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Zonisamide as an Adjunctive Treatment to Cognitive Processing Therapy for Veterans With Posttraumatic Stress Disorder and Comorbid Alcohol Use Disorder: A Pilot Study

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Background and Objectives: There are high rates of comorbid alcohol use disorder (AUD) among those who have posttraumatic stress disorder (PTSD). Ideally, treatment for comorbidity should address both disorders simultaneously. Zonisamide, an anticonvulsant, may be effective in decreasing alcohol use and may attenuate symptoms of PTSD. Treatment strategies can include medication in combination with a proven evidence-based psychotherapy designed to treat PTSD, such as cognitive processing therapy (CPT).
Methods: This 12-week pilot study was designed to test feasibility, acceptability, and preliminary efficacy of zonisamide (400 mg) as an adjunct to CPT for veterans with PTSD and comorbid AUD. Veterans ($n = 24$) with PTSD and current alcohol dependence were randomized in a 3:1 ratio to receive zonisamide or placebo in a double-blind fashion. All subjects received CPT enhanced to include sessions addressing drinking behavior.
Results: Subjects overall reported a significant decrease in drinking outcomes, craving, and symptoms of PTSD. Zonisamide was well-tolerated and easily administered with CPT, which was also well-tolerated. Exploratory analysis of comparison of groups suggests there was no advantage of zonisamide vs placebo in drinking or PTSD outcomes. There was a numeric but nonsignificant higher rate of abstinence with zonisamide (50%) vs placebo (33%).
Conclusion and Scientific Significance: The interpretation of the results is limited by the pilot nature of this study. The combination of psychosocial treatment with medication management mimics real-world treatment. In order to isolate the individual contributions of medication vs psychotherapy a much larger study would need to be conducted. (Am J Addict 2020;00:00–00)

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BACKGROUND

In the general adult population, posttraumatic stress disorder (PTSD) has a lifetime prevalence rate of 6.8% and a 12-month prevalence rate of 3.6%. It is a serious psychiatric disorder that tends to be chronic with one-third of the sufferers having symptoms more than 10 years after experiencing the traumatic event.[1,2] Some groups are more likely than the general population to suffer from PTSD, and that includes veterans, particularly those who have experienced combat. A recent meta-analysis of 33 studies evaluating prevalence rates among OEF/OIF veterans reported prevalence rates of 23%.[3] These high prevalence rates are accompanied by an increase in intensity in treatment utilization at Veterans Affairs (VAs) nationwide.

There is a high rate of comorbidity with alcohol use disorder (AUD) in individuals with PTSD.[4,5] Among veterans, 63% of those that met criteria for AUD (please note that most of these studies used criteria for alcohol dependence, but for simplicity, we are using alcohol use disorder throughout) or use of other substances also met criteria for PTSD.[6] Individuals diagnosed with comorbid PTSD and AUD tend to be more impaired and have poorer treatment prognosis than those diagnosed with PTSD or AUD alone. In particular, veterans with probable comorbid PTSD and AUD compared with veterans with probable PTSD or probable AUD alone, were found to have lower cognitive, physical, and mental health functioning and poor quality of life.[7] Treatment of comorbidity ideally includes addressing both disorders simultaneously, since leaving one disorder untreated can lead to relapse and/or exacerbation of the other. While there are established pharmacotherapies to treat PTSD and AUD alone, there are no medications approved to treat

the patients who have comorbid disorders.[8] There has been interest in developing a medication that helps decrease drinking behavior and also attenuates symptoms of PTSD. Another alternative is focusing on medications that would be delivered in conjunction with other treatments for PTSD, such as with one of the effective evidence-based treatments (EBT) established to treat PTSD.[9]

The anticonvulsant zonisamide has shown some promise in treating AUD symptoms. Zonisamide has properties similar to topiramate and is thought to act by indirectly facilitating γ-aminobutyric acid (GABA) inhibitory neurotransmission and indirectly reducing glutamate neurotransmission.[10] By this mechanism, zonisamide may reduce both the rewarding effects of alcohol consumption and the unpleasantness of drinking cessation, including alcohol urge or "craving." The effects on GABA may also explain its anxiolytic properties in patients with AUD and patients with refractory anxiety.[11-13] A few open-label studies using zonisamide in AUD (as noted above, these studies were conducted using criteria for alcohol dependence [AD])[12,14] showed that zonisamide was well-tolerated and associated with reduced drinking. In another study, zonisamide was more effective than diazepam in treating alcohol withdrawal syndrome.[15] These findings were validated in randomized, double-blind studies showing that zonisamide reduced drinking in AUD.[16,17] A more recent study showed that zonisamide was similar to topiramate in reducing drinking outcomes, in both quantity (drinks consumed per day) and frequency (percent days drinking, and percent days heavy drinking) compared with placebo with fewer side effects.[17]

Anticonvulsants have shown promise in PTSD treatment as well.[18-22] While zonisamide has not been formally tested for PTSD, a pilot study that used zonisamide as an adjunct to anxiolytic therapy in patients with marked anxiety provided preliminary evidence for zonisamide's efficacy in reducing anxiety symptoms. Given zonisamide's similarity to topiramate in terms of its neuropharmacologic effects and efficacy in other clinical syndromes, and potential as a mood-stabilizing and anxiolytic, zonisamide is worth testing as a potential pharmacotherapy for symptoms of PTSD.[11,23-26]

Given that treatment of PTSD is a high priority, the Veterans Health Administration (VHA) and the Department of Defense (DoD) have invested considerable resources in providing access to EBT to veterans. This includes cognitive processing therapy (CPT),[27] which is based on an information processing theory of PTSD and is an integration of psychoeducation and cognitive therapy. Currently, according to multiple clinical practice guidelines, CPT is recommended as one of the gold standard treatments for PTSD.[9] The National Institute for Health and Care Excellence (NICE) and the VA/DoD clinical practice guidelines recommend a co-occurring disorder not preclude access to recommended EBT treatments.[9,28] In fact, one promising treatment option in treating AUD and comorbid PTSD is use of combined treatment of pharmacotherapy for AUD and psychotherapy for PTSD.[8]

Some pilot data has suggested that CPT can be used in patients who have comorbid substance use disorders, although this has been primarily using retrospective case reviews or tested in individuals who are not currently actively using.[29] Our group has piloted the use of CPT in veterans with comorbidity with AUD:CPT is ideally suited to include modules on discussing use of substances. Use of CPT (cognitive therapy only version of CPT) in comorbidity follows the standard 12-session therapy, and integrates alcohol use in the cognitive worksheets (eg, A-B-C, challenging beliefs, patterns of problematic thinking worksheets to be completed on alcohol use), and addresses the role of drinking throughout highlighting the possible association between AUD and PTSD. We have reported on its effective use in combination with an established pharmacotherapy for AUD, disulfiram; CPT was effective in treating symptoms of PTSD, and alcohol use decreased after initiation of disulfiram.[30] Other groups have also reported on the use of CPT in comorbid AUD[31] or with participants who also have hazardous drinking.[32] Results suggest that CPT is well-tolerated, and is associated with reductions in symptoms of PTSD[31,32] and hazardous drinking.[32]

The current study reports on a 12-week pilot study, which was designed to test the feasibility, safety, and efficacy of combining zonisamide (400 mg/d) as an adjunct to CPT for veterans with PTSD and comorbid AUD. The study was designed as a pilot and in order to gain experience with zonisamide and its utility and acceptability in combination with an EBT and to evaluate for preliminary efficacy. In order to gain maximum experience with zonisamide, the study used an unbalanced design where subjects were randomized to active treatment in a 3:1 ratio.

METHODS

Design

This was a 12-week, randomized, placebo-controlled study in veterans diagnosed with DSM-IV AD and PTSD. The study was approved by both the Human Subjects Subcommittees of the VA Connecticut Healthcare System (West Haven, CT) and the Yale Human Investigations Committee (New Haven, CT). Participants were randomized to either zonisamide (400 mg) or placebo in the ratio 3:1. All participants also received up to 12 sessions of CPT.

Participants

One hundred forty-four individuals who were veterans were phone screened after responding to advertisements. One hundred twenty were excluded (for details see Fig. 1). After signing informed consent, participants underwent an initial assessment and screening. The screening consisted of a careful psychiatric and medical evaluation that also included screening for a potential alcohol withdrawal. Male and

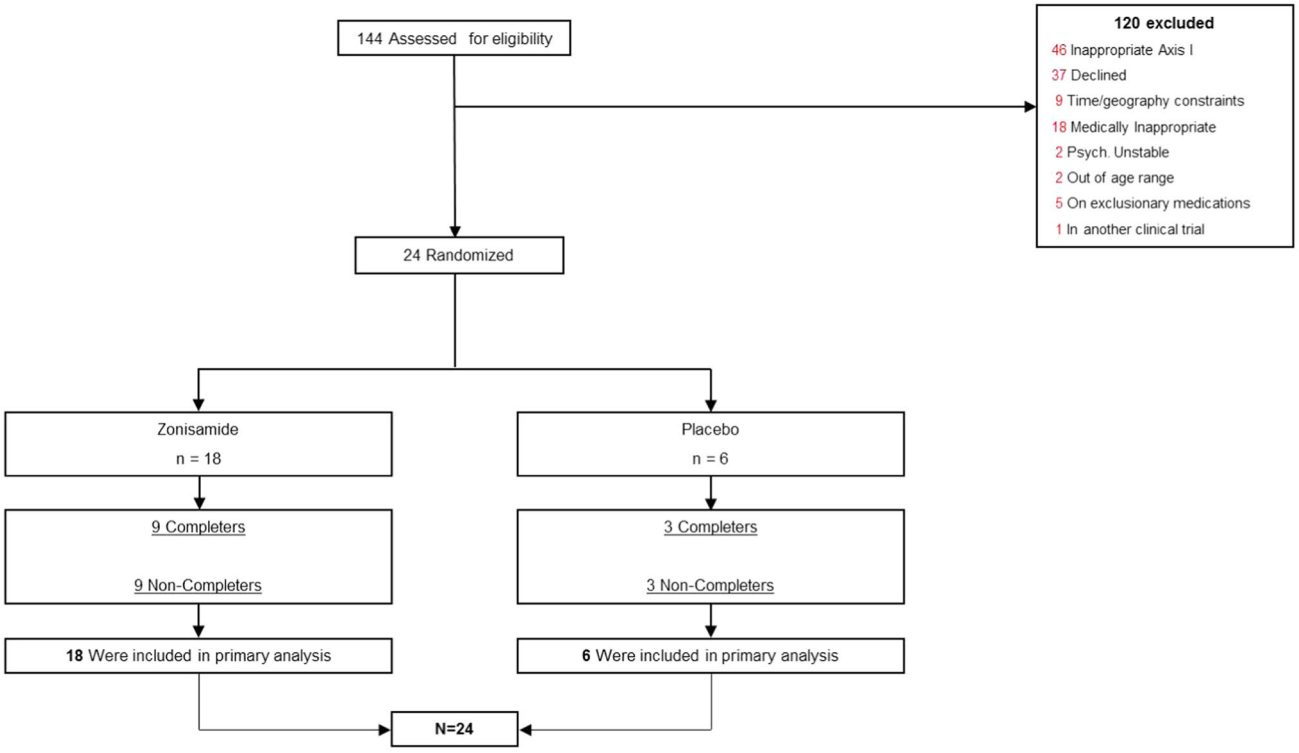

FIGURE 1. Consort table.

female participants were included if they were between 21 and 65 years old, met current criteria for primary AD (use of other substances was not an exclusion) and PTSD (determined using Structured Clinic Interview for DSM-IV Disorders [SCID])[33]; had at least one recent episode of heavy drinking (>4 standard drinks/sessions for men and >3 standard drinks/sessions for women) over the past 14 days, were medically and neurologically healthy, and for women, negative pregnancy test and use of acceptable method of contraception. Individuals were excluded if they had a current unstable medical condition, met current SCID criteria for a psychotic disorder or psychosis, were taking clozapine, lamotrigine, or had a history of an allergy to zonisamide or hypersensitivity to sulfonamides, were pregnant or lactating females, or already were receiving CPT.

Treatment

Participants ($n = 24$) were randomized (ratio 3:1) by the pharmacist (who was the only one with access to randomization codes) to either zonisamide or placebo. Zonisamide was titrated upward over 6 weeks to a maximum dose of 400 mg. At end of study (week 12), medication was tapered over 2 weeks. All medication was dispensed weekly in blister packs, and in identical-looking capsules clearly labeled with date and time (am or pm) for administration. Medication side effects were monitored weekly throughout the study. We employed a number of strategies to insure compliance with the study medication. Before starting medication, each participant met with the nurse to go over medication regiment, possible side effects, and importance of compliance with study medication. The study nurse called each participant during the first week to discuss side effects and encourage compliance. Before each visit, participants received a reminder phone call about the appointment and were reminded to return the blister pack with the study medication. During each study visit, the blister pack medication was counted, and the participant was prompted to report any doubling of dose or missing days of study medication.

All subjects received CPT. CPT[34] was standardized to include: (a) psychoeducation about alcohol use as an avoidance of PTSD symptoms, (b) obtaining clinician administered weekly breathalyzers to measure blood alcohol level, (c) integrating alcohol use in the cognitive worksheets used with CPT (eg, A-B-C, challenging beliefs, patterns of problematic thinking worksheets to be completed on alcohol use), (d) addressing the role of drinking throughout treatment, and (e) encouraging the use and collection of daily diaries of alcohol use. The therapy was provided by two psychologists. Psychologists were trained in CPT through the VA rollout initiative; the psychoeducation about alcohol use was standardized in a manual. The two psychologists who developed and standardized the alcohol portion (EM, MG) trained other members of our team, who delivered the therapy (JJ, EO). Independent assessment of

veterans' PTSD and AD symptoms were obtained by another member of the research team; this was done to ensure that we obtain unbiased ratings of PTSD and AD symptoms.

Measures

Assessments included collection of demographic, diagnostic (Structured Clinic Interview for DSM-IV Disorders [SCID I]),[33] and clinical information that encompassed questions on drinking patterns using the Timeline Follow-Back (TLFB) method,[35] craving for alcohol using the Obsessive Compulsive Drinking Scale (OCDS),[36] PTSD symptoms using the Clinician Administered PTSD Assessment (CAPS)[37] for DSM-IV and PTSD Checklist for DSM-IV (PCL),[38] and side effects using SAFTEE.[39] All measures were administered by experienced and trained study personnel. All outcome measures were collected weekly except for the CAPS, which was administered every second week. The baseline TLFB collected drinking data on 90 days prior to randomization. There was also a 3-month follow-up visit.

Statistical Analysis

Descriptive statistics were used to summarize the data on $n = 24$ individuals that were included in the analysis. Baseline demographic characteristics for the medication groups (ZON vs PLA) were compared using χ^2 tests for categorical variables and using analysis of variance (ANOVA) for continuous variables. The analyses were performed on the modified intent-to-treat sample (ie, individuals who had some post-baseline outcome data). For the main drinking outcome measures, we used ANOVA that included medication (ZON vs PLA) as factors in the model. For the analysis of PTSD symptoms, and OCDS we used linear mixed models (LMMs). LMM were also used for the drinking outcomes over time in secondary analyses. We selected the appropriate correlation structure for each dependent variable based on Schwartz Bayesian information criterion (smaller is better). Medication group (ZON vs PLA) was entered as a between subject factor and time was used as a within subject factor. χ^2 tests were used for all categorical data. All analyses were performed using 24.0 version of SPSS. Statistical testing for the outcomes was at a two-tailed α level of .05. Post hoc comparisons (Fisher's least significant difference) were also included in the analysis.

RESULTS

Sample Characteristics

Twenty-four individuals were included in the analysis. Recruitment for the study began in September 2013 and finished in October 2015. Of those, 18 were assigned to zonisamide and 6 to placebo. The groups consisted of middle-aged (mean age of the sample = 45.2, SD = 12.5), mostly men (91.6%) who had severe symptoms of PTSD (mean total CAPS score = 68.7, SD = 22.5) and drank heavily in the 3 months before starting the study (mean heavy drinking days = 40.7, SD = 29.8). Details of the demographic characteristics can be found in Table 1.

Compliance

The targeted dose in this study was 400 mg/d. The starting dose was 100 mg, increased to 200 mg for 2 weeks, 300 mg for another 2 weeks, and 400 mg at week 6 and until the end of the 12-week study. At the end of study (week 12), taper was conducted over 2 weeks. The average maximum dose was 327.8 (SD = 101.7) and the modal maximum dose was 400 mg. A majority of the subjects reached the maximum dose (16/24 or 66.6%). Participants complied with their medication regiment (54.1%) with no differences in compliance between the groups (55.5% in the ZON group vs 50% in the PLA group). There were only three subjects who dropped out due to side effects, they included one for sedation (assigned to PLA), one for GI issues (assigned to ZON), and one for a rash (assigned to ZON). Another three dropped out during week 1 for unknown reasons, of those one was assigned to PLA and the other two to ZON.

Half of the sample in this study completed all 12 research visits and from those that dropped out, we collected number of drinking days and PTSD symptom data on 66.6% in both groups. The rates of CPT completion were similar between the groups (33.3% in the ZON group vs 33.3% in the PLA group) with 37.5% of the participants (9/24) completing all 12 sessions and 50% completing at least 9 sessions (12/24). The average number of CPT sessions was 7 with no differences between the groups.

Drinking Outcomes

Drinking significantly decreased with treatment but there were no differences between the treatment groups on the number of drinking days ($F_{1,22} = 1.58$, $P = .22$) ($d = 0.54$), number of heavy drinking days ($F_{1,22} = 0.08$, $P = .78$) ($d = 0.15$), or the drinks per drinking day ($F_{1,22} = 0.78$, $P = .78$). Mixed model analysis that included time and treatment group produced similar results with significant time effects ($P < .05$) and no significant time × group interactions (effect size ranges from $d = 0.35$ to 0.46) (Table 2).

There was some evidence of differences between groups in abstinence rates, which was high in this group. Complete abstinence rates were 45.8% of the participants reporting complete abstinence during the 12 weeks of treatment and 70.8% of participants reported greater than 90% abstinence during treatment. The complete abstinence rates between the medication groups were higher in the zonisamide group (50% in ZON group and 33.3% in the PLA group), but did not differ statistically ($\chi^2 = 0.50$, $P = .48$). Similarly, a larger percentage of those with >90% abstinence were in the ZON group (ZON = 77.7% vs PLA = 50%), although this also was not statistically significant ($\chi^2 = 1.7$, $P = .19$) (for details on all outcome measures refer Table 2).

TABLE 1. Demographics/clinical characteristics of participants

Variables	Zonisamide ($n = 18$)		Placebo ($n = 6$)		Statistics
	Mean	SD	Mean	SD	F, P
Age	44.28	12.94	47.83	11.57	0.356, .557
	n	%	n	%	χ^2, P
Gender					
Male	18	100.00	4	66.67	6.545, .011
Female	0	0.00	2	33.33	
Race/ethnicity					
Caucasian	7	38.89	3	50.00	1.022, .600
African American	7	38.89	1	16.67	
Hispanic	4	22.22	2	33.33	
Marital status					
Single	8	44.44	1	16.67	5.526, .137
Married/cohabitating	7	38.89	1	16.67	
Separated/divorced	2	11.11	3	50.00	
Widowed	1	5.56	1	16.67	

	Drinking and PTSD characteristics				
	Mean	SD	Mean	SD	F, P
CAPS scores					
Total	67.33	23.82	72.83	19.60	0.259, .616
Re-experience	21.77	9.40	23.16	7.13	0.109, .745
Avoidance	31.27	11.72	29.83	7.96	0.078, .783
Hypervigilance	23.77	6.85	26.50	6.97	0.704, .411
Alcohol consumption					
No. of drinking days	46.88	30.25	51.00	22.09	0.093, .764
No. of heavy drinking days	43.94	30.12	31.50	29.57	0.763, .392

CAPS = Clinician Administered PTSD Assessment; PTSD = posttraumatic stress disorder.

Alcohol Craving

There was a significant decrease in overall craving for alcohol measured by the OCDS ($F_{12, 31.6} = 2.2$, $P = .03$). The same was true for obsessions with drinking ($F_{12, 47.3} = 2.2$, $P = .03$), and compulsions ($F_{12, 28.3} = 2.1$, $P = .04$) over the 12 weeks of treatment. Although the reduction in alcohol craving was greater in the zonisamide group, group differences did not reach statistical significance for any OCDS measures.

PTSD Symptoms

PTSD symptoms measured using the CAPS decreased significantly over the treatment period ($F_{6, 36.1} = 11.1$, $P = .001$) without any group differences and no significant time × group interactions ($d = 0.28$) (see Fig. 2 for total CAPS cores).

The results were similar for the three CAPS subscales. The analysis of self-reported PTSD symptoms, using the PCL, produced the same results for time ($F_{12, 32.9} = 3.5$, $P = .002$) without significant interactions, indicating that participants felt a significant decrease in the PTSD symptoms over the course of treatment.

Side Effects

Medication in this study was well-tolerated with no differences between the groups in the reporting of side effect most commonly associated with anticonvulsants. Most frequently reported side effects on zonisamide were difficulty in sleeping (33.3% on ZON vs 29.4% on PLA) and depressed mood (33.3% on ZON vs 23.5% on PLA). Other side effects were extreme tiredness/fatigue (16.6% on ZON vs 17.6% on PLA), feeling drowsy (16.6% on ZON vs 11.7% on PLA), decreased sex drive (16.6% on ZON vs 35.3% on PLA), anger/irritability (16.6% on ZON vs 17.6% on PLA), and difficulty with memory (16.6% on ZON vs 17.6% on PLA).

Adverse Effects

There were three reports (two on placebo and one on zonisamide) of adverse events that were submitted to the Human Subject Subcommittee but did not meet criteria for serious and unanticipated. One participant was hospitalized for intoxication and suicidal ideation (on placebo) shortly after randomization (decision = unrelated). The second subject was taken to the ER after a fall (on placebo) (decision = possibly related). He reported that his back "went out" (had a history of

TABLE 2. Means and standard errors for main outcome measures

	Zonisamide ($n = 18$)		Placebo ($n = 6$)			Statistics	
	Mean	SE	Mean	SE	Effect size (d)	F	P
Drinking over 12 weeks of treatment							
Drinks per drinking day	5.60	1.83	2.70	1.23	0.49	Drug, 0.78	.38
Drinking days	7.44	3.56	17.33	8.64	0.54	Drug, 1.57	.22
Heavy drinking days	5.50	2.60	4.16	2.44	0.15	Drug, 0.07	.78
Craving (OCDS)							
Total score						Drug, 0.18	.67
Baseline	18.28	2.31	11.48	4.15	0.51	Time, 2.20	.03
Week 12	5.34	2.59	11.92	4.75		Drug × Time, 0.96	.50
Obsessions						Drug, 0.04	.84
Baseline	7.14	1.07	4.61	1.88	0.35	Time, 2.15	.03
Week 12	2.42	1.18	4.39	2.15		Drug × Time, 0.78	.66
Compulsions						Drug, 0.69	.41
Baseline	11.18	1.45	8.13	2.60	0.58	Time, 2.14	.04
Week 12	2.93	1.63	7.43	3.02		Drug × Time, 0.69	.74
PTSD symptoms							
CAPS							
Total score						Drug, 0.83	.37
Baseline	67.33	5.49	72.83	9.51	0.43	Time, 11.14	<.01
Week 12	30.83	6.02	23.80	11.21		Drug × Time, 0.93	.48
Total hyperarousal						Drug, 0.20	.65
Baseline	23.77	1.83	26.50	3.17	0.41	Time, 8.64	<.01
Week 12	12.28	2.03	9.06	3.80		Drug × Time, 1.14	.35
Total avoidance						Drug, 2.91	.10
Baseline	31.27	2.44	29.83	4.23	0.66	Time, 12.43	<.01
Week 12	12.16	2.73	5.93	5.18		Drug × Time, 1.19	.33
Total re-experience						Drug, 0.001	.98
Baseline	21.77	2.03	23.16	3.52	0.16	Time, 14.91	<.01
Week 12	7.21	2.20	7.70	4.06		Drug × Time, 0.57	.75
PCL							
Total score						Drug, 0.01	.99
Baseline	38.66	3.74	39.16	6.47	0.13	Time, 3.51	<.01
Week 12	18.92	4.08	22.89	7.40		Drug × Time, 0.61	.81

CAPS = Clinician-Administered PTSD Scale; OCDS = Obsessive Compulsive Drinking Scale; PCL = PTSD Checklist for *DSM-IV*.

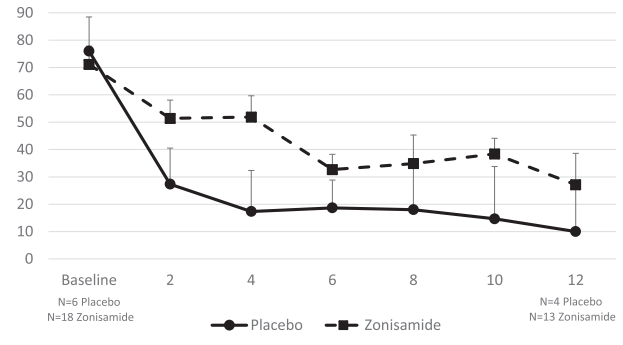

FIGURE 2. Effects of zonisamide on self-reported CAPS total scores across the medication treatment period. CAPS = Clinician-Administered PTSD Scale.

back problems). He also reported feeling dizzy and tired—due to pneumonia and dehydration (according to hospital notes). The third participant reported breast swelling and noticed a small lump (on zonisamide) 1 week after completing the study (decision = possibly related). He did not seek medical attention for another 6 months. After medical investigation, the final diagnosis was subareolar abscess and lactiferous duct fistula.

DISCUSSION

This study was designed to evaluate the feasibility, acceptability, and preliminary efficacy of using zonisamide (400 mg) as an adjunct to CPT in veterans with PTSD and comorbid AUD. Subjects as a group, all of whom were treated with CPT, reported a significant decrease in both

drinking outcomes, craving, and symptoms of PTSD. Zonisamide was well-tolerated in this pilot study and while definitive conclusions cannot be drawn there is evidence that zonisamide might be of interest for further exploration in AUD. In contrast, there was no promising evidence that it was effective in further reducing symptoms of PTSD.

Zonisamide had a favorable side effect provide and its tolerability is evidenced by a majority of participants reaching the maximum dose and few dropouts due to the side effect profile. Its use was easily incorporated into treatment with an EBT that was trauma-focused; this is important clinically as zonisamide requires titration. Although preliminary in nature, exploratory analysis suggested that zonisamide did not add benefit beyond the behavioral intervention as it was not superior to placebo in any outcomes. The only suggestion of benefit was in the domain of drinking outcomes, since it was noted that there was more abstinence and less alcohol craving with zonisamide compared with placebo, although the results were nonsignificant. Zonisamide efficacy in AUD is currently under evaluation (clinicaltrials.gov) in two larger randomized controlled trials. The results from the present study suggest it can be used safely in those with comorbidity.

One of the main findings of this study is that CPT can be used effectively in patients with PTSD who are actively drinking. It has been previously reported that CPT can be used in those with comorbid AUD[31] and in those with hazardous drinking. It should be noted that Kaysen et al[31] did not report on drinking outcomes. In the present study, drinking outcomes were collected and subjects as a group decreased drinking, had high rates of abstinence or near-abstinence (>90%), and reported a decrease in craving. This adds to the growing body of literature that suggests that trauma-focused EBTs can be used safely in the dually diagnosed. Most of the evidence is with prolonged exposure (PE), modified for substance use,[40] but CPT is also trauma-focused and can be used in this context. CPT may be particularly suitable for patients with comorbidity since sessions can be easily adapted to include psychoeducation highlighting the possible association between AUD and PTSD (eg, high co-occurrence, the likelihood that improving PTSD symptoms can impact one's ability to manage AUD symptoms such as thoughts and cravings) as well as cognitive restructuring involving AUD and PTSD. During CPT, the patients learn to identify patterns of thoughts about the trauma and its consequences that keep them stuck from recovering (ie, "Stuck Points"), and then learn to examine and challenge stuck points in order to develop a healthier approach to their thoughts and feelings. Cognitive restructuring involved with CPT, focused on restructuring maladaptive thoughts about oneself, others, and the world, and can also promote recovery from alcohol use.[31,41]

The average number of completed CPT sessions in this study was 7 and 37.5% ($n = 9$) of the sample completed all 12 sessions. There are acknowledged barriers to both implementing and receiving psychotherapies for PTSD, with high dropout in trauma-focused treatments in general (36%),[42] and higher dropout among veterans (50%).[43] In a large-scale study examining veterans newly enrolled in a PTSD clinic ($n = 1924$) who completed at least one CPT or PE session, the median number attended was 5 out of 12 sessions (range of 2-9 sessions).[44] In a systematic review examining attrition rates among veterans and service members, the overall dropout was 36%, with a considerable range (from 5% to 78.2%).[42] While it was thought that dropout was lower in clinical trials due to higher motivation and more vigorous retention efforts, authors found dropout did not differ by substance use disorder. The dropout rate in this study is consistent with these data.

It should be noted that while CPT is designed for 12 sessions, Mott et al[45] have reported that in order to meet the definition of "completer," an adequate dose of CPT is seven or more sessions. This takes into account early responders and is based on prior research showing good end-state criteria in 7.5 sessions.[45,46] This suggests that an average of about 7 sessions[46] may be sufficient for good PTSD outcome. The significant drop in PTSD symptoms in this study, even in those who did not complete all 12 sessions of CPT, may suggest that fewer number of sessions may be sufficient to achieve good functioning. It is possible that veterans who dropped out of CPT after the first month were early responders in the present study. While our small sample prevented further and more detailed analysis of this issue, dismantling CPT to determine which aspects are important would be an important future study. Our rates of completion are slightly lower than those reported in Kaysen's chart review of CPT completion among PTSD-diagnosed veterans with and without concurrent AUD,[31] although in the present study subjects were currently drinking. The rates of the current study are comparable to other trauma-focused interventions examining dual diagnosis populations,[47] although lower than those reported in samples with PTSD only.[46,48-50] Consistent with previous research,[31,51] trauma-focused treatment was associated with trauma symptom improvement over time despite an AUD diagnosis. Results support evidence that PTSD and substance use should be addressed concurrently rather than sequentially[52] and prior research suggested that trauma-focused treatments (vs nontrauma-focused) show superior results.[53]

In this study, PTSD symptoms significantly decreased from highly symptomatic CAPS overall score (mean = 68.7 at baseline) to mildly symptomatic (mean = 28.3). This decrease of over 40% is consistent with other studies using CPT.[54,55] What is clinically interesting from this study is the question of whether the large reduction in PTSD symptoms may have contributed to the high rates of abstinence. There is at least some emerging evidence that treating PTSD may improve substance use outcomes,[56] and that improvement of distress leads to improvement in both PTSD and substance use during trauma-focused treatment for PTSD.[57] These results are not consistent across all studies, although different methodology makes comparisons difficult.[58] Nevertheless,

this is an important area of study. It should also be noted that results from this study showed a nonsignificant group difference in CAPS scores between those who were treated with zonisamide (higher CAPS score) compared with those treated with placebo of over 20 points particularly early in treatment (week 4, see Fig. 2). Post hoc analysis at each time point showed that there were no statistically significant differences between groups. Whether this is a true finding, one that does not reach statistical significance because of the very small sample size, particularly with the small number assigned to placebo ($n = 6$) could not be determined. Nevertheless, these data are not promising in supporting further exploration of zonisamide's effect in the treatment of patients with PTSD.

The conclusions in this study were limited by the likelihood that it was underpowered for a medication effect owing to the small sample size and unbalanced medication assignment. All subjects received the psychotherapeutic intervention aimed at reducing PTSD symptoms, which also included coping skills targeting reduction of alcohol use; this may have produced a ceiling effect. Our effect sizes indicate that a much larger sample would be needed to show the superiority of zonisamide over placebo as an adjunctive treatment to CPT. While the study also shows zonisamide treatment can be incorporated to a platform of active trauma-focused psychotherapy, this also likely obscured medication effects. Further, without a comparison group for psychotherapy, we cannot determine whether another behavioral platform would produce similar results. Since the sample consisted of veterans who were mostly men, generalizability of our findings to women and civilians is limited. Because this study was initiated several years ago, the diagnostic criteria were assessed according to DSM-IV rather than DSM-5. While a 3-month follow-up was scheduled, the data have not been analyzed and given the small sample size the utility of these data is unclear. Another limitation is that there was no fidelity rating for the therapy.

Nevertheless, the findings from this pilot study do give some guidance on further areas of study. Zonisamide efficacy seems more likely in helping with drinking outcomes than PTSD symptoms. Interventions treating comorbidity ideally should treat both disorders. There is interest in finding a medication that can treat both disorders or using behavioral platforms that target both disorders (eg, Seeking Safety). The hope that monotherapy can treat comorbidity has been disappointing, as medications to treat both have often been found to treat only one disorder (eg, prazosin[59]) or sometimes neither.[60] The combination of psychosocial treatment with medication management is a promising option and does mimic real-world treatment. Several studies have successfully used combination treatment using a behavioral platform to treat PTSD and adding a medication to treat AUD.[61,62] To fully evaluate the combination of CPT and zonisamide, with the ability to isolate and understand the individual contributions of medication vs psychotherapy in AUD and PTSD, a much larger study would need to be conducted.

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