Naltrexone and Disulfiram Treatment Response in Veterans With Alcohol Dependence and Co-Occurring Problem-Gambling Features

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ABSTRACT

Background: Disordered gambling behavior frequently co-occurs with alcohol dependence and other psychiatric conditions. Using data from a previously published trial, we conducted secondary analyses to examine the influence of problem-gambling features on treatment outcome for alcohol dependence or co-occurring psychopathology assessed via *DSM-IV* criteria.

Methods: Two hundred fifty-four patients with alcohol dependence and co-occurring psychiatric disorders were treated for 12 weeks in an outpatient medication study conducted at 3 Veterans Administration outpatient clinics from October 1998 to March 2002. Randomization included assignment to 1 of 4 groups: (1) naltrexone alone, (2) placebo alone, (3) (open-label) disulfiram and (blinded) naltrexone, or (4) (open-label) disulfiram and (blinded) placebo. One hundred seventy-four participants were evaluated for the diagnostic inclusionary criteria for pathological gambling using the Massachusetts Gambling Screen. Primary outcome and secondary outcome measures assessed alcohol use and psychiatric domains.

Results: Forty-five of 174 participants (25.9%) exhibited problem-gambling features (acknowledged 1 or more inclusionary criteria for pathological gambling). A gambling-group–by-disulfiram interaction was observed for abstinence, with problem-gambling features not associated with beneficial response to disulfiram ($z=6.58$, $P=.01$). Participants with problem-gambling features reported significantly less improvement over time in general psychiatric functioning ($z=2.62$, $P=.01$), specifically within somatization ($z=3.77$, $P<.01$), phobic anxiety ($z=3.24$, $P<.01$), interpersonal sensitivity ($z=2.61$, $P=.01$), paranoid ideation ($z=2.32$, $P=.02$), and anxiety ($z=2.10$, $P=.04$) domains.

Conclusions: The association between problem-gambling features and poorer outcomes in alcohol and multiple nonsubstance psychiatric domains suggests the need for improved screening for gambling problems in dually diagnosed populations and for the development of empirically validated treatments for individuals with these disorders.

J Clin Psychiatry 2017;78(9):e1299–e1306
https://doi.org/10.4088/JCP.16m11220

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Pathological gambling is characterized by persistent and recurrent maladaptive patterns of gambling behavior, and estimated lifetime prevalence for US adults ranges from 0.4% to 1.6%, with population-based studies that use formal diagnostic criteria showing estimates at the lower end of this range[1–3] The diagnostic threshold for pathological gambling in the fourth edition of *The Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*) involves meeting 5 or more of 10 inclusionary criteria,[4] with *DSM-5* criteria utilizing a threshold of 4 or more of 9 inclusionary criteria for gambling disorder.[5] However, subsyndromal levels of pathological gambling may be experienced by up to 5% of the general population.[6] Subsyndromal pathological gambling, including levels of 1 or 2 inclusionary criteria of pathological gambling, has been associated with a broad range of co-occurring disorders[6,7] and other adverse health measures like low self-esteem, suicidality, and drug and alcohol use.[8–10] Despite associations between subsyndromal and syndromal pathological gambling and multiple psychiatric disorders, many treatment settings do not screen for pathological gambling, and research studies for nongambling psychiatric disorders do not include assessments of pathological gambling. As such, the potential influence of syndromal or subsyndromal pathological gambling on treatment outcome requires direct investigation.

Prior randomized clinical trials for alcohol dependence have often not assessed gambling behaviors to examine the possible influence of problem-gambling features on treatment outcome. Because some US Food and Drug Administration (FDA)–approved treatments for alcohol dependence (eg, opioid-receptor antagonists) have demonstrated effectiveness (albeit with some mixed results) in placebo-controlled trials of pathological gambling, there is some suggestion that particular treatments might be more effective in individuals with co-occurring problem-gambling features and alcohol dependence. For example, among individuals with pathological gambling, the presence of a

Clinical Points

- Few studies have investigated effects of problem-gambling features on alcohol treatment outcome in individuals with alcohol dependence and non–gambling-related co-occurring psychiatric disorders.
- One in 4 individuals with alcohol dependence exhibited problem-gambling features.
- Over the course of treatment, individuals with problem-gambling features showed less improvement in general psychiatric functioning, specifically within somatization, anxiety, paranoid-ideation, and interpersonal sensitivity domains, than those without such features.

family or personal history of alcoholism was associated with better pathological gambling treatment outcome in response to an opioid-receptor antagonist (either naltrexone or nalmefene).[11] Nalmefene has also demonstrated varying degrees of efficacy in the treatment of pathological gambling,[12,13] and naltrexone has been shown to reduce disadvantageous decision-making in a rodent gambling task,[14] providing further support for opioid antagonists in the treatment of pathological gambling. However, results from 1 randomized, double-blind, placebo-controlled trial of naltrexone for concurrent alcohol-use disorder and pathological gambling were not promising.[15]

We conducted a multicenter controlled trial of the efficacy of naltrexone and disulfiram alone and in combination in individuals with alcohol dependence and co-occurring psychopathology in a general mental health clinic (ie, nonresearch) setting.[16,17] The effectiveness of disulfiram for the treatment of pathological gambling remains unclear, since results have been mixed.[18,19] On the one hand, disulfiram has a proposed mechanism of action of inhibiting alcohol metabolism, suggesting a specificity for alcohol dependence. On the other hand, disulfiram may also inhibit dopamine β-hydroxylase, and this effect may account for its efficacy in drug addictions like cocaine dependence.[20] In a recent study of pathological gambling and comparison subjects, a functional allelic variant of the gene encoding dopamine β-hydroxylase was linked across diagnostic groups to subjective emotional responses and related corticostriatal-limbic brain activations.[21] These findings raise the possibility that disulfiram may be helpful in targeting specific emotional processing features in a transdiagnostic fashion.

Using data from an already published trial,[17] we investigated the influence of problem-gambling features on alcohol treatment outcome in individuals with alcohol dependence and non–gambling-related co-occurring psychiatric disorders. We hypothesized that (1) alcohol-dependent individuals would report high frequencies of problem-gambling features; (2) the presence of problem-gambling features would be associated with poorer alcohol treatment outcome; (3) naltrexone would result in greater effectiveness than disulfiram in alcohol-dependent individuals with co-occurring problem-gambling features; (4) the presence of problem-gambling features would be associated with poorer non–alcohol-dependence psychiatric outcomes generally; and (5) follow-up post hoc analyses would identify specific domains in which problem-gambling features would be associated with poorer non–alcohol-dependence psychiatric outcomes (eg, relating to affective processing, given co-occurrences between pathological gambling and affective disorders).

METHODS

Non–gambling-related findings involving the study sample have been described elsewhere.[17] The study was approved by the Human Subjects Subcommittee of the Veterans Administration (VA) Connecticut Healthcare System; the Northampton and Bedford, Massachusetts VA hospitals; and the Yale University Institutional Review Board. Each institution is affiliated with the New England Mental Illness Research, Education Clinical Center (MIRECC).

Participants

Men and women aged 18 years or older were recruited from patients treated in clinics at MIRECC facilities. Participants met current *DSM-IV* criteria for a major Axis I disorder and *DSM-IV* criteria for alcohol dependence based on the Structured Clinical Interview for *DSM-IV*.[22] Inclusion criteria required that all participants had been abstinent no more than 29 days, to ensure that the study included individuals with active alcohol dependence. Exclusion criteria included (1) unstable psychotic symptoms or serious current psychiatric symptoms, such as suicidal or homicidal ideation; (2) unstable medical illness or clinically significant abnormalities on laboratory tests (eg, liver function test results greater than 3 times normal values) or physical examination at screening visit; and (3) a need for medication with unfavorable interactions with naltrexone (eg, narcotics). Participants taking psychiatric medications had to be on a stable regimen (no medication changes) for at least 2 weeks prior to randomization. Participants were also required to be abstinent for 3 days prior to randomization. The stated goal of the study was complete abstinence.

Because participants were recruited from VA clinics, participants in the trial continued to receive psychiatric treatment as usual. All 3 VA clinics have intensive substance-abuse treatment programs that include intensive rehabilitation programs with aftercare and supported housing options. Most participants were already enrolled in the clinics before signing the informed consent, although a few responded to advertisements and entered treatment as a result of entering into the trial. After providing written informed consent, participants completed an intake assessment, which included psychiatric and physical examinations and laboratory assessments.

Procedures

Following completion of baseline assessments, 254 participants were randomized to 1 of 4 groups for a

Table 1. Baseline Demographic and Clinical Characteristics[a]

Variable	All Participants (N = 174) Mean (SD)	With PGF (n = 45) Mean (SD)	Without PGF (n = 129) Mean (SD)	PGF Group Differences t	P
Age, y	47.3 (8.7)	46.1 (9.8)	47.6 (8.2)	1.01	.31
Education, y	12.9 (1.9)	12.7(1.5)	13.0 (1.9)	0.79	.43
	Frequency (%)	Frequency (%)	Frequency (%)	χ^2	P
Male	171 (96.6)	44 (97.8)	125 (96.9)	0.09	.76
White	124 (70.1)	31 (68.9)	93 (72.1)	0.17	.68
Not married	139 (78.5)	35 (85.4)	104 (83.2)	0.11	.74
Employed full-time	101 (57.1)	34 (75.6)	67 (51.9)	**7.64**	**.01**
Current psychiatric diagnoses					
Major depressive disorder	117 (67.2)	30 (66.7)	87 (67.4)	0.01	.92
PTSD	73 (42.0)	18 (40.0)	55 (42.6)	0.10	.76
Bipolar I or II disorder	34 (19.5)	7 (15.6)	27 (20.9)	0.61	.43
Schizophrenia	9 (5.2)	4 (8.9)	5 (3.9)	1.71	.19
Anxiety disorder other than PTSD	35 (20.1)	7 (15.6)	28 (21.7)	0.79	.38
Cocaine use disorder	78 (44.8)	26 (57.8)	52 (40.3)	**4.11**	**.04**
Baseline psychiatric medication					
Any	143 (83.1)	38 (86.4)	105 (82.0)	0.43	.51
Antidepressant	127 (73.8)	34 (77.3)	93 (72.7)	0.36	.55
Anxiolytic	15 (8.7)	3 (6.8)	12 (9.4)	0.27	.60
Mood stabilizer	56 (2.5)	13 (29.6)	43 (33.6)	0.24	.62
Antipsychotic	37 (21.5)	9 (20.5)	28 (21.9)	0.04	.84
More than 1 type	71 (41.3)	17 (38.6)	54 (42.2)	0.17	.68
Baseline drinking measures	Mean (SD)	Mean (SD)	Mean (SD)	t	P
Years of alcohol use (lifetime) (n = 144)	26.7 (9.9)	27.5 (8.9)	26.4 (10.3)	−0.63	.53
Drinking days (out of 30) (n = 151)	16.1 (12.1)	16.5 (12.8)	15.9 (11.9)	−0.27	.79
Drinks per drinking day (n = 118)	18.9 (12.5)	18.6 (12.4)	19.0 (12.6)	0.14	.89
Percentage of heavy drinking days	13.0 (12.1)	12.8 (12.7)	13.1 (11.9)	0.17	.86
Alcohol Dependence Scale score	19.7 (8.4)	18.8 (9.0)	20.0 (8.3)	0.65	.52

[a]Bold denotes significant at $P < .05$.
Abbreviations: PGF = problem-gambling features, PTSD = posttraumatic stress disorder.

12-week trial: (1) open randomization to disulfiram 250 mg or no disulfiram and (2) randomization to naltrexone 50 mg or placebo in a double-blind fashion. This resulted in the following groups: (1) naltrexone alone, (2) placebo alone, (3) disulfiram and naltrexone, or (4) disulfiram and placebo. Details of the randomization have been previously described.[16,17] Medication adherence was monitored using the Microelective Events Monitoring System (MEMS) for each visit. Patients attended weekly medication check-ins with nursing staff who monitored compliance.

Assessments

Primary outcomes were measures of alcohol use. The Substance Abuse Calendar, based on the Timeline Follow-Back Interview,[23] was administered at each weekly visit. Craving was assessed weekly using the Obsessive Compulsive Drinking Scale (OCDS).[24]

One hundred seventy-four participants (administered at 2 of the 3 study sites) completed the Massachusetts Gambling Screen (MAGS).[25] The MAGS is a reliable and valid, self-report measure assessing *DSM-IV* criteria for pathological gambling.* If participants acknowledged 1 or more diagnostic criteria for pathological gambling during the past year, they were characterized as having problem-gambling features. Those acknowledging 5 or more criteria were characterized as having pathological gambling. The low frequency of pathological gambling necessitated the combination of at-risk and pathological groups, a strategy employed in prior gambling studies.[6,26–29] We have termed the combined group as *exhibiting problem-gambling features*. Psychiatric symptoms were assessed using the Brief Symptom Inventory (BSI)[30] administered by the research staff at baseline and every 2 weeks during treatment. Adverse effects and common adverse symptoms were evaluated by the research staff weekly using the Hopkins Symptom Checklist,[31] a self-report symptom inventory.

Data Analysis

Baseline demographic and substance-use variables, psychiatric diagnoses, psychiatric medications, and serum liver enzyme levels were compared between participants with and without problem-gambling features using χ^2 analyses for dichotomous and analysis of variance (ANOVA) for continuous variables. The primary outcome variables were percentage of heavy drinking days (defined as 5 or more standard drinks) and number of participants with total abstinence, calculated from the Substance Abuse Calendar data. Continuous primary and secondary variables (eg, BSI scores, serum levels, OCDS scores) were analyzed using random effects regression models[32,33] of a priori contrasts for

*The current study uses the term *pathological gambling* to refer to disordered gambling, since *pathological gambling* was used by *DSM-IV-TR*.[4]

Table 2. Alcohol Outcome Variables Grouped by Gambling Status[a]

Variable	With PGF (n = 45) Mean (SD)	Without PGF (n = 129) Mean (SD)	PGF Group Differences F	P				
Self-reported drinking								
% of heavy drinking days	2.9 (7.8)	3.6 (10.9)	0.17	.68				
	n (%)	n (%)	χ^2	P				
Participants with total abstinence	29 (64.4)	91 (70.5)	0.49	.48				
			Difference by PGF		Change Over Time		PGF by Time	
	Mean (SD)	Mean (SD)	z	P	z	P	z	P
Serum liver values, IU/L								
GGT (n = 165)								
Pre	57.0 (52.4)	72.0 (96.7)	0.36	.55	**6.73**	**<.01**	0.21	.89
Post	37.4 (43.0)	45.0 (73.6)						
SGOT (n = 174)								
Pre	30.6 (17.8)	33.3 (27.9)	0.05	.82	**4.77**	**<.01**	0.21	.89
Post	33.5 (40.4)	27.5 (21.1)						
SGPT (n = 173)								
Pre	37.4 (29.6)	33.4 (21.3)	0.00	.99	1.19	.31	1.07	.36
Post	37.7 (42.2)	28.6 (17.7)						
OCDS factor scores								
Obsessive score (n = 175)								
Pre	5.1 (3.6)	6.2 (4.2)	1.03	.31	**18.87**	**<.01**	1.08	.37
Post	2.4 (3.2)	2.6 (3.3)						
Compulsive score (n = 175)								
Pre	6.3 (4.0)	6.7 (5.1)	0.74	.39	**28.87**	**<.01**	0.76	.69
Post	2.3 (3.3)	2.6 (3.8)						
Total score (n = 175)								
Pre	11.4 (6.5)	12.9 (8.8)	0.93	.34	**29.50**	**<.01**	0.95	.49
Post	4.7 (6.2)	5.2 (6.8)						

[a]Bold denotes significant at $P < .05$.
Abbreviations: GGT = γ-glutamyl transferase, OCDS = Obsessive Compulsive Drinking Scale, PGF = problem-gambling features, SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamic pyruvic transaminase.

174 veterans who had completed the MAGS. The primary contrasts were (1) the combination of disulfiram/naltrexone versus either disulfiram or naltrexone alone; (2) disulfiram alone versus naltrexone alone; and (3) any medication versus placebo. ANOVA models were used for continuous outcomes not evaluated longitudinally (eg, consecutive days of abstinence).

RESULTS

Subject Characteristics

Demographic and baseline characteristics of the 174 veterans who were assessed for gambling behavior are presented (Table 1). Of the 174 participants, 11 (6.3%) met *DSM-IV* criteria for past-year pathological gambling while an additional 34 (19.5%) exhibited 1 to 4 criteria for pathological gambling. Forty-five participants (25.9%) were therefore classified as exhibiting problem-gambling features.

Although there were no significant differences between those with and without problem-gambling features on most demographic and psychiatric variables (Table 1), veterans with problem-gambling features were more likely to be employed full-time (75.6% vs 59.1%) ($\chi^2 = 7.64$, $P = .01$) and to have a current cocaine-use disorder (57.8% compared to 40.3%) ($\chi^2 = 4.11$, $P = .04$), compared to veterans without problem-gambling features.

Alcohol Use and Craving Outcomes by Gambling and Medication Status

Overall, there were no significant differences between those with and without problem-gambling features in percentage of heavy drinking days and the number of participants with total abstinence between groups (Table 2). No significant gambling-group–by–time interaction was noted for liver enzymes or alcohol cravings measures (ie, OCDS factor scores) (Table 2). Medication compliance did not differ between those with and without problem-gambling features.

There were significant interactions between problem-gambling features and medication condition (Table 3). The presence of problem-gambling features in those participants taking disulfiram was associated with a lower percentage of participants who achieved total abstinence from alcohol ($z = 6.58$, $P = .01$). As Table 3 shows, there were no significant gambling-group–by–medication-group interactions observed for naltrexone.

Measures of Non–Alcohol-Dependence Psychiatric Symptoms

A significant gambling-group–by-time interaction was observed for the overall BSI score ($z = 2.62$, $P = .01$), with problem-gambling features associated with poor psychiatric symptom improvement. In post hoc analyses, participants with problem-gambling features reported poorer outcome

Table 3. Outcome Variables in Treatment Groups

Variable	With PGF n (%)	Without PGF n (%)	Statistic χ^2	*P*
Condition				
Disulfiram/naltrexone (n = 44)	11 (25.0)	33 (75.0)	0.58	.90
Disulfiram/placebo (n = 42)	10 (23.8)	32 (76.2)		
Naltrexone (n = 43)	13 (30.2)	30 (69.8)		
Placebo (n = 45)	11 (24.4)	34 (75.6)		
	Mean (SD)	Mean (SD)	*F*	*P*
% Days medication compliance				
Disulfiram (n = 86)	74.9 (28.4)	78.7 (28.1)	0.53	.59
Naltrexone (n = 90)	81.7 (24.8)	81.5 (28.0)	−0.04	.97
Placebo (n = 83)	85.0 (22.2)	79.2 (28.7)	−0.82	.41

Naltrexone treatment	With Naltrexone				Without Naltrexone				2 × 2 ANOVA					
	With PGF (n = 24)	Without PGF (n = 63)	Naltrexone Groups Only		With PGF (n = 21)	Without PGF (n = 66)	No Naltrexone Groups		Naltrexone		PGF		PGF × Naltrexone	
	Mean (SD)	Mean (SD)	*t*	*P*	Mean (SD)	Mean (SD)	*t*	*P*	*F*	*P*	*F*	*P*	*F*, *P*	
% Heavy drinking days	4.3% (9.6)	3.6% (11.0)	−0.28	.78	1.3% (5.0)	3.6% (10.9)	1.38	.17	0.65	.42	0.22	.64	0.75, .39	
	n (%)	n (%)	χ^2	*P*	n (%)	n (%)	χ^2	*P*			*z*	*P*	*z*	*P*
Participants with total abstinence	14 (11.7)	43 (35.8)	0.76	.38	15 (12.5)	48 (40.0)	0.01	.91	1.14	.29	0.44	.51	0.24	.62

Disulfiram treatment	With Disulfiram				Without Disulfiram				2 × 2 ANOVA					
	With PGF (n = 24)	Without PGF (n = 63)	Disulfiram Groups Only		With PGF (n = 24)	Without PGF (n = 64)	No Disulfiram Groups Only		Disulfiram		Difference by PGF		PGF × Disulfiram	
	Mean (SD)	Mean (SD)	*t*	*P*	Mean (SD)	Mean (SD)	*t*	*P*	*F*	*P*	*F*	*P*	*F*	*P*
% Heavy drinking days	4.4% (10.2)	2.0% (7.2)	−1.19	.24	1.5% (4.7)	5.2% (13.5)	1.88	.06	0.01	.93	0.13	.72	2.98	.09
	n (%)	n (%)	*z*	*P*	n (%)	n (%)	*z*	*P*			*z*	*P*	*z*	*P*
Participants with total abstinence (n = 120)	11 (9.2)	52 (43.3)	**6.11**	**.01**	18 (15.0)	39 (32.5)	1.51	.22	0.01	.94	3.25	.07	**6.58**	**.01**

Abbreviations: ANOVA = analysis of variance, PGF = problem-gambling features.

with respect to multiple subscale scores on the BSI: anxiety ($z = 2.10$, $P = .04$), phobic anxiety ($z = 3.24$, $P < .01$), somatization ($z = 3.77$, $P < .01$), paranoid ideation ($z = 2.32$; $P = .02$), and interpersonal sensitivity ($z = 2.61$, $P = .01$) (Table 4).

DISCUSSION

This randomized, double-blind study is to our knowledge the first to examine systematically the influence of problem-gambling features on alcohol and psychiatric treatment outcomes in individuals with alcohol dependence and nongambling co-occurring Axis I disorders. The multiple strengths of the study, including the large sample size and multiple valid and reliable self-report and biological measures obtained, allow for examination of the interactive influences of problem-gambling features with medication effects in alcohol dependence. In contrast to prior alcohol treatment studies of naltrexone or disulfiram,[34–38] this study allowed for an assessment of problem-gambling features and had the power to identify between-group differences related to alcohol treatment outcome.

Hypothesis 1 (alcohol-dependent individuals will have high rates of problem-gambling features)

In this study, we determined the frequency of problem-gambling features in 174 treatment-seeking individuals with current *DSM-IV* alcohol dependence. Consistent with our first hypothesis, one-quarter (25.9%) of alcohol-dependent participants in this study reported past-year problem-gambling features. This finding is approximately 10 times that of problem-gambling features found in the general population (2.7%)[6] and consistent with frequencies found previously among individuals with alcohol dependence.[39–42]

Hypothesis 2 (problem-gambling features will be associated with poorer alcohol treatment outcome)

We found no significant differences between those with and without problem-gambling features for alcohol-dependence treatment outcomes. These findings suggest that alcohol outcome may be distinct from problem-gambling features, at least in the group of veterans with co-occurring alcohol dependence and psychopathology who participated in the current trial.

Hypothesis 3 (naltrexone will be more effective than disulfiram in alcohol-dependent individuals with problem-gambling features)

Although there were no significant gambling-group–by–medication-group interactions observed for naltrexone, problem-gambling features in those participants taking disulfiram were associated with a significantly lower percentage of participants who achieved total abstinence from alcohol. One explanation for this finding is that

Table 4. Psychiatric Outcome Measures Based on Gambling Status[a]

Brief Symptom Inventory Score	With PGF Mean (SD)	Without PGF Mean (SD)	Change Over Time *z*	Change Over Time *P*	Differences by Gambling At-Risk Level *z*	Differences by Gambling At-Risk Level *P*	Gambling At-Risk Level by Time *z*	Gambling At-Risk Level by Time *P*
Global Severity Index								
Pre	0.98 (0.70)	0.98 (0.63)	**14.79**	**<.01**	−1.02	.31	**2.62**	**.01**
Post	0.55 (0.61)	0.52 (0.57)						
Depression								
Pre	1.43 (0.97)	1.33 (0.87)	**−15.08**	**<.01**	−0.53	.60	0.41	.68
Post	0.63 (0.82)	0.71 (0.82)						
Anxiety								
Pre	0.86 (0.70)	0.90 (0.73)	**−11.96**	**<.01**	−0.70	.48	**2.10**	**.04**
Post	0.51 (0.57)	0.43 (0.55)						
Phobic anxiety								
Pre	0.64 (0.82)	0.72 (0.77)	**−8.17**	**<.01**	−1.41	.16	**3.24**	**<.01**
Post	0.45 (0.66)	0.39 (0.63)						
Obsessive compulsive								
Pre	1.12 (0.90)	1.13 (0.80)	**−12.71**	**<.01**	−0.37	.71	1.12	.26
Post	0.67 (0.81)	0.63 (0.74)						
Somatization								
Pre	0.47 (0.53)	0.58 (0.56)	**−6.56**	**<.01**	**−2.25**	**.02**	**3.77**	**<.01**
Post	0.36 (0.48)	0.31 (0.42)						
Paranoid ideation								
Pre	0.85 (0.71)	0.91 (0.78)	**−8.19**	**<.01**	−0.24	.81	**2.32**	**.02**
Post	0.66 (0.90)	0.55 (0.71)						
Psychoticism								
Pre	0.85 (0.71)	0.77 (0.59)	**−15.36**	**<.01**	−0.11	.91	−0.27	.79
Post	0.35 (0.44)	0.40 (0.53)						
Hostility								
Pre	0.71 (0.83)	0.59 (0.60)	**−9.43**	**<.01**	0.28	.78	1.22	.22
Post	0.30 (0.45)	0.26 (0.49)						
Interpersonal sensitivity								
Pre	0.90 (0.91)	1.03 (0.88)	**−9.72**	**<.01**	−1.51	.13	**2.61**	**.01**
Post	0.55 (0.76)	0.55 (0.86)						

[a]Bold denotes significant at $P < .05$.
Abbreviation: PGF = problem-gambling features.

problem-gambling features may worsen alcohol-treatment outcome and that only naltrexone, not disulfiram, may be able to counteract such influences by reducing the symptoms of both problem gambling[43,44] and alcohol dependence.[45,46] However, this interpretation remains speculative, as does the mechanism by which such an effect may operate.

Hypotheses 4 and 5 (problem-gambling features will be associated with poorer non–alcohol psychiatric outcomes generally and in specific domains)

Consistent with these hypotheses, this study found that the presence of problem-gambling features was associated with poorer non–alcohol-dependence psychiatric outcomes generally with less of a reduction in the Global Severity Index associated with the presence of problem-gambling features ($z = 2.62$, $P < .01$). A follow-up analysis indicated that the presence of problem-gambling features was associated with less improvement in the majority of psychiatric symptoms assessed, including in some but not all affective domains (specifically in domains related to anxiety but not depression). One possible explanation for this finding is that both at-risk/problem gambling and alcohol dependence may be independently associated with certain psychiatric symptoms (eg, anxiety). This finding is consistent with data from other studies indicating that both syndromal and subsyndromal levels of problematic gambling are associated with a broad range of psychopathology.[7] However, this explanation would not apply to depression in the current study, and the findings suggest that problem-gambling features may exert differential effects on depression and anxiety outcomes in this population. Although treatment of alcohol dependence resulted in an overall reduction of these symptoms for the entire group, the presence of problem-gambling features in a subset of alcohol-dependent participants appeared to continue to exert a maintaining influence on psychiatric symptoms overall and in specific domains, with the greatest impacts statistically appearing to relate to somatization ($z = 3.77$, $P < .01$) and phobic anxiety ($z = 3.24$, $P < .01$). The former relationship suggests that co-occurring somatic concerns warrant consideration in relationship to problem-gambling features and co-occurring alcohol dependence and psychiatric disorders, further indicating that co-occurring medical concerns that are associated with problem-gambling features be considered for their potential impact on treatment outcome. As medical conditions and related aspects like pain interference have been associated with problem-gambling features in cross-sectional or longitudinal studies,[47,48] additional research is needed to identify specific aspects of somatization that are linked to treatment outcome. While other statistically significant findings appear to resonate with the extant literature (eg, less of a decrease in paranoid ideation seen in

association with problem-gambling features resonates with findings of frequent pathological gambling and problem-gambling features in association with psychotic disorders[49]), the findings relating to somatization and phobic anxiety were the most robust statistically. Additional research is needed to clarify the relative influence of co-occurring disorders on psychiatric symptoms and develop more effective treatment strategies for individuals with alcohol dependence, co-occurring psychiatric disorders, and problem-gambling features.[50]

Strengths and Limitations

Strengths of this study include its large sample size and comprehensive assessment battery, including diagnostic, self-report, and biological assessments, to examine changes in behavior associated with medication changes in a "real world" clinical setting comprised of a psychiatric population with multiple co-occurring disorders. Several methodological limitations, however, deserve mention. First, this study was based on a predominately male veteran sample and the results may not generalize to other clinical settings. Second, problem-gambling features were assessed using only a self-report measure and with no corroboration from third parties. Therefore, the frequency of problem-gambling features found in this study may represent an underestimation or an overestimation. Additionally, the problem-gambling features group included a range of problem-gambling severity, and future studies with larger samples should examine syndromal gambling disorder versus those with subsyndromal problem-gambling features. Third, no measures of problem-gambling severity over time were obtained. Although we are able to examine influences of problem-gambling features on alcohol and other psychiatric outcomes, we cannot assess effects of naltrexone or disulfiram on problem-gambling outcomes in the sample. This inquiry is important given the previous research that has found naltrexone to be effective in several studies of individuals with pathological gambling without current substance-use disorders.[43,44] The current findings should be interpreted in light of their limitations. For example, the study used self-report data when assessing problem-gambling features and changes in psychopathology. Self-report data are reliant on honest self-disclosure of symptoms and may be vulnerable to response bias. Furthermore, additional measures of gambling behaviors would have been helpful. However, in order to minimize subject burden, the MAGS was used as the sole assessment of gambling behaviors. Another limitation of the current study was that we did not reduce the α for statistical significance using a Bonferroni correction as this approach has been reported to be overly conservative in this type of exploratory study.[33] As such, some of the differences significant at a threshold just below $P < .05$ (eg, those in Table 1) should be considered particularly cautiously.

CONCLUSIONS

In spite of these limitations, this study has both methodological and clinical importance. This is one of the first studies of which we are aware to systematically evaluate the influence of subsyndromal and pathological gambling on alcohol and psychiatric treatment outcomes. The poorer outcomes for the group with problem-gambling features suggest a need to understand better the nature of these relationships and enhance screening and prevention efforts related to all levels of problem-gambling features in individuals with alcohol dependence and co-occurring psychopathology. Clinicians who screen for problem-gambling features should be aware of treatment and counseling services, and prevention efforts targeting the public health concerns of alcohol consumption should include recognition of the co-occurrence with problem-gambling features.

Submitted: September 14, 2016; accepted March 8, 2017.

Potential conflicts of interest: None of the authors have any conflict of interest to report with respect to the content of the manuscript. **Dr Grant** has received research grants from the National Center for Responsible Gaming, Trichotillomania Learning Center, American Foundation for Suicide Prevention, NIDA, Forest, Psyadon, Takeda, and Brainsway; receives yearly compensation from Springer Publishing for acting as Editor-in-Chief of the *Journal of Gambling Studies*; and has received royalties from Oxford University Press, American Psychiatric Publishing, Norton Press, Johns Hopkins Press, and McGraw Hill. **Dr Potenza** has received financial support or compensation for the following: has consulted for Ironwood, Lundbeck, Shire, INSYS, RiverMend Health, Opiant/Lakelight Therapeutics, and Jazz; has received research support from Mohegan Sun Casino, the National Center for Responsible Gaming, and Pfizer; has participated in surveys, mailings, or telephone consultations related to drug addiction, impulse control disorders, or other health topics; has consulted for law offices and gambling entities on issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; has given academic lectures in grand rounds, CME events, and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. **Dr Petrakis** has consulted for Alkermes.

Funding/support: This research was supported by the VA New England VISN I Mental Illness Research, Education and Clinical Center (MIRECC); NIH grants RL1 AA017539 and RC1 DA028279; Center of Excellence in Gambling Research Awards (to Yale University and the Universities of Minnesota and Chicago) from the National Center for Responsible Gaming; and the National Center on Addiction and Substance Abuse (CASAColumbia).

Role of the sponsor: The sponsors had no role in the study design, study execution, data analysis, or manuscript preparation.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of any of the funding agencies including the Department of Veterans Affairs or the United States government.

Acknowledgments: We acknowledge a mentorship role of Bruce Rounsaville, MD, and participation in the main clinical trial by the VA New England VISN I MIRECC Study Group: Nitigna Desai, MD, at Bedford VAMC and Boston University School of Medicine; Kathleen Carroll, PhD, Yale University School of Medicine; Charla Nich, MS, Yale University School of Medicine; Charles E. Drebing, PhD, at Bedford VAMC and Boston University School of Medicine; Marylee Losardo, MSPA, at Bedford VAMC; Barbara E. Rofman, RN, MS, at Bedford VAMC; Wayne Costello (deceased), MEd, LMHC, at Northhampton VAMC; Christopher Cryan, BA, at Northhampton VAMC; Lynn Gordon, RN, MPA, LADC, at Northhampton VAMC; Arturo Monteiro, MD, at Northhampton VAMC; John Reino, CAGS, MA, LMHC, at Northhampton VAMC; Rachel Alpert at VA CT Healthcare and Yale University School of Medicine; Paul H. Desan, MD, PhD, at VA CT Healthcare and Yale University School of Medicine; Kathryn Keegan, RNC, at VA CT Healthcare; Diana Limoncelli, BA, at VA CT Healthcare and Yale University School of Medicine; Colette McHugh-Strong, JD, at VA CT Healthcare; Alison Oville, BA, at VA CT Healthcare; Christine Sicignano, BA, at VA CT Healthcare; and Louis Trevisan, MD, at VA CT Healthcare and Yale University School of Medicine.

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