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Predicting Response to Opiate Antagonists and Placebo in the Treatment of Pathological Gambling

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Abstract

Rationale—Although opiate antagonists have shown promise in the treatment of pathological gambling (PG), individual responses vary. No studies have systematically examined predictors of medication treatment outcome in PG. Understanding clinical variables related to treatment outcome should help generate treatment algorithms for PG.

Objectives—We sought to identify clinical variables associated with treatment outcome in PG subjects receiving opiate antagonists.

Methods—284 subjects (137 [48.2%] women) with DSM-IV PG were treated in one of two double-blind placebo-controlled trials (16 weeks of nalmefene or 18 weeks of naltrexone). Gambling severity was assessed with the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling [PG-YBOCS] with positive response defined as ≥35% reduction in PG-YBOCS score for at least one month by study endpoint. Depression, anxiety, and psychosocial functioning were included in stepwise logistic regression analyses designed to identify clinical factors independently associated with treatment response.

Results—The clinical variable most strongly associated with a positive response to an opiate antagonist was a positive family history of alcoholism (p=.006). Among individuals receiving higher doses of opiate antagonists (i.e., nalmefene 50mg/d or 100mg/d or naltrexone 100mg/d or 150mg/d), intensity of gambling urges (PG-YBOCS urge subscale) was associated with a positive response on a trend level (p=.036). Among individuals receiving placebo, younger age was associated, on a trend level, with positive treatment outcome (p=.012).

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Conflicts of Interest

Dr. Grant has received research grants from Forest Pharmaceuticals, GlaxoSmithKline, and Somaxon Pharmaceuticals. Dr. Grant has also been a consultant to Pfizer Pharmaceuticals and Somaxon Pharmaceuticals and has consulted for law offices as an expert in pathological gambling.

Dr. Kim reports no competing interests.

Dr. Hollander has received a research grant from and served as a consultant to Somaxon.

Dr. Potenza consults for and is an advisor to Boehringer Ingelheim, receives research support from Mohegan Sun, has consulted for and has financial interests in Somaxon, and has consulted for law offices and the federal defender's office as an expert in pathological gambling and impulse control disorders.

Conclusions—A family history of alcoholism appears to predict response to an opiate antagonist in PG. Future research is needed to identify specific factors (e.g., genetic) mediating favorable responses.

Keywords

opiate antagonists; impulsivity; impulse control disorders; addiction; pharmacotherapy; placebo

Introduction

The efficacy of opiate antagonist treatment of pathological gambling (PG) has been established in three separate placebo-controlled studies (Kim et al. 2001; Grant et al. 2006; Grant et al. 2008). Opiate antagonists reduce urges associated with PG, reduce gambling behavior, and improve overall psychosocial functioning in individuals with PG (Kim et al. 2001; Grant et al. 2006; Grant et al. 2008). Nonetheless, 10% to 30% of PG patients treated with opiate antagonists do not demonstrate significant improvement (Kim et al. 2001; Grant et al. 2006; Grant et al. 2008). No studies have systematically examined predictors of medication treatment outcome in PG.

The rationale for the use of opiate antagonists in the treatment of PG stems from their effectiveness in treating other addictive disorders involving alcohol, heroin, and cocaine use (Martin et al. 1973; Kosten et al. 1989; Volpicelli et al. 1992; Anton et al. 1999). The efficacy of opiate antagonists in the treatment of addictive disorders, including PG, has been proposed to involve opioidergic modulation of mesolimbic dopamine circuitry. Behaviorally, opiate antagonist administration leads to diminished urges to engage in the addictive behavior and longer periods of abstinence (Mason et al. 1999; Kim et al. 2001), consistent with a mechanism of action involving ventral striatal dopamine systems (Broekkamp and Phillips 1979; Matthews and German 1984). Further work into defining which subtype of pathological gamblers will benefit most from opiate antagonists could enhance treatment strategies for PG and other impulse control disorders.

Alcohol dependence, a disorder with phenomenological and genetic links to PG (Blanco et al. 2001; Brewer and Potenza 2008; Slutske et al. 2000), responds favorably to opiate antagonists in many but not all studies (Anton et al. 2006; Krystal et al. 2001). Factors associated with a positive response to an opiate antagonist among alcohol dependent patients include strong alcohol cravings, a family history of alcoholism, and a euphoric response to alcohol (O'Brien 2005; Monterosso et al. 2001).

We sought to identify clinical variables associated with treatment outcome in PG subjects receiving opiate antagonists. We hypothesized that a family history of alcoholism and stronger urges to gamble would be associated with positive PG treatment outcome with opiate antagonists. We hypothesized that less severe PG would be associated with placebo response (Montgomery 1999).

Materials and Methods

Subjects

Data for this predictor analysis came from two separate double-blind placebo-controlled trials: a multi-center, 16-week study of nalmefene (n=207) (Grant et al. 2006) and a single-site, 18-week trial of naltrexone (n=77) (Grant et al. 2008). Both studies enrolled only individuals with DSM-IV PG, and subjects were randomly assigned to either placebo or medication in their respective study.

All subjects were required to score ≥5 on the South Oaks Gambling Screen (SOGS) (Lesieur and Blume 1987) and have gambled 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 for both studies included: 1) infrequent gambling (i.e. less than one time per week) that did not meet DSM-IV criteria for PG; 2) unstable medical illness or clinically significant abnormalities on laboratory tests, EKG, or physical examination at screening visit; 3) current pregnancy or lactation, or inadequate contraception in women of childbearing potential; 4) a need for medication other than nalmefene or naltrexone with possible psychotropic effects or medications with unfavorable interactions with nalmefene or naltrexone (e.g., narcotics); 5) lifetime history of bipolar disorder type I or II, dementia, schizophrenia, or any psychotic disorder; 6) current DSM-IV substance abuse or dependence with possible exception of nicotine dependence; 7) positive urine drug screen at screening; 8) initiation of psychotherapy or behavior therapy within 3 months prior to study baseline; 9) previous treatment with nalmefene or naltrexone; 10) clinically significant suicidality; and 11) 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.

After screening, subjects in the nalmefene study were randomly assigned in blocks of eight by using computer generated randomization (with no clinical information) to one of four conditions (1:1:1:1): placebo, or nalmefene doses of 25mg/day, 50mg/day, or 100mg/day. Similar randomization was performed in the naltrexone study with subjects assigned to one of four conditions: placebo or naltrexone doses of 50mg/day, 100mg/day, or 150mg/day. Of the total 284 subjects for the two studies, 214 subjects (75.4%) were assigned to active medication and 70 (24.6%) were assigned to placebo.

The nalmefene study was conducted at 15 outpatient psychiatric treatment centers in the United States from March 2002 through April 2003. Each treatment center's institutional review board approved the study and the informed consent. The naltrexone study was conducted at the University of Minnesota from September 2003 through June 2005. The institutional review board for the University of Minnesota approved the study and the informed consent. Potential risks of the study, as well as alternative treatments, were discussed with subjects. After complete description of each study, written informed consent was obtained. The studies were conducted in accordance with the Declaration of Helsinki.

Assessments

Psychiatric comorbidity was assessed using the Structured Clinical Interview for DSM-IV (First et al. 1995). A semi-structured, rater-administered questionnaire was used to collect clinical information on PG.

Investigators who were blind to subjects' group assignment administered outcomes measures at each visit. The primary outcome measure for both studies was the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS), a clinician-administered scale assessing gambling symptoms within the last seven days (Pallanti et al. 2005). The first five items of the PG-YBOCS comprise the gambling urge/thought subscale and the final five comprise the gambling behavior subscale.

Secondary measures included the *Sheehan Disability Scale (SDS)* (Sheehan 1983), a three-item self-report scale assessing psychosocial functioning; the *Hamilton Anxiety Rating Scale (HAM-A)* (Hamilton 1959), a clinician-administered scale that examines global

anxiety; and the *Hamilton Depression Rating Scale (HAM-D)* (Hamilton 1960), a 24-item, clinician-administered rating scale assessing severity of depression.

Family history assessment was performed using a semi-structured interview that asked PG probands about each first-degree relative's history of Axis I psychiatric disorders. Having at least one first-degree relative with alcoholism qualified as a positive family history.

Data Analyses

Treatment response was defined as a 35% or greater reduction in PG-YBOCS total score for at least one month by study endpoint. Treatment response using the PG-YBOCS weighed changes in urge/thoughts equally with behavior, and this definition of treatment response has been found to correlate with clinically significant changes in PG (Hollander et al. 2005). Subjects (n=214) receiving active medication were retained for predictor of response analysis, and 70 subjects assigned to placebo were analyzed for placebo response.

Individual variables were examined with univariate Cox regression models. Models were run separately by study as well as combined. Predictor analysis results did not differ between nalmefene and naltrexone. In addition, predictor analysis results did not differ based on dose of nalmefene or naltrexone (except gambling urges, see below), and therefore all doses were combined for analyses. A multivariate Cox model was then performed using backward stepping. The multivariate model was applied only to the pooled sample where those variables measured in both studies could be used. Study source was entered into this multivariate model. The nalmefene and naltrexone groups differed on several baseline variables (sex, race/ethnicity, education, baseline gambling severity, and psychosocial functioning), and these variables were entered into the multivariate model.

Separate Cox models were evaluated to explore the relationship between baseline PG-YBOCS urge and clinical response to higher doses (defined as the two highest doses of 3 active doses administered in each study) of opiate antagonists. An interaction term was included in models for each study separately as well as with both studies combined. All comparison tests were two-tailed. Because we performed multiple comparisons, we used an adjusted alpha level of $p<.01$; we did not adjust the alpha level to reflect all statistical comparisons because this is the first study of this topic and is therefore exploratory; in addition, the Bonferroni correction tends to be overly conservative (Rosner 1995).

Results

Subject Characteristics

284 subjects with DSM-IV PG were recruited. Demographics and clinical characteristics at baseline are presented (Table 1). The nalmefene and naltrexone groups differed on several baseline variables which were factored into the multivariate model. (Table 1). Demographics and baseline clinical characteristics, however, did not differ between those assigned to active medication and placebo.

The 284 subjects reported a mean age (±SD) at PG onset of 29.0 (± 11.4) years [range 13–59] with a lag time of 11.1 (± 11.5) years [range <1–40] from starting to gamble and meeting criteria for PG. Only 86 (30.3%) had ever attended Gamblers Anonymous, and only 54 (19.0%) had sought prior professional mental health treatment for gambling.

Of the 284 subjects, 137 (48.2%) played non-strategic games only (e.g., slots, bingo, lottery, pull tabs, and video poker), 44 (15.5%) played only strategic games (e.g., blackjack, poker), and 103 (36.3%) played both non-strategic and strategic games. Type of gambling activity was not associated with response to opioid antagonists.

Although subjects with current bipolar, psychotic and substance use disorders were excluded, the enrolled subjects reported clinically important current co-occurring disorders. Sixty-eight subjects (23.9%) met criteria for mood disorders (major depressive disorder [n=47], depressive disorder NOS [n=21]) 21 (7.4%) for anxiety disorders (social phobia [n=8], panic disorder [n=6], anxiety disorder NOS [n=7]), and 7 (2.5%) for eating disorders (binge eating disorder [n=6] and bulimia nervosa [n=1]). 118 subjects (41.5%) used tobacco daily. Neither co-occurring disorders nor tobacco use were associated with treatment response.

Response to Opiate Antagonists

Results of multivariate analyses provided similar results when the nalmefene and naltrexone studies when analyzed separately and when analyzed together. Therefore, data from the nalmefene and naltrexone groups were combined to obtain increased power, and the results presented are for all subjects assigned to opiate antagonist treatment (Table 2).

A family history of alcoholism demonstrated the most robust association with positive treatment response to opiate antagonists (HR=1.74, 95% CI =1.17 – 2.58, p=.006). No other variable was significant at $p<0.01$. Although baseline urges to gamble did not predict treatment response for the entire sample, when analyzed by medication dose, baseline urges were associated, on a trend level, with response to higher doses of opiate antagonists (i.e. nalmefene 50mg or 100mg or naltrexone 100mg or 150mg) 2 (parameter estimate = 1.77; SE= 0.84; Wald χ^2 =4.41; p= .036; HR= 5.86; HR 95% CI=1.12–30.6).

Response to Placebo

Variables associated with placebo response are presented in Table 3. The variable most robustly associated with placebo response was age (HR=0.70; HR 95% CI=0.52–0.92; p=. 012), but no variable was significant at $p<0.01$. Younger subjects were more likely to respond to placebo. For each age increase of 10 years, subjects were approximately 30% less likely to respond to placebo.

Discussion

Although multiple medications appear efficacious in treating PG (Dell'Osso et al. 2006), prior studies did not systematically investigate clinical factors associated with positive response. In this examination of two large, placebo-controlled studies of opiate antagonists, several important findings emerge. The associations of a positive family history of alcoholism and strong gambling urges with positive treatment response to opiate antagonists in PG is consistent with studies of these drugs in the treatment of alcohol dependence (e.g., high alcohol craving and family history of alcoholism associated with better outcomes) (O'Brien 2005; Monterosso et al. 2001; Krishnan-Sarin et al. 2007). Although many individuals with PG respond clinically to opiate antagonists, not everyone demonstrates a positive response (Grant et al. 2006; Grant et al. 2008). This differential treatment response may reflect individual biological differences such as those associated with opiate antagonist response in alcohol dependent subjects. A more complete understanding of biological factors associated with opiate antagonist treatment of PG might be attainable through neuroimaging and genetic data. Nonetheless, this study suggests that readily attainable clinical information can be used to guide pharmacotherapy selection for PG.

The finding of a positive family history influencing treatment response also suggests a genetic predisposition to response to opiate antagonists across diagnostic groups and a possible endophenotype. Amongst alcohol dependent individuals, a commonly occurring allelic variant of the mu-opioid receptor gene is associated with treatment response to

naltrexone (Oslin et al. 2003; Ray and Hutchison 2007). The extent to which this finding extends to PG subjects warrants direct investigation.

PG urge severity appeared to have some association with treatment response but only at the higher doses of the opiate antagonists. These findings are consistent with a separate study associating strong gambling urges at treatment onset with clinical response to high-dose opiate antagonists (Kim et al. 2001). The precise relationship between gambling urges and the mechanism of action of opiate antagonists in the treatment of PG requires further examination; e.g., in studies investigating neural correlates of gambling urges before and after opiate antagonist treatment.

Placebo response is important to understand, particularly as it is frequently observed in controlled trials of PG (Grant and Potenza 2007). Factors associated with opiate antagonist response were not associated with placebo response. Contrary to our hypothesis, a milder form of PG did not predict placebo response. This may have been due to the fact that the trials required at least moderately severe PG for study entry and therefore the range of PG severity was limited. In addition, because each trial had foru arms (three with medication), the studies had a relatively small number of subjects assigned to placebo. Larger studies with a broader range of PG severity are needed to further address the placebo response seen in this disorder (Grant and Potenza 2007). Young age at treatment onset was associated with placebo response on a trend level. Although no longitudinal studies have examined how long a placebo response may last in PG, prior medication studies suggest that a placebo response may subside over several months (Hollander et al. 2000). These findings suggest that younger individuals who appear to respond to open-label opiate antagonist treatment be followed closely in case they are placebo responders. In non-PG samples, placebo response involves dopamine release in the nucleus accumbens (Scott et al. 2007), and this mechanism is hypothesized to operate across diagnostic groups (de la Fuente-Fernández et al. 2006). The extent to which this mechanism pertains to placebo response in PG and to age-related changes in mesolimbic dopamine function (Chambers et al. 2003) requires direct investigation.

This study represents to our knowledge the first systematic examination of clinical measures associated with treatment outcome in PG, but there exist several limitations. First, PG is a chronic disease that may require long-term therapy. By design, these studies did not assess treatment effects beyond the acute 16 or 18 week periods. Factors associated with long-term outcome require further evaluation. Second, these studies enrolled subjects seeking pharmacological treatment and excluded those with certain mental health concerns. Given these exclusion criteria (e.g. no comorbidity with bipolar disorder or current substance use disorders), these results may not generalize to the larger population of people with PG.

The identification of readily measurable, clinical variables (family history of alcoholism and intensity of gambling urges at treatment onset) that are related to response to opiate antagonist treatment has important clinical and theoretical implications. Clinically, the information can be used to help identify patients who might respond best to treatment with opiate antagonists. As other medications (e.g., serotonin reuptake inhibitors, mood stabilizers) have shown promise in treating PG, future studies should investigate which specific clinical measures are associated with response to these treatments. From a theoretical perspective, the similarities between factors related to opiate antagonists in the treatments of PG and alcohol dependence lend further support to a close relationship between the disorders and the consideration of PG as a “behavioral” addiction.

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All procedures comply with the current laws of the United States of America.

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TABLE 1

Baseline Demographic and Clinical Characteristics of 284 Subjects with Pathological Gambling Treated with Opiate Antagonists

Variable	Total Sample (N=284)	Nalmefene Study (N=207)	Naltrexone Study (N=77)	Statistic
Subjects assigned to: n(%)				
Drug	214 (75.4)	156 (75.4)	58 (75.3)	X^2 =0.000; df=1;
Placebo	70 (24.6)	51 (24.6)	19 (24.7)	p=0.995
Age, mean (± SD) [range], yrs	45.9 (11.4) [19–72]	45.9 (11.4) [19–72]	47.8 (9.6) [21–66]	t-test=−1.301; df=282; p=0.195
Sex, n (%)				X^2 =6.932; df=1;
Female	137 (48.2)	90 (43.5)	47 (61.0)	p=0.009
Race/Ethnicity, n (%).				
Caucasian	235 (82.7)	165 (79.7)	70 (90.9)	X =9.15; df=2
African-American	29 (10.2)	28 (13.5)	1 (1.3)	p=0.010
Other	20 (7.1)	14 (6.8)	6 (7.8)	
Marital Status, n (%)				
Never married	64 (22.5)	48 (23.2)	16 (21.3)	X^2=0.20; df=2;
Married	117 (41.2)	85 (41.1)	32 (42.7)	p=0.903
Separated/Divorced/Widowed	103 (32.3)	74 (35.7)	29 (36.0)	
Education, n (%)				
High school graduate or less	103 (36.3)	73 (35.3)	30 (39.0)	X^2=13.66; df=2;
Some college	148 (52.1)	118 (57.0)	30 (39.0)	p=0.001
College graduate or post-graduate	33 (11.6)	16 (7.7)	17 (22.0)	
PG-YBOCS total, mean (± SD)	21.7 (5.1)	23.3 (5.1)	18.6 (4.9)	t-test= 6.977; df=282; p<.0001
Sheehan Disability Scale, mean (±SD)	14.4 (4.2)	14.7 (3.7)	13.4 (6.5)	t-test= 2.106; df=282 p=0.036

PG-YBOCS=Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling

TABLE 2

Relationship Between Demographic and Clinical Variables and Response to Opiate Antagonists in 214 Subjects with Pathological Gambling Who Received Active Medication

Baseline Variable	Parameter Estimate	SE	Wald χ^2	p-value	Hazard Ratio	HR 95%CI
Age	0.04	0.09	0.15	0.699	1.04	0.79 – 1.07
Gender	0.01	0.20	<0.01	0.952	1.01	0.75 – 1.48
Race/Ethnicity	0.01	0.27	<0.01	0.965	1.01	0.81 – 2.07
Marital Status	0.12	0.20	0.36	0.549	1.13	0.67 – 1.34
Education	0.42	0.25	2.79	0.094	1.52	0.85 – 1.95
PG-YBOCS total	−0.02	0.03	0.74	0.390	0.98	0.94 – 0.99
PG-YBOCS urges/thoughts	0.02	0.06	0.12	0.729	1.02	0.91 – 1.14
PG-YBOCS behavior	−0.04	0.03	1.73	0.189	0.96	0.91 – 1.01
Sheehan Disability Scale	−0.02	0.03	0.49	0.485	0.98	0.93 – 1.01
HAM-D	0.02	0.03	0.25	0.620	1.02	0.97 – 1.08
HAM-A	−0.01	0.03	<0.01	0.983	1.00	0.95 – 1.05
Positive family history of alcohol use disorders	**0.55**	**0.20**	**7.53**	**0.006**	**1.74**	**1.17 – 2.58**
Prior treatment for pathological gambling	−0.04	0.27	0.02	0.882	0.96	0.64 – 1.58

PG-YBOCS=Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling; HAM-D=Hamilton Depression Rating Scale; HAM-A=Hamilton Anxiety Rating Scale

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TABLE 3

Relationship Between Demographic and Clinical Variables and Treatment Response in 70 Subjects with Pathological Gambling Who Received Placebo

Baseline Variable	Parameter Estimate	SE	Wald χ^2	p-value	Hazard Ratio	HR 95% CI
Age	−0.36	0.14	6.29	0.012	0.70	0.52 – 0.92
Gender	−0.19	0.35	0.31	0.575	0.82	0.42 – 1.62
Race/Ethnicity	0.81	0.53	2.29	0.130	2.25	0.79 – 6.39
Marital Status	−0.19	0.36	0.26	0.608	0.83	0.41 – 1.69
Education	−0.41	0.34	1.42	0.233	0.66	0.34 – 1.30
PG-YBOCS total	−0.03	0.03	1.19	0.276	0.97	0.91 – 1.03
PG-YBOCS urges/thoughts	−0.03	0.06	0.37	0.545	0.97	0.87 –1.08
PG-YBOCS behavior	−0.08	0.06	1.90	0.168	0.93	0.83 –1.03
Sheehan Disability Scale	0.03	0.03	0.96	0.328	1.03	0.97 – 1.09
HAM-D	−0.01	0.04	0.01	0.985	1.00	0.93 – 1.09
HAM-A	0.01	0.04	0.03	0.854	1.01	0.93 – 1.08
Positive family history of alcohol use disorders	0.36	0.37	0.97	0.324	1.44	0.98 – 1.63
Prior treatment for pathological gambling	0.11	0.44	0.07	0.795	1.12	0.48–2.65

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