BACKGROUND: Gambling disorder is a disabling illness experienced by 1% to 3% of adults. Pharmacologic management of gambling disorder has produced mixed results, with some but not all studies showing medication to be more effective than placebo. Ecopipam may offer promise for treating gambling disorder because of its antagonism of dopamine-1 receptors.

METHODS: Twenty-eight individuals with gambling disorder were enrolled and received ≥1 dose of oral ecopipam in an 8-week trial (1 week placebo lead-in, 6 weeks of medication (50 to 100 mg/d as needed), and 1 week follow-up. Participants were enrolled between September 2010 and June 2011 at 3 sites in the United States. Change from baseline to study endpoint on the Yale-Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS) was the primary outcome measure.

RESULTS: Treatment was associated with statistically significant reductions in the PG-YBOCS total score (baseline score of 25.6 reduced to 14.0 at study endpoint; \( P < .001 \)) and PG-YBOCS subscales (Thought-Urge and Behavior, \( P < .001 \)).

CONCLUSIONS: These findings suggest that pharmacologic targeting of the dopamine-1 receptor may be beneficial in gambling behavior. Placebo-controlled, double-blind studies are warranted to confirm these preliminary findings.

KEYWORDS: addiction, dopamine, ecopipam, gambling
INTRODUCTION

Gambling disorder is a worldwide public health problem characterized by persistent and recurrent maladaptive patterns of gambling. Past-year adult prevalence rates for gambling disorder are estimated at 1% to 3%. Because untreated gambling disorder is associated with impaired functioning, reduced quality of life, and high rates of bankruptcy and divorce, validated treatments are needed to optimize mental health care and long-term outcomes.

Controlled clinical trials evaluating pharmacologic treatments for gambling disorder have demonstrated that opioid antagonists, n-acetylcysteine, and lithium may be promising options for reducing gambling urges, thoughts, and behaviors. Similarly, variations of cognitive-behavioral therapy are established treatments for gambling disorder, although trained therapists are not plentiful. Not all individuals receiving pharmacologic treatment report symptom improvement, and no medication has been approved by the FDA for gambling disorder. Yet, based on neurobiological evidence for brain dysfunction, pharmacologic options continue to hold promise for gambling disorder.

Gambling urges may contribute to maintenance and relapse in gambling disorder. Individuals with gambling disorder who report moderate to high gambling urges at treatment onset demonstrate significant symptom improvement with the opioid antagonist naltrexone, and gambling urge intensity has been positively associated with treatment outcome among individuals receiving the opioid antagonists naltrexone or nalmefene. Not everyone, however, responds to or can tolerate an opiate antagonist. Given the clinical significance of self-reported gambling urges, additional pharmacologic agents that target urges are needed.

Ecopipam is a selective antagonist of the D1-dopamine receptor family (composed of D1 and D5 subtypes). Clinical studies suggest that ecopipam acts to block the euphoric effects of drugs and thereby reduces cravings associated with other addictions such as cocaine use. This effect on urges or cravings may be because of ecopipam’s antagonism of dopamine-1 receptors, particularly in the ventral striatum. Given that ecopipam has shown some effect in reducing cravings associated with drug addiction, it may have a similar effect on urges and subsequent gambling behavior in gambling disorder. This pilot study examined the efficacy and tolerability of ecopipam in treating gambling disorder. We hypothesized that ecopipam would reduce the severity of gambling urges, thereby reducing gambling behavior and improving overall function.

METHODS

Men and women age 18 to 75 with a primary diagnosis of gambling disorder were recruited via newspaper or poster advertisements from September 2010 to June 2011.

Inclusion criteria included: 1) met diagnostic criteria for gambling disorder on the clinician-administered Structured Clinical Interview for Pathological Gambling (SCI-PG); 2) a minimum score of ≥18 on the Yale-Brown Obsessive Compulsive Scale modified for Pathological Gambling (PG-YBOCS); 3) gambling urges of at least moderate intensity (corresponding to a score of ≥2 on the first question of the PG-YBOCS); and 4) reporting ≥2 episodes of gambling behavior within the 2-week period leading up to screening. In addition, 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 (ie, <1 time per week) that does not meet diagnostic criteria for gambling disorder; 2) unstable medical illness or clinically significant abnormalities on physical examination or abnormal laboratory results; 3) history of seizures; 4) having a myocardial infarction within 6 months; 5) current pregnancy or lactation, or inadequate contraception in women of childbearing potential; 6) lifetime history of bipolar disorder type I or II, dementia, or any psychotic disorder based on the Structured Clinical Interview for DSM-IV (SCID); 7) current or recent (past 3 months) substance use disorder, except nicotine dependence; 8) history of a major depressive episode in the past 2 years; 9) active suicidal ideation/thoughts within 12 months preceding study participation; 10) history of attempted suicide; 11) clinically significant suicidality (on the Columbia Suicide Severity Rating Scale); 12) a first-degree relative with a major depressive episode that resulted in any psychiatric hospitalization or suicide (attempted or completed); 13) a need for medication other than ecopipam with possible effects on gambling symptoms (ie, serotonergic antidepressants, lithium, or naltrexone) or unfavorable interactions with ecopipam (ie, dopamine agonist); 14) positive urine drug screen.
(cocaine, amphetamine, methamphetamine, THC, benzodiazepines, barbiturates, PCP, opiates) at screening; 15) initiation of psychotherapy or behavior therapy specifically for gambling disorder within 3 months before study baseline (excluding marital counseling); 16) previous treatment with ecopipam; and 17) treatment with investigational medication or depot neuroleptics within 3 months, with fluoxetine within 6 weeks of study entry.

To avoid interactive effects that might obscure a drug effect, individuals attending Gamblers Anonymous were allowed to participate if attendance had been ongoing for at least 6 months before study entry. Participants who started individual therapy or Gamblers Anonymous, based on their self-report, were discontinued from the study.

The institutional review board for each university site approved the study and the informed consent procedures. Investigators discussed potential risks of the study, as well as alternate treatments, with recruits. After being given a complete description of the study and the opportunity to ask questions, the enrollees provided voluntary written informed consent. This study was carried out in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

Study design
The study consisted of a 1-week placebo lead-in period, followed by 6 weeks of ecopipam, and then a 1-week follow-up visit via telephone to assess adverse events. All participants were blinded to treatment assignment throughout the study. The informed consent stated that participants would receive both drug and placebo during the study but not exactly when each would be given.

After a complete medical and psychiatric examination (SCID performed by an experienced clinician), all eligible participants received matching placebo tablets for 1 week and were instructed to take one 50-mg tablet whenever they felt the urge to gamble. They were instructed that a second placebo tablet could be taken within the 24-hour period if the urge to gamble recurred or if the original urge did not abate. Participants were told they were not permitted to take >2 tablets in any 24-hour period, and they were given a diary and told to write down when they took ecopipam and how many tablets were taken. Study doses were based on PET studies showing that 100 mg of oral ecopipam saturated brain D1/5 receptors and on other clinical studies showing that these doses were well-tolerated. Previous data suggest that ecopipam reaches maximal concentrations (T<sub>max</sub>) at 2 hours after dosing.

Participants were reimbursed for their time ($25 per visit given at the end of the study) and received parking or bus tokens to compensate for transportation to the study center.

Efficacy and safety assessments
Participants were evaluated every week for the initial 5 weeks (including screening and baseline) and at the final visit. One week after the final visit, they were contacted via telephone to assess any new or previously reported adverse events. Between visits, participants monitored their ecopipam use using a daily written log.

The primary outcome measure was the total score on the PG-YBOCS. This reliable and valid, 10-item, clinician-administered scale rates gambling symptoms within the last 7 days.

Secondary measures used at each study visit included subscales of the PG-YBOCS (the gambling urge/thought subscale comprises the first 5 items of the PG-YBOCS, and the gambling behavior subscale comprises items 6 to 10); Gambling Symptom Assessment Scale (G-SAS), Clinical Global Impressions-Improvement and Severity scales (CGI), Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HAM-A), Sheehan Disability Scale, and the Columbia Suicide Severity Rating Scale (C-SSRS). In addition, the percentage of “responders” at each visit was quantified; response was defined a priori as a ≥35% reduction in PG-YBOCS total score.

Because of potential psychiatric side effects of ecopipam, safety assessments done at each visit included the 17-item HDRS and the C-SSRS. The protocol stated that any participant endorsing suicidal thoughts at any time was to be removed from the study and provided with appropriate clinical intervention (eg, hospitalization if needed). In addition, participants were contacted via telephone during the weeks between later visits to
assess suicidality and adverse events. Other safety assessments (sitting blood pressure, heart rate, adverse effects, and concomitant medications) were documented at each visit. Investigators recorded concomitant medications, including dosage, start and stop dates, and reason for use. Laboratory assessments (eg, clinical chemistry, hematology, and urine toxicology) and urine pregnancy tests were performed at screening and final visit.

**Data analysis**

In all efficacy analyses, only participants who returned for at least 1 visit after starting medication were included, and a last observation carried forward approach was used. Effects of treatment on clinical measures were quantified using repeated-measures analysis of variance. The non-parametric Cochran Q test was used to analyze the binary responder variable. For this pilot study, statistical significance was defined as $P < .05$ uncorrected throughout, unless indicated otherwise in the text.

**RESULTS**

**Baseline characteristics**

Thirty-five individuals with gambling disorder provided written voluntary consent and were enrolled in the study. Seven did not receive ecopipam and discontinued during the placebo phase: 2 for violation of compliance, 2 for unstable medical condition, 2 lost to follow-up, and 1 for reporting positive answers on the C-SSRS. The remaining 28 (mean age 45.0 ± 14.4 years [range 21 to 68]; 12 [42.9%] female) were included in the analysis. Baseline characteristics are presented in TABLE 1. On average, the participants had a moderately severe form of gambling disorder at study entry, as indicated by PG-YBOCS total score.

**Clinical variables**

Clinical measures at each time point, along with baseline vs end-of-study statistical comparisons, are indicated in TABLE 2. Highly significant improvements occurred across the range of clinical outcome measures during ecopipam treatment. The primary outcome variable—change from baseline on the PG-YBOCS total score—reached statistical significance by the week-2 visit (ie, after 1 week of ecopipam treatment). Although the mean change in PG-YBOCS scores during the study appears more pronounced than changes on the secondary measures, mean reductions on the CGI and G-SAS also were statistically significant.

Participants used a median of 38 tablets (range, 3 to 94) over the 6 weeks of ecopipam treatment. During the placebo week, they took a median of 10 tablets.

Twenty-two (78.6%) of 28 enrollees completed the 8-week trial. Completers and non-completers showed no statistically significant pretreatment differences on any measures. Among the 6 who failed to complete the study, 2 were lost to follow-up, 2 withdrew by their choice, 1 was terminated for noncompliance, and 1 experienced an adverse effect (depressed mood).

**Adverse events and blood parameters**

In the intent-to-treat population, mood and anxiety symptoms were unchanged during the trial: the mean HAM-A scores changed from 2.5 (±2.5) at baseline to 3.1 (±3.1) at study endpoint ($T = 0.82; P = .418$), and mean HDRS scores were essentially unchanged—3.6 (±2.6) at baseline and 3.6 (±3.3) at study endpoint ($T = 0.00; P = 1$) (TABLE 2).

Ecopipam was generally well-tolerated; adverse effects reported by participants were mild to moderate and resolved without sequelae (TABLE 3). Nineteen (67.9%) of the 28 participants reported at ≥1 adverse event. Twelve events were considered mild, 6 moderate, and none severe. A participant who initiated antidepressant medication (amitriptyline) for anxiety during the study was not removed because no evidence indicates that amitriptyline influences the symptoms of gambling disorder. The investigator did not report this as an adverse event because no change was observed in the individual’s HDRS or HAM-A scores.
The most common adverse event was anxiety (n = 4; 14.3%). Adverse events generally affected the central nervous system (CNS) and GI system. CNS symptoms included anxiety, drowsiness, fatigue, depression, and headache. GI symptoms included vomiting and constipation. Rhinorrhea (n = 2) and fever (n = 2) also were reported. Adverse events reported by a single subject at any time during the study included right arm pain, cold symptoms, right eye twitching, overeating, chest pain, diarrhea, leg cramps, insomnia, jitteriness, anhedonia, nausea, dizziness, restlessness, indigestion, decreased appetite, increased smoking, sedation after second pill, coughing, increased appetite, grogginess, vivid dreams, abdominal pain, acne, animal bite (leg), tremors, and sneezing. One serious adverse event reported for 1 participant (abdominal pain requiring hospitalization) was deemed to be unrelated to the study medication. Laboratory values and vital signs showed no significant changes during the study. Although ecopipam has been reported to reduce body weight, our participants' body weight did not change significantly during the study.

### DISCUSSION

This pilot study—to our knowledge the first to examine the efficacy of a dopamine-1 receptor antagonist in treating gambling disorder—demonstrated that gambling symptoms improved significantly in most trial participants. These findings support the idea that dopaminergic system activation is likely the primary mediator of gambling’s reinforcing properties.

The dopamine-1 receptor in particular may play a key role in addiction, as supported by findings that dopamine-1 antagonists:

- blunt the reinforcing effects of drugs of abuse in animals
- block stress-induced reinstatement of addiction-seeking behavior
- may play a role in promoting increased inhibition of motor responses

Although the exact mechanism of ecopipam in gambling disorder is speculative, our findings suggest that pharmacologic modulation of the dopamine system at the dopamine-1 receptor reduces gam-

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**TABLE 2**

| Changes on primary and secondary measures across visits |
|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| PG-YBOCS total score | 25.6 (4.1) | 22.1 (3.7) | 19.7 (5.8) | 14.4 (6.6) | 13.7 (7.0) | 10.8 (5.9) | 12.6 (8.5) | 14.7*a | 6,116 | <.0001 |
| PG-YBOCS urges/thought subscale score | 12.9 (2.6) | 11.5 (2.2) | 10.8 (2.9) | 8.2 (2.9) | 7.3 (3.5) | 6.7 (3.7) | 6.8 (4.2) | 10.6*a | 6,114 | <.0001 |
| PG-YBOCS behavior subscale score | 13.0 (2.0) | 10.6 (2.4) | 9.0 (3.8) | 6.4 (4.2) | 6.6 (4.3) | 4.2 (3.4) | 6.1 (4.6) | 13.7*a | 6,111 | <.001 |
| Responder, n (%) | — | 1 (3.6) | 9 (32.1) | 15 (53.6) | 16 (57.1) | 17 (60.7) | 15 (53.6) | 48.2^b | 6 | <.0001 |
| CGI-severity | 4.6 (0.8) | 4.3 (0.6) | 4.0 (0.7) | 3.5 (0.9) | 3.5 (1) | 3.1 (1) | 3.2 (1.2) | 6.6^a | 6,114 | <.0001 |
| G-SAS total score | 32.1 (6.3) | 25.8 (7.1) | 27.1 (7) | 22.5 (9.9) | 22.3 (10) | 18.0 (10.2) | 20.5 (11.5) | 6.8^a | 6,113 | <.0001 |
| Hamilton – Anxiety | 3.6 (2.6) | 3.0 (2.7) | 3.1 (3.1) | 2.2 (2.5) | 2.3 (2.5) | 2.3 (2.5) | 3.3 (3.1) | 1.55 | 6,128 | >.16 |
| Hamilton – Depression | 2.5 (2.5) | 2.5 (2.9) | 2.6 (2.8) | 1.9 (2.2) | 2.5 (2.9) | 2.5 (3.1) | 3.0 (3.4) | 1.20 | 6,128 | >.30 |

**Sheehan Disability Scale**

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<th>Work</th>
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<td>CGI Minimal</td>
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</table>

Last observation carried forward. All values shown as mean ± SD, unless otherwise indicated.

*a F-test.

^b Chi-square Test of Goodness Fit.

CGI: Clinical Global Impression Improvement; G-SAS: Gambling Symptom Assessment Scale; PG-YBOCS: Pathological Gambling Modification of the Yale-Brown Obsessive Compulsive Scale.
bling behavior and may be doing so via reduction in gambling urges.

This study has clinical importance as the first pharmacologic study in gambling disorder that allowed participants to use medication “as-needed” instead of on a schedule. Compliance with treatment, including medication, has been problematic in previous studies of individuals with gambling disorder.46 Because of potential compliance issues and the side effects associated with ecopipam, this study sought to use medication only when the person had urges to gamble.

Although ecopipam may be a promising treatment for gambling disorder, prior pharmacologic studies have shown that particular treatments have not been effective for all individuals with gambling disorder.1 In this study, the medication was specifically focused on gamblers endorsing moderate urges to gamble. In gambling disorder, urges have been shown to be a particularly useful clinical marker for other pharmacotherapies and therefore may be an important subtype for which to tailor treatment.19 Although this notion requires additional study, one future direction for treating gambling disorder may be to better define its subtypes to guide pharmacologic treatment selection.

Our study has important limitations. Foremost, clinician bias may have influenced the results because the design was single-blind. Positive responses not attributable to the study medication may have occurred (eg, positive effects of regular therapist contact and/or participants feeling obliged to meet the expectations of the research). In addition, placebo response rates in gambling disorder studies have been high (up to 72%).47

Our results may be at least in part the result of a placebo effect, although interestingly the 1-week placebo lead-in period eliminated only 1 participant.

Gambling disorder is a chronic disease that may require long-term therapy. By design, our study did not assess treatment effects beyond a 6-week treatment period. A longer course of treatment possibly could have resulted in continued and greater reductions in gambling symptoms.

We enrolled subjects seeking pharmacologic treatment, not psychotherapy. Therefore, our results may not generalize to all people with gambling disorder. The few exclusionary criteria in this study (eg, most psychiatric disorders were not grounds for exclusion) suggest, however, that this sample may generalize to a large population of individuals with gambling disorder. Because we enrolled individuals who were taking stable doses of psychotropic medications (eg, bupropion and selective noradrenergic reuptake inhibitors), these medications might have affected treatment outcomes. Treatment response did not differ based on whether or not a participant was taking other psychotropics, however, and this evidence suggests that positive outcomes were not simply the result of ecopipam augmenting another agent.

This investigation suggests that ecopipam taken “as-needed” may be effective in acute treatment of gambling disorder. The single-blind design and small number of participants limit the interpretation of the efficacy results, but our findings support the use of controlled designs for future investigations of dopamine-1 antagonists for gambling disorder. As effective treatments emerge, screening for gambling disorder by physicians and mental health care providers becomes increasingly important to providing timely treatment.

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REFERENCES

ECOPIPAM FOR GAMBLING

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