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Noradrenergic *vs* Serotonergic Antidepressant with or without Naltrexone for Veterans with PTSD and Comorbid Alcohol Dependence

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The wars in Iraq and Afghanistan are associated with high rates of post-traumatic stress disorder (PTSD) and comorbid alcohol use disorders. The pharmacotherapy of these comorbid conditions has received relatively little study. The current study compared the serotonin uptake inhibitor, paroxetine, to the norepinephrine uptake inhibitor, desipramine. It also evaluated the adjunctive efficacy of the Food and Drug Administration (FDA)-approved alcoholism pharmacotherapy, naltrexone, relative to placebo. Four groups of predominately male veterans ($n = 88$) meeting current diagnostic criteria for both alcohol dependence (AD) and PTSD were randomly assigned under double-blind conditions to one of four groups: paroxetine + naltrexone; paroxetine + placebo; desipramine + naltrexone; desipramine + placebo. Main outcome measures included standardized scales that assessed symptoms of PTSD and alcohol consumption. Paroxetine did not show statistical superiority to desipramine for the treatment of PTSD symptoms. However, desipramine was superior to paroxetine with respect to study retention and alcohol use outcomes. Naltrexone reduced alcohol craving relative to placebo, but it conferred no advantage on drinking use outcomes. Although the serotonin uptake inhibitors are the only FDA-approved medications for the treatment of PTSD, the current study suggests that norepinephrine uptake inhibitors may present clinical advantages when treating male veterans with PTSD and AD. However, naltrexone did not show evidence of efficacy in this population. This study was registered with ClinicalTrials.gov, registration number NCT00338962 and URL: http://clinicaltrials.gov/ct2/show/NCT00338962?term = desipramine+AND+alcohol+dependence+AND+depression&recr = Closed&rank = 1.
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INTRODUCTION

Exposure to combat is a risk factor for mental health problems, notably the development of post-traumatic stress disorder (PTSD). The Iraq (Operation Iraqi Freedom) and Afghanistan (Operation Enduring Freedom) wars are the largest ground operations since the Vietnam War, and veterans from these recent conflicts have prevalence rates of PTSD between 6–12% (Erbes *et al*, 2007; Hoge *et al*, 2004, 2006). Among those seeking mental health care at the Veterans Administration nationally, PTSD accounted for 52% of the mental health diagnoses overall, and 13% of the diagnoses in Operation Enduring Freedom/Operation Iraqi Freedom veterans (Seal *et al*, 2007). Psychiatric comorbidity is an important factor in the treatment of PTSD. It is estimated that 80% of individuals with PTSD also suffer from another Axis I psychiatric disorder (Foa *et al*, 2000). In men, the most common co-occurring disorder is alcohol abuse or dependence (51.9%), and in women, it is the fourth most common diagnosis (27.9%; Fear *et al*, 2010; Kessler *et al*, 1995). Those individuals with comorbid alcohol dependence (AD) report more symptoms of PTSD in all three clusters (re-experiencing, avoidance, and hyper-arousal) compared with those individuals with PTSD alone (Read *et al*, 2004; Riggs *et al*, 2003; Saladin *et al*, 1995). The comorbidity of PTSD and alcoholism is also associated with poorer alcohol-related outcomes, greater impairment in vocational functioning and quality of life, and increased risk for suicide (Brief *et al*, 2004; Johnson, 2008; Keane *et al*, 1988; Kosten and Krystal, 1988). Although there are approved medications for both PTSD and AD alone, the efficacy of these medications in comorbid populations is unclear. Given the high need for effective treatments for

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patients with comorbidity, evaluating the efficacy of pharmacotherapies for this patient population is a high clinical priority.

Serotonergic reuptake inhibitors (SRI) are the first-line treatment for PTSD, but there is a paucity of data comparing their efficacy to alternative treatment mechanisms. The SRIs paroxetine and sertraline are the only Food and Drug Administration (FDA)-approved pharmacotherapies for PTSD. The efficacy of these medications may be more robust in non-veteran and predominately female patient populations (Hertzberg *et al*, 1999; Smajkic *et al*, 2001), including a negative clinical trial in predominately male veterans (Friedman *et al*, 2007). Although an open-label study suggested that sertraline reduced PTSD symptoms and alcohol consumption (Brady *et al*, 1995), a larger randomized, placebo controlled study ($n=94$) showed no significant overall effect of sertraline on symptoms of PTSD or alcohol consumption (Brady and Sinha, 2005).

Noradrenergic mechanisms are implicated in the pathophysiology of PTSD (Krystal and Neumeister, 2009), but norepinephrine reuptake inhibitors (NRI) have not been tested adequately for military-related PTSD. A small, negative trial with desipramine in combat-related PTSD (Reist *et al*, 1989) was followed by a randomized comparison that showed the NRI reboxetine was of equal efficacy to an SRI (Spivak *et al*, 2006).

To date, there are no definitive trials of the combinatorial efficacy of antidepressants and the FDA-approved pharmacotherapies for alcoholism (acamprosate, naltrexone, and disulfiram). One study in veterans ($n=254$) found that naltrexone, disulfiram, or the combination of naltrexone and disulfiram did not differ from each other in efficacy, but were superior to placebo in improving drinking outcomes among alcohol-dependent patients with PTSD (Petrakis *et al*, 2006). Patients in this study remained on stable psychiatric pharmacotherapy regimens typical for PTSD, but this study did not randomly assign the PTSD medications, limiting the ability to explore the interactive effects of pharmacotherapies. Despite a negative clinical trial in veterans (Krystal *et al*, 2001), naltrexone is the only FDA-approved medication whose efficacy for alcoholism is supported by a large multi-center clinical trial conducted in the US (Anton *et al*, 2006).

The purpose of this study was to (1) evaluate and compare a noradrenergic antidepressant (desipramine) to the standard treatment for PTSD, with one of the FDA-approved serotonergic antidepressants (paroxetine) in a primarily veteran sample of participants with PTSD; (2) evaluate and compare their effectiveness in those participants with PTSD and comorbid AD, and (3) evaluate the value of the addition of the FDA-approved medication naltrexone in decreasing alcohol consumption.

SUBJECTS AND METHODS

Subjects

This study was approved by the Human Subjects Subcommittees of the VA Connecticut Healthcare System (West Haven, CT), and the Bedford VA Medical Center (Bedford, MA). Both VAs are affiliated with the New England Mental Illness Research Education and Clinical Center (MIRECC). The study was also approved by the Yale Human Investigations Committee (New Haven, CT). The present sample ($n=88$) consisted of veterans ($n=81$) and non-veterans ($n=7$). The participants were outpatients from the MIRECC-affiliated clinics ($n=42$ from CT, and $n=46$ from MA), who met DSM-IV criteria for current PTSD and AD, determined by structured clinical interview (First *et al*, 1996), who were abstinent no more than 29 days. Non-veterans in this sample were recruited through advertisements in the community and local newspapers. 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, desipramine, or paroxetine, including liver function tests over three times the normal level. Subjects could not be taking medications thought to influence alcohol consumption (such as naltrexone, disulfiram, or acamprosate). Subjects were also required to be abstinent for 2 days before randomization (see Figure 1).

Treatments

After providing written informed consent, subjects completed an intake assessment, which included a physical examination, laboratory assessments, diagnostic, and psychiatric evaluation. Following completion of baseline assessments, 88 subjects were randomized to one of four groups for a 12-week trial. Randomization included (1) desipramine 200 mg per day or paroxetine 40 mg per day, and (2) randomization to naltrexone 50 mg or placebo in a double-blind fashion. This resulted in the following four groups, (1) paroxetine + naltrexone, (2) paroxetine + placebo, (3) desipramine + naltrexone, and (4) desipramine + placebo. Study medications were dispensed in blister packs (during the 2-week titration period for antidepressants) and packaged in separate bottles (after titration for 10 weeks), so subjects received two bottles, one labeled 'naltrexone/antidepressant study medication' and the other 'naltrexone study medication'. Desipramine was started at a dose of 25 mg per day. The dose was gradually increased over 2 weeks to 200 mg per day. Paroxetine was started at 10 mg per day and the dose was gradually increased over 2 weeks to 40 mg per day. Naltrexone was started at 25 mg the first day and 50 mg per day for the rest of the treatment. Medication compliance was monitored at every visit for each bottle. All subjects also received Clinical Management/Compliance Enhancement therapy (Carroll *et al*, 1998) administered by trained research personnel.

Assessments

Primary outcomes were measures of PTSD severity and alcohol use. PTSD symptom severity was assessed biweekly by the clinician administered PTSD scale for DSM-IV (CAPS; Blake *et al*, 1990). The Alcohol Dependence Scale (ADS; Skinner and Horn, 1984) was administered at baseline to characterize the severity of AD. The Substance Abuse Calendar, based on the Timeline Followback Interview (Sobell and Sobell, 1992), was administered by highly trained research personnel at each weekly visit to collect a detailed self-report of daily alcohol and other substance use

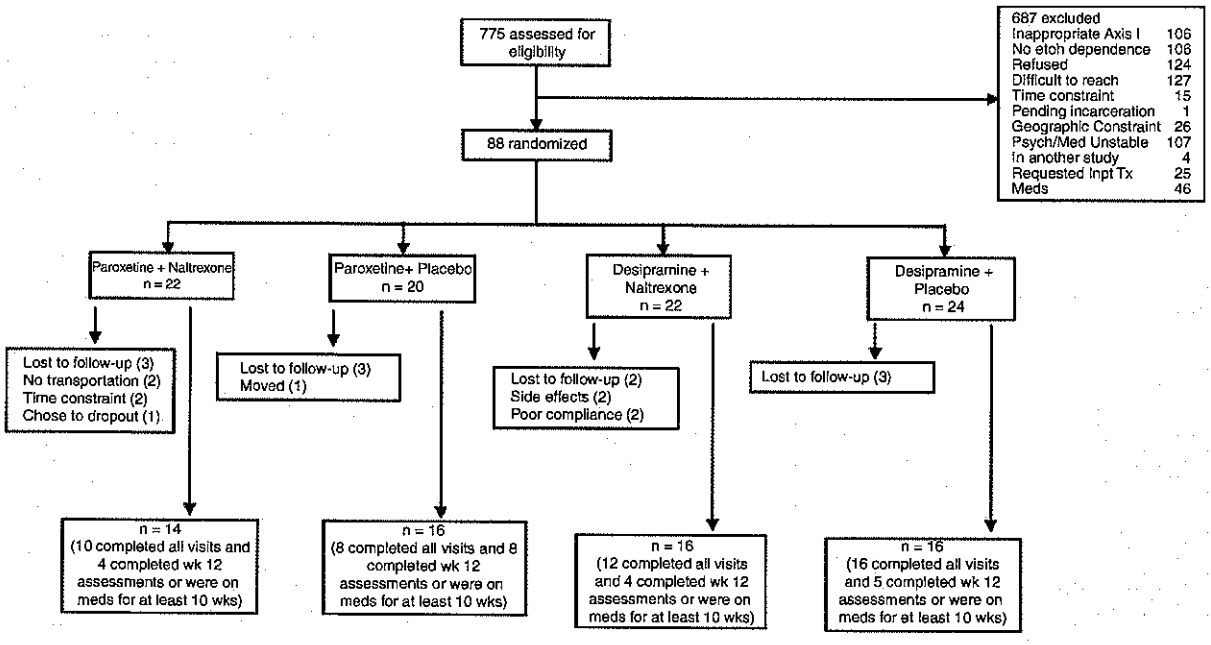


Figure 1 Flowchart describing the screening and randomization distribution for the participants in the study.

throughout the 84-day treatment period, as well as for the 90-day period before randomization. Alcohol consumption was confirmed using serum gamma-glutamyl transferase (GGT), collected four times during the study (baseline, week 4, week 8, and week 12). Craving was assessed weekly using the Obsessive Compulsive Drinking and Abstinence Scale (OCDS; Anton *et al*, 1996).

Side effects and common adverse symptoms were evaluated by the research staff weekly, using a modified version of the Systematic Assessment for Treatment Emergent Events (Levine and Schooler, 1986). The symptoms that are known to be associated with treatment with desipramine, paroxetine, and naltrexone were specifically screened for on a weekly basis. The symptoms were then clustered into the following categories: gastrointestinal, emotional, cold and flu symptoms, skin, sexual, neurological, and cardiac.

Data Analysis

Descriptive statistics were used to summarize the data on all randomized subjects. All continuous variables were examined for adherence to the normal distribution using normal probability plots and Kolmogorov–Smirnov tests. The alcohol data was not normally distributed. Log transformations were applied, but normality was not achieved. Therefore, the alcohol data was ranked and nonparametric tests for repeated measures analysis were used (Brunner *et al*, 2002). Baseline demographic characteristics for the four treatment groups (paroxetine + naltrexone, paroxetine + placebo, desipramine + naltrexone, desipramine + placebo) were compared using χ^2-tests for categorical variables, and using analysis of variance for continuous variables. The analyses were on the intent-to-treat sample. The nonparametric, repeated measures analysis for the drinking data was performed in SAS Version 9.1.3. All other analyses were performed using 17.0 Version of SPSS. All statistical testing was at a two-tailed alpha level of 0.05. Bonferonni adjustments were applied to the analysis of CAPS subscales (three subscales; $\alpha = 0.016$), the alcohol data (three drinking outcome measures; $\alpha = 0.016$), craving data (two subscales: $\alpha = 0.025$), and the comparison of side effects (seven symptom groups; $\alpha = 0.007$).

The outcome variables included: a) PTSD symptoms (change from baseline CAPS total scores and change from baseline scores on CAPS subscales); and b) measures of alcohol consumption (average number of drinks per week, percent heavy drinking days, and drinks per drinking days) and craving (OCDS scores). Mixed-effects models were used to assess changes in PTSD symptoms and alcohol consumption over time. To understand better the differences among the four treatment groups, data were analyzed comparing desipramine to paroxetine, naltrexone to placebo, and their interaction in the same model. The treatment comparisons were between-subject factors in the models, and time (12 weeks) was used as a within-subject factor (when applicable). The use of the mixed-effects models approach for the analysis of our data has several specific advantages. Unlike traditional repeated measures analyses, mixed-effects models allow for different numbers of observations per subject, use of all available data on each subject, and are unaffected by randomly missing data. They also provide flexibility in modeling the correlation structure of the data (Gueorguieva and Krystal, 2004).

RESULTS

Demographic Characteristics

The subjects for this study were participants ($n = 88$) who met current DSM-IV criteria for PTSD and AD (see Table 1). The participants were middle aged (mean age = 47.1, SD = 8.9), predominately Caucasian (75%), and male

Table 1 Demographic and Drinking Characteristics of the Sample

	Totals N = 88	Par+Nal n = 22	Par+Pla n = 20	Des+Nal n = 22	Des+Pla n = 24	Statistics
	Mean, SD	Mean, SD	Mean, SD	Mean, SD	Mean, SD	F, p
Age	47.1, 8.90	45.14, 6.71	49.15, 8.95	47.05, 9.96	47.04, 9.71	703, 0.553
Gender	n, %	n, %	n, %	n, %	n, %	χ^2, p
Male	80, 90.1	22, 100	19, 95	18, 81.8	21, 87.5	5.14, 0.162
Female	8, 9.1	0, 0	1, 5	4, 18.2	3, 12.5	—
Ethnicity						
Caucasian	66, 75	16, 72.3	14, 70	19, 86.3	17, 58.3	2.43, 0.876
African American	19, 21.6	5, 22.7	5, 25	3, 13.6	6, 25	—
Other	3, 3.4	1, 4.5	1, 5	0, 0	1, 4.2	—
Marital status						
Single	22, 25	7, 35	1, 5	7, 31.8	7, 29.2	14.10, 0.119
Married/cohabitating	12, 13.6	1, 4.5	6, 30	4, 18.2	1, 4.2	—
Separated/divorced	52, 59.1	13, 59.1	12, 60	11, 50	16, 66.7	—
Widowed	2, 2.3	1, 4.5	1, 5	0, 0	0, 0	—
Measures of alcohol consumption						
	Mean, SD	Mean, SD	Mean, SD	Mean, SD	Mean, SD	F, p
Number of drinking days 1 month before randomization	19.9, 9.99	19.09, 8.85	19.85, 10.54	22.59, 8.13	18.21, 11.96	0.805, 0.495
Drinks per drinking day 1 month before randomization	23.55, 19.28	28.66, 30.00	17.97, 9.06	21.91, 15.25	25.01, 15.70	1.18, 0.322
Heavy drinking days within last month	18.16, 10.66	16.77, 8.70	18.30, 11.37	20.18, 10.02	17.46, 12.51	415, 0.743
% heavy drinking days 1 month before randomization	60.53, 35.55	55.91, 28.97	61, 37.88	67.27, 33.41	58.19, 41.70	415, 0.743
Total ADS scores	21.45, 8.78	20.52, 8.42	20.32, 6.22	20.09, 9.58	24.42, 9.81	1.286, 0.285
GGT analysis[a]	69.10, 65.25	99.75, 96.93	70.59, 62.02	57.09, 36.63	53.50, 48.05	2.282, 0.086

Abbreviations: ADS, Alcohol Dependence Scale; Des, desipramine; GGT, gamma-glutamyl transferase; Nal, naltrexone; Par, paroxetine; Pla, placebo.
[a]Only 83 of the 88 participants had a GGT analysis; $n = 20$ for Par+Nal; $n = 17$ for Par+Pla.

(90.1%), and the majority were either separated or divorced (59.1%; please see Table 1). There were no differences in age, sex, ethnicity, or marital status, based on treatment assignment in this sample. However, there were site differences on the basis of ethnicity ($\chi^2_1 = 8.3$, $p = 0.015$), with 62% ($n = 26/42$) Caucasians of the sample in West Haven in comparison with 87% ($n = 40/46$) of the sample in Bedford. The sample consisted primarily of veterans (81/88 or 92%) and some non-veterans (7/88 or 8%). Participants were not on any psychiatric medications before starting study, with the exception of sleep medications that were taken as needed ($n = 6$).

For the drinking baseline variables, data was collected for 90 days. Comparisons were made for each drinking variable (number of drinking days, drinks per drinking days, heavy drinking days, and % heavy drinking days) over each 30-day period (three times). As there were no differences in the overall drinking patterns over the three separate months before randomization, data is presented for the 30-day period before enrollment in the study. The participants in this study were heavy drinkers who drank on average 23.5 (SD = 19.3) standard drinks on a drinking day, drank on average 19.9 (SD = 9.9) days in a month, with more than half of their drinking days (mean = 18.16, SD = 10.7) in the past 30 days being heavy drinking days (five or more standard drinks). As shown in Table 1, there were no significant differences between the treatment groups at baseline in drinking days, drinks per drinking days, heavy drinking days, percent heavy drinking days, GGT levels, or ADS scores. However, there were site differences based on ADS scores ($F_{1,84} = 4.44$, $p = 0.038$); participants in West Haven had lower ADS scores (mean = 19.52, SD = 1.32) than participants in Bedford (mean = 23.41, SD = 1.29).

Medication Dosing and Treatment Retention

Antidepressant medication was increased using a taper for all participants according to the predetermined schedule outlined earlier to a maximum dose of 200 mg for desipramine and 40 mg for paroxetine. Participants who could not tolerate the highest dose in either condition were brought to lower doses. In the group taking desipramine, 74% were tapered to the maximum dose of 200 mg, whereas in the group taking paroxetine, 79% were tapered to the maximum dose of 40 mg, indicating that the majority of the participants were able to tolerate the medications.

The average maintenance dose for subjects that were on medication for at least 4 weeks was 187.2 (SD = 31.7) for desipramine and 39.7 (SD = 1.4) for paroxetine.

In this sample of individuals, 49/88 or 55.7% completed the entire trial. There were significantly more completers in the desipramine group ($n = 30/46$, 65%) than in the paroxetine group ($n = 19/42$, 45%; $\chi^2_1 = 3.551$, $p = .05$). Subjects in the desipramine group also took medication longer (mean = 61.41 days, SD = 31.2) than those in the paroxetine group (mean = 45.48 days, SD = 34.6; $F_{1,84} = 4.99$, $p = 0.02$), and desipramine significantly increased the duration (days in the study) of study retention ($\chi^2_1 = 3.7$, $p = 0.053$; please see Figure 2).

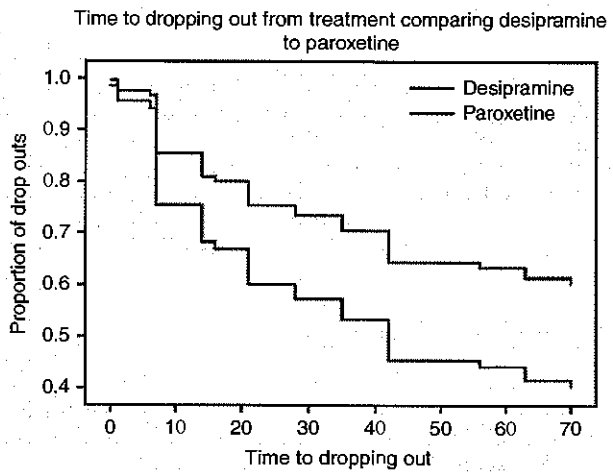


Figure 2 Survival curve of treatment retention comparing desipramine with paroxetine.

Naltrexone did not significantly influence the rate of study completion ($\chi^2_1 = .414$, $p = .52$) and did not significantly increase the duration of study retention (naltrexone: 49.89 ± 35.3 SD; placebo: 57.73 ± 31.92; $\chi^2_1 = 0.01$, $p = 0.916$). There were no significant differences among the treatment groups, based on rates of study retention ($\chi^2_1 = 0.84$, $p = 0.36$).

PTSD Symptom Outcomes

The CAPS data were analyzed using change from baseline CAPS scores in the model to control for baseline symptoms of PTSD (please see Table 2). There was a significant decrease in CAPS scores over time ($F_{6108.8} = 2.175$, $p = 0.051$) and no significant interactions of treatment with time (desipramine/paroxetine by time $F_{6108.8} = 1.249$, $p = 0.287$; naltrexone/placebo by time $F_{6108.8} = 0.813$, $p = 0.562$), and no significant three-way interaction (please see Figure 3). Similarly, there was a significant decrease in each of the three CAPS subscale scores over time, but after Bonferonni adjustment was applied to the analysis ($\alpha = 0.016$), no treatment effects or interactions were significant.

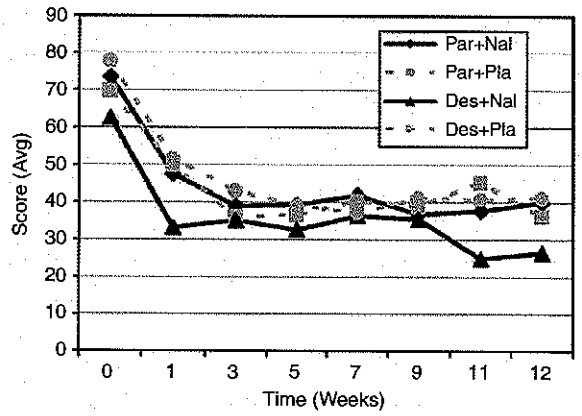
Alcohol Use Outcomes

Relative to paroxetine, desipramine significantly reduced the percentage of heavy drinking days ($F_{1.84} = 7.22$, $p = 0.009$)

Table 2 PTSD and Depression Outcome Scores at Beginning and End of Treatment

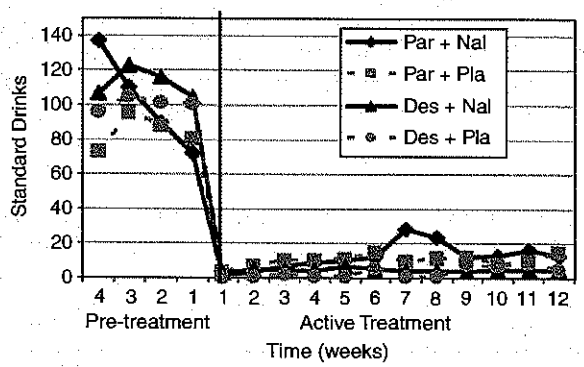
	Paroxetine+Naltrexone	Paroxetine+Placebo	Desipramine+Naltrexone	Desipramine+Placebo	Time
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	F, p
CAPS					
Pre	73.54 (5.007)	69.810 (5.166)	62.500 (5.047)	77.833 (4.832)	49.633, 0.00
Post	40.024 (5.53)	36.591 (5.570)	26.751 (5.353)	41.392 (4.949)	—
Re-experience					
Pre	18.640 (1.863)	17.619 (1.918)	15.909 (1.874)	21.417 (1.794)	22.803, 0.00
Post	9.513 (1.926)	9.069 (2.059)	7.295 (2.010)	9.350 (1.842)	—
Avoidance					
Pre	32.221 (2.245)	29.667 (2.314)	26.227 (2.261)	31.083 (2.165)	41.289, 0.00
Post	17.038 (2.315)	14.459 (2.467)	9.697 (2.408)	18.354 (2.221)	—
Hyperarousal					
Pre	22.573 (1.677)	22.524 (1.726)	20.364 (1.687)	25.333 (1.615)	30.670, 0.00
Post	13.430 (1.734)	13.398 (1.890)	9.811 (1.809)	13.925 (1.658)	—
HAM-D					
Pre	13.273 (1.112)	10.950 (1.167)	11.195 (1.132)	13.167 (1.065)	8.570, 0.00
Post	9.328 (1.256)	8.238 (1.299)	8.563 (1.201)	8.943 (1.117)	—

Abbreviations: CAPS, clinician administered PTSD scale; HAM-D, Hamilton depression scale; PTSD, post-traumatic stress disorder.



Par = Paroxetine; Nal = Naltrexone; Pla = Placebo; Des = Desipramine

Figure 3 Post-traumatic stress disorder (PTSD) symptoms measured using total clinician administered PTSD scale for DSM-IV (CAPS) scores over the entire 12 weeks of treatment for four treatment conditions.



Par = Paroxetine; Nal = Naltrexone; Pla = Placebo; Des = Desipramine

Figure 4 Number of standard drinks per week during pre-treatment (4 weeks) and during active treatment (12 weeks) for the four treatment conditions.

and drinks per drinking days ($F_{1.84} = 5.04$, $p = 0.027$). Participants significantly reduced their weekly alcohol consumption during the study (time: $ATS_{6.82} = 4.3$, $p = 0.0001$), and 51% of participants remained abstinent throughout the study. Also, after adjusting for multiple comparisons, there was a significant interaction for time by desipramine/paroxetine treatment on the number of drinks per week ($ATS_{6.82} = 2.46$, $p = 0.018$; please see Figure 4), indicating that the desipramine-treated subjects had a greater reduction in their drinking over time compared with the paroxetine-treated subjects.

There were no significant effects of naltrexone on any of the drinking outcomes, including average number of drinks per week, percentage of heavy drinking days, and drinks per drinking days.

Craving. OCDS total scores decreased significantly over time ($F_{12104.8} = 6.87$, $p = 0.0001$). Naltrexone, relative to placebo, significantly decreased craving ($F_{1582.0} = 6.39$, $p = 0.012$; naltrexone = 19.88 (SD = 12.89) at baseline, placebo = 21.1 (SD = 12.89) at baseline, compared with naltrexone = 6.7 (SD = 14.07) at endpoint, placebo = 8.3 (SD = 13.38) at endpoint). There were no significant differences in craving between the desipramine *vs* paroxetine-treated subjects (desipramine = 20.0 (SD = 12.61) at baseline, paroxetine = 21.0 (SD = 13.19) at baseline, compared with desipramine = 6.1 (SD = 13.09) at endpoint, and paroxetine = 9.4 (SD = 14.45) at endpoint) and no significant two-way or three-way interactions. OCDS (obsessions and compulsions) subscale scores decreased significantly over time. After Bonferonni adjustment was applied to the analysis ($\alpha = 0.025$), no treatment effects or interactions were significant.

GGT levels. GGT levels declined over time in the entire sample ($F_{3121.8} = 3.3$, $p = 0.022$). This reduction was significantly greater in the desipramine-treated participants ($F_{1229.5} = 5.08$, $p = 0.02$; desipramine baseline = 55.2, paroxetine baseline = 86.4; desipramine week 4 = 48.7, paroxetine week 4 = 46.1; desipramine week 8 = 41.7, paroxetine week 8 = 47.1; desipramine week 12 = 37.5, paroxetine week 12 = 57.1). Naltrexone did not significantly affect GGT levels.

Depression Symptom Outcomes

There was a significant decrease in the 17-item Hamilton Depression scores over time ($F_{7405.6} = 8.57$, $p = 0.0001$) and no significant interactions of treatment with time (desipramine/paroxetine by time $F_{7418.2} = 0.834$, $p = 0.970$; naltrexone/placebo by time $F_{7418.1} = 0.152$, $p = 0.994$), and no significant three-way interaction (please see Table 2).

Adverse Events

There were five medical adverse events in this study; one in the desipramine + naltrexone group, two in the desipramine + placebo group, one in paroxetine + naltrexone group, and one in the paroxetine + placebo group. One study participant died in a work-related fatality that occurred 4 weeks after study medications were discontinued, and was deemed to be unrelated to the study. Among participants receiving desipramine, two reported dizziness or lightheadedness, one participant treated with this medication-developed tachycardia. These cases were managed by careful clinical monitoring and, in some cases, adjusting their desipramine dose. One participant in the paroxetine + placebo group experienced a seizure and study medication was discontinued.

There were four psychiatric adverse events in this study. Two participants were incarcerated related to alcohol intoxication (desipramine + placebo; paroxetine + naltrexone). One participant was hospitalized for severe anxiety (paroxetine + placebo). One participant (paroxetine + placebo) reported suicidal ideation 9 weeks after study medication was discontinued, which was deemed to be unrelated to study medication.

Side Effects

Desipramine-treated participants reported significantly more gastrointestinal symptoms (abdominal pain, nausea, vomiting, loss of appetite, constipation, diarrhea, aftertaste, dry mouth, coughing up blood, vomiting blood, black/bloody/light stool,

yellow eyes, weight gain, and increased thirst) than paroxetine-treated subjects ($F_{1,84}=7.67$, $p=0.007$). After adjustment for multiple comparisons ($\alpha=0.007$), there were no other statistically significant differences in side effect reporting across the groups.

DISCUSSION

The current data provide the strongest evidence to date that NRIs might have a role in the treatment of individuals with PTSD and comorbid AD. In this study, desipramine had a comparable efficacy to paroxetine for PTSD symptoms, despite a prior literature questioning the efficacy of desipramine (Reist *et al*, 1989). Further, desipramine was superior in reducing alcohol consumption, as it significantly reduced the percentage of heavy drinking days and the number of drinks per week compared with paroxetine, confirmed by a significant decrease in GGT levels. However, there was no main effect of naltrexone on PTSD symptoms, and the combination of desipramine and naltrexone did not confer any clinical advantages.

Revisiting the role of NRIs in PTSD treatment is timely. Tricyclic antidepressants with NRI activity were among the first pharmacotherapies for PTSD supported by double-blind, placebo-controlled clinical trials (Frank and Thase, 1999). The superior tolerability profile for SRIs over tricyclic antidepressants, the emergence of definitive pharmacotherapy trials supporting the efficacy of SRIs for PTSD (Brady *et al*, 2000; Marshall *et al*, 2001; Tucker *et al*, 2001), the absence of definitive NRI trials for PTSD, and the negative preliminary findings with desipramine (Reist *et al*, 1989), all contributed to waning interest in NRI treatment for PTSD. More recently, the emergence of drugs that block the α_1 noradrenergic receptor, such as prazosin (Raskind *et al*, 2007) and risperidone (Berger *et al*, 2009; Rothbaum *et al*, 2008) as promising treatments for the re-experiencing and hyperarousal symptoms of PTSD, converges with evidence of (a) the capacity of NRIs to attenuate noradrenergic activation (Charney and Heninger, 1985) and (b) of preliminary support for the NRI, reboxetine for PTSD (Spivak *et al*, 2006). These findings indicate that after 25 years of research, noradrenergic hyperactivity remains an important target for the treatment of PTSD (Van der Kolk, 2004).

The superior efficacy of desipramine to paroxetine for reducing heavy drinking may be particularly important for veterans with PTSD. SRIs appear to have mixed effects on drinking among patients diagnosed with PTSD, increasing drinking in some subgroups, whereas reducing drinking in others (Brady and Sinha, 2005). Similarly the efficacy of SRIs for reducing drinking among patients with comorbid depression has been questioned (Pettinati, 2001, 2004). NRIs have not been studied previously in patients with AD and PTSD, but a prior study provided suggestive evidence that desipramine reduced drinking only in alcohol-dependent patients with comorbid depression (Mason *et al*, 1996). Interestingly, the improved alcohol use outcomes were not reflected in improved symptoms of PTSD, but perhaps a longer study would address this issue.

In contrast to a prior report from our group (Petrakis *et al*, 2006), naltrexone did not reduce drinking in participants in this study. Differences in the design or execution of the current study may have influenced the opposing findings. The current study differs from the prior one in that participants were specifically recruited for this clinical trial on the basis of comorbid PTSD and AD. In contrast, the prior report was a secondary subgroup analysis of a larger study that recruited participants with a variety of psychiatric disorders. Also, participants in the prior study were on long-standing pharmacotherapies for PTSD, whereas participants in the current study either started or changed antidepressant medications while also being randomized to naltrexone or placebo. The failure to replicate the prior finding may be related to the smaller sample size and reduced statistical power in the current study. We acknowledge that our study was powered to detect medium to large effect sizes, and we do not have sufficient power to detect smaller effect sizes. The aforementioned study is consistent with secondary analyses of a prior VA multicenter study of naltrexone. This study reported that the increased risk for relapse to alcohol use among patients requiring the introduction of antidepressants for psychiatric symptoms may be mitigated by naltrexone (Krystal and Neumeister, 2009). Although naltrexone worsens symptoms associated with noradrenergic hyperactivity in human laboratory models (Charney and Heninger, 1986; Rosen *et al*, 1999), it did not worsen PTSD symptoms and in fact was well-tolerated by participants in this study.

Several issues limit conclusions that may be drawn from the current findings. First, the current findings may not generalize to all patients, such as women and non-veterans. Women may show superior SRI responses relative to tricyclic antidepressants for the treatment of both major depression and PTSD. The absence of an SRI and NRI efficacy difference in the current study may reflect the predominately male study sample. The results of the current study are consistent with other reports that evaluated the efficacy of an SRI for PTSD in predominately male veterans (without comorbidity) and showed no group differences in PTSD outcomes (Friedman *et al*, 2007). It should be noted that the studies differ in methodology, as one study used a placebo comparison whereas the current study used an active comparison. Second, drinking outcomes in SRI clinical trials for AD may be influenced by factors such as the age of onset of pathological drinking and of PTSD (Brady *et al*, 2000; Kranzler *et al*, 1996); these factors were not collected in this study. Third, this study compared desipramine and paroxetine with the objective of distinguishing the effects of NRI and SRI treatment for PTSD. However, desipramine is not truly a selective NRI. Recent evidence of the preliminary efficacy of prazosin in reducing PTSD symptoms (Raskind *et al*, 2007) suggests that a medication that has the capacity to block α_1 adrenergic receptors (Richelson, 2003) may be related to its efficacy in treating symptoms of PTSD. This important issue limits the capacity of the current findings to inform the question as to whether highly selective NRIs would be preferred for the treatment of this population over medications that block *both* the norepinephrine transporter and α_1 adrenergic receptors. Also, this study could not address the combinatorial impact of blockade of serotonin and norepinephrine transporters, ie, SNRIs. These drugs have shown preliminary

efficacy for PTSD (Davidson *et al*, 2006; Pae *et al*, 2007; Richelson, 2003). Their efficacy in AD is untested.

Overall, this study provided support for further investigation of desipramine treatment for participants with comorbid PTSD and AD. Although paroxetine, but not desipramine, is FDA-approved for PTSD treatment, the current study did not fmd a significant difference between desipramine and paroxetine with respect to their effectiveness in treating PTSD symptoms. Further, in this sample of predominately male veterans, desipramine significantly reduced heavy drinking compared with paroxetine, making it an important possible therapeutic agent in treating this population of patients.

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DISCLOSURE

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