A Double-Blind, Placebo-Controlled Study of the Opiate Antagonist Naltrexone in the Treatment of Pathological Gambling Urges

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Objective: Pathological gambling (PG) is a disabling disorder experienced by approximately 1% of adults and for which few empirically validated treatments exist. This study examined the efficacy and tolerability of the opioid antagonist naltrexone in adults with PG who have urges to gamble.

Method: An 18-week, double-blind, placebo-controlled trial was conducted to evaluate the safety and efficacy of 3 doses of oral naltrexone for PG. Seventy-seven individuals with DSM-IV-TR PG were randomly assigned to naltrexone (50 mg/day, 100 mg/day, or 150 mg/day) or placebo. Subjects were assessed with the Pathological Gambling Adaptation of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS), the urge and behavior subscales of the PG-YBOCS, the Gambling Symptom Assessment Scale (G-SAS), the Clinical Global Impressions-Severity of Illness scale (CGI-S), and measures of depression, anxiety, and psychosocial functioning. Data were collected from September 2002 to June 2005.

Results: Outcomes did not significantly differ between the various doses of naltrexone. Subjects assigned to naltrexone had significantly greater reductions in PG-YBOCS total scores ($p = .0094$), gambling urges ($p = .0053$), and gambling behavior ($p = .0134$) compared to subjects assigned to placebo. Subjects assigned to naltrexone also had greater improvement in overall gambling severity (reflected in the CGI-S scores) ($p = .0080$) and in psychosocial functioning ($p = .0177$) than subjects assigned to placebo. A completer analysis ($N = 49$) demonstrated significantly greater improvement on all variables for subjects assigned to naltrexone. A sex analysis demonstrated that men and women did not differ significantly in their response to naltrexone.

Conclusion: Subjects assigned to naltrexone demonstrated statistically significant reductions in gambling urges and behavior in PG. Low-dose naltrexone (50 mg/day) appeared as efficacious as higher doses (100 mg/day and 150 mg/day), and all doses were well tolerated.

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Pathological gambling (PG), a significant public health problem, is characterized by persistent and recurrent maladaptive patterns of gambling. PG is associated with impaired functioning, reduced quality of life, bankruptcy, divorce, and suicide.[1–5] Past-year adult prevalence rates for PG are estimated at 1%.[6,7] PG occurs more frequently in primary care (6.2% of outpatients)[8] and psychiatric (6.9% of inpatients) settings.[9] Untreated PG can impair functioning in multiple domains.[10] Empirically validated treatments for PG are therefore needed to optimize mental health care.

Few randomized controlled clinical trials have evaluated medication treatments for PG, and those trials in which medications have shown promise have not been successfully replicated.[11] Given its efficacy in the treatment of alcohol and opiate dependence,[12–14] the opioid receptor antagonist naltrexone was previously examined in the treatment of PG.[15,16] In a 12-week, double-blind, placebo-controlled study of naltrexone, 75% of naltrexone-treated subjects were either "much improved" or "very much improved" by the Clinical Global Impressions-Improvement scale (CGI-I) compared to 24% of those receiving placebo.[17] In a post hoc analysis, this previous study demonstrated that naltrexone was more effective in gamblers with more severe urges.

This study sought to replicate and extend the findings from the previous trial. Unlike the previous study, we enrolled PG subjects with a range of co-occurring disorders and extended the treatment trial to 18 weeks. Because of the hypothesized mechanism of action of naltrexone (i.e., modulation of mesolimbic dopamine)[18,19] and the previous findings of naltrexone's ability to reduce urges in PG,[17] the current study sought to enroll only those

individuals with PG who reported gambling secondary to urges or cravings. We hypothesized that naltrexone would reduce the severity of gambling urges and thereby improve gambling behavior and patients' overall functioning.

METHOD

Subjects

Men and women aged 18 to 75 years with a primary diagnosis of PG based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR),[20] were recruited by newspaper advertisements for medication treatment. All subjects met the DSM-IV-TR criteria for PG as assessed by the clinician-administered Structured Clinical Interview for Pathological Gambling (SCI-PG).[21] All subjects were required to have at least moderate urges to gamble as determined by a score of 2 or higher on item 1 of the Gambling Symptom Assessment Scale (G-SAS)[17]; a minimum score of 5 on the South Oaks Gambling Screen (SOGS);[22] and gambling behavior within 2 weeks prior to enrollment. Women's participation required negative results on a beta–human chorionic gonadotropin pregnancy test and stable use of a medically accepted form of contraception.

Exclusion criteria included (1) infrequent gambling (i.e., less than 1 time per week) that did not meet DSM-IV-TR criteria for PG; (2) unstable medical illness or clinically significant abnormalities on laboratory tests, electrocardiogram, or physical examination at screening visit; (3) current pregnancy, lactation, or inadequate contraception in women of childbearing potential; (4) a need for medication with possible psychotropic effects other than naltrexone or for medications with unfavorable interactions with naltrexone (e.g., narcotics); (5) lifetime history of bipolar disorder type I or II, dementia, schizophrenia, or any psychotic disorder determined by Structured Clinical Interview for DSM-IV (SCID); (6) current DSM-IV-TR substance abuse or dependence; (7) positive urine drug screen at screening (except for cannabis); (8) initiation of psychotherapy or behavioral therapy within 3 months prior to study baseline; (9) previous treatment with naltrexone; (10) baseline score of 26 or higher on the 24-item Hamilton Rating Scale for Depression (HAM-D); (11) baseline score of 26 or higher on the Hamilton Rating Scale for Anxiety (HAM-A); (12) clinically significant suicidality; or (13) treatment with investigational medication or depot neuroleptics within 3 months, with fluoxetine within 4 weeks, or with other psychotropics within 2 weeks prior to study baseline.

The institutional review board for the University of Minnesota approved the study and the informed consent. One investigator discussed potential risks of the study, as well as alternative treatments, with subjects. After complete description of the study, subjects provided written informed consent. This study was carried out in accordance with the Declaration of Helsinki. Data were collected from September 1, 2002, to June 30, 2005.

Study Design

Dose range selection was based on naltrexone's clinical and pharmacokinetic data and on PG studies using naltrexone.[15,17] Studies with naltrexone in PG have suggested that relatively high doses (i.e., 2–3 times the recommended therapeutic dose approved for alcohol dependence) may be needed to elicit a therapeutic response in PG.[15,17] Thus, we selected naltrexone doses of 50 mg/day, 100 mg/day, and 150 mg/day.

After screening, eligible subjects entered a 1-week placebo lead-in, followed by 17 weeks of double-blind naltrexone or placebo. All eligible study subjects received placebo for 1 week. Beginning at week 2, subjects not found to be placebo responders (i.e., 50% reduction in the total score of the G-SAS[17]) were randomly assigned (in block sizes of 8, using computer-generated randomization with no clinical information) to the following 4 conditions: naltrexone 50 mg/day, 100 mg/day, 150 mg/day, or placebo. To minimize nausea, treatment for all subjects was initiated at 25 mg/day naltrexone or placebo equivalent for 2 days, and then the dose was increased to 50 mg/day or placebo equivalent. In addition, all subjects were given ondansetron 4 mg/day for the first 3 days of medication to reduce nausea. To protect the blind, a third investigator (B.K.H.) saw each subject at week 2 (when adverse events due to naltrexone were most likely to occur) to assess improvement and side effects. That investigator did not see study subjects at any other study visit.

At week 3, subjects randomly assigned to 50 mg/day continued at that dose, while subjects randomly assigned to naltrexone 100 mg/day or 150 mg/day were raised to the higher doses. At this point, all subjects had reached the doses to which they were randomly assigned, and no further changes in dosing were made. Subjects who were significantly noncompliant with study procedures (i.e., more than 3 consecutive days of not taking medication) were discontinued from the study. Study drug compliance was assessed by inserting riboflavin (25 mg tablet) into each study capsule and using urine florescence tests.

Screening Assessments

Subjects were evaluated at entry into the study by the SCI-PG, a reliable and valid diagnostic instrument using criteria for DSM-IV-TR PG.[21] Psychiatric comorbidity was assessed using the SCID.[23] Medical history, physical examination, electrocardiogram, and routine laboratory testing were obtained. Investigators assessed PG symptoms using the Pathological Gambling Adaptation of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS).[24] Subjects reported severity of PG symptoms using the SOGS[22] (screening visit only) and the

self-rated G-SAS.[17] Anxiety symptom severity was rated with the HAM-A.[25] Depressive symptoms were assessed using the HAM-D.[26] Psychosocial functioning was evaluated using the self-report version of the Sheehan Disability Scale (SDS).[27]

Efficacy and Safety Assessments

Subjects were seen weekly for 8 weeks and then every 2 weeks for the remaining 10 weeks of the study. The primary outcome measure was the PG-YBOCS.[24] The PG-YBOCS is a reliable and valid, 10-item, clinician-administered scale that rates gambling symptoms within the last 7 days, on a severity scale from 0 to 4 for each item. (Total scores range from 0 to 40, with higher scores reflecting greater illness severity.)

The first 5 items of the PG-YBOCS comprise the gambling urge/thought subscale (time occupied with urges/thoughts; interference and distress due to urges/thoughts; resistance against and control over urges/thoughts), and items 6–10 comprise the gambling behavior subscale (time spent gambling and amount of gambling; interference and distress due to gambling; ability to resist and control gambling behavior).

Secondary measures that were used at each study visit included:

Gambling Symptom Assessment Scale. Subjects completed the G-SAS[17] at each study visit. The G-SAS is a 12-item, reliable and valid, self-rated scale assessing gambling urges, thoughts, and behaviors during the previous 7 days. Each item is rated 0 to 4, with a possible total score of 48. Higher scores reflect greater severity of PG symptoms.

Clinical Global Impressions-Severity of Illness scale. The Clinical Global Impressions-Severity of Illness scale (CGI-S)[28] consists of a reliable and valid 7-item Likert scale used to assess severity in clinical symptoms. The CGI-S was used at each visit. Scoring ranges from 1 = "not ill at all" to 7 = "among the most extremely ill." The CGI-S was used to refer specifically to gambling severity, not overall psychopathology.

Sheehan Disability Scale. The SDS[27] is a 3-item, reliable and valid self-report scale that assesses functioning in 3 areas of life: work, social or leisure activities, and home and family life. Scores on the SDS range from 0 to 30.

Hamilton Rating Scale for Anxiety. The HAM-A[25] is a reliable and valid, clinician-administered, 14-item scale that provides an overall measure of global anxiety.

Hamilton Rating Scale for Depression. The HAM-D[26] is a valid and reliable, 24-item, clinician-administered rating scale assessing severity of depressive symptoms.

Safety assessments at each visit included evaluations of sitting blood pressure, heart rate, and weight. Adverse effects were documented and included time of onset and resolution, severity, action taken, and outcome. The investigator recorded use of concomitant medications in terms of daily dosage, start and stop dates, and reason for use. Liver function tests were drawn every 2 weeks during the study. Naltrexone compliance was monitored by a urine florescence test at each visit.

Data Analysis

Demographic and baseline visit characteristics for naltrexone and placebo groups were compared using χ^2 and analysis of variance (ANOVA) to determine if group differences existed at random assignment. Primary and secondary measures were examined using repeated-measures ANOVA modeling analyses (PROC MIXED, SAS/STAT Software for Windows, version 8.2, SAS Institute Inc., Cary, N.C.). The baseline value of the measure being analyzed was used as a covariate. A time trend (linear) was included in all models. A treatment-by-time interaction was examined for all models but was removed due to lack of significance. The covariance structure of the repeated-visit data was modeled as autoregressive. The difference in the overall level of posttreatment values, the main effect for treatment, was the test of primary interest. Initial modeling was performed on the 3 active levels. Final modeling was performed comparing placebo with the combined active arms. Analyses were performed on all available data as well as for the completers. All available postrandomization data were first analyzed, and a secondary, supportive analysis of completers was performed. All comparison tests were 2-tailed, and an α level of .05 was used to determine statistical significance.

A retrospective power analysis was performed using a bootstrap approach.[29] Five thousand resampling iterations were performed, and significance was achieved in 68% of the 4-level treatment variable. The 2-level active/placebo dichotomy displayed 69% power. These results indicate that the significant findings reported are not likely to be based on chance.

RESULTS

Subject Characteristics

There were no significant differences among the 3 naltrexone groups on baseline characteristics, study outcomes, treatment completion, medication compliance, or adverse drug experiences. Therefore, data from the naltrexone groups were combined, and the results presented are naltrexone and placebo group comparisons. Demographics at baseline are presented (Table 1). There were no statistically significant imbalances regarding age, sex, marital status, education, or gambling severity between treatment groups.

The subjects as a whole reported a mean ± SD age at pathological gambling onset of 36.3 ± 11.9 years (range, 14–59 years) with a lag time of 11.2 ± 10.7 years

Table 1. Demographic Characteristics of 77 Subjects With DSM-IV-TR Pathological Gambling at Baseline, by Treatment Group[a]

Characteristic	Placebo (N = 19)	Naltrexone (N = 58)
Age, mean ± SD, y	44.7 ± 9.67	47.8 ± 9.65
Sex, male, N (%)	9 (47.4)	21 (36.2)
Race/ethnicity, white, N (%)	16 (84.2)	54 (93.1)
Marital status, married, N (%)	11 (57.9)	21 (36.2)
Education, ≥ 12 y, N (%)	16 (84.2)	54 (93.1)

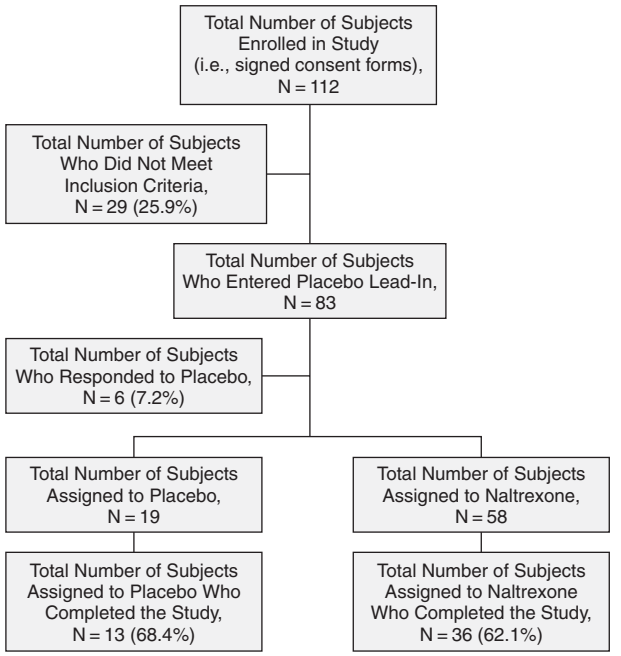
[a]There were no statistically significant differences between groups.

(range, < 1–40 years) from starting to gamble and meeting criteria for pathological gambling. On average, the group spent a mean ± SD of 13.1 ± 7.4 hours (range, 6–32 hours) each week gambling and lost a mean ± SD total of $535.54 ± $449.68 (range, $100–$1750) each week. The majority of the group (51.9%; N = 40) identified nonstrategic forms of gambling (e.g., slot machines, pull tabs, lottery, bingo) as their primary type of gaming. Although many subjects had multiple triggers, the most common triggers of the urge to gamble were having money (72.7%; N = 56), stress (61.0%; N = 47), loneliness (50.6%; N = 39), and advertisements (50.6%; N = 39). Even though 25 (32.5%) had committed some criminal act due to gambling and 13 (16.9%) had declared bankruptcy due to gambling, only 32 (41.6%) had ever attended Gamblers Anonymous, and only 15 (19.5%) had sought outpatient mental health treatment for gambling.

Although subjects with current bipolar, psychotic, and substance use disorders were excluded, the enrolled subjects reported clinically important current comorbidities. Forty-seven subjects (61.0%) reported symptoms consistent with major depressive disorder, 16 (20.8%) had an anxiety disorder (e.g., social phobia, panic disorder, anxiety disorder not otherwise specified), 13 (16.9%) had another impulse control disorder (most commonly compulsive buying, compulsive sexual behavior, or kleptomania), and 5 (6.5%) had an eating disorder (e.g., binge eating disorder and bulimia nervosa). Comorbidities did not differ between treatment groups, and no particular comorbidity was associated with treatment response.

Figure 1 shows subject number and disposition throughout the study. A total of 49 (63.6%) completed the 18-week study. Thirteen (68.4%) of 19 subjects assigned to placebo and 36 (62.1%) of 58 subjects assigned to naltrexone completed the 18-week trial. The rate of completion of the study did not differ between treatment groups. Of the 28 subjects who failed to complete the study, 20 either withdrew consent for personal reasons or were unable to comply with the study schedule. Five withdrew due to adverse events, and 3 felt the study was not helping their gambling. Reasons for study withdrawal did not significantly differ between groups.

Figure 1. Subject Flow in the Study



Efficacy Results

Analysis of the 3 active arms failed to demonstrate any significant increase in effects associated with increased dose. Hence, the active arms were combined and compared to placebo. Significantly better results were observed for those assigned to naltrexone on the primary efficacy variable, the PG-YBOCS total scores (F = 7.16; df = 1,66; p = .0094; Table 2). A significant treatment effect, which continued throughout the study, was first detected after 6 weeks on active medication (p = .0002). Of those subjects assigned to naltrexone, 23 (39.7%) were able to abstain from all gambling for at least 1 month, whereas only 2 (10.5%) assigned to placebo attained complete abstinence from gambling for at least 1 month (Fisher exact = .023).

PG-YBOCS urge/thought and behavior subscale results were consistent with the total score, and the difference among groups was statistically significant on the urge subscale (F = 8.32; df = 1,66; p = .0053) and behavior subscale (F = 6.46, df = 1,66; p = .0134; Table 2). On the urge/thought subscale, differences became significant after 6 weeks of active treatment (p = .005), whereas behavior actually improved significantly after only 3 weeks of active treatment (p = .0443).

G-SAS analysis (Table 2) demonstrated statistically significant differences between groups in patient-reported gambling symptoms (F = 6.08, df = 1,66; p = .0162). Consistent with the PG-YBOCS total score response, response on the G-SAS was seen after 6 weeks of active

Table 2. Treatment Response of Pathological Gambling Subjects Assigned to Placebo or Naltrexone (intent-to-treat population)

	Baseline, Mean ± SD		End Point, Mean ± SD				
Variable	Placebo	Naltrexone	Placebo	Naltrexone	Test[a]	p Value	Effect Size[b]
PG-YBOCS total score	18.6 ± 4.90	16.9 ± 6.60	12.9 ± 9.31	9.7 ± 8.12	7.16	.009	3.05
PG-YBOCS urge/thought subscale score	10.2 ± 2.66	9.5 ± 3.54	7.1 ± 4.73	5.5 ± 4.16	8.32	.005	1.66
PG-YBOCS behavior subscale score	8.4 ± 2.80	7.4 ± 3.62	5.8 ± 4.79	4.2 ± 4.17	6.46	.013	1.49
G-SAS total score	29.5 ± 5.63	26.9 ± 8.28	21.2 ± 9.80	15.7 ± 9.47	6.08	.016	3.71
CGI–S score	4.6 ± 1.02	4.5 ± 1.08	3.6 ± 1.44	3.0 ± 1.50	7.48	.008	0.542
HAM-D score	9.89 ± 4.05	8.48 ± 3.81	9.13 ± 6.32	6.61 ± 1.28	7.76	.007	0.692
HAM-A score	10.3 ± 4.26	8.89 ± 4.15	9.64 ± 4.11	6.76 ± 0.43	13.38	< .001	0.908
Sheehan Disability Scale score	13.4 ± 6.52	10.0 ± 6.38	8.4 ± 7.39	4.8 ± 6.45	5.91	.018	2.40

[a]Repeated Measures ANOVA; F value (df = 1,66).
[b]Differences in response between placebo and active groups adjusted for baseline level.
Abbreviations: ANOVA = analysis of variance, CGI-S = Clinical Global Impressions-Severity of Illness scale, G-SAS = Gambling Symptom Assessment Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = 24-item Hamilton Rating Scale for Depression, PG-YBOCS = Pathological Gambling Adaptation of the Yale-Brown Obsessive Compulsive Scale.

Table 3. Percentage of Subjects Reporting Adverse Drug Events

Adverse Drug Event	Placebo Group (N = 19)	Naltrexone Group (N = 58)	p Value[a]
Headache	47.4	39.7	.599
Nausea	36.8	60.3	.111
Diarrhea	31.6	13.8	.096
Constipation	15.8	5.2	.156
Dry mouth	10.5	13.8	1.00
Dizziness	5.3	10.3	.674
Insomnia	0	12.1	.183

[a]Fisher exact test.

treatment (p = .0015). The CGI-S scale also demonstrated significant improvement after 6 weeks of active treatment and showed significantly greater response by study endpoint (F = 7.48; df = 1,66; p = .0080; Table 2).

Mean values in HAM-A and HAM-D scores remained at low levels throughout the study in both treatment groups, but the subjects assigned to naltrexone demonstrated statistically significant improvement in both depression and anxiety scores (F = 13.38, df = 1,66; p < .0001; Table 2).

Subjects assigned to naltrexone also demonstrated significantly greater response with respect to psychosocial functioning. The total SDS score demonstrated statistically significant differences between the 2 groups (F = 5.91, df = 1,66; p = .0177; Table 2). In addition, the subscale scores of the SDS also demonstrated statistically significant differences between the active and placebo groups on the 3 functional domains: work/school (F = 8.75, df = 1,60; p = .0044); social life/leisure activities (F = 8.35, df = 1,65; p = .0052); and family life/home responsibilities (F = 16.27, df = 1,65; p = .0001).

Analyses performed on the subset of 49 subjects who completed the study demonstrated significant reductions on all measures consistent with the intent-to-treat analyses. An analysis of sex demonstrated that both men and women responded equally well to naltrexone, and there were no significant sex differences in response.

Safety and Tolerability

The incidence and severity of adverse experiences in naltrexone-treated subjects were consistent with prior studies,[15–17] and no unusual experiences were reported (Table 3). Because subjects may have reported more than 1 adverse experience, however, it was not possible to accurately determine for individual subjects which particular adverse event resulted in treatment discontinuation. Most adverse experiences were of mild-to-moderate intensity and most commonly occurred during the first week of drug treatment. There were no statistically significant differences in the incidence of adverse events between groups. There were no clinically significant changes in laboratory testing, including liver function tests, during treatment with naltrexone.

DISCUSSION

This randomized, double-blind clinical trial found naltrexone to be superior to placebo in the treatment of PG across a spectrum of illness-specific and global outcome measures. The results demonstrate that naltrexone treatment reduces the symptoms associated with PG, specifically urges to gamble. In addition, this is the first double-blind confirmatory pharmacological study in PG, and it extends our previous findings[17] by demonstrating that naltrexone is beneficial, safe, and well tolerated for as long as 4 to 5 months.

The efficacy of naltrexone in this study lends further support to the hypothesis that pharmacologic manipulation of the opiate system may target core symptoms of PG, such as urges.[30] Opioid antagonists have been effective in treating other addictive disorders involving alcohol, heroin, and cocaine use.[12–14,31] The efficacy of opioid antagonists in the treatment of addictive disorders, including PG, has been proposed to involve opioidergic modulation of mesolimbic dopamine circuitry. Behaviorally, opioid antagonist administration leads to diminished urges to engage in the addictive behavior and longer periods of

abstinence,[17,30,32] consistent with a mechanism of action involving ventral striatal dopamine systems.[18,33] Further work into defining the precise manner in which opioid antagonists mediate their beneficial effects and which subtype of pathological gamblers will benefit most from opioid antagonists could enhance treatment strategies for PG and other impulse control disorders.

Adverse events reported in this study were consistent with naltrexone's previously reported safety profile.[16,17,34] No dose of naltrexone resulted in hepatotoxicity, and this may be, in part, due to limiting subjects' use of concomitant nonsteroidal analgesics.[17] Although there has been concern that opioid antagonists might engender depression, depression and anxiety scores (HAM-D and HAM-A) actually improved with treatment.

Although several medications have demonstrated early promise in the treatment of PG, this study represents the only confirmatory medication trial in PG performed to date, but there are several limitations. First, PG is a chronic disease that may require long-term therapy. Although this study is one of the longest medication trials for PG, the study did not assess treatment effects beyond the acute 18-week treatment period, and longer-term effects thus require further evaluation. It is possible that a longer course of therapy could result in continued and even greater reductions in gambling symptoms. Alternatively, naltrexone's therapeutic effects in PG might not endure beyond 18 weeks. Second, we enrolled subjects seeking pharmacological treatment, not psychotherapy, and excluded those with severe mental health issues. Given these exclusion criteria (e.g., no comorbidity with bipolar disorder or current substance use disorders), these results may not generalize completely to the larger population of people with PG. The study did, however, include subjects with depression and anxiety disorders, and it thus appears more representative than many previous treatment studies.[35] Third, although subjects were excluded if they had lifetime bipolar I or II disorders, it is possible that some may have had histories of subsyndromal mania or hypomania. If present, this may have led to discontinuation for some of these subjects taking medication, as naltrexone could possibly have induced subtle mood destabilization. More detailed assessments of subsyndromal mood symptoms are needed for future studies. Fourth, the subjects assigned to placebo demonstrated improvement over time. Although this placebo effect is a confounder, examination of the relative pattern over time demonstrates that the treatment signal outweighed the placebo effect. Fifth, this study did not include behavioral therapy. Effective behavioral treatments for PG are emerging,[36–38] and they should be considered in conjunction with pharmacotherapies.

This investigation suggests that naltrexone may be effective in the acute treatment of PG when subjects report urges to gamble. As effective treatments for PG emerge, it becomes increasingly important that physicians and mental health care providers screen for PG in order to provide timely treatment.

Drug names: fluoxetine (Prozac and others), naltrexone (Vivitrol, ReVia, and others), ondansetron (Zofran and others).

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