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Gender Differences in Predictors of Treatment Attrition with High Dose Naltrexone in Cocaine and Alcohol Dependence

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Abstract

Recently, we reported that naltrexone at 150mg/day significantly decreased cocaine and alcohol use for men, but not women with co-occurring cocaine and alcohol dependence. The present study is an exploratory investigation of predictors that explain the different gender response to naltrexone, with a particular focus on differential predictors of treatment attrition. No significant predictors were associated with treatment discontinuation in men. Women, however, were more likely to discontinue treatment when reporting severe pre-treatment psychiatric problems, or nausea while in treatment. Further research on the impact of pre-treatment and in-treatment gender differences with naltrexone is warranted.

Keywords

Naltrexone; cocaine dependence; alcohol dependence; adverse events; nausea; treatment attrition

Introduction

Naltrexone, an opioid antagonist, is a FDA-approved medication for alcohol dependence.¹ It has been shown to be efficacious, but good adherence is necessary for successful outcomes.^{2–5} For example, naltrexone treatment is significantly advantageous over placebo, only when alcohol dependent patients maintain high medication adherence.^{6, 7} In recent investigations, patients' reports of nausea during naltrexone treatment predicted poor medication adherence^{8–10} and treatment discontinuation.¹¹ Nausea is one of the most common adverse events reported in naltrexone treatment,^{11, 12} and O'Malley et al⁸ previously reported there may be gender differences in the experience of this side effect, possibly due to increased sensitivity of the opioid pathways in women compared to men.⁸ Thus, patients' experience of naltrexone-associated nausea may limit its effectiveness, via poor medication adherence, and this finding may be seen more frequently in women than in men.

In a large randomized, double-blind, placebo-controlled investigation of high-dose naltrexone (150mg) in cocaine and alcohol dependent (CAD) patients, Pettinati et al.¹³ reported that men in naltrexone treatment (vs., placebo) reduced their cocaine and alcohol use, whereas women taking naltrexone had poorer outcomes than the women taking placebo. In addition, there

appeared to be an intriguing but non-significant difference in treatment attrition rates between the two subgroups of naltrexone-treated men and women (27.6% vs. 45.8%, respectively), but not in placebo subgroups. Given the trends of women discontinuing treatment at a higher rate than men in naltrexone condition and more frequent reports of nausea in female (vs. male) patients, Pettinati et al.¹³ suggested that a high daily dose of naltrexone (150 mg/day) might be problematic for women. In contrast, one preclinical study reported that a 100 mg/day dosage of naltrexone was safe and well-tolerated in both men and women.¹⁴ Two previous studies reported gender differences in outcome among alcohol dependent samples,^{11, 15} but did not explore whether the outcome differences between men and women were medication-related.

Despite the promising results of the large clinical trial of high-dose naltrexone treatment for CAD men, the gender disparity in response to high-dose naltrexone raises important clinical issues, such as potential gender differences in naltrexone-associated adverse events and treatment non-adherence. The present exploratory study is a secondary analysis evaluating whether there are gender-specific differences in predictors of treatment attrition between CAD men and women who received a high-dose of naltrexone versus placebo, with one of two types of psychosocial therapies. Variables affecting differential outcome or attrition for men and women, including experience of nausea,^{8, 13} substance use,¹⁶ and severity of psychiatric problems^{17–20} were considered. We chose six variables to predict treatment attrition for men and women. They included: 1) randomized medication treatment condition (high-dose naltrexone or placebo); 2) randomized psychosocial treatment condition [cognitive behavioral therapy (CBT) or a medical management treatment model (BRENDA)²¹]; 3) psychiatric severity prior to treatment, as women present with more severe psychiatric problems than men prior to substance use treatment, leading to treatment attrition^{17–20}; 4) experience of nausea, which is the most common adverse effect associated with the standard dose and high-dosage naltrexone, and a more frequently reported adverse event in women than men in naltrexone treatment^{8, 13}; 5) alcohol use during treatment; and 6) cocaine use during treatment.

Methods

Participants

Participants were cocaine dependent and alcohol dependent (DSM-IV) patients between the ages of 18 and 65 who were seeking treatment at a university-affiliated outpatient, substance addiction treatment research facility in Philadelphia, PA. Detailed descriptions of the participants have been reported elsewhere.¹³

Of the 229 patients who were administered medical and psychosocial evaluations, laboratory tests, and Structured Clinical Interview for DSM-IV,²² 164 patients (116 men and 48 women) were eligible for the study (i.e., met all of the inclusion criteria and did not meet any exclusion criteria), provided written consent, and were randomized. This study was approved by the University of Pennsylvania Institutional Review Board.

Measures

Self-reported Substance Use—Time-line Follow-Back (TLFB)²³ techniques were used to gather self-reports of detailed daily alcohol and cocaine use at the weekly treatment visits. In studies with alcohol and drug dependent populations, there has been good agreement between TLFB data and collateral and biological data.^{24–26} The primary outcome TLFB measures were the frequencies of alcohol and cocaine use. TLFB was administered by a trained research technician at baseline assessment and at each weekly visit throughout the trial.

Psychiatric Severity—The psychiatric severity composite score of the Addiction Severity Index 5 (ASI-5)²⁷ was used to obtain the severity of psychiatric problems. ASI-5 has

demonstrated moderate to excellent internal consistency, test, retest, and inter-rater reliabilities in different groups of substance abusers.^{28, 29} A trained research technician at the baseline assessment administered the ASI-5.

Report of Nausea—A research physician met with patients weekly and gathered information about adverse events. Subjects were asked to report any new symptoms, the number of days experiencing the symptoms, and the severity of symptoms ranging from “very mild” to “very severe.” The research physician also recorded any medical decisions or resolutions taken by the physician.

Treatment Attrition—Treatment attrition was defined as discontinuing medication treatment, either high-dose naltrexone or placebo, for three or more consecutive weeks over the planned treatment course. Medication discontinuation was monitored by weekly pill counts (i.e., blister packs).

Procedures

This was a randomized, placebo-controlled, double-blind factorial (2×2) 12-week trial of naltrexone/placebo and psychosocial treatments for CAD. Participants were randomly assigned to one of the following four treatment conditions: naltrexone-CBT (33 males, 11 females); naltrexone-BRENDAs (25 males, 13 females); placebo-CBT (26 males, 11 females); or placebo-BRENDAs (32 males, 13 females). Participants assigned to the placebo condition were prescribed placebo pill(s) of identical appearance in identical packaging. During the trial, participants were scheduled to meet weekly with a research physician for medications, and either a BRENDA or CBT clinician for the psychosocial intervention. Research Technicians met with the participants weekly to obtain various study-related measures. Detailed descriptions of the procedures have been reported elsewhere.¹³

Manually-guided CBT, an individual psychotherapy treatment based on the relapse prevention model of Marlatt and Gordon³⁰ and adapted by Carroll³¹ for treatment of CAD, was conducted by CBT-trained, experienced, masters- or doctoral-level therapists in 45-minute weekly sessions for the duration of the 12-week treatment trial. BRENDA is a primary care based, manualized psychosocial intervention to enhance treatment adherence and motivation to achieve health.^{21, 32} Participants assigned to the BRENDA condition attended weekly 30-minute individual meetings with a BRENDA-trained and experienced nurse practitioner during the 12-week treatment period.

Data Analyses

All randomized participants were included in the data analysis, regardless of whether the subject discontinued treatment. Subjects were not dropped from any study activity, unless they specifically requested that they not be contacted. The frequency of nausea was obtained by dividing the number of reports of nausea (i.e., severity ranging from mild to very severe) by the number of meetings held between the subject and the research physician. Students' t-tests and chi-square analyses were conducted to examine the gender differences within the continuous variables (e.g., psychiatric severity, frequency of nausea reporting, alcohol and cocaine use) and categorical variables (e.g., type of randomized treatments and treatment attrition), respectively.

We performed two separate logistic regression analyses, for men and women, to predict treatment attrition, using six predictor variables: 1) medication treatment (high-dose naltrexone or placebo); 2) psychosocial treatment (CBT or BRENDA); 3) psychiatric severity at baseline; 4) frequency of nausea reporting during the treatment; 5) frequency of cocaine use during the treatment; and 6) frequency of alcohol use during the treatment. Missing data for alcohol and

cocaine use were imputed as drug use (“positive”); that is a standard practice in clinical trials.³³ Although the purpose of the current study is to examine the interaction between gender and covariate variables in a model predicting the treatment attrition, our analyses will be limited to two separate gender analyses due to an unbalanced and small sample. Because the current study is exploratory, a backward stepwise selection based on likelihood ratio (LR) statistics were used to fit the model, using an alpha entry criterion of .05 and an alpha deletion criterion of .10. All analyses were conducted using the SPSS 12.0 software package.

Results

Gender differences on selected pre-treatment and in-treatment variables

Demographic pre-treatment and in-treatment data have been previously described in more detail elsewhere.¹³ Of relevance to the present study, men and women overall did not differ in their age, proportion of days of cocaine and alcohol use in treatment, and treatment attrition rates.

Women did significantly report nausea more frequently ($t=2.17$, $df=152$, $p=0.02$) and higher psychiatric severity ($t=2.13$, $df=154$, $p=0.04$) than men (Table 1). However, within the medication groups, different patterns emerged between men and women on outcome-related variables, in particular, treatment attrition.

Predictors of Treatment Attrition

Results of logistic regression of treatment attrition for men and women with the six main predictors (i.e., medication treatment, psychosocial therapies, psychiatric severity, nausea reporting, cocaine use and alcohol use) are presented in Table 2. The final models for men and women from the backward stepwise elimination analyses are presented in Table 3.

In a model containing all six predictors for women, the overall likelihood ratio (G statistic) was 46.41 (d.f.=6) and $X^2(6) = 11.30$ ($p=0.08$) (Table 3). Backward elimination began with a full model containing all variables, and the final model for women included psychiatric severity and frequency of nausea ($X^2 = 8.18$, $p=0.02$) (Table 4). The estimated odd ratios (OR) and 95% CI were calculated for both variables. Women with higher psychiatric severity (OR = 23.89, 95% CI=1.04 to 547.27, $p= 0.05$) and higher frequency of nausea (OR = 43.45, 95% CI = 1.01 to 1864.43, $p= 0.05$) were more likely to dropout from the treatment.

For men, the overall likelihood ratio (G statistic) for a model containing the six variables was 123.36 (d.f.=6) and $X^2(6) = 13.18$ ($p=0.04$) (Table 3). In a backward stepwise elimination analysis, the final model contained both medication group and psychosocial therapy group as the significant factors predicting the treatment attrition (130.16, d.f. = 6; $X^2(6) = 6.38$, $p=0.04$). The results suggest that the men who were assigned to placebo condition (OR = 0.47, 95% CI=0.21 to 1.08, $p= 0.08$) and the men who were assigned to BRENDA condition (OR = .50, 95% CI=0.22 to 1.14, $p= 0.10$) were more likely to dropout from the treatment than those who were assigned to either naltrexone or CBT, respectively (Table 4).

Discussion

Previously, Pettinati et al.¹³ found that CAD women and men had different treatment outcomes with high-dose naltrexone treatment, in which CAD men reduced their cocaine and alcohol use whereas women did not. In the present exploratory study, we attempted to investigate potential explanations for the gender differences in outcome, focusing on treatment attrition.

Our findings indicate that women generally reported nausea more frequently than men. While the overall attrition differences between men and women were not statistically significant, the

differential rates of attrition between the subgroup of naltrexone-treated men and women approached significance. In attempting to predict treatment attrition, we found that men receiving placebo treatment and BRENDA were more likely to discontinue treatment. However, women reporting higher psychiatric problem severity and more frequent bouts with nausea in treatment were more likely to dropout from treatment.

In our study, high psychiatric severity was a predictor for CAD women discontinuing the treatment. Women obtained significantly higher psychiatric severity scores than men at baseline. Sixty-three percent of women and 46% of men reported high psychiatric symptoms prior to entering the treatment. If psychiatric severity, as demonstrated in our analysis, is making a significant impact on treatment attrition (and, subsequently, on their substance use), female patients with pre-treatment psychiatric symptoms may require symptom management (e.g., pharmacotherapy or psychotherapy) at the onset of substance use treatment. This would be an important clinical issue, given the high prevalence co-occurring substance use and mental disorders.^{34, 35}

In general, the research findings on attrition rates between male and female substance abusers in various treatment settings are mixed.^{18, 19, 36, 37} In a recent injectable naltrexone trial using various doses, nausea was the only adverse event (AE) that occurred differentially for women and men in 10% or more patients, and the rate of nausea was significantly higher for women at a higher dosage (vs. placebo).¹¹ Additionally, higher doses of naltrexone (vs. lower doses and placebo) resulted in higher rate of treatment discontinuation, secondary to adverse events (e.g., nausea), although the difference in attrition was not examined between men and women.¹¹ Our findings are in line with those found in naltrexone-treated, alcohol dependent patients from O'Malley et al.,⁸ who previously reported that female alcohol dependent patients receiving naltrexone (50mg) were 7.2 times more likely to experience nausea than male patients, and that experiences of nausea was significantly associated with poor medication adherence and treatment discontinuation. These findings suggest that high-dose naltrexone treatment affects women differently.^{8, 38, 39} Due to sample size limitations, potential interaction effects of nausea and gender with treatment condition (naltrexone vs. placebo) on attrition were not examined. However, our data suggest there exist differential, though non-significant rates of both nausea and psychiatric severity for men and women in the two different treatment conditions. Future trials using naltrexone in female alcohol disordered patients, with or without cocaine dependence should focus on the impact of nausea and psychiatric problems on treatment attrition and treatment response.

Although our results have a number of potential implications for treating female CAD patients with high-dose naltrexone, due to the exploratory nature of the study, we cannot come to a definite conclusion. Clinically, our findings indicate that female CAD patients may require closer supervision during high-dose naltrexone treatment, especially given the possibility of gender effect in one naltrexone trial with large enough female alcoholic sample.¹¹ In one recent preclinical study with rhesus macaques,⁴⁰ a variant of the μ -opioid receptor gene (OPRM1C77G) was linked to increased alcohol consumption and preference, as well as alcohol intoxication, in male macaques only; this gender effect suggests μ -opioid receptor blockade may impact alcohol consumption and treatment response dissimilarly for men and women. Preliminary genetic research investigations indicate that alcohol dependent patients with certain genotypes respond better to naltrexone than those without comparable genetic profiles.⁴¹⁻⁴³ Identifying specific genotypes of CAD women, who do not experience naltrexone-associated side effects and who responds positively to naltrexone treatment, would enhance the effectiveness of high-dose naltrexone treatment (on genomic approach, see O'Brien (2008)).⁴⁴

The interpretation of our findings needs to be examined in light of the following methodological limitations. First, our findings are specific to outpatient treatment-seeking CAD patients, and may not be representative of the general CAD population. Second, the ratio between male and female subjects in our sample was unbalanced. The number of female subjects was small, although this male-female distribution is within the expected range in the treatment sample.^{8, 36} Due to these sample-related limitations, we were only able to conduct two separate logistic regression analyses, each for men and women, rather than directly examining the interaction effects between gender and the predictors in our regression model. Similarly, potentially relevant interactional term, such as the interactional effect between cocaine or alcohol use and gender, was not included in the model due to sample size limitations. Given that this is an exploratory study, further research is needed to examine any gender differences in naltrexone treatment using an ample and a comparable number of female subjects per group to investigate the gender interaction. Third, although the use of logistic regression is the most appropriate statistical test in our investigation, the backward stepwise elimination procedures require a number of statistical tests. Thus, additional predictors increase the likelihood of Type I error occurring in analyses. It is recommended that cross-validation samples be conducted in future investigations, in order to reduce the risk of Type I error.

In conclusion, our findings showed a significant relationship between treatment discontinuation, and psychiatric problem severity and frequency of nausea in CAD women in high-dose naltrexone treatment. For men, those in placebo and BRENDA treatments were more likely to discontinue treatment. Further research is needed on how outcomes may be affected by gender differences in pre-treatment characteristics as well as potential pharmacokinetic-differential effects of high-dose naltrexone.

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Table 1

Gender Differences in Baseline, Predictor and Dependent Variables.

	<u>Overall</u>			<u>PLAC</u>		<u>NAL</u>	
	Male Total (n=116) ^a	Female Total (n=48)	Male (n=58) ^b	Female (n=24)	Male (n=58) ^c	Female (n=24)	
<u>Demographics</u>							
Age, M (s.d.)	39.0 (7.5)	39.3 (5.8)	39.8 (8.0)	38.3 (5.8)	38.2 (6.8)	40.3 (5.8)	
Caucasian, n (%)	31 (26.7)	8 (16.7)	14 (24.1)	3 (12.5)	17 (29.3)	5 (20.8)	
<u>Variables of Interest</u>							
Psychiatric severity, M (s.d.)	0.29 (0.23) *	0.39 (0.26)	0.28 (0.25)	0.35 (0.27)	0.30 (0.21)	0.42 (0.25)	
Percentage of Nausea Reporting, M (s.d.)	0.06 (0.14) *	0.13 (0.20)	0.03 (0.09)	0.12 (0.23)	0.09 (0.17)	0.14 (0.17)	
<u>% Days of Use (in treatment):</u>							
<i>Alcohol, M% (s.d.)</i>	11.75 (15.2)	12.28 (14.5)	14.35 (16.2)	9.83 (12.0)	9.06 (13.7)	14.84 (16.6)	
<i>Cocaine, M% (s.d.)</i>	8.51 (12.4)	10.03 (15.1)	10.87 (14.1)	7.11 (11.1)	6.07 (9.9)	13.09 (18.1)	
<u>Dependent Variable</u>							
Treatment Attrition, n (%)	48 (41.4)	20 (41.7)	29 (43.1) ^d	9 (37.5) ^d	19 (16.4) ^d	11 (45.8) ^d	

*
p < 0.05^aTest of Male vs. Female^bTest of Male vs. Female in Placebo condition only^cTest of Male vs. Female in Naltrexone condition only^dPercentage within treatment condition

Note: M= Mean; M%= Mean percentage; s.d.= Standard deviation; NAL= high dose naltrexone; PLAC= placebo

Logistic Regression Odds Ratio (OR) and 95% Confidence Intervals for Predicting Treatment Attrition.

Table 2

Predictor Variables	Men			Women		
	OR	CI	p	OR	CI	p
Medication ^a	0.409	0.16–1.02	0.06	0.664	0.15–2.86	0.58
Therapy ^b	0.522	0.22–1.24	0.14	0.579	0.13–2.57	0.47
Psychiatric Severity	4.599	0.67–31.38	0.12	19.259	0.65–572.82	0.09
Adverse Event- Nausea	8.906	0.26–306.27	0.23	51.758	0.77–3468.87	0.07
Cocaine Use	0.967	0.92–1.02	0.22	1.052	0.97–1.14	0.21
Alcohol Use	1.038	0.99–1.09	0.10	0.993	0.92–1.07	0.85

^aPlacebo was the reference category (coded 0) and naltrexone was the comparison category (coded 1)

^bBRENDa was the reference category (coded 0) and CBT was the comparison category (coded 1)

Note. A backward stepwise selection based on likelihood ratio (LR) statistics were used to fit the model, using an alpha entry criterion of .05 and an alpha deletion criterion of .10; Treatment attrition was the comparison category (coded 1), and treatment continuance was the reference category (coded 0); OR=odds ratio; CI=confidence interval.

Table 3

Logistic Regression Odds Ratio (OR) and 95% CI for Remaining Variables in the Final Model for Men and Women.

Men			
Predictor Variables	OR	CI	p
<i>NAL</i> ^a	0.473	0.21–1.08	0.077
<i>CBT</i> ^b	0.498	0.22–1.14	0.098
Women			
Predictor Variables	OR	CI	p
<i>Psychiatric Severity</i>	23.894	1.04–547.27	0.047
<i>Adverse Event- Nausea</i>	43.45	1.01–1864.43	0.049

^aPlacebo was the reference category (coded 0) and naltrexone was the comparison category (coded 1)^bBRENDA was the reference category (coded 0) and CBT was the comparison category (coded 1)

Note. A backward stepwise selection based on likelihood ratio (LR) statistics were used to fit the model, using an alpha entry criterion of .05 and an alpha deletion criterion of .10; Treatment attrition was the comparison category (coded 1), and treatment continuance was the reference category (coded 0); OR=odds ratio; CI=confidence interval; NAL= high dose naltrexone; PLAC= placebo.