Original Investigation

Concurrent Naltrexone and Prolonged Exposure Therapy for Patients With Comorbid Alcohol Dependence and PTSD
A Randomized Clinical Trial

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IMPORTANCE Alcohol dependence comorbid with posttraumatic stress disorder (PTSD) has been found to be resistant to treatment. In addition, there is a concern that prolonged exposure therapy for PTSD may exacerbate alcohol use.

OBJECTIVE To compare the efficacy of an evidence-based treatment for alcohol dependence (naltrexone) plus an evidence-based treatment for PTSD (prolonged exposure therapy), their combination, and supportive counseling.

DESIGN, SETTING, AND PARTICIPANTS A single-blind, randomized clinical trial of 165 participants with PTSD and alcohol dependence conducted at the University of Pennsylvania and the Philadelphia Veterans Administration. Participant enrollment began on February 8, 2001, and ended on June 25, 2009. Data collection was completed on August 12, 2010.

INTERVENTIONS Participants were randomly assigned to (1) prolonged exposure therapy plus naltrexone (100 mg/d), (2) prolonged exposure therapy plus pill placebo, (3) supportive counseling plus naltrexone (100 mg/d), or (4) supportive counseling plus pill placebo. Prolonged exposure therapy was composed of 12 weekly 90-minute sessions followed by 6 biweekly sessions. All participants received supportive counseling.

MAIN OUTCOMES AND MEASURES The Timeline Follow-Back Interview and the PTSD Symptom Severity Interview were used to assess the percentage of days drinking alcohol and PTSD severity, respectively, and the Penn Alcohol Craving Scale was used to assess alcohol craving. Independent evaluations occurred prior to treatment (week 0), at posttreatment (week 24), and at 6 months after treatment discontinuation (week 52).

RESULTS Participants in all 4 treatment groups had large reductions in the percentage of days drinking (mean change, −63.9% [95% CI, −73.6% to −54.2%] for prolonged exposure therapy plus naltrexone; −63.9% [95% CI, −73.9% to −53.8%] for prolonged exposure therapy plus placebo; −69.9% [95% CI, −78.7% to −61.2%] for supportive counseling plus naltrexone; and −61.0% [95% CI, −68.9% to −53.0%] for supportive counseling plus placebo). However, those who received naltrexone had lower percentages of days drinking than those who received placebo (mean difference, 7.93%; $P = .008$). There was also a reduction in PTSD symptoms in all 4 groups, but the main effect of prolonged exposure therapy was not statistically significant. Six months after the end of treatment, participants in all 4 groups had increases in percentage of days drinking. However, those in the prolonged exposure therapy plus naltrexone group had the smallest increases.

CONCLUSIONS AND RELEVANCE In this study of patients with alcohol dependence and PTSD, naltrexone treatment resulted in a decrease in the percentage of days drinking. Prolonged exposure therapy was not associated with an exacerbation of alcohol use disorder.

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Alcohol dependence and posttraumatic stress disorder (PTSD) are highly comorbid,[1] yet little is known about how best to treat this large, highly dysfunctional, and distressed population. Even though studies of treatments for alcohol dependence do not exclude patients with PTSD, symptoms of PTSD are not targeted with these treatments.[2,3] The failure to address PTSD is deleterious because patients with alcohol dependence and PTSD relapse sooner than patients with alcohol dependence and other comorbid Axis I psychiatric diagnoses.[3] In contrast, treatment studies for PTSD typically exclude patients with comorbid alcohol dependence[4] because of the concern that alcohol dependence will interfere with the patient's ability to benefit from PTSD treatment[5] or fear that the PTSD treatment will exacerbate drinking behavior.[6,7]

Previous trials of concurrent therapies for substance use disorders and PTSD have demonstrated improvements in PTSD, but have not shown clear benefits for the treatment of substance use disorder.[6,8] Only 1 published randomized trial used cognitive behavioral therapy for alcohol dependence plus 150 mg of sertraline (or placebo) for PTSD.[9] Alcohol use and PTSD symptoms decreased during treatment, but the study design did not allow separating the unique effects of cognitive behavioral therapy from the effects of the medication.

We compared the efficacy of naltrexone, which is an evidence-based treatment for alcohol dependence,[10-12] and prolonged exposure therapy, which is an evidence-based treatment for PTSD,[4,13] separately and in combination, along with supportive counseling. Naltrexone is hypothesized to decrease drinking via attenuation of craving for alcohol, and prolonged exposure therapy is hypothesized to reduce drinking via amelioration of PTSD symptoms that can lead to self-medication with alcohol. Our 2 × 2 study design tested the hypotheses that (1) participants receiving naltrexone would show significantly greater reductions in drinking than those receiving placebo; (2) participants receiving prolonged exposure therapy would show greater reductions in PTSD symptom severity than those who do not receive prolonged exposure therapy; and (3) participants receiving combined treatment would show superior outcomes in both decreased drinking and PTSD severity.[14]

Methods

Participants

Participants were treatment-seeking individuals recruited through advertisements and professional referrals to the University of Pennsylvania's Center for the Treatment and Study of Anxiety and the Philadelphia Veterans Affairs Hospital. The demographic and trauma information collected at baseline appear in **Table 1**. Inclusion criteria were (1) current PTSD and alcohol dependence according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*)[15]; (2) clinically significant trauma-related symptoms, as indicated by a score of at least 15 on the PTSD Symptom Severity Interview (PSS-I)[16,17]; and (3) heavy drinking in the past 30 days, defined as an average of more than 12 standard alcohol drinks per week with at least 1 day of 4 or more drinks determined by the Timeline Follow-Back Interview (TFBI).[18] Exclusion criteria were (1) current substance dependence other than nicotine or cannabis; (2) current psychotic disorder (eg, schizophrenia, bipolar disorder); (3) clinically significant suicidal or homicidal ideation; (4) opiate use in the month prior to study entry; (5) medical illnesses that could interfere with treatment (eg, AIDS, active hepatitis); or (6) pregnancy or nursing.

Procedure

The University of Pennsylvania institutional review board approved the protocol. After receiving written informed consent, participants completed an intake assessment, which included a physical examination, laboratory assessments, and a psychiatric evaluation. Eligible participants completed a baseline evaluation and were then randomly assigned to 1 of 4 treatment groups in which they received 100 mg/d of naltrexone or placebo plus prolonged exposure therapy or no prolonged exposure therapy. Prior to beginning treatment, participants completed outpatient medical detoxification (≥3 consecutive days of abstinence from alcohol) measured via self-report and breath testing for alcohol. During detoxification, oxazepam was administered as needed to manage symptoms of alcohol withdrawal. All patients received supportive counseling focused on medication management (see treatment descriptions below). Participant enrollment began on February 8, 2001, and ended on June 25, 2009 (**Figure 1**). Data collection was completed on August 12, 2010.

Measures

The PSS-I[16,17] is a clinician-rated interview corresponding to the *DSM-IV*[15] symptom criteria. It was administered by evaluators, who were blinded to group assignment, prior to treatment, every 4 weeks during treatment, at posttreatment (week 24), and at follow-up (weeks 38 and 52). The PSS-I has a range of scores from 0 to 51 with higher scores indicating more severe PTSD symptoms.

The TFBI[18] is an interview that uses a calendar method to assess when and how much alcohol was consumed. The TFBI was used to calculate the percentage of days drinking (PDD) at pretreatment, each visit during treatment, posttreatment (week 24), and 6 months after treatment discontinuation (week 52). Because the number of days between assessment points varied, we presented drinking days as a percentage of total days. For descriptive purposes, we also calculated the number of days drinking in the past 90 days at baseline and week 52. Higher scores for PDD and drinking days in the past 90 days indicate worse drinking outcomes.

The Penn Alcohol Craving Scale[19] is a 5-item self-administered measure of alcohol craving during the prior week that was completed at every visit. The range of possible scores is 0 to 30, with higher scores indicating a higher level of craving.

Treatments

Naltrexone is an opiate antagonist approved by the US Food and Drug Administration to treat alcohol dependence. The target dose of naltrexone was 100 mg/d, starting with 50 mg/d for

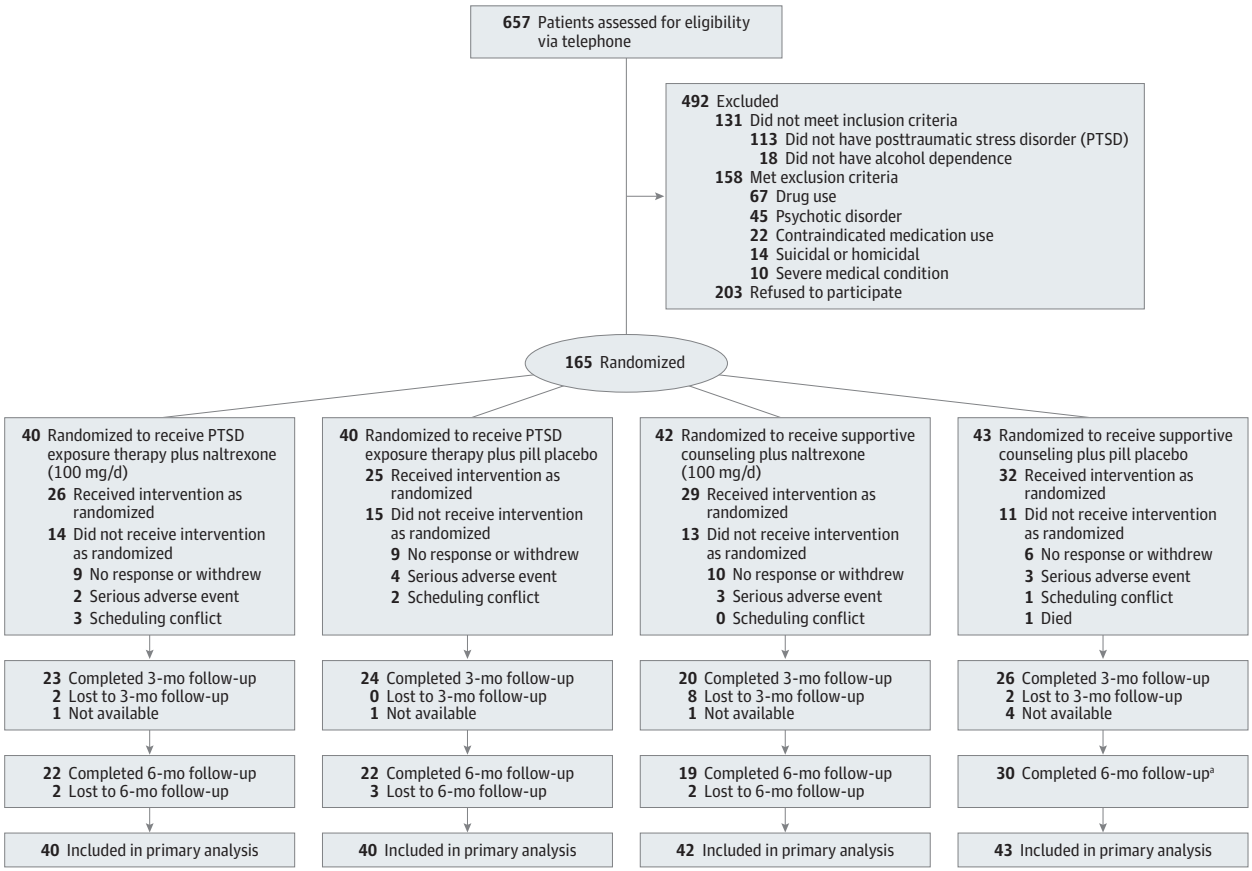
Table 1. Baseline Characteristics[a]

	PTSD Exposure Therapy		Supportive Counseling	
	Plus Naltrexone (n = 40)	Plus Placebo (n = 40)	Plus Naltrexone (n = 42)	Plus Placebo (n = 43)
Age, mean (95% CI), y	40.1 (36.7-43.5)	44.7 (41.8-47.7)	44.9 (41.8-47.9)	41.2 (38.6-43.9)
Sex				
Female	13 (32.5)	13 (32.5)	16 (38.1)	15 (34.9)
Male	27 (67.5)	27 (67.5)	26 (61.9)	28 (65.1)
Race/ethnicity				
Black	30 (75.0)	28 (70.0)	21 (50.0)	26 (60.5)
White	9 (22.5)	8 (20.0)	19 (45.2)	14 (32.6)
Hispanic	1 (2.5)	3 (7.5)	2 (4.8)	1 (2.3)
Native American	0	0	0	1 (2.3)
Other	0	1 (2.5)	0	1 (2.3)
Types of trauma				
Sexual assault	12 (30.0)	11 (27.5)	11 (26.2)	8 (18.6)
Physical assault	16 (40.0)	12 (30.0)	18 (42.9)	16 (37.2)
Combat	4 (10.0)	7 (17.5)	4 (9.5)	4 (9.3)
Other	8 (20.0)	10 (25.0)	9 (21.4)	15 (34.9)
Time since trauma, mean (SD), y	12.3 (13.5)	10.3 (13.0)	12.2 (13.2)	10.3 (12.2)

Abbreviation: PTSD, posttraumatic stress disorder.

[a] Values are expressed as number (percentage) unless otherwise indicated. All participants received supportive counseling.

Figure 1. Flow of Participants Through the Trial



All participants received supportive counseling.
[a]Some participants who did not complete the 3-month follow-up returned to complete the 6-month follow-up.

a minimum of 3 days and titrating up within 1 week; 3 patients were unable to tolerate the 100-mg/d dose and were titrated down to 50 mg/d. The 100-mg/d dose of naltrexone used in this study is higher than the 50-mg/d dose recommended for treatment of alcohol dependence, but much lower than the 300-mg/d dose that has been associated with elevations in liver enzyme levels.[20] Compliance with the dosing regimen was monitored by weekly pill counts during the first 3 months and by biweekly counts for the next 3 months.

Prolonged exposure therapy consisted of 12 weekly 90-minute sessions followed by 6 biweekly sessions and included repeated imaginal exposure (ie, revisiting and recounting traumatic memories) and processing the memory (ie, discussing thoughts and feelings related to revisiting the memory).[21] Participant homework consisted of repeated listening to a recording of the recounting made during the session, and repeated in vivo exposure to safe situations he/she avoided because of trauma-related distress. When the participant demonstrated no or minimal distress when recounting the traumatic memory and confronting traumatic reminders, any remaining sessions focused on other psychosocial problems.

Supportive counseling was based on the BRENDA model,[22] which combines medication management with compliance enhancement techniques based on motivational interviewing.[23] All participants received eighteen 30- to 45-minute sessions of supportive counseling, administered by a study nurse, which included dispensing medication, monitoring compliance, assessing and providing education about alcoholism, and offering support and advice concerning drinking. Visits were weekly during the first 3 months and biweekly during the remaining 3 months.

For more details about the treatment methods and sample, see Foa and Williams.[24]

Data Analyses

Two-tailed tests adopting an α level of .05 were conducted to test differences in change in outcomes among treatment groups. We conducted piecewise growth modeling using hierarchical linear and nonlinear modeling (version 6.34)[25] to estimate different slopes during the treatment phase and the follow-up phase.[26] Hierarchical linear and nonlinear modeling is robust to missing data due to dropout during treatment and follow-up.[27] Using hierarchical linear and nonlinear modeling does not exclude any data, thus rendering replacement or imputation for missing values unnecessary.[28] A nonlinear model (natural log number of weeks) fit the data best for the PSS-I and alcohol craving outcomes; for PDD, a piecewise model with a hyperbolic transformation of the number of weeks fit the data best.

All change parameters were modeled as random effects. The main effects of treatment were evaluated by coding time variables such that intercept terms of the piecewise growth models represented posttreatment outcome levels (ie, centering the time variables at posttreatment), and by including dummy-coded treatment group variables as predictors of the intercept. A graphical examination of the growth curve results revealed potential treatment differences in change over time during the follow-up period. Therefore, we conducted exploratory tests for the following interactions during follow-up: prolonged exposure therapy × time, naltrexone × time, and prolonged exposure therapy × naltrexone × time. Dummy-coded variables and interaction terms for prolonged exposure therapy and naltrexone were included in the level 2 component of the model as predictors of the change parameter during follow-up. The Cohen *d* statistic is reported for between-group effect sizes (d = 0.25 for small, d = 0.50 for medium, and d = 0.80 for large[29]). All analyses were conducted with the intent-to-treat sample.

The Mplus statistical software version 5.1 was used for a Monte Carlo simulation post hoc power analysis, which used parameter estimates from the data analysis to provide estimates of obtained power.[30,31] These analyses produced power estimates of 0.90 or higher to detect medium (d = 0.50) effect size differences of 20.6 to 22.8 for change in PDD and 7.1 to 10.2 for change in PTSD severity (on the PSS-I) during treatment. The analyses also produced power estimates of 0.90 or higher to detect medium effect size differences of 17.4 to 18.1 for PDD and 7.1 to 8.4 for PTSD severity (PSS-I) during follow-up. Exploratory χ^2 analyses were conducted to examine differences in the percentage of participants classified as having achieved low PTSD severity (ie, ≤10 on the PSS-I at 6 months after treatment discontinuation).

Results

Preliminary Analyses

There were 165 participants with PTSD and alcohol dependence. Fifty-three participants (32.1%) dropped out of the study prior to the end of the treatment period. This rate did not significantly differ (χ^2_3 = 1.55; P = .67) across treatment groups (n = 165): 35% for prolonged exposure therapy plus naltrexone, 38% for prolonged exposure therapy plus placebo, 31% for supportive counseling plus naltrexone, and 26% for supportive counseling plus placebo. Twelve participants were removed from the study because of serious adverse events (serious suicidal ideation, n = 7; serious medical illness, n = 3; psychotic symptoms, n = 1; death, n = 1; however, none of these events was determined to be related to the study). Analysis of variance and χ^2 analysis revealed no significant differences for demographic and pretreatment outcome variables across groups (Table 1). The median number of years since the index trauma was 5.15 (25th percentile, 1.34; 75th percentile, 20.21).

Treatment Adherence

Prolonged Exposure Therapy

On average, participants completed a mean of 6.18 (SD, 3.86) exposure sessions in the prolonged exposure therapy plus naltrexone group vs a mean of 6.48 (SD, 3.49) sessions in the prolonged exposure therapy plus placebo group (P = .73). Treatment adherence for prolonged exposure therapy was monitored by 3 doctoral-level clinicians. Of the total prolonged exposure therapy sessions provided, 15% were randomly selected to assess treatment adherence. The overall ad-

Table 2. Summary of the Piecewise Growth Curve Models for Percentage of Days Drinking and Craving to Drink[a]

	Mean (95% CI), % of Days				
	Pretreatment (Wk 0)	Posttreatment (Wk 24)	Change Between Pretreatment and Posttreatment	Follow-up (Wk 52)	Change Between Posttreatment and Follow-up
Drinking					
PTSD exposure therapy					
Plus naltrexone	71.2 (62.5 to 79.9)	7.3 (1.9 to 12.7)	−63.9 (−73.6 to −54.2)	8.8 (3.3 to 14.3)	1.5 (−0.9 to 3.8)
Plus placebo	78.6 (71.4 to 85.6)	13.4 (5.5 to 21.1)	−63.9 (−73.9 to −53.8)	18.9 (8.8 to 29.1)	5.6 (0.2 to 11.0)
Supportive counseling					
Plus naltrexone	75.4 (67.1 to 83.5)	3.5 (0.1 to 6.8)	−69.9 (−78.7 to −61.2)	21.5 (10.6 to 32.4)	18.0 (13.2 to 22.8)
Plus placebo	74.1 (66.4 to 81.8)	13.2 (7.3 to 19.2)	−61.0 (−68.9 to −53.0)	27.3 (14.7 to 40.0)	14.1 (8.8 to 19.4)
Craving to drink					
PTSD exposure therapy					
Plus naltrexone	17.9 (15.8 to 20.1)	5.1 (3.4 to 6.7)	−13.6 (−16.1 to −11.2)	6.0 (4.0 to 8.1)	1.0 (−1.2 to 3.2)
Plus placebo	19.2 (16.3 to 22.1)	9.1 (6.1 to 12.2)	−10.1 (−13.5 to −6.63)	6.9 (4.2 to 9.7)	−2.1 (−5.2 to 1.0)
Supportive counseling					
Plus naltrexone	17.7 (15.3 to 20.0)	8.0 (6.0 to 10.1)	−9.8 (−12.3 to −7.2)	7.4 (4.2 to 10.6)	−0.6 (−3.4 to 2.3)
Plus placebo	18.7 (16.7 to 20.7)	10.3 (8.2 to 12.4)	−8.7 (−11.4 to −6.1)	8.9 (6.4 to 11.4)	−1.4 (−3.4 to 0.7)

Abbreviation: PTSD, posttraumatic stress disorder.

[a] All participants received supportive counseling.

herence rate was 96%. Three adherence raters performed separate ratings on 10% of the sessions. Interrater reliability was 97.8% (95% CI, 91.7%-99.9%).

Medication

The average number of days of detoxification was 4.45 (range, 3-14 days). All but 10 participants were able to reach and remain on 100 mg/d of naltrexone; 9 were titrated down to 50 mg/d and 1 participant refused medication and dropped out of the study. There were 141 participants (85%) who met criteria for adherence to medication and supportive counseling (defined as ≥80% adherence to medication and attendance to supportive counseling): 34 (85.0%) in the prolonged exposure therapy plus naltrexone group, 34 (85.0%) in the prolonged exposure therapy plus placebo group, 36 (85.7%) in the supportive counseling plus naltrexone group, and 37 (86.0%) in the supportive counseling plus placebo group. Differences between groups were not statistically significant (P = .99).

Drinking Outcome

Participants in all groups reported reductions in PDD during treatment (**Table 2**). At posttreatment, a significant main effect of naltrexone emerged (mean difference = 7.93%, P = .008, d = 0.42) such that patients receiving naltrexone had lower PDD (mean, 5.38%; 95% CI, 2.23% to 8.54%) than patients receiving placebo (mean, 13.29%; 95% CI, 8.45% to 18.12%). At posttreatment, the main effect of prolonged exposure therapy (P = .51) and the interaction of naltrexone × prolonged exposure therapy (P = .53) were not statistically significant. During the 6 months following treatment discontinuation, a significant prolonged exposure therapy × time interaction emerged (P = .01, d = 0.41) such that patients receiving prolonged exposure therapy had a mean change in PDD during follow-up of 3.6% (95% CI, −2.2% to 9.5%), which was not significant, whereas patients not receiving prolonged exposure therapy exhibited a mean increase in PDD during follow-up of 15.9% (95% CI, 8.8% to 23.1%). The interactions of naltrexone × time (P = .98) and prolonged exposure therapy × naltrexone × time (P = .39) were not statistically significant during follow-up.

All groups showed reductions in alcohol craving during treatment (Table 2). A significant main effect of naltrexone emerged (mean difference = 3.14, P = .008, d = 0.43) at posttreatment such that the 2 naltrexone groups had less alcohol craving (mean craving, 6.6; 95% CI, 5.2-7.9) than the 2 placebo groups (mean craving, 9.7; 95% CI, 7.9-11.6). Neither the main effect of prolonged exposure therapy (P = .08) nor the interaction of prolonged exposure therapy × naltrexone (P = .44) was significant at posttreatment. During follow-up, the interactions of prolonged exposure therapy × time (P = .55), naltrexone × time (P = .66), and prolonged exposure therapy × naltrexone × time (P = .63) were not statistically significant, with none of the groups exhibiting significant changes in alcohol craving during follow-up.

PTSD Outcome

All 4 groups showed reductions in PSSI (or PTSD symptoms) during the treatment period (**Table 3**). The main effect of prolonged exposure therapy at posttreatment was not significant (mean difference = 2.63, P = .15, d = 0.23). At posttreatment, the main effects of naltrexone (P = .70) and the interaction of prolonged exposure therapy × naltrexone (P = .80) were also not significant. The interactions of prolonged exposure therapy × time (P = .55), naltrexone × time (P = .66), and prolonged exposure therapy × naltrexone × time (P = .63) were not statistically significant for the follow-up period.

In an exploratory analysis, 70.0% of participants in the prolonged exposure therapy plus naltrexone group achieved a low level of PTSD severity (ie, ≤10 on the PSS-I at 6 months after

Table 3. Summary of the Piecewise Growth Curve Models for Posttraumatic Stress Disorder (PTSD) Symptoms[a]

PTSD Symptom Severity Interview	Mean (95% CI), % of Days				
	Pretreatment (wk 0)	Posttreatment (wk 24)	Change Between Pretreatment and Posttreatment	Follow-up (wk 52)	Change Between Posttreatment and Follow-up
PTSD exposure therapy					
Plus naltrexone	30.3 (27.7 to 32.9)	12.2 (8.2 to 16.1)	−19.1 (−23.1 to −15.09)	7.9 (4.1 to 11.8)	−4.1 (−7.6 to −0.6)
Plus placebo	27.7 (24.7 to 30.8)	13.3 (9.3 to 17.3)	−16.1 (−20.8 to −11.3)	10.8 (6.3 to 15.2)	−2.5 (−6.3 to 1.3)
Supportive counseling					
Plus naltrexone	27.1 (24.7 to 30.8)	15.3 (12.2 to 18.3)	−12.40 (−15.79 to −8.97)	10.9 (7.2 to 14.6)	−4.2 (−8.1 to −0.3)
Plus placebo	27.5 (25.4 to 29.6)	15.5 (12.4 to 18.6)	−11.6 (−14.1 to −9.1)	11.1 (8.2 to 14.1)	−4.3 (−6.9 to −1.6)

[a] All participants received supportive counseling.

treatment discontinuation) vs 55.0% of participants in the prolonged exposure therapy plus placebo group, 43.9% of the supportive counseling plus naltrexone group, and 37.2% of the supportive counseling plus placebo group (P = .02).

Discussion

This is the first study, to our knowledge, that used a design which allowed for separate examination of the effects of an evidence-based medication for alcohol dependence (naltrexone), an evidence-based psychotherapy for PTSD (prolonged exposure), and their combination, on both drinking and PTSD symptoms among individuals with comorbid alcohol dependence and PTSD. Participants in all 4 groups showed a significant reduction in PDD. However, at posttreatment, participants who received naltrexone showed significantly lower PDD than participants who received placebo. This finding is consistent with previous studies showing that naltrexone is an effective treatment for alcohol dependence.[10-12] One hypothesized mechanism of naltrexone's effect on drinking is through the attenuation of alcohol craving.[32] The results of the current study support this hypothesis; participants who received naltrexone had lower cravings for alcohol than those who received placebo.

All 4 groups showed a significant reduction in PTSD symptoms during treatment. However, there was no increased improvement in PTSD symptoms from prolonged exposure therapy compared with supportive counseling, which is inconsistent with a large body of evidence that prolonged exposure is an effective treatment for PTSD.[4,13] This null finding may be due to the fact that all participants received supportive counseling. Perhaps the nonspecific factors involved in supportive counseling masked some of the unique effects of prolonged exposure therapy. In addition, attendance to prolonged exposure therapy sessions was lower in this study than in other trials of prolonged exposure therapy.[33] The relatively low number of prolonged exposure therapy sessions received by the participants, combined with the fact that all participants received supportive counseling, prevents strong conclusions about the efficacy of prolonged exposure therapy on PTSD in patients with alcohol dependence and PTSD.

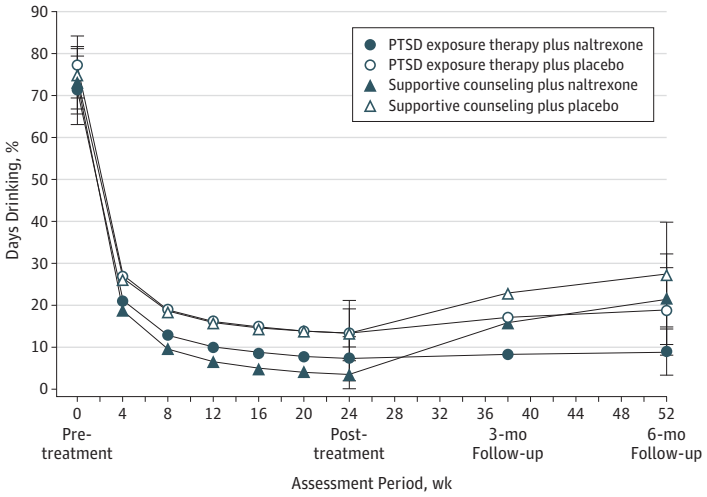
Importantly, our findings indicated that prolonged exposure therapy was not associated with increased drinking or alcohol craving, a concern that has been voiced by some investigators.[34] In fact, reduction in PTSD severity and drinking was evident for all 4 treatment groups. This finding contradicts the common view that trauma-focused therapy is contraindicated for individuals with alcohol dependence and PTSD because it may exacerbate PTSD symptoms and thereby lead to increased alcohol use.[6,7]

Participants in this study were followed up for 6 months after treatment discontinuation. During this follow-up period, participants who received prolonged exposure therapy retained low drinking levels, whereas participants who did not receive prolonged exposure therapy had a higher relapse rate. Exploratory analyses suggest that naltrexone plus prolonged exposure therapy vs naltrexone alone, prolonged exposure therapy alone, or supportive counseling alone was associated with a lower rate of relapse of alcohol dependence, as measured by PDD (**Figure 2**). Further evidence that prolonged exposure therapy may reduce the rate of relapse comes from our findings of the main effect of prolonged exposure therapy on PDD during follow-up. This finding suggests that receiving prolonged exposure therapy plus naltrexone protects patients with alcohol dependence and PTSD from relapse in drinking after treatment discontinuation.

To our knowledge, this study is the first randomized trial of patients with comorbid alcohol dependence and PTSD to demonstrate significant differences in outcomes between an active treatment and a control comparison.[6,9] This may be due to differences between the treatments that were used in the current study and those used in the other studies. Brady et al[9] used sertraline for treating PTSD and cognitive behavioral therapy for treating alcohol dependence, neither of which have been found to have strong effects on the respective target disorder. Hien et al[6] used the Seeking Safety treatment program, a type of cognitive behavioral therapy that targets substance use disorders and comorbid PTSD, which has not gained strong support for its efficacy with either disorder. Our results highlight the importance of selecting treatments with strong evidence for their efficacy with both disorders when treating patients with alcohol dependence and PTSD.

As noted above, attendance to prolonged exposure therapy sessions was low relative to our previous PTSD treatment studies. However, our previous studies excluded patients with PTSD and comorbid alcohol dependence. Low adherence to therapy has been found in other studies of patients with PTSD and sub-

Figure 2. Mean Percentage of Days Drinking During Treatment and Follow-up



No. of patients									
PTSD exposure therapy									
Plus naltrexone	40	40	38	34	34	31	28	26	21
Plus placebo	40	40	39	34	33	29	28	25	23
Supportive counseling									
Plus naltrexone	42	41	37	34	34	31	31	28	19
Plus placebo	43	41	40	36	36	35	34	32	26

Preliminary growth curve analyses indicated that change during treatment was nonlinear and modeling time using a hyperbolic transformation of the number of weeks (time = 1 − [1/{weeks + 1}]) yielded the best fit to the data with drastic decreases in percentage of days drinking during the earlier part of treatment that flattened out over time. Error bars indicate 95% confidence intervals; PTSD, posttraumatic stress disorder.

stance use disorders. For example, Hien et al[35] found that only 12.2% of patients completed all 12 sessions of the Seeking Safety treatment program. The relatively low adherence to prolonged exposure therapy sessions may be explained in part by our clinical observation that participants in the study experienced multiple life difficulties (eg, homelessness, health problems). This observation is consistent with Drapkin et al's[36] findings. It is encouraging to note, however, that patients who received 6 or more sessions of prolonged exposure therapy benefitted substantially from treatment, suggesting that a relatively low dose of prolonged exposure therapy is effective in this population.

Several caveats should be noted. First, because of concern for the safety of these highly impaired patients, supportive counseling was provided for all 4 treatment groups. As a result, we were unable to evaluate the separate contribution of this intervention to the overall outcome. Second, attendance to prolonged exposure therapy sessions was relatively low, therefore the efficacy of a full treatment dose of prolonged exposure therapy on PTSD and drinking behavior could not be evaluated. Future research should examine ways to increase treatment adherence in this population. Third, we relied on pill counting to assess adherence to medication; the use of more sophisticated methods may have increased the reliability of assessing adherence to medication. Fourth, medication management and prolonged exposure therapy were delivered by separate clinicians. This model may be less readily applicable in mental health community clinics or primary care settings because it requires greater logistical coordination than an integrated model in which both interventions would be delivered by the same clinician. Despite these limitations, our trial demonstrates that (1) patients with comorbid alcohol dependence and PTSD benefit from naltrexone treatment; (2) prolonged exposure therapy is not associated with exacerbation of alcohol dependence; and (3) combined treatment with naltrexone and prolonged exposure therapy may decrease the rate of relapse of alcohol dependence for up to 6 months after treatment discontinuation.

ARTICLE INFORMATION

Author Contributions: Dr Foa had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Foa, Bux, Oslin, O'Brien, Riggs, Volpicelli.
Acquisition of data: Foa, Yusko, Bux, Oslin, Imms, Riggs.
Analysis and interpretation of data: Foa, Yusko, McLean, Suvak, Oslin, O'Brien.
Drafting of the manuscript: Foa, Yusko, McLean, Suvak, Bux, Imms.
Critical revision of the manuscript for important intellectual content: Foa, Oslin, O'Brien, Riggs, Volpicelli.
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