Sertraline Treatment of Pathological Gambling: A Pilot Study

Jerónimo Saiz-Ruiz, M.D., Ph.D.; Carlos Blanco, M.D., Ph.D.; Angela Ibáñez, M.D., Ph.D.; Xavier Masramon, B.Sc.; Margarita M. Gómez, M.D.; María Madrigal, M.D.; and Teresa Díez, M.D.

Objective: Several open-label and double-blind studies have suggested that selective serotonin reuptake inhibitors may be useful in the treatment of pathological gambling. The purpose of this study was to evaluate the efficacy of sertraline in the treatment of pathological gambling.

Method: Sixty patients meeting the DSM-IV criteria for pathological gambling were treated for 6 months in a double-blind, flexible-dose, placebo-controlled study of sertraline 50 to 150 mg/day. Data were collected from November 1998 to January 2001. The primary outcome measure assessing change in clinical status was the responder rate with respect to the Criteria for Control of Pathological Gambling Questionnaire (CCPGQ). Secondary measures included the Clinical Global Impressions scale (CGI) (Severity of Illness and Improvement subscales), and Visual Analogue Scales assessing gambling frequency, severity, amount, and improvement. Concomitant medication and psychotherapy were not allowed during the study.

Results: At the end of the study, 23 sertraline-treated subjects (74%) and 21 placebo-treated subjects (72%) were considered as responders on the CCPGQ ($p = .9$). Similar results were obtained when the CGI-Improvement scale limited to symptoms of pathological gambling was used as an outcome measure. Sertraline was well tolerated throughout the study.

Conclusion: Sertraline was not statistically significantly superior to placebo in the overall sample. The power of the study was limited by the high placebo-response rate and the small sample size.

(J Clin Psychiatry 2005;66:28–33)

Received Dec. 4, 2003; accepted June 28, 2004. From the Department of Psychiatry, Hospital Ramón y Cajal, Universidad de Alcalá, Madrid, Spain (Drs. Saiz-Ruiz and Ibáñez); the Department of Psychiatry, Columbia University, New York, N.Y. (Dr. Blanco); the R&D Department—Medical Unit, Pfizer-Euroclin Institute, Barcelona, Spain (Mr. Masramon); and Pfizer SA, Medical Unit, Department of Neuroscience, Madrid, Spain (Drs. Gómez, Madrigal, and Díez).

Financial support from Pfizer Spain, S.A.

Dr. Saiz-Ruiz has received grant/research support from Eli Lilly (Spain) and has participated in speakers' or advisory boards for Bristol-Myers Squibb (Spain). Dr. Blanco has received grant/research support from GlaxoSmithKline and BioTie. Dr. Ibáñez has received grant/research support from Pfizer S.A.

Corresponding author and reprints: Carlos Blanco, M.D., Ph.D., Department of Psychiatry, Columbia University, 1051 Riverside Drive, Unit 69, New York, NY 10032 (e-mail: cb255@columbia.edu).

Pathological gambling is characterized by a persistent pattern of continued gambling despite its adverse consequences.[1] Once thought to be relatively uncommon, it is now estimated that pathological gambling has a lifetime prevalence among adults of 1.6% and among adolescents of 3.9%.[2,3]

Little is known to date about the etiology of pathological gambling. Previous studies suggest that norepinephrine, dopamine, and β-endorphins may be involved in its pathophysiology.[4–6] Two twin studies[7–9] have suggested a genetic vulnerability for pathological gambling in males. Furthermore, one of the studies[8] found a shared genetic vulnerability for pathological gambling and alcohol abuse or dependence. Studies of molecular biology[10–13] have found associations between pathological gambling and specific alleles in the dopamine receptor, the serotonin transporter, and the gene coding for monoamine oxidase A. Recent studies using neuroimaging techniques[14,15] have also suggested reduced activity in the left ventromedial prefrontal cortex and decreased activity in some brain regions, including frontal and orbitofrontal cortex, basal ganglia, thalamus, and ventral anterior cingulate activity, in response to gambling-related stimulus.

Based on the conceptualization of pathological gambling as an impulse-control disorder, an obsessive-compulsive spectrum disorder, or a hybrid of those 2 conditions,[16] several lines of evidence have implicated the serotonergic system in the pathophysiology of pathological gambling.[17–19] Two small open-label studies have suggested that fluvoxamine[20] and citalopram[21] might be efficacious in the treatment of pathological gambling, but subsequent placebo-controlled studies of fluvoxamine[22,23] and paroxetine[24,25] have obtained mixed results. The goal of this study was to examine the tolerability and efficacy of sertraline in the treatment of pathological gambling.

METHOD

Subjects

Patients attending the Pathological Gambling Outpatient Program of the Department of Psychiatry of Hospital Ramón y Cajal in Madrid, Spain, participated in this pilot study. The Institutional Review Board of Hospital Ramón y Cajal approved the protocol prior to the beginning of the

study. All subjects met DSM-IV criteria for pathological gambling and signed informed consent prior to their entry into the study. Data were collected from November 1998 to January 2001.

Exclusion criteria were (1) current comorbid major depressive disorder; (2) current or lifetime history of bipolar disorder, schizophrenia, or other psychotic disorder; and (3) alcohol or substance dependence or abuse in the past 3 months. Concomitant psychotropic medication was not allowed during the study, and all previous ineffective psychotropic medications were discontinued before study start. Patients undergoing individual or group psychotherapy or participating in Gamblers Anonymous were excluded. Individuals with an unstable coexisting medical condition were not eligible for the study. Women's participation was contingent upon negative results of a β-human chorionic gonadotropin pregnancy test and stable use of a medically accepted form of contraception.

Study Design

Patients were evaluated at entry by a semistructured psychiatric interview for pathological gambling and by the Structured Clinical Interview for DSM-IV (SCID)[26] to assess psychiatric comorbidity. Medical history was obtained, and physical examination, electrocardiogram, and routine laboratory testing were performed.

Patients eligible for the study were randomly assigned to 24 weeks of double-blind treatment with either sertraline or matched placebo. Following randomization, treatment was initiated at 50 mg/day of sertraline or placebo equivalent during week 1. Sertraline could be increased to 100 mg/day at the end of week 4 and up to 150 mg/day from the end of week 8 until the end of the study, based on clinical response and tolerability. Reductions in the dosage of study medication to the next previous level were allowed if a patient was experiencing a side effect; once the side effect subsided, the dosage could be titrated back up. Subjects who missed 30 or more days of medication were discontinued from the study.

Efficacy and Safety Assessments

Investigators administered the Criteria for Control of Pathological Gambling Questionnaire (CCPGQ) (J.S.-R., unpublished data, 1997) to patients. The CCPGQ is composed of 5 questions: "Do you have an urge to gamble?" "Can you control the impulse to gamble or try to resist it?" "Do you feel anxious, depressed or irritable?" "Has your gambling problem substantially decreased?" and "Do you still gamble?" The internal consistency of these questions measured with Cronbach coefficient alpha was 0.89, indicating that the 5 questions have a high degree of internal consistency. The correlation between overall score of the CCPGQ and the Clinical Global Impressions (CGI) scale score (as measured by Pearson r) was equal to 0.85. All individual questions of the CCPGQ also had high correlations, ranging from $r = 0.52$ (question 3) to $r = 0.82$ (all $df = 58$, $p < .001$), suggesting convergent validity of the CCPGQ.

Investigators also rated gambling severity using the CGI-Severity of Illness (CGI-S) and CGI-Improvement (CGI-I) subscales limited to symptoms of pathological gambling (PG-CGI-I).[27] Other secondary measures included patient self-rated 100-mm Visual Analogue Scales (VAS) for frequency, severity, amount, and improvement of gambling and the South Oaks Gambling Screen (SOGS).[28] The VAS were constructed based on the VAS used to measure drug craving.[29] The PG-CGI-I and VAS scales were assessed at baseline and weeks 2, 4, 8, 12, 16, 20, and 24, whereas the SOGS was assessed at baseline and termination only.

Because pathological gambling is categorized as an impulse-control disorder, the Eysenck Impulsiveness Questionnaire (EIQ)[30] was included to investigate whether changes in gambling behavior were associated with changes in impulsivity and to test whether sertraline was associated with specific score changes in the total EIQ or any of its subscales. The EIQ consists of 3 subscales: impulsiveness, venturesomeness, and empathy. *Impulsiveness* characterizes individuals who behave without thinking or realizing the risk involved in their actions, *venturesomeness* measures sensation-seeking, and *empathy* quantifies sociability.

At each visit, safety assessments included evaluations of weight, sitting blood pressure, and heart rate. Adverse effects were documented, and documentation included time of onset, duration, severity, action taken, and outcome. Use of concomitant medications was recorded in terms of daily dosage, stop and start dates, and reason for use. Compliance was monitored by pill count, and patients were counseled if found to be noncompliant.

Data Analysis

The main comparison of interest was sertraline versus placebo in the intent-to-treat (ITT) population. The ITT population comprised all patients randomly assigned to double-blind study medication who had a baseline assessment and had taken at least 1 dose of medication. Statistical analyses used the last-observation-carried-forward (LOCF) data-set.

Patients were considered responders if they answered "Yes" to the second and fourth questions of the CCPGQ. Patients who were lost to follow-up or withdrew consent prior to the completion of the study were considered nonresponders. CCPGQ responder rate was the primary outcome measure assessing change in clinical status.

The χ^2 statistic was used to compare the proportion of patients in each treatment group that obtained a rating of 1 or 2 on the PG-CGI-I subscale at endpoint. Efficacy analyses for the VAS, SOGS, and EIQ (and its subscales) were performed using t tests and analysis of covariance

Table 1. Disposition of Patients Randomly Assigned to Placebo (N = 33) or Sertraline (N = 33)

Status	Placebo, N (%)	Sertraline, N (%)
Withdrawn prior to end of treatment	14 (42.4)	15 (45.4)
Insufficient clinical response	1 (3.0)	1 (3.0)
Adverse event	0 (0.0)	2 (6.1)
Protocol violation	2 (6.1)	2 (6.1)
Lost to follow-up	9 (27.3)	5 (15.2)
Withdrew consent	2 (6.1)	3 (9.1)
Other	0 (0.0)	2 (6.1)
Completed treatment	19 (57.6)	18 (54.6)

(ANCOVA) for the 24-week treatment period using baseline as covariate. Temporal course of response to treatment was also examined using a mixed effects model for longitudinal data that included age at onset of pathological gambling, age of the patient at the time of the assessment, and sex as covariates. Response curves for each treatment group were examined and differences compared. All statistical tests were 2-sided and performed at the $\alpha = .05$ level of significance.

The number and intensity of adverse events were compared between groups using t tests. The proportion of patients who discontinued treatment because of adverse events and the incidence of clinically significant laboratory abnormalities were compared between treatment groups using Fisher exact test.

RESULTS

Demographic and Clinical Characteristics

A total of 66 patients (mean age, 38.9; SD, 11.6 years; 6 women [10%]) were randomly assigned to sertraline (N = 33) or placebo (N = 33). Of those, 31 in the sertraline group and 29 in the placebo group who took at least 1 dose of medication are included in the efficacy analysis. Patient disposition during the study is presented in Table 1. Baseline clinical characteristics of the patients in the sertraline and placebo groups included in the efficacy analysis and a summary of the treatment efficacy results are shown in Table 2.

Treatment Efficacy

Treatment with sertraline did not yield significantly greater efficacy than placebo at any point during the study as assessed by the CCPGQ. By week 2, 26 patients (84%) in the sertraline group and 20 patients (69%) in the placebo group were considered responders ($\chi^2 = 1.9$, df = 1, p = .17). At the last visit, 23 sertraline-treated subjects (74%) and 21 placebo-treated subjects (72%) were classified as responders ($\chi^2 = 0.02$, df = 1, p = .88). Response rates using the PG-CGI-I scale followed a slightly different pattern but also failed to find differences between sertraline and placebo. By week 2, 19 patients (61%) in the sertraline group and 13 patients (45%) in the placebo group were considered responders ($\chi^2 = 1.6$, df = 1, p = .2). At the last visit, 21 sertraline-treated subjects (68%) and 19 placebo-treated subjects (66%) were responders ($\chi^2 = 0.03$, df = 1, p = .9).

There were no significant differences between the groups in VAS scores for frequency of gambling, amount of money gambled, severity of gambling, or improvement using LOCF analysis (Table 2) or mixed random regression models (not shown). Similarly, there were no differences between the groups in score changes on the overall EIQ or any of its subscales (Table 2). Analyses of covariance on the EIQ and its subscales, using baseline values of the overall scale or the subscales, as appropriate, also failed to identify sertraline as a predictor of change in any of these measures (not shown).

An ANCOVA on the SOGS (N = 44) found an adjusted mean decrease of –6.6 (SD = 4.0) in the sertraline group versus –4.3 (SD = 5.4) in the placebo group (t = 1.91, df = 1, p = .06). Time to diagnosis of pathological gambling was the only significant predictor of outcome (β = –0.27, standard error of β [SE] = 0.09, p = .004), indicating that longer time from diagnosis to treatment resulted in worse outcome.

Tolerability

Mean dose at the end of the study was 95 mg/day in the sertraline group versus 100 mg/day in the placebo group. In the sertraline group, at the end of the study, 12 patients were taking 50 mg/day, 10 patients were taking 100 mg/day, and 9 patients were taking 150 mg/day. In the placebo group, at endpoint, 9 patients were taking 50 mg/day, 11 patients were taking 100 mg/day, and 9 patients were taking 150 mg/day. Sertraline was well tolerated. Most patients in the sertraline group (71%) and the placebo group (62%) experienced at least 1 side effect. Common side effects (i.e., higher than 10%) included dyspepsia (N = 10, 32%), headache (N = 8, 26%), dizziness (N = 6, 19%), insomnia (N = 4, 13%), and diarrhea (N = 4, 13%). None of the side effects had a significantly higher frequency in the sertraline than in the placebo group. In the sertraline group, 2 patients (6%) dropped out, one due to diarrhea and the other due to hypertension, and none in the placebo group dropped out due to side effects (Fisher exact test, p = .5).

Of the 66 randomized patients, 53 (80%) completed at least a month of the study, 49 (74%) completed at least 2 months, 44 (67%) completed 3 months, 42 (64%) completed 4 months, 40 (61%) completed 5 months, and 37 (56%) completed the full pilot study. There was no differential attrition between the groups at any point during the study.

DISCUSSION

This study did not find significant differences between sertraline and placebo for the treatment of pathological gambling. Two facts may help explain the apparent dis-

Table 2. Demographic Characteristics and Treatment Responses of Patients Treated With Placebo or Sertraline for Pathological Gambling (intent-to-treat population)

	Baseline		Endpoint				
Variable	Placebo (N = 29)	Sertraline (N = 31)	Placebo (N = 29)	Sertraline (N = 31)	Test	df	p Value
Gender, N (%)							
Male	26 (89.7)	28 (90.3)					
Female	3 (10.3)	3 (9.7)					
Age, mean (SD), y	40.4 (12.3)	37.5 (10.9)					
Duration of pathological gambling, mean (SD), y	8.3 (6.9)	7.1 (6.3)					
CCPGQ responders, N (%)	0 (0)	0 (0)	21 (72)	23 (74)	$\chi^2 = 0.02$	1	.9
PG-CGI-I responders, N (%)	0 (0)	0 (0)	19 (66)	21 (68)	$\chi^2 = 0.03$	1	.9
EIQ subscale scores, mean (SD)							
Impulsiveness (range, 0–19)	9.6 (0.9)	8.2 (0.7)	8.2 (0.6)	7.9 (0.6)	t = 0.25	42	.8
Venturesomeness (range, 0–16)	7.7 (0.9)	7.2 (0.8)	7.1 (0.4)	7.3 (0.5)	t = 0.41	42	.7
Empathy (range, 0–19)	13.1 (0.6)	13.6 (0.6)	12.7 (0.4)	13.7 (0.4)	t = 1.63	42	.1
South Oaks Gambling Screen total score, mean (SD)	12.0 (2.5)	11.5 (1.9)	7.4 (4.5)	5.1 (3.9)	t = 1.91	42	.06
Visual Analogue Scale subscale scores, mean (SD)							
Frequency of gambling (0 = never to 100 = very often)	75.5 (20.8)	70.3 (21.8)	15.2 (22.2)	12.8 (23.9)	t = 0.39	58	.7
Amount gambled (0 = nothing to 100 = very much)	74.1 (22.4)	75.7 (16.4)	19.4 (27.8)	15.5 (29.1)	t = 0.55	58	.6
Severity of gambling (0 = well to 100 = very severe)	80.3 (21.5)	82.7 (17.3)	26.5 (32.0)	34.7 (34.9)	t = –0.95	58	.3

Abbreviations: CCPGQ = Criteria for Control of Pathological Gambling Questionnaire, EIQ = Eysenck Impulsiveness Questionnaire, PG-CGI-I = Clinical Global Impressions scale-Improvement, symptoms of pathological gambling.

crepancy between our findings and the results of prior studies. First, some of the evidence for the efficacy of SSRIs in pathological gambling comes from small open trials,[20,21] which do not control for possible placebo effects, and whose efficacy therefore has to be considered preliminary.

Second, the 4 published controlled trials of SSRIs for pathological gambling[22–25] have obtained mixed results. An early crossover trial with fluvoxamine including 15 patients[23] found an order effect in the treatments, curtailing the possibility of drawing valid inferences on drug-placebo differences from that study. A second clinical trial (N = 45) comparing paroxetine versus placebo[25] found the active medication superior to placebo. A placebo-controlled study conducted by our group and including 32 patients[22] found fluvoxamine to be efficacious in the subgroup of younger, male pathological gamblers, but not in the overall sample. Finally, a recent multicenter study[24] (N = 76) also failed to find differences between paroxetine and placebo.

Thus, the results of the present study are not inconsistent with previous findings regarding the efficacy of SSRIs and suggest that subgroups of pathological gamblers may need to be identified for which SSRIs are superior to placebo. Several cross-sectional studies have identified differences among subgroups of pathological gamblers based on demographic characteristics,[31–35] preferred type of gambling activity,[36] history of legal problems,[37] and presence or absence of comorbidity.[38–40] However, longitudinal studies are sorely needed to test the predictive validity of these subgroups regarding the course of the disorder and their response to treatment.

A second finding of our study, which helps explain the positive results of open studies but the less conclusive results of randomized trials, is the moderate to high placebo response rate found in the controlled trials: 50% in Hollander and coworkers' crossover study,[23] 23% in Kim and colleagues' parallel-group study,[25] 33% in our fluvoxamine study,[22] and 49% in the recent multicenter paroxetine study.[24] Although our sample size was not large enough to conduct formal pattern analyses, the similarity of rates of response between the 2 treatment groups and the presence of early response followed by relapse in some individuals suggest that an important component of the effect of the drug could be nonspecific. One possibility for future studies would be to consider the inclusion of a placebo run-in phase in the design. However, the timing of the response to placebo has varied substantially across past studies, posing difficulties in deciding the length of such a placebo run-in phase.[22–24]

The reasons for the high placebo response rate in this and previous studies are unknown but deserve careful consideration because, without a better understanding of them, they will continue to substantially limit the statistical power of any future placebo-controlled trial for pathological gambling. As has been previously suggested,[24] it is possible that asking subjects to be more aware of their behaviors may have served the function of covert relapse prevention therapy, an intervention with preliminary evidence of efficacy in pathological gambling.[41,42] It is also possible that clinic visits to see the physician and the establishment of a therapeutic alliance may explain a substantial portion of the treatment effect. Alternatively, the motivational states of the subjects may have influenced response, a potential predictor that has yet to be examined in the outcome literature on pathological gambling. Regardless of the reason, the pattern of response of pathological gamblers to sertraline, characterized by early but

sometimes inconsistent response and lack of significant differences with placebo, appears less supportive of pathological gambling as an obsessive-compulsive spectrum disorder and more consistent with the conceptualization of pathological gambling as a (nonpharmacologic) addiction.

Importantly, time from diagnosis to treatment predicted response to treatment. Because pathological gamblers usually wait years from the onset of their disorder until they seek treatment,[43] our findings suggest that interventions that facilitate early detection and treatment of pathological gambling may have a significant impact on the outcome of treatment.

Sertraline was well tolerated, the same as other SSRIs in clinical trials for pathological gambling. The types of adverse events reported in this study correspond to the safety profile of sertraline established by research for depression and other disorders.[44]

The results of this study in combination with the results of the multicenter paroxetine trial raise questions about the efficacy of SSRIs for pathological gambling. Studies with placebo lead-in phases may be necessary to decrease the signal-to-noise ratio and detect the potential therapeutic effects of SSRIs for pathological gambling. At the same time, although psychosocial interventions appear promising,[45,46] their specificity remains to be tested. In contrast to pharmacologic treatments, which have focused on decreasing impulsivity, psychosocial strategies have emphasized the role of motivation and cognitions in the treatment of pathological gambling.[41,42]

Although pathological gamblers have high response rates once they seek treatment for their disorder, very few appear to seek such treatment. A research and public health priority is to decrease health care system barriers to the treatment of pathological gamblers. A recent study[43] found that pathological gamblers' shame and secrecy are the main reasons to delay treatment, suggesting that public interventions directed at increasing awareness and decreasing stigma may be important strategies to improve the long-term outcome of individuals with pathological gambling, but further work is needed to identify and decrease additional barriers.

The present study and our previous trial with fluvoxamine[22] also suggest that even when patients enter treatment and improve from their symptoms, they often drop out of treatment. Although there is little systematic knowledge of the outcome of pathological gamblers after they stop treatment, preliminary data suggest that they are at high risk for relapse.[47] Therefore, another priority in the treatment of pathological gamblers is the design and testing of strategies that may increase motivation to seek and remain in treatment. Finally, although the majority of patients in this study improved, a third of the patients in each group did not respond to treatment, despite their lack of comorbidity. Future research should attempt to identify modifiable biological and psychological predictors of treatment resistance to improve the outcome of patients with pathological gambling.

This study has several limitations. First, the mean dose of sertraline was only 95 mg/day, substantially lower than the dose used in the treatment of other impulse-control disorders.[48–50] It is possible that higher doses may have yielded even higher response rates to medication than the ones found in the study. However, other controlled trials of pathological gambling or other impulse-control disorders using higher doses of other SSRIs have not reported higher response rates than the ones found in this study.[22,48–50]

Second, patients in this study had lower scores on the EIQ than have been previously reported.[51] It is possible that higher scores on the EIQ may be related to differential response to sertraline and placebo. Future studies should collect measures of impulsivity and investigate whether level of impulsivity is related to treatment response.

Third, the onset of pathological gambling was determined by clinical interview, possibly limiting the reliability of such information. Fourth, although the CCPGQ had good internal validity, data were not collected to assess its test-retest or interrater reliability. However, the high correlation of the CCPGQ with the CGI scale scores and the similar conclusions reached by our analyses using either scale suggest that our results are robust.

Fifth, the high placebo response limited the power of our study. If the proportion of responders found in our study is an accurate estimate of true response rates to sertraline and placebo in pathological gambling, a sample size of 185 patients per treatment arm would have been necessary to find a significance difference at the conventional $\alpha = .05$ level.

Finally, the sample was composed mostly of men. However, our prior controlled trial with fluvoxamine[22] found lower response rates for women than for men, and other studies of pathological gambling have not reported higher response rates in women, suggesting that a different gender composition of the sample would be unlikely to have yielded a higher response rate.

In conclusion, we found high rates of response to both sertraline and placebo in this study. Future studies should investigate the specific and generic effects of pharmacologic and psychosocial treatments of pathological gamblers and the mechanisms of action of those effects.

Drug names: citalopram (Celexa), paroxetine (Paxil and others), sertraline (Zoloft).

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press; 1994
2. Shaffer HJ, Hall MN. Estimating the prevalence of adolescent gambling disorders: a quantitative synthesis and guide toward standard gambling nomenclature. J Gambl Stud 1996;12:193–214

3. 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
4. Roy A, Adinoff B, Roehrich L, et al. Pathological gambling: a psychobiological study. Arch Gen Psychiatry 1988;45:369–373
5. Bergh C, Eklund T, Sodersten P, et al. Altered dopamine function in pathological gambling. Psychol Med 1997;27:473–475
6. Shinohara K, Yanagisawa A, Kagota Y, et al. Physiological changes in Pachinko players: beta-endorphin, catecholamines, immune system substances and heart rate. Appl Human Sci 1999;18:37–42
7. Eisen SA, Lin N, Lyons MJ, et al. Familial influences on gambling behavior: an analysis of 3359 twin pairs. Addiction 1998;93:1375–1384
8. Slutske WS, Eisen S, True WR, et al. Common genetic vulnerability for pathological gambling and alcohol dependence in men. Arch Gen Psychiatry 2000;57:666–673
9. Winters KC, Rich T. A twin study of adult gambling behavior. J Gambl Stud 1999;14:213–225
10. Pérez de Castro I, Ibáñez A, Torres P, et al. Genetic association study between pathological gambling and a functional DNA polymorphism at the D4 receptor gene. Pharmacogenetics 1997;7:345–348
11. Comings DE, Gade R, Wu S, et al. Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. Mol Psychiatry 1997;2:44–56
12. Ibáñez A, Perez de Castro I, Fernandez-Piqueras J, et al. Genetic association study between pathological gambling and DNA polymorphic markers at MAO-A and MAO-B genes. Mol Psychiatry 2000;20: 105–109
13. Pérez de Castro I, Ibáñez A, Saiz-Ruiz J, et al. Genetic contribution to pathological gambling: association between a functional DNA polymorphism at the serotonin transporter gene (5-HTT) and affected males. Pharmacogenetics 1999;9:397–400
14. Potenza MN, Leung HC, Blumberg HP, et al. An FMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers. Am J Psychiatry 2003;160:1990–1994
15. Potenza MN, Steinberg MA, Skudlarski P, et al. Gambling urges in pathological gambling: a functional magnetic resonance imaging study. Arch Gen Psychiatry 2003;60:828–836
16. Blanco C, Moreyra P, Nunes EV, et al. Pathological gambling: addiction or compulsion? Semin Clin Neuropsychiatry 2001;6:167–176
17. Moreno I, Saiz-Ruiz J, Lopez-Ibor JJ. Serotonin and gambling dependence. Hum Psychopharmacol 1991;6:9–12
18. Blanco C, Orensanz Munoz L, Blanco Jerez CR, et al. Pathological gambling and MAO activity: a psychobiological study. Am J Psychiatry 1996;153:119–121
19. DeCaria CM, Begaz T, Hollander E. Serotonergic and noradrenergic function in pathological gambling. CNS Spectr 1998;3:38–47
20. Hollander E, DeCaria CM, Mari E, et al. Short-term single-blind fluvoxamine treatment of pathological gambling. Am J Psychiatry 1998;155:1781–1783
21. Zimmerman M, Breen RB, Posternak MA. An open-label study of citalopram in the treatment of pathological gambling. J Clin Psychiatry 2002;63:44–48
22. Blanco C, Petkova E, Ibáñez A, et al. A pilot placebo-controlled study of fluvoxamine for pathological gambling. Ann Clin Psychiatry 2002;14: 9–15
23. 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
24. Grant JE, Kim SW, Potenza MN, et al. Paroxetine treatment of pathological gambling: a multi-center randomized controlled trial. Int Clin Psychopharmacol 2003;18:243–249
25. Kim SW, Grant JE, Adson DE, et al. A double-blind placebo-controlled study of the efficacy and safety of paroxetine in the treatment of pathological gambling. J Clin Psychiatry 2002;63:501–507
26. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV-Patient Edition (SCID-I/P, Version 2.0). New York, NY: Biometric Research, New York State Psychiatric Institute; 1995
27. 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
28. 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
29. Tiffany ST, Singleton E, Haertzen CA, et al. The development of a cocaine craving questionnaire. Drug Alcohol Depend 1993;34:19–28
30. Eysenck SBG, Pearson PR, Easting G, et al. Age norms for impulsiveness, venturesomeness, and empathy in adults. Pers Individ Dif 1985;6: 613–619
31. Grant JE, Kim SW. Gender differences in pathological gamblers seeking medication treatment. Compr Psychiatry 2002;43:56–62
32. Ibáñez A, Blanco C, Moreryra P, et al. Gender differences in pathological gambling. J Clin Psychiatry 2003;64:295–301
33. Tavares H, Martins SS, Lobo DSS, et al. Factors at play in faster progression for female pathological gamblers: an exploratory analysis. J Clin Psychiatry 2003;64:433–438
34. Ladd GT, Petry NM. Gender differences among pathological gamblers seeking treatment. Exp Clin Psychopharmacol 2002;10:302–309
35. Potenza MN, Steinberg MA, McLaughlin SD, et al. Gender-related differences in the characteristics of problem gamblers using a gambling helpline. Am J Psychiatry 2001;158:1500–1505
36. Petry NM. A comparison of treatment-seeking pathological gamblers based on preferred gambling activity. Addiction 2003;98:645–655
37. Potenza MN, Steinberg MA, McLaughlin SD, et al. Illegal behaviors in problem gambling: analysis of data from a gambling helpline. J Am Acad Psychiatry Law 2000;28:389–403
38. Lesieur HR, Blume SB. Evaluation of patients treated for pathological gambling in a combined alcohol, substance abuse and pathological gambling treatment unit using the Addiction Severity Index. Br J Addict 1991;86:1017–1028
39. Ladd GT, Petry NM. A comparison of pathological gamblers with and without substance abuse treatment histories. Exp Clin Psychopharmacol 2003;11:202–209
40. Grant JE, Kim SW. Demographic and clinical features of 131 adult pathological gamblers. J Clin Psychiatry 2001;62:957–962
41. Petry NM, Roll JM. A behavioral approach to understanding and treating pathological gambling. Semin Clin Neuropsychiatry 2001;6: 177–183
42. Hodgins DC, Petry NM. Cognitive and behavioral treatments. In: Grant JE, Potenza MN, eds. Pathological Gambling: A Clinician's Guide. Washington, DC: American Psychiatric Publishing Inc; 2004:169–187
43. Tavares H, Martins SS, Zilberman ML, et al. Gamblers seeking treatment: why haven't they come earlier? Addict Disord Treat 2002;1: 65–69
44. Fabre LF. A double blind, multicenter study comparing the safety and efficacy of sertraline with placebo in major depression. Biol Psychiatry 1991;21:353S
45. Sylvain C, Ladouceur R, Boisvert JM. Cognitive and behavioral treatment of pathological gambling: a controlled study. J Consult Clin Psychol 1997;65:727–732
46. Petry NM, Kelley J, Boccuzzi J, et al. Cognitive-behavioral treatment for pathological gambling: a randomized trial. Presented at the 62nd annual meeting of the College on Problems in Drug Dependence; June 2000; San Juan, Puerto Rico
47. Stinchfield R, Winters KC. Outcome of Minnesota's gambling treatment programs. J Gambl Stud 2001;17:217–245
48. Koran LM, Chuong HW, Bullock KD, et al. Citalopram for compulsive shopping disorder: an open-label study followed by double-blind discontinuation. J Clin Psychiatry 2003;64:793–798
49. Ninan PT, McElroy SL, Kane CP, et al. Placebo-controlled study of fluvoxamine in the treatment of patients with compulsive buying. J Clin Psychopharmacol 2000;20:362–366
50. Black DW, Gabel J, Hansen J, et al. A double-blind comparison of fluvoxamine versus placebo in the treatment of compulsive buying disorder. Ann Clin Psychiatry 2000;12:205–211
51. Blaszczynski A, Steel Z, McConaghy N. Impulsivity in pathological gambling: the antisocial impulsivist. Addiction 1997;92:75–87