Naltrexone and Disulfiram in Patients with Alcohol Dependence and Comorbid Post-Traumatic Stress Disorder

Ismene L. Petrakis, James Poling, Carolyn Levinson, Charla Nich, Kathleen Carroll, Elizabeth Ralevski, and Bruce Rounsaville

Background: *Although disulfiram and naltrexone have been approved by the Food and Drug Administration for the treatment of alcoholism, the effect of these medications on alcohol use outcomes and on psychiatric symptoms is still unknown in patients with co-occurring disorders post-traumatic stress disorder (PTSD).*

Methods: *Patients (n = 254) with a major Axis I psychiatric disorder and comorbid alcohol dependence were treated for 12 weeks in a medication study at three Veterans Administration outpatient clinics. Randomization included (1) open randomization to disulfiram or no disulfiram; and (2) double-blind randomization to naltrexone or placebo. This resulted in four groups: (1) naltrexone alone; (2) placebo alone; (3) disulfiram and naltrexone; or (4) disulfiram and placebo. Outcomes were measures of alcohol use, PTSD symptoms, alcohol craving, GGT levels and adverse events.*

Results: *93 individuals (36.6%) met DSM-IV criteria for PTSD. Subjects with PTSD had better alcohol outcomes with active medication (naltrexone, disulfiram or the combination) than they did on placebo; overall psychiatric symptoms of PTSD improved. Individuals with PTSD were more likely to report some side effects when treated with the combination.*

Conclusions: *The results of this study suggest that disulfiram and naltrexone are effective and safe for individuals with PTSD and comorbid alcohol dependence.*

Key Words: Alcohol, disulfiram, dual diagnosis, naltrexone, Post-Traumatic Stress Disorder (PTSD)

Naltrexone and disulfiram are two of only three medications approved by the Food and Drug Administration (FDA) for the treatment of alcohol dependence, which affects about 14% of the population (Rieger et al 1990). Both were approved for use in uncomplicated alcohol dependence and have only rarely been studied in individuals with comorbid Axis I psychiatric disorders. A small but growing literature has suggested that both naltrexone and disulfiram may be used safely in patients with comorbid psychiatric disorders (Larson et al 1992; Croop et al 1997; Salloum et al 1998; Maxwell and Shinderman 2000; Morris et al 2001; Mueser et al 2003). However, whether there is variability in the efficacy and safety of naltrexone, disulfiram or combined medication when used with diagnostic specific subgroups is still an important clinical question.

Post-traumatic stress disorder (PTSD) is a serious anxiety disorder with an estimated lifetime prevalence of 8% in the general population, but is higher in patients with alcohol dependence (Kessler et al 1995). Comorbidity of PTSD and alcohol dependence is associated with more severe symptoms of PTSD, higher risk of relapse to alcohol, a higher rate of psychosocial and medical problems, and higher utilization of inpatient hospitalization (Jacobsen et al 2001). Therefore, evaluating the effect of approved pharmacotherapies for treating alcoholism in patients with co-occurring PTSD is of clinical importance.

Another important clinical issue is what effect naltrexone and disulfiram have on the specific psychiatric symptoms of PTSD. A small literature does exist evaluating the effect of naltrexone on PTSD symptoms in non-alcohol dependent individuals because of its mechanism of action on the opioid receptor. Two early reports showed improvements in PTSD symptoms with naltrexone (Bills and Kreisler 1993) and the opioid antagonist nalmefene (Glover 1993) in patients diagnosed with PTSD. A more recent but short term, open label study with naltrexone (Lubin et al 2002) reported significant but not clinically meaningful reduction of only the re-experiencing and hyperarousal symptoms in PTSD patients. One case report has suggested that naltrexone may actually exacerbate some psychiatric symptoms associated with PTSD, particularly rage and explosive behavior (Ibarra et al 1994).

There is even less available data for disulfiram. Early reports suggested disulfiram precipitates a number of psychiatric symptoms including delirium, depression, anxiety symptoms, mania and psychosis (as reviewed by Larson et al 1992). However, most of these reports date before 1970 when dosages of 1 to 2 grams were used and the definitions of the psychiatric symptoms were not standardized. Aside from these early clinical reports, however, there are few studies of the use of disulfiram in patients with comorbid psychiatric disorders. Since disulfiram acts centrally by inhibiting dopamine beta-hydroxylase resulting in an excess of dopamine and decreased synthesis of norepinephrine, there exists the potential that disulfiram may precipitate psychotic and depressive symptoms (Fisher 1989). We conducted the first large scale study comparing the disulfiram and naltrexone, alone and in combination, as treatment for alcohol dependence in a veteran population with a heterogeneous set of comorbid mental disorders, many of whom were concurrently receiving pharmacotherapy for their symptoms (Petrakis et al 2005).

The purpose of the present study was (1) to evaluate the relationship between the diagnosis of PTSD and alcohol use in terms of treatment response to disulfiram and naltrexone, alone and in combination; (2) to evaluate what effect these medications may have on the specific psychiatric symptoms of PTSD; and (3) the relationship between diagnosis of PTSD or no PTSD on side effects and adverse events in response to disulfiram and naltrexone alone and in combination.

Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

Address reprint requests to Ismene Petrakis, M.D., VA Connecticut Healthcare System, #116-A, 950 Campbell Avenue, West Haven, CT 06516; E-mail: ismene.petrakis@yale.edu.

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Methods

Subjects

This study was approved by the Human Subjects Subcommittee of the VA Connecticut Healthcare System and the Northampton and Bedford, Massachusetts VA's, which are all affiliated with the New England Mental Illness Research and Education Clinical Center (MIRECC). The present sample (n = 254) consisted of outpatients from the MIRECC-affiliated clinics who met criteria for a current DSM IV major Axis I disorder and alcohol dependence, determined by structured clinical interview (SCID) (First et al 1996), who were abstinent no more than 29 days. The Alcohol Dependence Scale (ADS) (Skinner 1984) was also administered at baseline to characterize the severity of alcohol dependence. Those individuals on psychiatric medication were on a stable regimen (no changes) of psychiatric medication for at least 2 weeks prior to randomization. Exclusion criteria included unstable psychotic symptoms or serious current psychiatric symptoms, such as suicidal or homicidal ideation, or medical problems that would contraindicate the use of naltrexone and disulfiram, including liver function tests over 3 times the normal level. Subjects were also required to be abstinent for 3 days prior to randomization and the stated goal of the study was complete abstinence.

Treatments

After providing written informed consent, subjects completed an intake assessment, which included a physical examination, laboratory assessments and an interview with a psychiatrist. Following completion of these baseline assessments, 254 subjects were randomized to one of four groups for a 12-week trial. Randomization included (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. The use of a placebo control condition for disulfiram may lead to the temptation for individuals to sample alcohol in order to "test" the blind, leaving questions about safety and the ability to maintain a true medication blind. For that reason, individuals were randomized to either disulfiram or no disulfiram, and disulfiram was dispensed in an open-label fashion. The dispensing of naltrexone was placebo-controlled and double-blind.

Study medications were dispensed in bottles with Microelective Events Monitoring (MEMS) caps in order to monitor compliance at every visit. All subjects also received weekly Clinical Management/Compliance Enhancement therapy (Carroll et al 1998) administered by trained research personnel. The methods from this study were described in more detail previously (Petrakis et al 2005).

Assessments

Primary outcomes were measures of alcohol use. The Substance Abuse Calendar, based on the Timeline Follow-Back Interview (Sobell and Sobell 1992), was administered by a research assistant at each weekly visit to collect a detailed self-report of daily alcohol and other substance use throughout the 84-day treatment period as well as for the 90-day period prior to randomization. Alcohol consumption was confirmed using serum gamma-glutamyl transferase (GGT). Craving was assessed weekly using the Obsessive Compulsive Drinking and Abstinence Scale (OCDS) (Anton et al 1996). PTSD symptoms were assessed by the research staff at the baseline and biweekly during treatment by the Clinician Administered PTSD Scale (CAPS) (Blake et al 1990) for those subjects with PTSD (n = 93).

Side effects and common adverse symptoms were evaluated by the research staff weekly using the self-report Hopkins Symptom Checklist (HSCL) (Derogatis et al 1974). The symptoms that are known to be associated with naltrexone and disulfiram treatment were specifically screened for and have been described in detail previously (Petrakis et al 2005). For the purposes of this analysis, the symptoms were then clustered into the following categories: gastrointestinal, emotional, cold and flu symptoms, skin, sexual, neurological, severe and cardiac.

Data Analysis

Demographic, and substance use variables, serum liver enzyme levels, and psychiatric medications at baseline were compared between subjects with the diagnosis of PTSD and those without using chi-square analyses for dichotomous and analysis of variance for continuous variables. The primary outcome variables were the number of drinking days and the number of heavy drinking days (defined as 5 or more standard drinks) per week calculated from the substance abuse calendar data. Primary and secondary outcomes with repeated measures were analyzed using random effects regression models (Hedeker et al 1991) of a priori contrasts for the intent to treat sample. 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. Analyses of variance (ANOVA) models were used for continuous outcomes not evaluated longitudinally (e.g., days in treatment, consecutive days of abstinence, adverse events).

Results

The subjects for this study were all 254 veterans who were enrolled in the MIRECC Naltrexone Disulfiram Treatment Trial (Petrakis et al 2005). The subject characteristics have been previously described in more detail elsewhere (Petrakis et al 2005). Within the entire sample 93 (36.6%) met current DSM-IV criteria for PTSD, while 161 (63.4%) did not. There were no differences in age, sex, or ethnicity in a comparison of the sub-sample of patients who had PTSD and those without (See Table 1). Of those with PTSD, 10 individuals had PTSD and alcohol dependence only, 42 had one other lifetime Axis I diagnosis, 28 had 2 diagnoses, 10 had 3 diagnoses and 3 individuals had 4 diagnoses. The most common secondary psychiatric diagnoses were Major Depressive Disorder (n = 65) and cocaine dependence (n = 35). Other diagnoses included bipolar disorder, schizophrenia, schizoaffective disorder, panic disorder and generalized anxiety disorder. Two hundred and twenty (86.6%) subjects were prescribed psychiatric medications during the study. There were no significant prescribing pattern differences in patients with PTSD versus those without PTSD.

As a measure of baseline substance use, drinking data were reported for the first 30 days of the baseline data that was collected for 90 days before they entered treatment. As shown in Table 1, individuals with PTSD reported fewer baseline years of drinking than subjects without PTSD (24.5 ± 8.9, 26.9 ± 9.8, respectively; $\chi 2$ = 3.74, p = .05) yet had more symptoms of alcohol dependence as measured by the ADS (23.9 ± 8.8, compared to 21.2 ± 8.5, $\chi 2$ = 5.84, p = .02). There were no differences in drinking days, drinks per drinking day, percent heavy drinking days or baseline GGT levels.

Table 1. Baseline Characteristics

	Current PTSD				
	Yes $n = 93$		No $n = 161$		Statistics
Variable	mean	sd	mean	sd	F, p
Age	46.3	7.0	47.1	8.9	.56, .45
Gender	*n*	%	*n*	%	X^2, p
Male	91	36.8	156	63.2	.20, .65
Female	2	28.6	5	71.4	
Ethnicity					
White	73	78.5	116	72.1	1.88, .60
Black	14	15.1	29	18.0	
Hispanic	4	4.3	8	5.0	
Other	2	2.2	8	5.0	
Measures of Alcohol Consumption					
ETOH use lifetime	24.5	8.9	26.9	9.8	3.74, .05
Drinking days	15	11.8	14.9	12.1	.01, .92
Drinks per drinking day	21.3	14.1	18.4	12.1	2.08, .15
% Heavy drinking days	45.8	38.6	45.2	40.4	.01, .91
Baseline ADS Score	23.9	8.8	21.2	8.5	5.84, .02
Prescribed Psychiatric Meds at Baseline					
Any	79	85	141	87.6	.35, .55
Antidepressant	71	76.3	118	73.3	.29, .59
Antianxiety	12	12.9	15	9.3	.79, .37
Mood stabilizer	29	31.2	58	36	.61, .43
Antipsychotics	20	21.5	38	23.6	.15, .70
More than one med	41	44.1	69	42.9	.03, .85
GGT					
Pre ($n = 190$)	72.8	101.0	66.9	76.6	.21, .64

PTSD, post-traumatic stress disorder; ADS, Alcohol Dependence Scale; GT, Gamma-glutamyl transferase.

Treatment Retention

Treatment retention was defined as the number of days between the first and last medication dose taken based on the MEMS data. There were no significant differences in overall retention in the group of subjects with PTSD and those without. There was a significant interaction between diagnosis and medication group on retention, where subjects with PTSD stayed in treatment longer if they were assigned to active medication compared to those assigned to placebo ($F_{1, 250} = 4.51$, $p = .03$).

Alcohol Use and Craving Outcomes

In the entire sample, subjects significantly decreased their alcohol use from baseline to post-treatment in all outcome measures. There was a very high overall rate of abstinence (177 or 69.7% of total sample reported 100% abstinence) during the active phase of the study. Overall, subjects assigned to either naltrexone or disulfiram reported significantly fewer drinking days per week ($F_{1, 2810} = 5.71$, $p = .02$) and more consecutive days of abstinence ($F_{1, 246} = 4.49$, $p = .04$) than those assigned to placebo. There were no significant differences by treatment condition in the percent of heavy drinking days or in the number abstinent for the entire study period. There were no advantages in any of the measures of alcohol consumption for subjects who received both medications compared to those treated with either active medication alone.

Overall, there was no significant effect of the diagnosis of PTSD on the maximum consecutive days of abstinence, the percent of heavy drinking days or the number of subjects abstinent for the entire study period (see Table 2). There was a significant interaction between PTSD diagnosis and medication condition on several alcohol outcomes including maximum consecutive days of abstinence (see Figure 1) and the percent of heavy drinking days. In each case, the group of subjects with PTSD that was treated with medication (disulfiram or naltrexone) had significantly more consecutive days of abstinence ($F_{1, 246} = 6.10$, $p = .01$), and a lower percent of heavy drinking days ($F_{1, 246} = 3.92$, $p = .05$) than those treated with placebo. However, there was no interaction of PTSD diagnosis and medication condition on the number of subjects who were abstinent for the entire medication period.

Regarding biological measures, there was no significant effect of diagnosis (PTSD vs. no PTSD) on measures of GGT over time. There were no significant interactions between diagnoses (PTSD vs. no PTSD) and medication condition in measures of GGT.

Based on the OCDS (Anton et al 1995), subjects in all groups reported significantly lower measures of craving over time. There was a significant difference between the PTSD versus no PTSD group, where the subjects with PTSD reported higher craving overall than those without PTSD ($z = 2.38$, $p = .02$). Further, there was a significant interaction between PTSD diagnosis and medication group on craving, where those treated with either disulfiram or naltrexone reported significantly lower scores over time than those treated with placebo ($z = -3.80$, $p = 0.00$); this effect is likely due to disulfiram as those treated with disulfiram reported significantly lower scores over time than those treated with naltrexone ($z = -2.95$; $p = .00$). As outlined in Table 2, the most dramatic decrease was in the group treated with disulfiram alone, where OCDS scores were reduced from 17.7 to 5.2 (71%)

Table 2. Primary Outcome Variables by Diagnosis of Post-Traumatic Stress Disorder (PTSD)

	Disulfiram/ Naltrexone		Disulfiram/ Placebo		Naltrexone		Placebo		By Psychiatric Diagnosis	Interaction (tx contrast PTSD)[a]			
	Mean (sd)		Mean (sd)		Mean (sd)		Mean (sd)		*df* = 1 *F*, *p*	DN vs DP *F*, *p*	DP vs N *F*, *p*	Any med vs P *F*, *p*	
Maximum consecutive days of abstinence													
No PTSD (*n* = 161)	69.6 (21.9)		67.1 (25.6)		66.0 (27.2)		66.1 (26.9)		.23, .63	.73, .39	.40, .53	6.10, .01	
PTSD (*n* = 93)	68.2 (28.6)		75.7 (21.0)		68.7 (23.8)		49.7 (34.7)						
% Days abstinent													
No PTSD	96.1% (9.8%)		95.9% (10.7%)		96.5% (7.5%)		95.2% (11.0%)		1.55, .20	.32, .57	1.00, .32	2.79, .10	
PTSD	97.8% (5.7%)		97.7% (10.5%)		94.1% (15.7%)		89.7% (19.0%)						
% Heavy drinking days													
No PTSD	3.5% (9.3%)		4.0% (10.6%)		2.8% (6.7%)		3.5% (8.8%)		.52, .47	.41, .52	1.27, .26	3.92, .05	
PTSD	1.7% (4.4%)		2.2% (10.5%)		5.4% (15.5%)		9.6% (17.6%)						
Abstinent for entire study period[a]	*n* (%)		*n* (%)		*n* (%)		*n* (%)		x^2, *p*	x^2, *p*	x^2, *p*	x^2, *p*	
No PTSD	29 (65.9)		29 (72.5)		21 (63.6)		31 (70.5)		.60, .44	.02, .89	.10, .75	.01, .92	
PTSD	17 (81.0)		22 (84.6)		17 (65.4)		11 (55.0)						
OCDS total score Change over time[b]	Mean (sd)	*n*	Mean (sd)	*n*	Mean (sd)	*n*	Mean (sd)	*n*	z, *p*	z, *p*	z, *p*	z, *p*	Time z, *p*
Pre													
No PTSD	13.2 (7.9)	43	10.2 (8.6)	40	10.7 (7.2)	33	13.1 (8.1)	43	2.38, .02	−1.04, .29	−2.95, .00	−3.80, .00	−12.30, .00
PTSD	13.3 (9.7)	21	17.7 (8.9)	26	14.6 (8.2)	25	12.9 (6.6)	20					
Post													
No PTSD	6.4 (8.7)	34	3.2 (4.9)	30	4.7 (5.7)	28	3.4 (5.1)	37					
PTSD	4.8 (5.9)	18	5.2 (6.3)	25	7.7 (8.7)	24	9.0 (11.5)	14					
GGT	Mean (sd)	*n*	Mean (sd)	*n*	Mean (sd)	*n*	Mean	*n*	z, *p*	z, *p*	z, *p*	z, *p*	Time z, *p*
Pre													
No PTSD	75.7 (57.3)	29	79.1 (108.3)	28	61.4 (67.0)	25	52.4 (65.6)	32	.19, .85	−.01, .99	−.49, .62	.14, .89	−4.76, 0.00
PTSD	70.6 (60.8)	17	82.8 (100.6)	19	45.4 (25.5)	23	63.4 (79.1)	16					
Post													
No PTSD	31.1 (18.7)	24	42.8 (59.2)	22	38.3 (34.9)	24	32.2 (32.4)	29					
PTSD	40.7 (30.3)	17	54.3 (72.3)	20	33.3 (20.2)	18	29.8 (12.9)	12					

[a] Percent is within treatment group by psychiatric diagnosis.
[b] Obsessive Compulsive Drinking and Abstinence Scale.

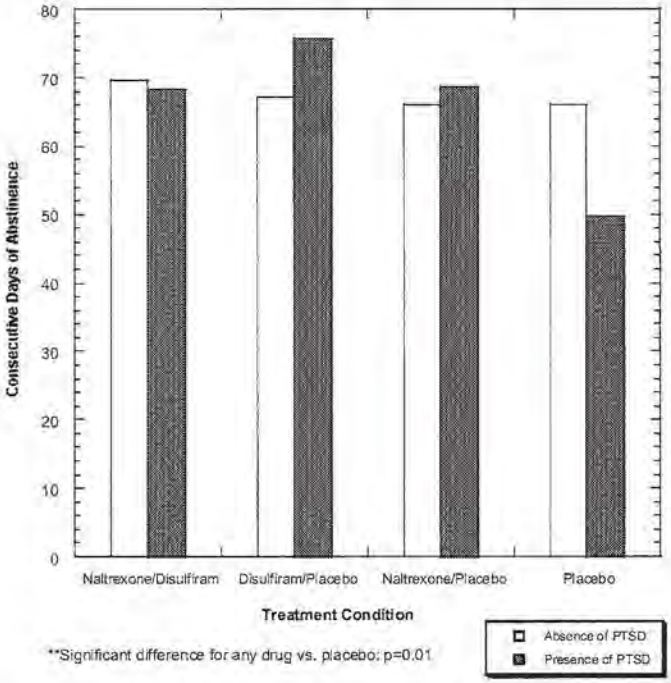


Figure 1. Maximum consecutive days of abstinence during active treatment for subjects with PTSD versus those without by treatment condition.

in contrast to placebo-treated subjects where OCDS scores were reduced from 12.9 to 9.0 (31%).

Effect of Study Treatments PTSD Symptoms

Based on the CAPS-SX, as a group, the sub-sample of subjects with PTSD (n = 87, 6 of the 93 individuals had missing data) showed a significant decrease in PTSD symptoms over time in total CAPS-SX score ($z = -3.22$, $p = .00$) and in all 3 of the CAPS-SX subscales (see Table 3). Over the course of treatment, subjects treated with disulfiram had significantly lower total scores over time ($z = -1.99$, $p = .05$), and lower hyperarousal scores over time ($z = -2.02$, $p = .04$) compared to those on naltrexone. Subjects on either naltrexone or disulfiram alone had lower re-experiencing symptoms over time ($z = 2.48$, $p = .01$) compared to those on the combination of naltrexone and disulfiram.

The group of subjects who had any alcohol use during treatment (n = 24) and the group of subjects with no alcohol use (n = 63) were analyzed separately. Those who sampled alcohol during treatment did not have a significant improvement over time in the total CAPS-SX score or in any of the subscales. Those who had no alcohol use reported a significant decrease in the total CAPS-SX scores over time ($z = -3.21$, $p = .00$) and in each of the subscales over time ($z = -2.10$, $p = .04$ for re-experiencing; $z = -2.91$, $p = .00$ for avoidance and $z = -3.25$, $p = .00$ for hyperarousal). Over the course of treatment, subjects treated with disulfiram had significantly lower total scores over time ($z = -2.65$, $p = .01$), lower hyperarousal scores over time ($z = -2.94$, $p = .00$) and lower avoidance scores over time ($z = -2.53$, $p = .01$) compared to those on naltrexone. Subjects on either naltrexone or disulfiram alone had lower re-experiencing symptoms over time ($z = 2.17$, $p = .03$) compared to those on the combination of naltrexone and disulfiram.

Safety and Side Effects

Overall, there were significant differences between the side effects reported by the PTSD group and non-PTSD group, where subjects with PTSD were more likely to report gastrointestinal ($F_{1, 246} = 3.84$, $p = .05$), emotional ($F_{1, 246} = 9.46$, $p = .00$), cold flu ($F_{1, 246} = 6.81$, $p = .01$) and neurological symptoms ($F_{1, 246} = 5.84$, $p = .02$) than those without PTSD. There was a significant interaction between the diagnosis of PTSD and medication condition, where those subjects treated with the combination of medications who also had PTSD were more likely to report cardiac ($F_{1, 246} = 13.65$, $p = .00$) and sexual side effects ($F_{1, 246} = 5.00$, $p = .03$) than those on either medication alone.

There were 6 serious adverse events in subjects with PTSD out of a total of 14 for the entire sample (Petrakis et al 2005). The adverse events in the subjects who had PTSD included 3 medical hospitalizations (one disulfiram/naltrexone-treated individuals had an alcohol-disulfiram reaction, another disulfiram/naltrexone-treated individual had a cardiac event; and one placebo-treated individual had a drug and alcohol overdose); one psychiatric hospitalization (disulfiram/placebo treated) and there was one death (naltrexone treated). One individual with PTSD and comorbid bipolar disorder also had a medical hospitalization

Table 3. Secondary Outcome Variables

	Disulfiram/ Naltrexone		Disulfiram/ Placebo		Naltrexone		Placebo		Time	Treatment Contrasts by Time: DN vs DP or N	DP vs N	Any med vs P
Variable	Mean (sd)	n	Mean (sd)	n	Mean (sd)	n	Mean (sd)	n	z, p	z, p	z, p	z, p
CAPS[a]												
Pre	43.22 (19.09)	18	38.48 (19.66)	23	37.76 (19.87)	25	31.73 (21.67)	15	−3.22, .00	.83, .40	−1.99, .05	−.11, .91
Post	37.80 (29.31)	15	28.65 (18.61)	23	33.26 (22.02)	23	26.00 (18.24)	12				
Re-experience												
Pre	8.89 (8.86)	18	10.52 (7.17)	23	8.60 (7.39)	25	8.93 (9.10)	15	−1.96, .05	2.48, .01	−1.12, .26	1.13, .26
Post	11.53 (10.94)	15	9.35 (8.08)	23	7.35 (7.38)	23	7.00 (5.61)	12				
Avoidance												
Pre	15.67 (9.51)	18	14.30 (8.23)	23	14.32 (8.21)	25	10.47 (9.09)	15	−2.95, .00	.19, .85	−1.83, .07	−.76, .45
Post	11.93 (10.47)	15	9.61 (8.69)	23	12.13 (9.29)	23	7.92 (8.43)	12				
Hyperarousal												
Pre	18.67 (9.06)	18	15.65 (8.77)	23	16.04 (7.27)	29	12.33 (8.58)	15	−3.51, .00	−1.00, .32	−2.02, .04	−.68, .49
Post	14.33 (11.57)	15	11.00 (7.17)	23	14.78 (7.68)	26	11.08 (8.96)	12				

[a] Clinician Administered PTSD Scale, administered to subjects with PTSD (n = 91, 6 of the 93 individuals had missing data).

for acute axonal neuropathy and was in the disulfiram/placebo group. This individual had previously discontinued study medication and at the time of the event was being prescribed nefazodone and valproic acid. The non-fatal cardiac events occurred after patient had discontinued study medications for other reasons; the death was thought to be cardiac but determined not to be study related since the individual had been non compliant with the study, including the medication, for many weeks.

Discussion

The results of this 12 week randomized trial of disulfiram and naltrexone for alcohol use in alcohol dependent patients with comorbid Axis I disorders suggest that (1) subjects with PTSD had better alcohol outcomes on active medication, either naltrexone, disulfiram or the combination, than they did on placebo; (2) psychiatric symptoms of PTSD improved over time and were not adversely affected by these medications. In fact, for several symptoms of PTSD, individuals treated with disulfiram showed significantly more improvement over time than those treated with naltrexone; and (3) individuals with PTSD were more likely to report some side effects when treated with the combination of medications.

The results of this study suggest that individuals with PTSD and comorbid alcohol dependence are particularly well suited to pharmacotherapy for treatment of their alcohol dependence. There is even some suggestion that they may respond particularly well to disulfiram. This may simply reflect a more positive outcome in response to a more aggressive treatment for the alcohol use disorder, namely the use of disulfiram, a powerful antidipsotropic medication. Alternatively there may be something about the mechanism of disulfiram that makes it particularly effective in this group of patients. Stress is often reported as a major factor in the relapse to substances of abuse, perhaps by leading to an increase in craving (Piazza et al 1990; Shaham and Stewart 1995; Erb et al 1996; Sinha et al 1999). This may be particularly relevant for individuals with PTSD and comorbid alcohol dependence. It has been hypothesized that the noradrenergic system in the brain may mediate both symptoms of hyperarousal in PTSD and the increased risk for substance abuse seen in these patients (Koob 1999). This may explain why PTSD patients misuse sedative drugs like alcohol. Medications that dampen this response may be effective in treating patients with comorbid PTSD and alcohol dependence by both alleviating symptoms of PTSD and decreasing alcohol consumption. Disulfiram's effect in the central nervous system (CNS) is a central inhibition of dopamine beta-hydroxylase, resulting in an excess of dopamine and decreased synthesis of norepinephrine (Karamanakos et al 2001). One may hypothesize that disulfiram's effect would be to both alleviate symptoms of PTSD and decrease alcohol consumption by decreasing the vulnerability to stress-induced relapse. If this were true, disulfiram should be particularly effective in the hyperarousal symptoms, which are mediated by the noradrenergic system. This was supported by results from this study that showed patients treated with disulfiram had lower hyperarousal scores over time than those on naltrexone. Of note, this effect was seen in the group that did not relapse, but not in the group that drank during the study. Similar effects were also seen in this sub-sample for the avoidance symptoms.

Contrary to some reports, there was no evidence from this trial that either disulfiram or naltrexone worsen the specific symptoms of PTSD. Further, in this study in which subjects achieved a high rate of abstinence, there were no "re-emergence" effects of psychiatric symptoms. In fact, the best outcomes were in those individuals who were abstinent throughout the trial. This is in contrast to reports that central nervous system (CNS) depressants actually improve PTSD symptoms (Bremner et al 1996) and subjects who decrease alcohol use have anecdotally reported that this worsens clinical symptoms of PTSD. It must be noted, however that in this trial the subjects enrolled had been deemed psychiatrically stable and the majority (86.6%) were on a stable dose (at least 2 weeks prior to randomization) of a concurrent psychiatric medication. Re-emergent psychiatric symptoms were likely adequately treated with the current psychiatric medications.

A strength of this study is its large sample size and comprehensive assessment battery to examine diagnostic-specific psychiatric symptoms as well as alcohol consumption. Limitations included first of all, a predominately male VA sample, hence the results may not be generalizable to other clinical settings. Second, subjects were concurrently being treated with a variety of psychotropic medications, and the effect of specific interactions or combinations on alcohol use, an area of interest, could not be determined. In fact, some recent literature has suggested that specific combinations may be particularly effective in the treatment of alcohol dependence for those with comorbid Axis I disorders (Farren and O'Malley 1999). Third, because of the different methods of study medication administration (open-label disulfiram vs. placebo-controlled, double blind administration of naltrexone), the head-to-head comparison of the efficacy of these medications may be confounded by other non-pharmacologic factors. For example, individuals on disulfiram may have been more motivated to abstain than those who were taking naltrexone. In addition, this was a highly motivated group of participants who all had entered treatment for their alcohol dependence and were willing to be randomized to disulfiram. While this resulted in good overall outcomes and compliance rates, significant treatment effects nevertheless emerged. It must be noted that the results from this trial may not be generalizable to all dually diagnosed individuals, particularly those who are not motivated for treatment and who represent a serious clinical challenge (Herbeck et al 2005).

This was the first randomized clinical trial to evaluate substance use outcomes and diagnostic-specific symptoms with the most commonly used FDA approved medications to treat alcoholism. While the changes in alcohol consumption were modest, the findings were accompanied by other clinically meaningful differences, including better treatment retention for those on active medication, lower rates of craving and overall improvement in PTSD symptoms. The better outcomes for the group of patients who remained abstinent suggest the importance of treating comorbid alcohol dependence in patients with comorbid PTSD. The results suggest disulfiram and naltrexone are effective and safe pharmacotherapeutic agents for this group of patients and should be considered in the clinical management of patients with PTSD and alcohol dependence.

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