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Naltrexone and Cognitive Behavioral Therapy for the Treatment of Alcohol Dependence:

Do sex differences exist?

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Abstract

Background—Sex differences in regards to pharmacotherapy for alcoholism is a topic of concern following publications suggesting naltrexone, one of the longest approved treatments of alcoholism, is not as effective in women as in men. This study was conducted by combining two randomized placebo controlled clinical trials utilizing similar methodologies and personnel in which the data was amalgamated to evaluate sex effects in a reasonable sized sample.

Methods—211 alcoholics (57 female; 154 male) were randomized to the naltrexone/CBT or placebo/CBT arm of the two clinical trials analyzed. Baseline variables were examined for differences between sex and treatment groups via analysis of variance (ANOVA) for continuous variable or chi-square test for categorical variables. All initial outcome analysis was conducted under an intent-to-treat analysis plan. Effect sizes for naltrexone over placebo were determined by Cohen's D (d).

Results—The effect size of naltrexone over placebo for the following outcome variables was similar in men and women (%days abstinent (PDA) d=0.36, %heavy drinking days (PHDD) d=0.36 and total standard drinks (TSD) d=0.36). Only for men were the differences significant secondary to the larger sample size (PDA p=0.03; PHDD p=0.03; TSD p=0.04). There were a few variables (GGT at wk-12 change from baseline to week-12: men d=0.36, p=0.05; women d=0.20, p=0.45 and drinks per drinking day: men d=0.36, p=0.05; women d=0.28, p=0.34) where the naltrexone effect size for men was greater than women. In women, naltrexone tended to increase continuous abstinent days before a first drink (women d-0.46, p=0.09; men d=0.00, p=0.44).

Conclusions—The effect size of naltrexone over placebo appeared similar in women and men in our hands suggesting the findings of sex differences in naltrexone response might have to do with sample size and/or endpoint drinking variables rather than any inherent pharmacological or biological differences in response.

Keywords

sex differences; naltrexone; alcoholism

Introduction

While sex differences in regards to pharmacotherapy for alcoholism has not been a major focus of interest, this issue is quickly becoming a topic of concern following two recent publications suggesting naltrexone, one of the longest approved treatments of alcoholism, is not as effective

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in women as in men (Garbutt et al., 2005; Hernandez-Avila et al., 2006). Specifically, Garbutt and colleagues (2005) examined the efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence, and reported that treatment effects among men taking naltrexone versus placebo was highly significant, whereas naltrexone was not significantly better than placebo in women. Similarly, Hernandez-Avila and colleagues (2006) reported that only men showed a greater reduction in drinks per day following daily oral naltrexone but the effect of targeted naltrexone did not show an sex by medication interaction.

The multi-site nature of the long acting naltrexone study (Garbutt et al., 2005) with subsequent increased variability over single site studies, and a disproportionately lower number of women compared to men, may have led to a spurious/chance conclusion that women respond significantly less to naltrexone than men. Also, there may have been something unique about the long acting injected naltrexone in women compared to men and extrapolation for this study to oral naltrexone efficacy might not be warranted. The Hernandez-Avila daily-naltrexone dosing arm, where a sex by medication interaction was reported, had a relatively small sample size (n=72) with more men (about 2/3 of the sample) than women (about 1/3 of the sample). Furthermore, this study recruited “problem drinkers” who drank less and were less severe than most alcohol dependent patients entering most naltrexone treatment trials. It is also important to note that the Garbutt (2005) and Hernandez-Avila (2006) articles are not consistent with the findings of the predominantly male sample (35 of 41 subjects) of hazardous drinkers, treated with oral naltrexone and two brief counseling visits, in the Davidson and colleagues study, which reported no sex effects on outcome (Davidson et al., 2004). Most other studies either do not report sex differences or do so with caveats suggesting sample size of statistical power limitations (Anton et al., 2006). Therefore, it is still unclear as to whether naltrexone works as well in woman as in men especially in those who are alcohol dependent and taking oral naltrexone.

Garbutt and colleagues (2005) reported the adverse event rates for injectable naltrexone (Vivitrol) were similar between both sexes, except for nausea, which was significantly greater in women at the lowest dose examined - a noted clinical phenomenon. A total of forty-three subjects, across both doses examined, did not complete the trial due to adverse events. The percentage of women in this group of non-completers was not reported. Similarly sex effects on medication compliance also remain unknown because studies to date do not report on this issue. Since side effects might influence compliance, which in turn might influence naltrexone treatment efficacy (Baros et al., 2007; Pettinati et al., 2000), it would be important to better understand whether there is sex based differential compliance to naltrexone. Neither the Vivitrol trial (Garbutt et al., 2005) or Hernandez-Avila study (Hernandez-Avila et al., 2006) reported adverse event data in relationship to compliance. In these reports, sex differences in treatment outcome were not primary objectives and therefore analyses of the causation of these effects were limited.

In this light, it is clear that more data is needed to elucidate the differences in men and women in naltrexone responsiveness for alcohol dependence. Understanding how the side effect profile of naltrexone impacts trial completion, as well as overall treatment outcome, differently between men and women is a very salient and timely issue. Given the sex differences of the long acting injectable naltrexone study results, clinicians might be hesitant to use naltrexone, oral or injectable, with women. More information in this area will have an important impact on the treatment of women alcoholics.

The present study explores how efficacy and side effects of naltrexone differ and interact in women and men based on data from two combined clinical trials for the treatment of alcohol dependence with naltrexone and cognitive behavioral therapy (Anton et al., 2005; Anton et al., 1999). We examined 1) whether sex differences in baseline characteristics might serve as

predictors for treatment outcomes 2) do treatment outcomes differ for women and men and 3) do study and medication adherence or side effect profile differ in women compared to men.

Materials and Methods

Study Procedures

Data collected from two previously reported alcohol-treatment clinical trials (Anton et al., 1999), referred to as Study #1, (Anton et al., 2005), referred to as Study #2 were amalgamated for the present analysis. Both clinical trials were randomized placebo controlled 12-week medication trials using 50 mg of naltrexone or placebo daily. Study #1 utilized CBT only (total sample size N=131) while Study #2 randomized subjects to either CBT or MET (total sample size N=160). Therefore, only the data collected for those subjects randomized to the CBT arm in Study #2 were combined with that from Study #1. Subjects (N=211) utilized in this post-hoc analysis included 131 (38 women, 93 men) participants from Study #1 and 80 (19 women, 61 men) participants from Study #2.

The clinical trials share a similar study timeline. Both studies evaluated participants over 12 weeks (84 days) of treatment with either naltrexone (50 mg daily) or placebo and CBT (based on the Project MATCH manual). Drinking during this time was the main unit of analysis. For both trials, laboratory samples, for CDT and GGT, were drawn within a 5-10 day period prior to randomization (baseline) and at wk-12. These two time points were used to calculate percent change in CDT from baseline to wk-12 (%CDT, Bio-Rad, Hercules, CA; CDT, CDT Tech, Axis-Shield, Oslo) and GGT as outcome measures of drinking and liver function. Reports of adverse events and physical symptom checklist were collected weekly in Study #1 and only at weeks 2, 6, and 12 in Study #2 using the same patient self-reported and health care professional rated checklists. In order to calibrate both trials for side effect tracking, the reports of adverse events were analyzed via events reported at any time during treatment (i.e., irrespective of time of occurrence).

Recruitment and Baseline Assessment

Subjects were outpatient alcohol dependent participants recruited from advertisements and who were randomized to the alcohol-treatment clinical trials mentioned above. The inclusion/exclusion criterions for both trials were quite similar and are summarized in Table 1. Briefly, all subjects were dependent on alcohol but not on other substances (except potentially nicotine), did not have other major axis 1 (DSM III R study 1 or DSMIV study 2) psychiatric diagnoses, and were medically stable. Liver enzymes (ALT, AST) of all participants had to be less than 2.5 times the upper limit of normal at time of randomization. The major differences in the inclusion and exclusion criteria between the trials are italicized and include differences in diagnositic drinking criteria (time line follow-back method (tlfb)), previous medicated inpatient detoxifications, and the lack of exclusion of current of marijuana use/abuse in Study #2. All subjects were assessed over a 3-5 day period and needed to be abstinent from alcohol for at least 5 days in each study prior to double blind randomization to naltrexone or placebo. Both studies were approved by the Institutional Review Board at the Medical University of South Carolina and signed informed consent for study participation was obtained from each participant.

Treatment and Assessment

All subjects in this report received manualized CBT based on the Project MATCH manual (Kadden et al., 1992). They could receive a maximum of 12 sessions (once weekly) over the trial and had the potential for 2 emergency sessions (rarely utilized). All therapists were trained and certified either during Project MATCH or by a Project MATCH certified therapist. The senior CBT therapist conducted therapy supervision weekly. All subjects received identical

appearing naltrexone or placebo capsules in blister packs and were instructed to take one capsule daily. Subjects were seen by a health care professional (physician or nurse) and assessed for side effects weekly in Study #1 and at baseline, weeks 2, 6 and 12 in Study #2. At these times subjects were also seen by a research assistant for alcohol consumption quantification using the timeline follow-back calendar method (Sobell et al., 1988) which forms the basis of the drinking data reported.

Compliance

Medication compliance was determined for both trials using urine riboflavin measurement at weeks 2, 6, and 12. A participant was considered medication compliant at week 2, 6, and 12 via urine riboflavin analysis if the measurement, defined a priori, was ≥ 1,500 ng for that week. A participant was considered medication compliant for the entire 12-week treatment period if 2 out of 3 measurements were positive (≥ 1,500 ng). If a sample was not obtained during one of the specified visits (weeks 2, 6, or 12), the participant was considered noncompliant for the missed visit (Baros et al., 2007).

Statistics

ANCOVA (using study entry variable (e.g., drinks per drinking day (90-day tlfb), %days abstinent (90-day tlfb), %heavy drinking days (90-day tlfb), and total standard drinks (90-day tlfb)) as a covariate where appropriate) and chi-square tests were used to examine differences in baseline variables, treatment efficacy and side effect profile (SPSS 11 analytic package). All outcome analyses were conducted under an intent-to-treat analysis plan. Effect sizes for naltrexone over placebo were determined by Cohen's D. Drinking outcome variables (drinks per drinking day, % days abstinent, days to first drink, % heavy drinking days, and total standard drinks) were evaluated in the following ways: main effect of drug group (naltrexone vs. placebo), main effect of sex (men vs. women), and interaction of drug group and sex. Given the small size and the need to explore effects of naltrexone within sex, an independent analysis within sex was conducted on outcome variables of interest. Side effects (focusing on nausea, falling asleep, staying asleep, decreased appetite, headache, dizziness, fatigue, and sexual dysfunction - the most common medication specific adverse effects) were examined between naltrexone and placebo treated subjects within each sex group using ANOVA.

Results

The salient demographic variables and baseline characteristics for the 211 subjects of this analysis are shown in Table 2. There were no significant sex or treatment group differences in age, race, employment, martial or smoking status. ANOVA indicated drinks per drinking day differed by sex (female=10±5; male=12±5; p=0.001) and that the effect of treatment varied by sex (naltrexone=11±5; placebo=12±5; p=0.03) (out of last 90 days). There were no main effects of sex or treatment in alcohol dependence scale score or %days drinking in the past 90-days.

Completion rates for males (80% placebo, 81% naltrexone) and females (86% placebo, 93% naltrexone) showed no main effect of sex (p=0.12) or treatment (p=0.40) and no significant interaction (p=0.44). Compliance ratio for males (67% placebo, 68% naltrexone) and females (82% placebo, 66% naltrexone) showed no main effect of sex (p=0.35) or treatment (p=0.26) and no significant interaction (p=0.23). The key drinking outcome variables (drinks per drinking day, % days abstinent, days to first drink, %heavy drinking days, and total standard drinks) are shown in Table 3. For men, ANCOVA indicated a significant effect of naltrexone compared to placebo on drinks per drinking day (p=0.05, d=0.36), %days abstinent (p=0.03, d=0.36), %heavy drinking days (p=0.03, d=0.36) and total standard drinks (p=0.04, d=0.36). Although the effect sizes for the aforementioned variables were comparable to that seen with men, only days to first drink was significant at a trend level in women (p=0.09, d=0.46).

CDT and GGT are biological markers that are often utilized to measure alcohol consumption. Percent change (baseline to wk-12) in CDT and GGT, are shown in Table 4. Although both CDT and GGT exhibited a greater reduction in the naltrexone group compared to placebo the only significant reduction was observed in GGT for men (p=0.03, d=0.41) although the effect size of this reduction was similar for both markers in both sexes.

Table 5 lists adverse events reported at any time during treatment (day 1 through day 84). Women treated with naltrexone reported more nausea (p=0.01) and difficulty staying asleep (p=0.001) than women in the placebo group. Also, women treated with naltrexone tended to report less difficulty falling asleep (p=0.09) compared to those on placebo group. Men treated with naltrexone tended to report more headaches (p=0.08), dizziness (p=0.09), and greater reduction in appetite (p=0.09) than those men on placebo. When the differential side effect of nausea was accounted for in the intent-to-treat analysis (Table 3) the pattern of results were not significantly altered, indicating that the experience of nausea in women was not a salient factor on how well they did in treatment.

Discussion

This report is an attempt to evaluate sex differences in naltrexone's effectiveness by evaluating multiple baseline characteristics for predictability of outcome as well as multiple outcome measures and side effects of naltrexone in a study population comprising 27% women. The only baseline variable with a significant difference between treatment groups (naltrexone vs. placebo) and an interaction of sex by treatment was drinks per drinking day (out of past 90 days). This indicates that women tend to drink less than men, a commonly known fact, and that those women assigned to the naltrexone arm of the study drank significantly less than those women assigned to the placebo arm of the study. We controlled for this event by using drinks per drinking day (past 90 days) as a covariate in the intent-to-treat analysis.

Contrary to reports that alcoholic women treated with naltrexone did not have significant treatment effects, we found that naltrexone had a significant effect on increasing the continuous abstinent days before a first drink in women. An effective treatment of alcoholism is to eliminate or reduce alcohol consumption and alcohol related problems. Naltrexone's ability to significantly increase the days to first drink in women implies that naltrexone could be an effective treatment for alcohol dependence in women. The utility of naltrexone over placebo in women is supported by effect sizes of 0.28 to 0.46 in our hands which are similar to, or larger than, those for men in this study and comparable to, or larger than, those reported in meta-analytic studies on naltrexone in general (Bouza et al., 2004; Kranzler and Van Kirk, 2001; Streeton and Whelan, 2001). The effect size of naltrexone over placebo was similar in women and men for the following variables: %days abstinent, %heavy drinking days, drinks per drinking day, total standard drinks and GGT. However, only for men were the differences significant secondary to the larger sample size. These findings should be viewed as exploratory in nature since the goal of these studies was not to definitively determine the utility of naltrexone in women alcoholics. In addition, the magnitude of the effects must be seen in light of a study done in an academic setting, with highly motivated subjects who received CBT by trained professionals. Similar effects might not be achieved in different settings, or with different patients and/or treatment providers. Nevertheless, these data could guide others in setting appropriate sample sizes for studying naltrexone, and perhaps other opiate antagonist effects, in women.

Most adverse events were mild to moderate in severity but did not preclude participation. Women reported more nausea and men tended to report decreased appetite, increased headache and dizziness when taking naltrexone. Furthermore, women on naltrexone did significantly better than placebo on several sleep parameters.

The majority of prior studies examining sex differences and alcohol have focused on either the differences in the development of alcohol dependence, the physiological and psychological consequences of alcohol use, abuse and dependence, and post-treatment functioning. For example, research indicates men consume alcohol more frequently and in greater amounts than women (Anthony and Echeagaray-Wagner, 2000). Although men are more likely to use alcohol and become dependent (Grant, 1997), women have more negative consequences. Despite fewer years of heavy drinking than alcoholic men, women develop an increased sensitivity to alcohol-induced brain damage (Hommer, 2003; Mann et al., 1992) including increased risk of stroke (English et al., 1995); increased development of cirrhosis (Loft et al., 1987; Mezey et al., 1988) and increased prevalence of peripheral neuropathy (Ammendola et al., 2000). Since women exhibit a rapid development of drinking problems, referred to as “telescoping” (Piazza et al., 1989; Randall et al., 1999), and seek treatment sooner than men (Fillmore, 1987) the timeframe for intervention fades more quickly for women compared to men, making earlier effective treatment more critical.

A considerable amount of attention is focused on the development of pharmacotherapies for the treatment of alcohol dependence. Despite evidence indicating a difference in the developmental patterns of alcoholism and physiology of alcoholism based on sex, the development of pharmacotherapies for the treatment of alcohol dependence has historically not been based on sex. This report provides evidence that the treatment of alcohol dependence in women with naltrexone does produce positive outcomes but that the significance of these positive outcomes may be limited by sample size, variability of response or both. The need to re-examine the utility of the current pharmacotherapies for the treatment of alcohol dependence by sex is great. In light of the recent publications reporting the lack of effect of naltrexone in women compared to men, further analysis of this pharmacotherapy for the treatment of alcohol dependence in women is warranted.

In the present study, it is possible that the lack of multiple significant outcomes of naltrexone effects in women might have to do with the sample size and/or type of drinking variables examined rather than any inherent pharmacological or biological differences in naltrexone response. The results of this study should provide direction in resolving the controversy over the effectiveness of naltrexone in women. To this end, research focused on the outcomes of women in alcohol clinical trials is necessary to identify the specific needs of women that will not only improve their outcome, but to also enhance awareness of the scientific community to the important fact that sex differences in treatment need to be examined and reported.

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Table 1

Inclusion and Exclusion Criteria for the Study #1 and Study #2 Naltrexone Trials

Study #1	**Study #2**
Inclusion criteria	Inclusion criteria
1. Age: 21-65	1. Age: 21 to 70 years
2. Meeting the DSM-III R criteria for alcohol dependence	2. Meeting the DSM-IV criteria for alcohol dependence
3. Drink on average ≥ 5 sdu/day in past 30 days	*3. Drink on average ≥ 5 sdu/day men, ≥ 4 sdu/day women for past 90 days*
4. Resided within 1 hr of clinic	4. Reside within 50 miles of clinic
5. Stable living situation and collateral	5. Stable living situation and collateral
6. Maintain sobriety for 5 days before randomization	6. Maintain sobriety for 5 days before randomization
7. No Previous inpatient medicated detoxification	*7. No more than 1 previous inpatient medicated detoxification*
Exclusion Criteria	Exclusion Criteria
1. Other current drug abuse or dependence (including marijuana)	*1. Current abuse of other psychoactive substances except for marijuana and nicotine*
2. Ever having abused opiates	2. Ever having abused opiates
3. Current major psychiatric disorder	3. Current major psychiatric disorder
4. Serious/unstable medical condition	4. Serious/unstable medical condition
5. Current psychotropic or anti-seizure meds or disulfram	5. Current use of disulfram, anti-seizure meds, or psychoactive medication use
6. Pending legal charges except DUI	6. Pending legal charges for any violent crime
7. Liver function test alt and ast > 2.5 times normal	7. Liver function test alt and ast > 2.5 times normal
	8. Use of an opiate antagonist in the month before
	9. Pregnancy, nursing, or lack of reliable birth control

Table 2

Demographics and drinking variables of the study sample for subjects assigned to naltrexone or placebo and cognitive behavorial thearpy (CBT)

	Women				Men			
	Naltrexone		Placebo		Naltrexone		Placebo	
	N=29		N=28		N=78		N=76	
	N	%	N	%	N	%	N	%
Race (%Caucasian)	24	83	25	89	67	86	64	84
Employed Full Time	21	72	21	75	70	90	68	89
Married	13	45	11	39	34	44	38	50
Smoking	16	55	10	34	47	60	34	45
	mean±sd		mean±sd		mean±sd		mean±sd	
Age	43±9		46±10		44±11		42±9	
Alcohol Dependence Scale	16±6		18±8		16±7		15±7	
% Days Drinking (out of last 90 days)	82±23		80±23		81±18		81±22	
Drinks per drinking day[a] (out of last 90 days)	8±4		11±6		13±5		12±5	

[a]There is a significant difference between sex (p=0.001) and treatment (p=0.03).

Table 3

Key drinking outcome variables (mean ± sd)

	Women				Men			
	NTX N=29	PLC N=28	p	Cohen's d	NTX N=78	PLC N=76	p	Cohen's d
Drinks[a] per drinking day	2±3	4±4	0.34	0.28	3±4	4±5	0.04	0.36
% Days Abstinent[b]	89±16	82±23	0.16	0.41	86±24	76±29	0.03	0.36
Days To First Drink	44±36	28±33	0.09	0.46	42±37	37±37	0.44	0.00
% Heavy Drinking Days [c]	4±9	7±14	0.38	0.36	5±15	9±14	0.14	0.36
Total Standard Drinks [b]	33±59	72±131	0.25	0.36	55±128	100±157	0.04	0.36

p is comparing NTX to PLC-ANCOVA using baseline as covariate

NTX =naltrexone ; PLC = placebo

[a] a drink is defined as 12 ounces of beer, 1.5 ounces of liquor or 5 ounces of wine

[b] %days abstinent, % heavy drinking days and total standard drinks out of 84 days

[c] a heavy drinking day is ≥ 5 drinks for men or ≥ 4 drinks for women

Table 4

Percent change in CDT and GGT, week-12 from baseline (mean ± sd)

	Women		p	Cohen's d	Men		p	Cohen's d
	NTX N=27	PLC N=25			NTX N=64	PLC N=59		
% Δ in CDT	-15.2±19	-9.5±31	0.44	0.20	-19±29	-11±36	0.17	0.28
	N=28	N=25			N=64	N=60		
% Δ in GGT	-27.6±24	-14.4±39	0.14	0.41	-38±32	-16±73	0.03	0.41

CDT = carbohydrate-deficient transferring; GGT = gamma-glutamyltransferase NTX=naltrexone ; PLC = placebo

Table 5

Adverse events at any time during treatment

	Women		p	Men		p
	NTX N=29	PLC N=28		NTX N=78	PLC N=76	
Nausea	38%	8%	0.01	13%	10%	0.82
Falling Asleep	24%	46%	0.09	23%	24%	0.77
Staying asleep	17%	54%	0.00	36%	31%	0.79
Decreased Appetite	17%	12%	0.56	25%	12%	0.09
Headache	48%	41%	0.47	34%	19%	0.08
Dizzy	7%	8%	0.91	13%	3%	0.09
Fatigue	52%	41%	0.33	31%	30%	0.93
Sexual Dysfunction	21%	35%	0.26	32%	35%	0.63

p is comparing NTX (naltrexone) to PLC (placebo).