Topiramate Treatment of Alcohol Use Disorder in Veterans with Posttraumatic Stress Disorder: A Randomized Controlled Pilot Trial

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Background: The course of posttraumatic stress disorder (PTSD) is frequently and severely complicated by co-occurring alcohol use disorder (AUD), yet there are few reports of pharmacologic treatments for these comorbid conditions. The objective of this pilot study was to obtain a preliminary assessment of the efficacy and safety of topiramate in reducing alcohol use and PTSD symptoms in veterans with both disorders.

Methods: This was a prospective 12-week, randomized, double-blind, placebo-controlled pilot trial of flexible-dose topiramate up to 300 mg/d in 30 veterans with PTSD and AUD. The primary outcome measure was frequency of drinking. Secondary outcomes consisted of other measures of alcohol use and PTSD symptom severity.

Results: Within-group analyses showed that topiramate treatment was associated with significant reductions in frequency and amount of alcohol use and alcohol craving from baseline through week 12. Between-group analyses showed that topiramate reduced frequency of alcohol use and alcohol craving significantly more than placebo and tended to reduce drinking amount. Topiramate treatment was also associated with decreased PTSD symptom severity and tended to reduce hyperarousal symptoms compared with placebo. Topiramate transiently impaired learning and memory, with significant recovery by the end of treatment.

Conclusions: These preliminary results indicate that in veterans with co-occurring PTSD and AUD, topiramate may be effective in reducing alcohol consumption, alcohol craving, and PTSD symptom severity—particularly hyperarousal symptoms. Topiramate was associated with transient cognitive impairment but was otherwise well tolerated.

Key Words: Topiramate, Clinical Trial, Alcohol Use Disorder, Posttraumatic Stress Disorder, Cognition.

A MONG CIVILIAN AND military personnel with posttraumatic stress disorder (PTSD), up to 52% suffer from comorbid alcohol use disorders (AUDs; Baker et al., 2009; Kessler et al., 1995). The co-occurrence of AUDs and PTSD is associated with poor psychosocial and medical outcomes, high rates of hospitalization, and impaired psychoso-

cial functioning (McCarthy and Petrakis, 2010), pointing to an urgent need to improve treatment options for the many veterans who suffer from these disorders.

To date, there have been few reported pharmacotherapy studies focused on these co-occurring conditions (Brady et al., 1995, 2005; Foa et al., 2013; Petrakis et al., 2006, 2012) and no consensus is readily available regarding the optimal use of medications (McCarthy and Petrakis, 2010; Sofuoglu et al., 2014). Evidence has recently emerged showing efficacy for topiramate in reducing problematic alcohol use (Johnson and Ait-Daoud, 2010) as well as independently showing topiramate's efficacy in reducing PTSD symptoms. Topiramate has been found to increase the proportion of days abstinent from alcohol use and to reduce the number of heavy drinking days and drinks per drinking day (Baltieri et al., 2008; Johnson et al., 2003, 2007; Kranzler et al., 2014; Rubio et al., 2009) and to reduce alcohol craving when compared with placebo (Johnson et al., 2003; Rubio et al., 2009) in AUD patients *without* PTSD. One exception to the generally positive findings was a controlled trial during residential detoxification treatment in which topiramate only showed a trend toward superiority to placebo, possibly due to the presence of

intensive psychosocial interventions applied to both treatment groups (Likhitsathian et al., 2013).

Topiramate has also been proposed as a possible treatment for PTSD, based on its pharmacological GABA/glutamate profile; specifically, its effects as a GABA agonist and its ability to block glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)/kainite signaling (Berlant and van Kammen, 2002; Sofuoglu et al., 2014). Topiramate has shown partial effectiveness in reducing PTSD symptoms in patients *without* AUD in 3 open trials (Alderman et al., 2009; Berlant, 2004; Berlant and van Kammen, 2002) and 3 small-to-medium sized controlled trials (Lindley et al., 2007; Tucker et al., 2007; Yeh et al., 2011). In a placebo-controlled trial in veterans, topiramate treatment was associated with greater improvement in PTSD re-experiencing symptoms when used to augment standard PTSD pharmacotherapy, although with more adverse effects (AEs) and higher dropout (Lindley et al., 2007). Topiramate also showed significantly greater reductions in PTSD re-experiencing symptoms than placebo in nonveterans with PTSD (Tucker et al., 2007). The most recent of the controlled trials in a civilian sample found that topiramate significantly reduced PTSD symptom severity as compared to placebo, with particular effectiveness in reducing re-experiencing and avoidance/numbing symptom clusters (Yeh et al., 2011).

There have been no controlled trials of topiramate to examine its effects in reducing alcohol consumption and PTSD symptom severity in patients with co-occurring AUD and PTSD, although a small open trial of topiramate in male combat veterans with PTSD showed a reduction in PTSD symptoms and a decrease in the proportion of patients with high-risk drinking (defined as >43 drinks per week; Alderman et al., 2009). We therefore conducted a randomized, placebo-controlled pilot trial to provide a preliminary assessment of the efficacy and safety of topiramate during a 12-week course of treatment in 30 veterans with PTSD and AUD whose treatment goals were to reduce and possibly stop alcohol consumption. We tested 2 a priori hypotheses: (1) the topiramate group would have a *within-group* reduction in percent drinking days over the course of the 12-week trial; (2) in a *between-groups* analysis, the topiramate group would have fewer percent drinking days when compared to the placebo group. We also planned to explore the efficacy of topiramate in reducing the amount of alcohol use, alcohol craving, and PTSD symptom severity.

MATERIALS AND METHODS

Participants

All participants provided written informed consent prior to study and underwent procedures approved by the University of California, San Francisco, the San Francisco Veterans Affairs Medical Center (SF VAMC) and the Department of Defense. Participants were recruited, and all procedures took place at the SF VAMC in San Francisco, CA. Study participants were 30 veterans who met DSM-IV-TR (American Psychiatric Association, 2000) diagnostic criteria for both current alcohol dependence and PTSD. All partici-

pants also reported "at-risk" or "heavy" drinking in accordance with National Institutes of Health/National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria (at least 15 standard drinks per week on average over the 4 weeks prior to study entry for men and at least 8 standard drinks per week on average for women; Willenbring et al., 2009), and all expressed a desire to reduce alcohol consumption with the possible long-term goal of abstinence. Participants included patients who were still actively drinking as well as those who had stopped in the days prior to random assignment. Participants were free to access any other standard psychological or pharmacologic treatments for PTSD and any psychosocial treatments for AUD, but they could not receive other AUD pharmacotherapy. Participants were excluded if they met diagnostic criteria for psychotic disorders, bipolar disorder, and dementia were known to have any clinically significant unstable psychiatric or medical conditions, or had a suicide attempt or suicidal ideation in the 6 months prior to enrollment. Other exclusion criteria included acute alcohol withdrawal, history of either nephrolithiasis, narrow angle glaucoma or seizure disorder, current use of other anticonvulsant medications, topiramate use within the past 4 weeks, and concurrent participation in other treatment studies.

Procedure

This was a randomized, double-blind, placebo-controlled, flexible-dose (25 to 300 mg/d) pilot trial of topiramate augmentation treatment. Screening consisted of 2 to 3 visits within 1 week during which participants completed the measures and interviews described later. Those who met entry criteria began the treatment phase of the study consisting of 12 weekly visits. Participants were randomly assigned in a 1:1 ratio to receive either topiramate or placebo treatment. Randomization was stratified by gender and balanced using computer-generated block randomization with permuted block sizes of 6, created by a study statistician with no clinical involvement in the trial. The allocation list was given to an independent pharmacist who assigned participants to study group and dispensed study medication according to the randomization list. Participants and all research staff including raters were blinded to the assigned treatment. Study medication was provided in prepackaged bottles containing identical 25 or 100 mg capsules of either topiramate or placebo. Dosing followed the method of Johnson and colleagues (2007). The initial dose was 25 mg nightly for 1 week. The dose was increased to 50 mg/d in 2 divided doses in week 2; in week 3, the dose was increased to 100 mg/d; in week 4, to 150 mg/d; in week 5 to 200 mg/d, and in week 6, to 300 mg/d given as 100 mg in the morning and 200 mg in the evening. This final dose was maintained from week 6 through week 11. In week 12, study medication was tapered and discontinued. Dosing was flexible, in that the maximum daily dose was determined by tolerability—if participants experienced clinically significant AEs, then study medication dose would not be advanced, or, if needed, it would be decreased.

All participants also received weekly Medical Management counseling (Pettinati et al., 2005), a manual-driven, low-intensity supportive counseling method designed by the NIAAA to promote adherence to the medication regimen and reduction in alcohol use.

Measures

Demographics and Psychiatric Characteristics. All participants were administered the Substance Use Disorders sections of the Structured Clinical Interview for DSM-IV-TR (First et al., 2001). PTSD diagnosis was assessed with the Clinician-Administered PTSD Checklist (CAPS; Blake et al., 1995), a 30-item structured interview based on the DSM-IV. The CAPS instrument is divided into sections based on PTSD symptom clusters: Re-experiencing, Avoidance, and Arousal. A CAPS criterion was considered to be present if a participant endorsed a symptom with a score ≥1 in fre-

quency and ≥ 2 in severity rating. All participants completed the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and the Beck Anxiety Inventory (BAI; Beck et al., 1988) at baseline and were assessed for PTSD symptom severity with the PTSD Checklist (PCL; Weathers and Litz, 1994) at baseline, weeks 4, 8, and 12.

Alcohol Consumption, Craving, and Severity. Alcohol consumption frequency and amount were assessed using the Time Line Follow Back (TLFB; Sobell and Sobell, 1992; Sobell et al., 1985) interview which yields number of alcohol drinking days, number of heavy drinking days, and number of drinks per each day of drinking. The TLFB was administered at baseline to assess the 90-day period prior to the beginning of screening and then weekly at each subsequent treatment visit. Obsessive thoughts and compulsions associated with alcohol craving were measured using the Obsessive Compulsive Drinking Scale (OCDS; Anton et al., 1995) at baseline, weeks 4, 8, and 12. Severity of harmful and hazardous drinking was measured using the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) at baseline.

Auditory Verbal Learning and Memory. To assess areas of cognition known to be adversely affected by topiramate (Aldenkamp et al., 2000), participants completed the Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt, 1991) at baseline, weeks 6 and 12. HVLT-R includes total recall (learning) and delayed recall (memory).

Adverse Effects. AEs were collected weekly using a checklist of the 18 most common AEs associated with topiramate as indicated in the FDA-approved labeling for topiramate (Pharmaceuticals, 2012).

Statistical Analyses

Baseline characteristics for each group were compared using a *t*-test for continuous variables and Fisher's exact test for categorical variables. This pilot study was designed with adequate power to allow the primary outcome analysis of *within-group* change in percent drinking days from baseline through week 12 in the topiramate treatment condition. The study was also powered for a secondary, *between-groups* outcome analysis to detect a "signal" or statistical trend ($p < 0.10$) for a difference in percent drinking days between the topiramate and placebo condition over the 12 weeks of the trial. Percent drinking days was overdispersed, positively skewed count data. Our primary within-topiramate group analysis applied a random-intercept repeated subject negative binomial model, modeling week (baseline through week 12) as a continuous variable. Our secondary between-groups analysis examined the percent drinking days per week averaged over the treatment phase of the trial (weeks 1 to 12). The model included fixed effect for week, treatment group (topiramate and placebo), and the interaction between treatment group and week. The same approach was applied to the analyses of percent heavy drinking days, drinks per week, and average drinks per drinking day. Baseline alcohol consumption means were used as respective covariates in group comparisons to control for prestudy and study enrollment effects.

We used random-intercept linear mixed models to explore the efficacy for topiramate-related reduction in PTSD symptomatology, craving, and effects on measures of learning and memory. We first looked for an effect of week within the topiramate treatment condition and then tested for a signal (trend) for a difference between treatment groups. Baseline scores for PTSD symptoms, craving, learning and memory were used as covariates in group comparisons. We calculated percent change for each outcome measure by comparing baseline to the respective average of weeks 1 to 12. All analyses were intent to treat and used all observations from all weeks. Given the preliminary nature of this study, all statistical tests were held to an alpha of 0.05 and completed with SPSS v21 (IBM Corp., Armonk, NY).

RESULTS

Patient Characteristics

Baseline characteristics for the topiramate (TOP) and placebo (PLA) groups are shown in Table 1. Of the 30 participants, 14 were randomly assigned to TOP, 16 to PLA. All

Table 1. Participant Characteristics at Baseline (Means ± Standard Deviation)

	TOP	PLA
n (female)	14 (1)	16 (1)
Age (years)	49.5 ± 13.9	50.4 ± 12.8
Education (years)	12.9 ± 3.1	14.4 ± 1.9
Race		
Caucasian (Hispanic/Latino)	8 (2)	8
American Indian/Alaskan Native	1	0
Asian	1	1
African American	2	5
Pacific Island Native	0	1
Mixed race	2	1
Combat exposed, *n* (%)	10 (71)	12 (75)
Comorbid substance use disorder, *n* (%)	5 (36)	5 (32)
AUD residential TX, *n* (%)	4 (29)	2 (13)
AUD outpatient TX, *n* (%)	7 (50)	8 (50)
PTSD outpatient TX, *n* (%)	9 (65)	9 (56)
PTSD pharmacotherapy TX, *n* (%)	5 (37)	9 (56)
Alpha blocker (Prazosin) (%)	1 (7)	1 (6)
Antidepressants (%)	4 (29)	7 (44)
Buproprion (%)	0 (0)	1 (6)
Citalopram (%)	2 (14)	3 (19)
Fluoxetine (%)	0 (0)	1 (6)
Mirtazapine (%)	1 (7)	0 (0)
Setraline (%)	0 (0)	2 (13)
Venlafaxine (%)	1 (7)	0 (0)
Antipsychotic (Quetiapine) (%)	1 (7)	1 (6)
Anxiolytic (%)	0 (0)	2 (13)
Buspirone (%)	0 (0)	1 (6)
Hydroxyzine (%)	0 (0)	1 (6)
β-blocker (Propranolol) (%)	0 (0)	1 (6)
Sedative/hypnotic (%)	0 (0)	3 (19)
Temazepam (%)	0 (0)	1 (6)
Trazodone (%)	0 (0)	2 (13)
Stimulant (methylphenidate) (%)	1 (7)	0 (0)
BDI-II	23.4 ± 11.6	26.3 ± 12.3
BAI	20.4 ± 12.7	27.4 ± 13.3
AUDIT score	27.1 ± 7.9	23.0 ± 7.5
Days abstinent between last drink and initiation of study medication	12.8 ± 13.6	4.8 ± 9.2
Percent DD per week	73.3 ± 30.3	80.4 ± 21.5
Percent HDD per week	58.5 ± 33.7	72.6 ± 28.5
Avg. drinks[a] per week	52.4 ± 34.2	58.2 ± 25.4
Avg. drinks[a] per DD	11.1 ± 6.1	10.9 ± 4.7
Baseline CAPS total	72.8 ± 14.3	83.1 ± 17.3
Re-experiencing	18.2 ± 4.3	21.9 ± 6.9
Avoidance	31.1 ± 6.1	34.8 ± 8.9
Arousal	23.5 ± 6.7	26.4 ± 4.1

AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; CAPS, Clinician-Administered PTSD Scale; %DD, percent drinking day; HDD, heavy drinking day (>4 standard alcoholic drinks for men, >3 standard alcoholic drinks for women); PLA, placebo; PTSD, posttraumatic stress disorder; TOP, topiramate; TX, treatment. Drink consumption was averaged over 90 days preceding study consent.
[a]Standard alcoholic drink is defined as containing 13.6 g of pure alcohol.

participants were veterans of Vietnam, the Gulf Wars, or Iraq and Afghanistan with war-zone and/or civilian related trauma exposure. There were no differences between treatment group characteristics at baseline. Of the 30 participants enrolled, 4 TOP and 2 PLA attended a 30-day community-based residential rehabilitation treatment program that included a structured living environment with group therapy and individual case management. Participants were allowed to travel to and from the SF VAMC to participate in screening and study procedures. Medication was initiated when the participant passed our screening process and entered the active treatment phase, regardless of time spent in residential treatment.

Study Retention

Of the 30 randomized patients, 27 (90%) (TOP: 13/14 [92.9%]; PLA: 14/16 [87.5%]) completed the trial, attending week 12 study visit. TOP attended a significantly higher percent of study visits (94.2 ± 23.5%) than PLA (83.1 ± 37.5%) during weeks 1 to 12 ($p = 0.002$). Attrition was low in both groups over the course of the treatment phase (TOP = 1/14, PLA = 2/16). Subject flow is illustrated in Fig. 1. Of the 3 participants who did not complete the study: 1 TOP participant was lost to follow-up (failed to return to study), 1 PLA participant withdrew due to lack of time, and 1 PLA participant died of myocardial infarction, judged to be unrelated to the study. No participants dropped out because of AEs related to study medication. Difference in total attrition between TOP and PLA at week 12 was not statistically significant ($p = 0.556$).

Maximum Medication Dose and Adherence

As described previously, this was a flexible-dose study. The maximum study dose (300 mg/d) was adjusted to participant tolerance. The average maximum study medication
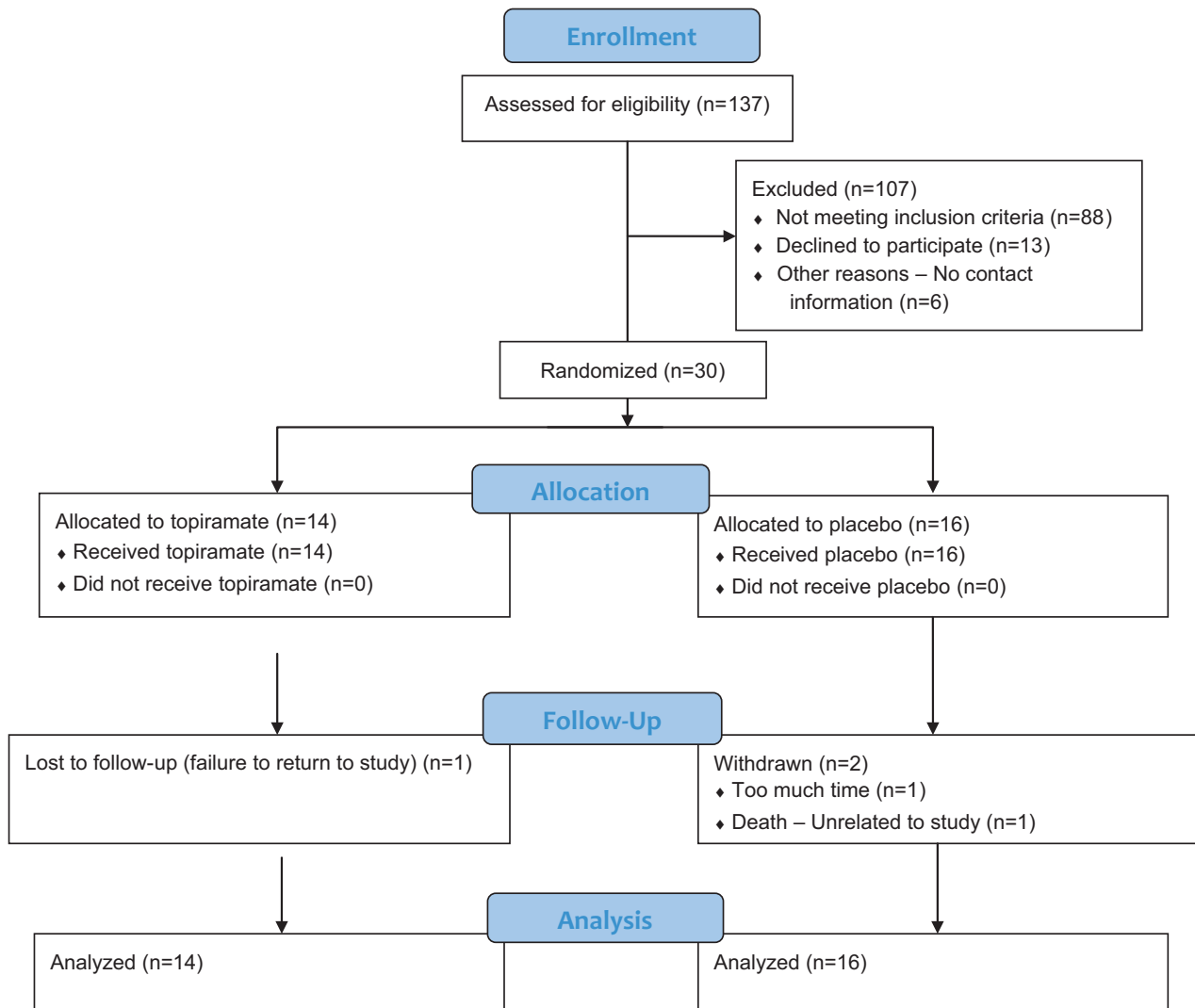

Fig. 1. CONSORT flow diagram.

dose reached in each of the study conditions was 286 ± 20 mg/d for TOP and 281 ± 45 mg/d for PLA. The difference in maximum dose reached by TOP and PLA was not statistically significant ($p = 0.248$).

Adherence was measured by self-report and verified by pill count. Medication adherence rate was the total dose (mg) self-reported taken/total dose prescribed $\times$ 100. Mean adherence rate was $63.1 \pm 20.3\%$ for TOP and $60.2 \pm 21.5\%$ for PLA, with no significant difference between groups.

Primary and Secondary Analyses of Percent Drinking Days

Our primary analysis demonstrated a significant decrease in percent drinking days from baseline through week 12 within TOP (Table 2). Our secondary analysis, illustrated in Fig. 2, showed a near-significant trend for a main effect of treatment ($p = 0.063$, incidence rate ratio = 0.430; 95% confidence interval = 0.18 to 1.05). There was not a significant treatment-by-week interaction. As we did not predict differential rates of change, we removed the insignificant interaction term and re-ran our between-group analysis, which revealed a significant main effect of treatment ($p = 0.036$, Table 2), with TOP having 51% less drinking days than PLA averaged during weeks 1 to 12.

Exploratory Analyses

Percent Heavy Drinking Days, Drinks per Drinking Day, and Standard Drinks per Week. Each univariate analysis examining reductions of percent heavy drinking days, standard alcohol drinks consumed per week, and standard alcohol drinks consumed per drinking day within TOP found significant reductions and are summarized in Table 2. Between-group comparisons revealed a trend for a main effect of treatment on standard drinks per week ($p = 0.099$, Table 2), with TOP having 55% fewer standard drinks during weeks 1 to 12 compared with PLA. We also observed a trend for a main effect of treatment on drinks per drinking day ($p = 0.057$, Table 2) with TOP having 61% fewer drinks per drinking day than PLA during weeks 1 to 12. There were no between-group effects for percent heavy drinking days. There were also no significant treatment by week interactions for any of these exploratory analyses. Removing the insignificant interaction terms from their respective model did not markedly change the degree of significance in group comparisons.

PTSD Symptom Outcome. Univariate analysis revealed a significant reduction within TOP in PTSD symptom severity as measured by the PCL total score and all 3 subscale scores from baseline through week 12 (Table 2). When compared to PLA, there were trends for main effects of treatment on PCL-total, $F(1, 48) = 2.81$, $p = 0.100$, and, as illustrated in Fig. 3, arousal scores, $F(1, 52) = 3.40$, $p = 0.071$, (Table 2). There were no significant treatment-by-week interactions for any PCL measure.

Table 2. TOP Within-Group and Between-Group Analyses for Alcohol Consumption, PTSD Symptoms and Alcohol Craving

| | Baseline | TOP within-group analysis | | | | | Between-groups analysis | | | | | |
	Mean ± SD	Weeks 1 to 12 Mean ± SD	%Δ	95% CI	IRR (β)	p-Value	TOP Weeks 1 to 12 Avg. Mean ± SD	PLA Weeks 1 to 12 Avg. Mean ± SD	p-Value	IRR (β)	95% CI	%Diff.
Alcohol consumption												
% DD	73.3 ± 30.3	19.5 ± 34.2	−74	0.82 to 0.98	0.89	0.019	19.5 ± 34.2	39.7 ± 36.5	0.036	0.38ᵃ	0.15 to 0.94	51
% HDD	58.5 ± 33.7	11.1 ± 27.1	−81	0.76 to 0.99	0.87	0.035	11.1 ± 27.1	16.8 ± 26.3	0.342	0.56	0.17 to 1.87	34
Std. drinks per week	52.4 ± 34.2	8.7 ± 19.0	−83	0.75 to 0.98	0.86	0.028	8.7 ± 19.0	19.3 ± 30.5	0.099	0.43	0.16 to 1.17	55
Drinks per DD	11.1 ± 6.1	1.9 ± 3.3	−83	0.74 to 0.96	0.83	0.008	1.9 ± 3.3	4.8 ± 6.5	0.057	0.45	0.20 to 1.02	60
PTSD symptoms												
PCL total score	57.1 ± 13.4	42.3 ± 16.4	−26	−1.84 to −0.62	(−1.22)	0.001	42.3 ± 16.0	49.0 ± 16.5	0.100	(−9.01)	−19.8 to 1.80	14
PCL B-reexperiencing	15.9 ± 5.2	12.3 ± 5.5	−23	−0.53 to −0.04	(−0.28)	0.026	12.3 ± 5.4	14.3 ± 5.5	0.155	(−2.75)	−6.57 to 1.08	14
PCL C-avoidance	23.9 ± 5.7	17.6 ± 7.4	−26	−0.73 to −0.20	(−0.46)	0.002	17.6 ± 7.2	19.9 ± 6.9	0.272	(−3.07)	−8.61 to 2.48	12
PCL D-Arousal	17.3 ± 4.8	12.4 ± 4.9	−28	−0.71 to −0.25	(−0.48)	0.000	12.4 ± 4.9	14.9 ± 5.0	0.071	(−3.23)	−6.74 to 0.29	17
Alcohol craving												
OCDS total	16.93 ± 8.70	5.53 ± 6.55	−67	−1.48 to −0.43	(−0.95)	0.002	5.53 ± 6.55	11.08 ± 8.12	0.025	(−7.02)	−13.1 to −0.91	50

%DD, percent drinking days; %HDD, percent heavy drinking days (>4 standard alcoholic drinks for men, >3 standard alcoholic drinks for women; standard alcoholic drink is defined as containing 13.6 g of pure alcohol); CI, confidence interval; IRR, incidence rate ratio (average relative change in outcome per week from baseline through week 12); %Δ, percent change (calculated by comparing baseline to the respective average of weeks 1 to 12); %Diff., percent difference (calculated by comparing weeks 1 to 12 averages between treatment groups); OCDS, Obsessive Compulsive Drinking Scale; PCL, PTSD Checklist; PTSD, posttraumatic stress disorder; TOP, topiramate.
[a] p-value of negative binomial model when the interaction term is removed.
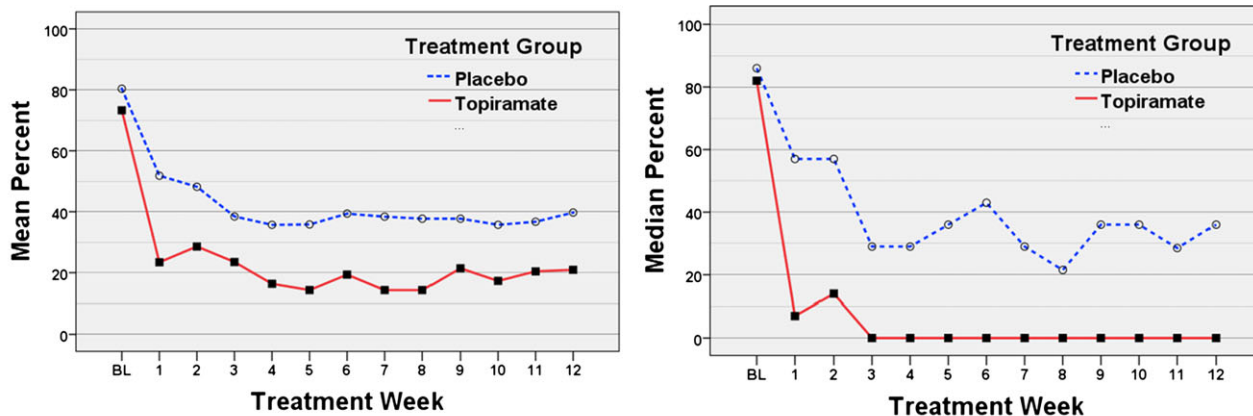
Abbreviation: BL, baseline weekly drinking average based on the 90 day period prior to the beginning of screening.

Fig. 2. Mean and median percent drinking days per week.
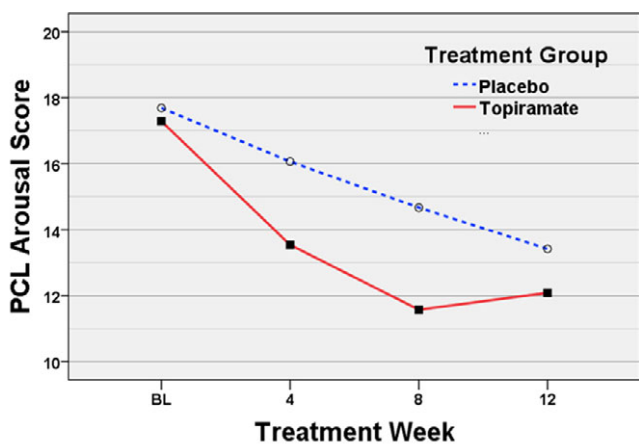
Abbreviation: BL, baseline PCL scores completed during screening.

Fig. 3. Mean posttraumatic stress disorder (PTSD) Checklist (PCL) arousal scores.

Alcohol Craving. As seen in Table 2, there was a significant reduction in OCDS scores from baseline through week 12 within TOP, $F(1, 14) = 15.17$, $p = 0.002$. When compared to PLA, there was a significant main effect of treatment, $F(1, 50) = 5.33$, $p = 0.025$. There was not a significant treatment by week interaction.

HVLT-R Total (Learning). There was a significant treatment by week interaction for HVLT-R total recall, $F(1, 21) = 6.63$, $p = 0.018$ (Fig. 4). Follow-up univariate analyses indicated that TOP decreased in performance between baseline and week 6, $F(1, 13) = 15.04$, $p = 0.002$, and then significantly regained some of that loss between weeks 6 and 12, $F(1, 12) = 17.59$, $p = 0.001$, whereas PLA did not show any change during these time intervals. Cross-sectional group comparisons showed no differences at baseline (TOP = 42.3 ± 10.3, PLA = 41.5 ± 13.8), significantly worse performance by TOP than PLA at weeks 6 ($p = 0.013$, TOP = 31.6 ± 8.4, PLA = 43.4 ± 15.3) and no significant

differences at week 12 (TOP = 41.0 ± 7.8, PLA = 44.8 ± 13.8).

HVLT-R Delayed Recall (Memory). There was a significant main effect of treatment, $F(1, 42) = 5.01$, $p = 0.031$, and week, $F(1, 22) = 6.23$, $p = 0.021$, suggesting differential treatment group performance between baseline and week 12 in HVLT-R delayed recall. There was no significant treatment by week interaction. Follow-up univariate analysis indicated that TOP decreased in performance between baseline and week 6, $F(1, 13) = 17.76$, $p = 0.001$, and then significantly regained part of that loss between weeks 6 and 12, $F(1, 12) = 6.50$, $p = 0.026$, whereas PLA did not show any significant change during these same intervals (Fig. 4). Cross-sectional group comparisons showed no differences at baseline (TOP = 46.4 ± 10.2, PLA = 44.13 ± 11.9), significantly worse performance of TOP compared with PLA at week 6 ($p = 0.028$, TOP = 31.3 ± 11.2, PLA = 42.4 ± 16.8). At week 12, TOP still tended to have worse performance than PLA ($p = 0.096$, TOP = 36.8 ± 8.8, PLA = 45.8 ± 15.0).

Adverse Events. Twelve (85.7%) TOP and 13 (81.3%) PLA participants experienced treatment-emergent adverse events during the trial. There were no significant differences between groups on any reported emergent adverse events. The most common reported emergent complaints were as follows: sleepiness, in 36% of TOP and 13% of PLA; loss of appetite in 29% of TOP and 38% of PLA; change in sense of taste in 21% of TOP and 31% of PLA; itching in 21% of TOP and 6% of PLA; diarrhea in 29% of TOP and 19% of PLA; and abnormal vision in 21% of TOP and 19% of PLA. Four participants—all of them PLA—experienced a total of 6 serious adverse events (SAEs).

Five of the 6 SAEs were conservatively categorized as "possibly" related to the study. Of the 4 participants with SAEs, 1 was hospitalized for suicidal ideation; 1 participant had 3 hospitalizations for chest pain; another participant had 1 hospitalization for chest pain; and 1 participant died
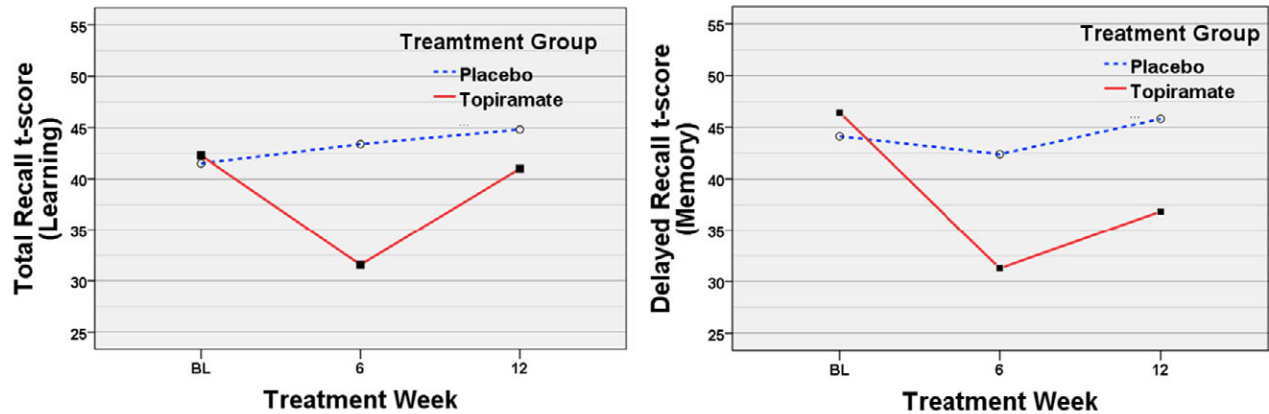
Abbreviation: BL, baseline learning and memory scores completed during screening.

Fig. 4. Mean Hopkins Verbal Learning Test-Revised total and delayed recall scores.

due to myocardial infarction, judged to be unrelated to the study.

DISCUSSION

The study described here is the first prospective trial of topiramate for co-occurring AUD and PTSD conducted in a cohort of veterans, whose goal was to reduce or stop alcohol use. The study was primarily powered to examine within-group changes in the topiramate condition, with secondary analyses intended to detect a between-groups signal of topiramate efficacy compared with placebo. As hypothesized, in the topiramate condition, treatment was associated with reduction in self-reported frequency and amount of alcohol use, alcohol craving, and PTSD symptoms from baseline to week 12. Of greater interest, topiramate tended to be more efficacious than placebo in reducing these measures of alcohol use and PTSD symptom severity. Overall, topiramate was well tolerated but was associated with transient reductions in learning and memory.

Topiramate's effects on reducing the frequency and amount of alcohol consumption and in reducing alcohol craving are in line with the findings of previously conducted studies of topiramate in AUD without PTSD (Baltieri et al., 2008; Johnson et al., 2003, 2007; Kranzler et al., 2014; Rubio et al., 2009). Topiramate's effects on PTSD symptom severity are also supportive of the promising findings of prior studies that examined participants with PTSD but without AUD (Lindley et al., 2007; Tucker et al., 2007; Yeh et al., 2011).

In contrast with other controlled topiramate studies of PTSD, we observed a trend toward greater reduction in PTSD arousal symptoms in TOP compared with PLA. Only 2 other controlled studies have demonstrated efficacy for topiramate in the treatment of PTSD symptoms compared with placebo (Tucker et al., 2007; Yeh et al., 2011), both showing reductions in re-experiencing and avoidance symptoms. Neither of those studies found topiramate to reduce

PTSD arousal symptoms. Our findings suggest that topiramate may target PTSD symptom clusters differently, dependent on the presence or absence of comorbid AUD. Topiramate may prove to be an especially useful treatment for those with comorbid AUD/PTSD who present with particularly troubling hyperarousal symptoms (e.g., irritability/ anger, hypervigilance, exaggerated startle response). This conclusion remains tentative as we did not study a PTSD group without AUD for comparison.

Topiramate's tolerability was evidenced in several ways. Surprisingly, adverse events did not occur at a significantly higher rate in participants treated with TOP as compared to PLA. Also, TOP participants had higher retention rates and reached a similar rate of medication adherence and dose (286 mg/d of a possible maximum target dose of 300 mg) compared with PLA. However, topiramate was associated with reductions in auditory/verbal learning and memory, although by week 12 there was recovery from the impairment in learning seen at mid-study. The topiramate-associated worsening of memory at week 6 also improved by end of study but continued to show impairment compared with placebo. Despite these test results, the TOP group did not report more subjective complaints of memory problems than the PLA group over the course of the trial. These findings are generally consistent with previously reported mixed observations on the effects of topiramate on learning and memory (Aldenkamp et al., 2000; Lee et al., 2003), but different from Likhitsathian and colleagues (2012) who found no decrease in cognitive functioning in an open trial of topiramate in AUD patients. Given the limited sample size, we were unable to conduct any meaningful statistical analyses to definitively conclude that the cognitive impairment observed in this population was caused only by topiramate treatment and was unrelated to continued alcohol consumption. At the least, our findings support the need to further delineate the effects of topiramate treatment on cognition in both active drinkers and continuous abstainers. Of note, there were no differences between groups in central nervous system adverse events,

which were associated with high dropout rates in a previous study of topiramate efficacy for PTSD (Lindley et al., 2007).

Strengths of this study included its double-blind, placebo-controlled, randomized design, intent-to-treat analyses, its focus on a veteran population, and the detailed measurement of both alcohol use and PTSD symptom severity. Moreover, while Likhitsathian and colleagues (2012) described cognitive changes in an open trial of topiramate in AUD, to our knowledge, we report the first placebo-controlled study of topiramate's neurocognitive AEs in a trial focusing on alcohol use. Limitations of the study include its sample size, consistent with the study's pilot nature, which may have decreased power to detect significant differences between topiramate and placebo despite there being large percent differences. Additionally, our small sample size did not allow for the examination of factors that may have influenced our outcomes, such as the moderating effects of concomitant treatment, genetics (Batki and Pennington, 2014; Kranzler et al., 2014), degree of motivation at study entry, or the presence of pretreatment abstinence. An additional limitation of this report is the reliance on self-report measures to assess drinking outcomes—although self-report at present remains the standard for alcohol use outcome measurement in clinical trials (Falk et al., 2010), for example, Fertig and colleagues (2012) and Litten and colleagues (2012). Despite these limitations, a priori hypothesis of detecting change within the topiramate group was confirmed, and signals for between-group differences in alcohol use and PTSD symptom severity were found to favor topiramate.

In sum, topiramate's effects on reducing alcohol consumption and craving in veterans whose goal was to reduce or stop alcohol use were generally in line with larger trials in AUD patients without PTSD. Topiramate's effects on reducing PTSD symptoms provide further support to the evidence available from several previous small open and controlled trials. While topiramate appeared to be safe and well-tolerated, the benefits in alcohol use reduction and PTSD symptom improvements must be interpreted in light of the apparent potential for transient cognitive decrements seen in the topiramate-treated participants. The results of this study warrant a larger investigation to more definitively assess the efficacy of topiramate treatment in reducing alcohol use and PTSD symptom severity in individuals with co-occurring AUD and PTSD.

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DISCLOSURE

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