive Compulsive Scale, modified for Pathological Gambling (PG-YBOCS),[19] which were significantly greater than those for treatment with placebo. In a placebo-controlled study lasting 6 months in 34 patients treated with fluvoxamine, Blanco-Jerez[21] found significantly greater reductions in time and money spent gambling per week in male and young pathological gamblers. In an open-label pilot study,[22] 7 of 8 patients treated with citalopram for 12 weeks were rated as responders according to the Clinical Global Impressions-Improvement scale (CGI-I). Finally, in an open-label study comparing patients receiving fluoxetine plus supportive psychotherapy with patients receiving supportive psychotherapy alone, significantly greater global improvement, as measured by the CGI-I, was shown for the combination treatment.[23]

To date, no study has investigated the utility of the SSRI paroxetine as a treatment for pathological gambling. In light of the studies described above indicating that SSRIs may be efficacious in the treatment of pathological gambling and considering the demonstrated efficacy of paroxetine as a treatment for OCD,[24] we conducted a double-blind, placebo-controlled study to evaluate the efficacy and safety of paroxetine in the treatment of pathological gambling. We hypothesized that paroxetine would not only improve the general status of patients suffering from pathological gambling, but also reduce the frequency and severity of gambling symptoms.

METHOD

Patient Selection

Patients were recruited by newspaper advertisements and by referrals for medication treatment. Patients 18 to 65 years of age fulfilling the DSM-IV[25] criteria for pathological gambling and scoring ≥ 5 on the South Oaks Gambling Screen (SOGS)[26] were enrolled if no other Axis I disorder as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[27] was present and if baseline scores on both the 17-item Hamilton Rating Scale for Depression (HAM-D)[28] and the Hamilton Rating Scale for Anxiety (HAM-A)[29] were ≤ 18 at the screening and baseline assessments. Concomitant psychotropic medication was not allowed. Psychotropic medications were discontinued at least 4 weeks before study start. Patients undergoing individual or group psychotherapy or participating in Gamblers Anonymous were excluded. Individuals with an untreated coexisting medical condition and women of childbearing potential who did not practice a reliable method of contraception were not eligible for the study.

The Institutional Review Board at the University of Minnesota, Minneapolis, approved the study protocol. Written informed consent from each patient was obtained before any study procedures were carried out.

Study Flow

Following the initial assessment, patients eligible for the study entered a 1-week placebo run-in phase. At the second (baseline) visit, patients were randomly assigned to receive double-blind study medication if they still met the eligibility criteria and if their initial score on the Gambling Symptom Assessment Scale (G-SAS)[30] had not decreased by 50%. Study medication was given for 8 weeks. The initial paroxetine dosage of 20 mg/day could be increased gradually to a maximum of 60 mg/day in increments of no more than 10 mg/week. The decision to increase the dosage of study medication was determined by the investigating physician at each study visit on the basis of tolerability and efficacy. During the study, reductions in the dosage of study medication to the next previous dosage level were allowed if a patient was experiencing a side effect; once the side effect subsided, the dosage could be returned to the previous level.

Outcome Measures and Safety Assessments

Changes in clinical status during the treatment phase were assessed at weekly intervals using the total score and gambling urge subscale score of the G-SAS. The G-SAS is a 10-item, self-rated scale designed to assess the average frequency, intensity, and duration of gambling symptoms. Individual items are scored on an ordinal scale ranging from 0 (symptom not present) to 8 (highest frequency or intensity), with each score representing the average of the past 7 days. Items 1 through 3 focus on gambling urges, items 4 and 5 address gambling-related thoughts, items 6 and 7 ask for the frequency and duration of actual gambling behavior, item 8 assesses the degree of subjective excitement experienced by an imminent gambling act, item 9 summarizes the subjective distress caused by gambling, and item 10 measures the amount of personal trouble (relationship, financial, legal, occupational, medical) caused by gambling. The test-retest reliability and

validity of the G-SAS have been demonstrated in open-label and double-blind studies of naltrexone treatment of pathological gambling.[30,31]

The change relative to baseline in the patients' overall gambling symptom status was assessed with the CGI.[32] This scale asks the rater to assess the symptom improvement on the basis of the rater's total experience with the specific patient population to which the patient belongs. In the present study, the CGI was limited to the assessment of changes in gambling symptoms from the baseline level (PG-CGI). In addition to the clinician-rated PG-CGI (PG-CGI-MD), each patient was asked to use the same scale to rate his or her own gambling symptoms (PG-CGI-PT) at each weekly visit.[33] Response to treatment was defined by a score of 1 ("very much improved") or 2 ("much improved") on the PG-CGI-MD. A further outcome measure was the reduction in the reported amount of money spent on gambling at the end of treatment relative to baseline. Although patients with major depression and anxiety disorders were excluded from the study, the severity of depressive and anxiety symptomatology was monitored during the study using the HAM-D and HAM-A.

At each study visit, information regarding side effects was obtained from spontaneous patient reports and investigator inquiry. Besides documented side effects, the overall evaluation of safety included scheduled physical examinations and laboratory tests.

Data Analysis

The main comparison of interest in this study was paroxetine versus placebo in the intent-to-treat study population. The intent-to-treat population comprised all patients who were randomly assigned to double-blind study medication and for whom at least 1 postbaseline efficacy assessment was available. Statistical analyses used the last-observation-carried-forward (LOCF) data set, in which the last available efficacy data from patients dropping out of the study are carried to successive timepoints.

For continuous variables, comparisons were based on the change from baseline scores. These were investigated by repeated measures analysis of variance (ANOVA) using the general linear model procedure in SPSS, version 10.0.[34] The dichotomous response data were analyzed using chi-square tests, with the proportion of patients fulfilling the response criteria being compared among the treatments. All hypotheses were 2-sided. The effect of interactions was assessed during the model-building process at the 10% level of significance, while all other statistical tests were performed at the 5% significance level.

RESULTS

Demographic and Baseline Characteristics

One hundred thirty-three potential patients were screened by telephone (112 were responding to advertisements; 21 were seeking treatment from referrals). Eighty-six potential patients made appointments for interviews. Of those 86 potential patients, 71 kept their appointments and were interviewed. Eighteen were excluded after the initial interview: 11 did not meet DSM-IV criteria for pathological gambling, 4 suffered from comorbid major depressive disorder, 2 suffered from comorbid alcohol abuse, and 1 suffered from bipolar disorder. Fifty-three patients met inclusion criteria and completed the single-week placebo run-in phase.

By the end of the 1-week placebo run-in phase, 2 patients were lost to follow-up and 6 (11.3%) were placebo responders (50% or greater reduction of the total G-SAS score). Forty-five patients were randomly assigned to receive either paroxetine (N = 23) or placebo (N = 22) and were included in the intent-to-treat population. Of the 45 subjects, 2 patients (both from the paroxetine group; 1 at visit 6 and 1 at visit 8) were unable to comply with the study schedule, and 2 (1 from the placebo group at visit 5, 1 from the paroxetine group at visit 7) discontinued treatment because of side effects. Forty-one patients (20 paroxetine, 21 placebo) completed all study visits. Demographics of the intent-to-treat population are presented in Table 1.

At baseline, the treatment groups were very similar with respect to mean age, mean SOGS and G-SAS scores, and mean HAM-A and HAM-D scores (Table 2). Baseline scores on the SOGS, G-SAS, CGI, HAM-A, and HAM-D correlated significantly with screening visit scores (Pearson correlation coefficient range, .550–.680, $p < .05$). The patients in the placebo group had lost on average 10% more (a mean of 7.7%) of their weekly income than the paroxetine patients during the week before study start, but this difference was not statistically significant. There was a greater proportion of women in the placebo group (77% versus 57% in the paroxetine group). Since the severity of pathological gambling symptoms at baseline was similar for men and women (total G-SAS score was 41.14 ± 10.81 for men and 43.35 ± 13.55 for women [$t = -0.537$, $df = 43$, $p = .594$]), it is assumed that this difference did not affect the analysis of the outcome measures.

Efficacy Assessments

At the 8-week study endpoint, the mean G-SAS total score had decreased by 52% in the paroxetine group compared with 23% in the placebo group. At all assessment timepoints, the reduction in the G-SAS total score in the paroxetine group was greater than in the placebo group, with the differences between the treatment groups being statistically significant at week 1 ($t = 4.348$, $df = 1$, $p = .043$), week 3 ($t = 5.298$, $df = 1$, $p = .026$), and weeks 6 through 8 ($t = 9.687$, $df = 1$, $p = .003$; $t = 9.999$, $df = 1$, $p = .003$; and $t = 4.411$, $df = 1$, $p = .042$; respectively) (Figure 1). At week 4, in the paroxetine group there was an increase in the mean G-SAS total score, which was due primarily to a single outlier.

Table 1. Demographic and Clinical Features of Patients With Pathological Gambling, Intent-to-Treat Population

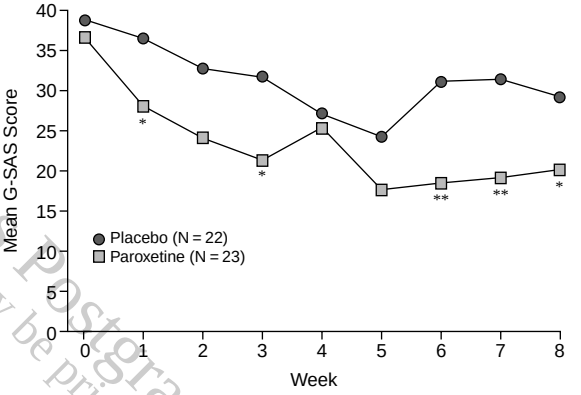
Characteristic	Paroxetine (N = 23)	Placebo (N = 22)
Age, mean (SD), y	49.3 (10.8)	49.3 (10.1)
Sex, N (%)		
Female	13 (56.5)	17 (77.3)
Male	10 (43.5)	5 (22.7)
Marital status, N (%)		
Single	3 (13.0)	6 (27.3)
Married	15 (65.2)	11 (50.0)
Divorced	4 (17.4)	5 (22.7)
Widowed	1 (4.3)	0
Race/ethnicity, N (%)		
White	21 (91.3)	22 (100.0)
African American	2 (8.7)	0
Education, N (%)		
Less than high school	1 (4.3)	2 (9.1)
High school graduate	11 (47.8)	10 (45.5)
Some college	6 (26.1)	5 (22.7)
College graduate	5 (21.7)	5 (22.7)
Forms of gambling, N (%)		
Slot machines	21 (91.3)	18 (81.8)
Bingo	6 (26.1)	2 (9.1)
Blackjack	5 (21.7)	3 (13.6)
Sporting events	4 (17.4)	6 (27.3)
Dice	4 (17.4)	2 (9.1)
Horse/dog track	2 (8.7)	1 (4.5)
Pull tabs	1 (4.3)	5 (22.7)
Lifetime history of a substance use disorder, N (%)	7 (30.4)	4 (18.2)
Probands with at least 1 first-degree relative with:		
Pathological gambling	10 (43.5)	10 (45.5)
Substance use disorder	14 (60.9)	11 (50.0)

Table 2. Baseline Characteristics of Patients With Pathological Gambling, Intent-to-Treat Population[a]

	Paroxetine (N = 23)		Placebo (N = 22)	
Characteristic	Mean	SD	Mean	SD
SOGS score	13.9	2.6	14.0	3.0
G-SAS score	37.0	10.9	38.9	13.1
Gambling urge G-SAS score	3.8	1.0	3.8	1.4
Time spent gambling, h/wk	11.1	5.7	13.6	10.4
Duration of gambling symptoms prior to the study, y	6.1	2.7	6.7	2.1
Weekly income, US $	712.5	332.2	732.4	335.3
Weekly income lost in previous week, %	44.2	40.1	51.9	35.2
HAM-D score	7.4	4.9	7.0	4.5
HAM-A score	8.8	6.1	8.7	5.0

[a]Abbreviations: G-SAS = Gambling Symptom Assessment Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, SOGS = South Oaks Gambling Screen.

Figure 1. Change From Baseline in the Mean Total Score of the Gambling Symptom Assessment Scale (G-SAS) During Treatment of Pathological Gambling With Paroxetine or Placebo[a]



[a]Asterisks represent pairwise comparisons, paroxetine versus placebo, for the difference in mean change from baseline in the LOCF intent-to-treat population. Abbreviation: LOCF = last observation carried forward.
*p < .05.
**p < .01.

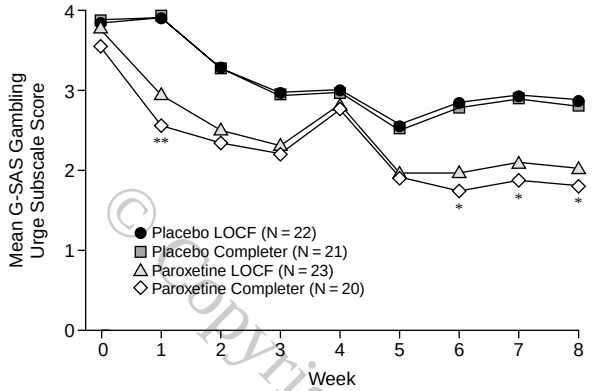
The gambling urge subscale of the G-SAS, which encompasses intensity, frequency, and duration of urges, reflects gambling-urge intensity since the last assessment. In the paroxetine group, the mean gambling urge subscale score decreased 37.9% at study endpoint compared with baseline, whereas there was only a 19.9% reduction for the placebo group. In the LOCF dataset, the reduction in the mean G-SAS gambling urge subscale score was numerically superior in the paroxetine group compared with the placebo group, but the differences were not statistically significantly greater (Figure 2). Among those patients completing the 8-week treatment (N = 41), however, the reduction in the G-SAS gambling urge subscale was significantly greater in the paroxetine group (N = 20) than in the placebo group (N = 21) at week 1 (t = 3.102, df = 39, p = .004) and at weeks 6 through 8 (t = 2.412, df = 39, p = .021; t = 2.300, df = 39, p = .027; and t = 2.221, df = 39, p = .032, respectively) (Figure 2).

Self-rated improvement as measured by the PG-CGI-PT was also significantly greater in the paroxetine than in the placebo group at weeks 6 through 8 (t = 4.879, df = 1, p = .033; t = 6.644, df = 1, p = .014; and t = 5.439, df = 1, p = .025; respectively) (Figure 3). From the clinician perspective, a similar result was obtained at weeks 7 and 8 (t = 5.423, df = 1, p = .025 and t = 6.448, df = 1, p = .015, respectively), where significantly greater proportions of patients in the paroxetine group achieved response as defined by a CGI-I score of 1 ("very much improved") or 2 ("much improved") (week 7: $\chi^2 = 6.505$, df = 1, p = .011 and week 8: $\chi^2 = 6.706$, df = 1, p = .010) (Figure 4).

Of the group treated with paroxetine, 11 (47.8%) were very much improved (equivalent to having stopped gambling), and 3 (13.0%) were much improved at the study endpoint using both the PG-CGI-MD and the PG-CGI-PT, while 3 (13.0%) had no change in pathological gambling symptoms at week 8. In comparison, 1 (4.5%) of the patients taking placebo was very much improved and 4 (18.2%) were much improved; 6 (27.3%) of the placebo group had no change in symptoms.

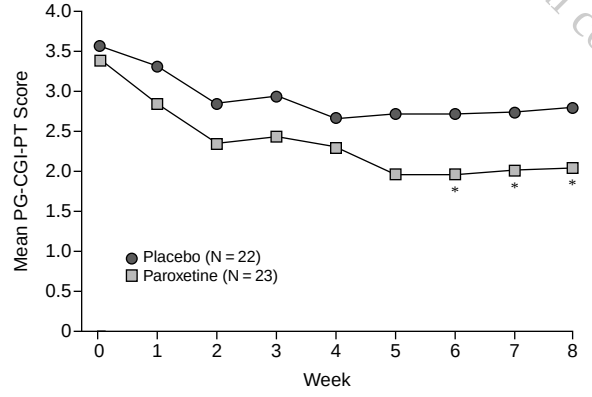
At the study conclusion, relative to baseline, the percentage of weekly income lost by gambling in the previous

Figure 2. Change From Baseline in the Mean Score of the Gambling Symptom Assessment Scale (G-SAS) Gambling Urge Subscale During Treatment of Pathological Gambling With Paroxetine or Placebo[a]



[a]Asterisks represent pairwise comparisons, paroxetine versus placebo, for difference in mean change from baseline in the LOCF population and completer populations. Abbreviation: LOCF = last observation carried forward.
*p < .05.
**p < .01.

Figure 3. Change in Mean Patient-Rated Clinical Global Impressions-Improvement Scale (PG-CGI-PT) Score During Treatment of Pathological Gambling With Paroxetine or Placebo[a]

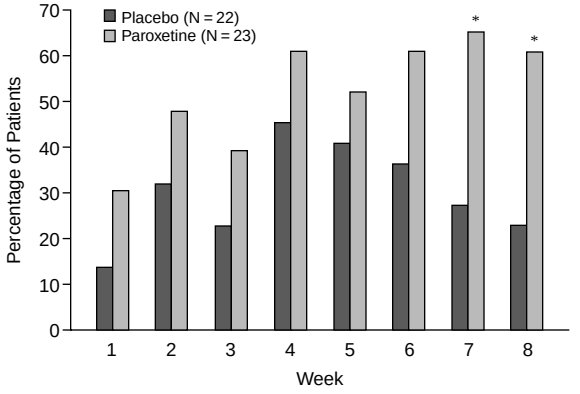


[a]Asterisks represent pairwise comparisons, paroxetine versus placebo, for difference in mean change from baseline in the LOCF intent-to-treat population. Abbreviation: LOCF = last observation carried forward.
*p < .05.

week was reduced by 20.2% in the paroxetine group and by 12.2% in the placebo group. The difference between the 2 treatments in this regard was not statistically significant (p = .456).

As measured by the HAM-D and HAM-A, the patients in both treatment groups exhibited on average low levels of depressive and anxiety symptoms at baseline (Table 2). Nonetheless, there was a drop in the depression and anxiety scores by approximately 50% in both groups, with no significant difference between the treatment groups at the

Figure 4. Percentage of Patients Achieving Response (CGI-I score = 1 or 2) During Treatment of Pathological Gambling With Paroxetine or Placebo[a]



[a]Asterisks represent pairwise comparisons, paroxetine versus placebo, for difference in mean change from baseline for the LOCF intent-to-treat population. Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, LOCF = last observation carried forward.
*p < .05.

end of the 8-week treatment (HAM-D score at endpoint: 3.37 ± 2.22 in the paroxetine group, 3.77 ± 2.69 in the placebo group [p = .402]; HAM-A score at endpoint: 4.67 ± 4.73 in the paroxetine group, 3.77 ± 2.69 in the placebo group [p = .917]).

Tolerability

The mean daily dose of paroxetine at the completion of the study was 51.7 ± 13.1 mg. Paroxetine was well tolerated, and only 1 patient in the paroxetine group dropped out of the study because of treatment-emergent adverse events. The most common adverse events in the paroxetine group were nausea (N = 6, 26.1%), headache (N = 4, 17.4%), and sweating (N = 4, 17.4%). Clinically significant changes in laboratory parameters or vital signs were not observed during the study.

DISCUSSION

The results of this 8-week trial indicate that paroxetine is effective in the treatment of pathological gambling. As measured by both the G-SAS and the CGI scales, the reduction in symptoms was significantly greater in the paroxetine than in the placebo group. The absolute reduction in gambling symptom severity—greater than 50% on G-SAS total score—is considered clinically relevant, particularly in light of the high baseline illness severity (mean SOGS scores of 13.9 and 14.0 for paroxetine and placebo, respectively) in the study sample. It is noteworthy that at the study endpoint more than 60% of the paroxetine patients and less than 25% of the placebo patients achieved clinical response using a generally accepted definition (the CGI). At study endpoint, there was less,

although not statistically significant, loss of weekly income in the paroxetine group compared with the placebo group. Our factor analytic data from a previous study suggest that the amount of money loss or frequency of gambling does not reflect gambling symptom severity accurately.[30] The frequency of gambling and amount of loss seem to be affected more by gamblers' income and money availability (clinical observation).

Similar to OCD and other impulse-control disorders, pathological gambling encompasses not only aberrant thought processes, but also specific objectifiable behaviors. Gambling behavior may fluctuate with availability of money, whereas urges to gamble and thoughts of gambling appear to be independent of gambling opportunities.[30,31] The G-SAS, which was employed in this study, documents changes in all of these domains of pathological gambling (urges, thoughts, behavior). This study supports previous findings that the G-SAS is a reliable and valid measure of change in pathological gambling symptoms.[30,31]

Paroxetine was found to be well tolerated. The types of adverse events documented in this study correspond to the safety profile of paroxetine established by research for depression and other indications.[24,35–37] Only 1 subject receiving paroxetine dropped out due to adverse events (nausea) exclusively associated with paroxetine.

The major limitation of this study is that our sample of pathological gamblers may not reflect the larger population of patients who suffer from pathological gambling. In the present study, the number of women (N = 30) was double that of men (N = 15). The literature, however, indicates that the rate of pathological gambling is twice as high among men compared with women.[38] Various factors might explain the fact that this study is inconsistent with earlier research. A larger-than-expected number of women in the study may have resulted from a gender-biased response from the newspaper advertisements or may reflect women's greater willingness to seek treatment. The gender distribution reported here may affect the generalizability of these findings to others with pathological gambling.

Pathological gambling has a reported high comorbidity with mood, anxiety, and substance use disorders.[39,40] Our study excluded patients with other Axis I disorders. Additionally, our subjects reported low HAM-A and HAM-D scores at baseline, suggesting little comorbid anxiety or depressive symptoms. Thus, our study sample may not represent the actual clinical population of patients with pathological gambling. Further controlled trials in patients with pathological gambling and comorbid disorders are necessary to test the effectiveness of paroxetine and other medications in a more naturalistic setting. The major focus of the present study, however, was the efficacy, not the effectiveness, of paroxetine.

In this study, positive effects of paroxetine, which were significantly greater than those of placebo, were seen from week 6, i.e., toward the end of the 8-week treatment phase and at doses generally greater than 40 mg/day. Although the reductions in symptom severity as measured by the G-SAS and the proportion of responders to paroxetine at study endpoint are considerable, it is clear that many patients still manifested appreciable levels of pathological gambling symptomatology. This point is borne out by the effects of treatment on scores on the gambling urge subscale of the G-SAS, since as a group only those paroxetine patients who completed 8 weeks of treatment showed improvement in core pathological gambling symptoms significantly greater than that of placebo. Thus, additional trials with larger patient samples and a longer treatment phase are required to determine whether treatment effects can be enhanced. This question is being addressed by the placebo-controlled 16-week trial that is currently ongoing at 5 investigative sites.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), naltrexone (Depade), paroxetine (Paxil).

REFERENCES

1. Shaffer HJ, Hall MN, Vander Bilt J. Estimating the prevalence of disordered gambling behavior in the United States and Canada: a research synthesis. Am J Public Health 1999;89:1369–1376
2. Shaffer HJ, Hall MN. Estimating the prevalence of adolescent gambling disorders: a quantitative synthesis and guide toward standard gambling nomenclature. J Gambling Stud 1996;12:193–214
3. Petry NM, Armentano C. Prevalence, assessment, and treatment of pathological gambling: a review. Psychiatr Serv 1999;50:1021–1027
4. Grant JE, Kim SW. Demographic and clinical features of 131 adult pathological gamblers. J Clin Psychiatry 2001;62:957–962
5. Phillips DP, Welty WR, Smith MM. Elevated suicide levels associated with legalized gambling. Suicide Life Threat Behav 1997;27:373–378
6. McElroy SL, Hudson JI, Phillips KA, et al. Clinical and theoretical implications of a possible link between obsessive-compulsive and impulse control disorders. Depression 1993;1:121–132
7. Cohen LJ, Simeon D, Hollander E, et al. Obsessive-compulsive spectrum disorders. In: Hollander E, Stein DJ, eds. Obsessive-Compulsive Disorders. Washington, DC: American Psychiatric Press; 1997
8. Doudet D, Hommer D, Higley JD, et al. Cerebral glucose metabolism, CSF 5-HIAA levels, and aggressive behavior in rhesus monkeys. Am J Psychiatry 1995;152:1782–1787
9. Virkkunen M, Goldman D, Nielsen DA. Low brain serotonin turnover rate (low CSF 5-HIAA) and impulsive violence. J Psychiatry Neurosci 1995; 20:271–275
10. Mehlman PT, Higley JD, Faucher I. Low CSF 5-HIAA concentrations and severe aggression and impaired impulse control in nonhuman primates. Am J Psychiatry 1995;151:1485–1491
11. Coccaro EF. Neurotransmitter correlates of impulsive aggression in humans. Ann N Y Acad Sci 1996;794:82–89
12. Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation: a possible prelude to violence. Science 2000;289: 591–594
13. Dohlberg OT, Iancu I, Sasson Y, et al. The pathogenesis and treatment of obsessive-compulsive disorder. Clin Neuropharmacol 1996;19:129–147
14. Dougherty D, Rauch SL. Serotonin-reuptake inhibitors in the treatment of OCD. In: Hollander E, Stein DJ, eds. Obsessive-Compulsive Disorders: Diagnosis, Etiology, Treatment. New York, NY: Marcel Dekker; 1997: 145–160
15. McElroy SL, Keck PE, Pope HG, et al. Pharmacological treatment of kleptomania and bulimia nervosa. J Clin Psychopharmacol 1989;9:358–360
16. Koran LM, Bullock KD, Hartston HJ, et al. Citalopram treatment of compulsive shopping: an open-label pilot study. In: New Research Abstracts of the 154th Annual Meeting of the American Psychiatric Association; May

9, 2001; New Orleans, La. Abstract NR537:145–146
17. Simeon D, Stein DJ, Gross S, et al. A double-blind trial of fluoxetine in pathologic skin picking. J Clin Psychiatry 1997;58:341–347
18. Hollander E, Frenkel M, DeCaria C, et al. Treatment of pathological gambling with clomipramine [letter]. Am J Psychiatry 1992;149:710–711
19. Hollander E, DeCaria CM, Mari E, et al. Short-term single-blind fluvoxamine treatment of pathological gambling. Am J Psychiatry 1998;155: 1781–1783
20. Hollander E, DeCaria CM, Finkell JN, et al. A randomized double-blind fluvoxamine/placebo crossover trial in pathological gambling. Biol Psychiatry 2000;47:813–817
21. Blanco-Jerez C. A long-term, double-blind, placebo-controlled study of fluvoxamine for pathological gambling. In: New Research Program and Abstracts of the 152nd Annual Meeting of the American Psychiatric Association; May 17, 1999; Washington, DC. Abstract NR126:97
22. Zimmerman M, Breen R, Posternak MA. An open-label study of citalopram in the treatment of pathological gambling. J Clin Psychiatry 2002; 63:44–48
23. De la Gandara JJ. Fluoxetine: open-trial in pathological gambling. In: New Research Program and Abstracts of the 152nd Annual Meeting of the American Psychiatric Association; May 20, 1999; Washington, DC. Abstract NR632:247
24. Zohar J, Judge R. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. Br J Psychiatry 1996;169:468–474
25. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
26. Lesieur HR, Blume SB. The South Oaks Gambling Screen (SOGS): a new instrument for the identification of pathological gamblers. Am J Psychiatry 1987;144:1184–1188
27. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P, Version 2.0). New York, NY: Biometric Research, New York State Psychiatric Institute; 1995
28. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
29. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
30. Kim SW, Grant JE, Adson DE, et al. Double-blind naltrexone and placebo comparison study in the treatment of pathological gambling. Biol Psychiatry 2001;49:914–921
31. Kim SW, Grant JE. An open naltrexone treatment study of pathological gambling disorder. Int Clin Psychopharmacol 2001;16:285–289
32. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
33. Bandelow B, Hajak G, Holzrichter S, et al. Assessing the efficacy of treatments for panic disorder and agoraphobia, 1: methodological problems. Int Clin Psychopharmacol 1995;10:83–93
34. Statistical Package for the Social Sciences, version 10.0. Chicago, Ill: SPSS Inc; 1999
35. Gunasekara NS, Noble S, Benfield P. Paroxetine: an update of its pharmacology and therapeutic use in depression and a review of its use in other disorders. Drugs 1998;55:85–120
36. Lecrubier Y, Bakker A, Dunbar G, et al. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. Acta Psychiatr Scand 1997;95:145–152
37. Ballenger JC, Wheadon DE, Steiner M, et al. Double-blind, fixed dose, placebo-controlled study of paroxetine in the treatment of panic disorder. Am J Psychiatry 1998;155:36–42
38. Volberg RA. The prevalence and demographics of pathological gamblers: implications for public health. Am J Public Health 1994;84:237–241
39. Specker SM, Carlson GA, Edmondson KM, et al. Psychopathology in pathological gamblers seeking treatment. J Gambling Stud 1996;12:67–81
40. Black DW, Moyer T. Clinical features and psychiatric comorbidity of subjects with pathological gambling behavior. Psychiatr Serv 1998;49: 1434–1439