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A randomized pilot trial of topiramate for alcohol use disorder in veterans with traumatic brain injury: Effects on alcohol use, cognition, and post-concussive symptoms

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Abstract

Background: Topiramate is an effective treatment for alcohol use disorder (AUD) and has also been used in the care of mild traumatic brain injury (mTBI). This pilot study aimed to obtain a preliminary assessment of topiramate's efficacy in reducing alcohol use and post-concussive symptoms, and its potential negative impact on cognitive function in 32 Veterans with co-occurring AUD and mTBI.

Methods: This was a prospective 12-week, randomized, double-blind, placebo-controlled pilot study of flexible-dose topiramate or placebo. Primary outcome was reduction of drinking days per week within the topiramate arm. Secondary outcomes included between group comparisons of alcohol use and craving, post-concussive symptoms, and cognitive function.

Results: Drinking days per week significantly decreased within both the topiramate and placebo arm. There were no significant treatment-by-week interactions on alcohol use/craving, or post-

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CRediT authorship contribution statement

David L. Pennington: Data curation, Formal analysis, Writing - original draft, Investigation, Writing - review & editing. **Jennifer Bielenberg:** Writing - origional draft, Investigation, Writing - review & editing. **Brooke Lasher:** Investigation, Writing - review & editing. **Ellen Herbst:** Investigation, Writing - review & editing. **Gary Abrams:** Conceptualization, Methodology, Writing - review & editing. **Tatjana Novakovic-Agopian:** Conceptualization, Methodology, Writing - review & editing. **Steven L. Batki:** Investigation, Funding acquisition, Formal analysis, Writing - review & editing.

Declaration of Competing Interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2020.108149.

concussive symptoms in intent-to-treat analyses. In per-protocol analyses, topiramate significantly reduced number of drinks per week compared with placebo. Topiramate transiently impaired verbal fluency and working memory. Processing speed, cognitive inhibition, and mental flexibility significantly improved between weeks 1 and 12, regardless of treatment arm.

Conclusions: Significant improvement occurred in both the topiramate and placebo groups over 12 weeks of treatment in alcohol use and post-concussive symptoms. Among treatment completers there was greater reduction of alcohol use in the topiramate arm. Topiramate was also associated with negative but transient effects on cognitive function. Results suggest both a possible benefit for topiramate treatment in reducing alcohol use and some potential for negative cognitive effects in Veterans with AUD and mTBI.

Keywords

Topiramate; Clinical trial; Alcohol use disorder; Traumatic brain injury; Cognitive function

1. Introduction

Military personnel are at substantially increased risk for traumatic brain injury (TBI) and alcohol use disorders (AUDs) compared with civilians (Brady et al., 2009; Substance Abuse and Mental Health Services Administration, 2007). Over 350,000 service members worldwide have a documented history of TBI, and those with TBI are noted to have increased risk of hazardous alcohol use (four or more drinks per day or more than seven drinks per week for women; five or more drinks per day or more than 14 drinks per week for men (National Institute on Alcohol Abuse and Alcoholism (NIAAA), 2007; Adams et al., 2012). Hazardous alcohol use can both predispose individuals to TBI and exacerbate existing TBI symptoms, thereby increasing vulnerability to future injuries (Schumm and Chard, 2012). Conversely, the cognitive impairments that accompany TBI can also increase predisposition to heavy alcohol use (Corrigan and Cole, 2008; Jorge et al., 2019; Polusny et al., 2011).

Mild TBI (mTBI) is the most common form of head injury, and is associated with increased risk for substance use disorders (Miller et al., 2013). Alcohol use pre- and post-TBI has also been associated with adverse neurological, psychiatric, and psychosocial outcomes, including posttraumatic seizures (Wiedemayer et al., 2002), depression (Jorge, 2005), decreased subjective well-being (Bogner et al., 2001; Bombardier et al., 2003; Olson-Madden et al., 2010), and higher rates of suicide (Teasdale and Engberg, 2001). These adverse consequences of heavy alcohol use with TBI underscore the importance of effective treatments for AUD in this understudied population.

While there are four Food and Drug Administration (FDA) approved medications for the treatment of AUD (acamprosate, disulfiram, and both oral and extended-release forms of naltrexone), there are no medications approved by the FDA specifically for the treatment of TBI symptoms. Medications used in the treatment of TBI generally target a specific persistent post-concussion symptom, e.g., headache, sleep problems, etc. (Department of Veterans Affairs, 2016). NIAAA recommendations endorse the consideration of medications for all patients with alcohol use disorders (National Institute on Alcohol Abuse

and Alcoholism (NIAAA, 2007), yet there have been few investigations regarding the effectiveness of medications for the treatment of AUD in individuals with TBI. At the time of this writing, there have been no reports of placebo-controlled trials of pharmacotherapy for the concurrent treatment of AUD and TBI symptoms in participants who were expressly selected to meet diagnostic criteria for both AUD and TBI. However, to date related work consists of one open and two controlled clinical trials. An open retrospective assessment of anticonvulsant treatment showed an association between divalproex and carbamazepine treatment and reduction of emotional lability and alcohol use in Veterans with TBI (Beresford et al., 2005). A controlled trial of valproate in patients with TBI, some of whom met criteria for AUD, has been completed (ClinicalTrials.gov NCT01760785) but results have not yet been published. Finally, a randomized, blinded trial comparing naltrexone to divalproex (with no placebo arm) in Veterans with AUD, some of whom had TBI and some of whom had PTSD showed a non-significant trend for greater improvement in alcohol use in the naltrexone treatment arm (Jorge et al., 2019).

Another anticonvulsant, topiramate, has characteristics that suggest potential utility in the treatment of co-occurring AUD and TBI. Topiramate has been shown in a number of controlled clinical trials to significantly reduce alcohol use in individuals with AUD (Blodgett et al., 2014) including a RCT with Veterans with co-occurring PTSD (Batki et al., 2014), a condition that is frequently comorbid with TBI (Stein and McAllister, 2009). Topiramate is also utilized in the care of TBI patients both as an anticonvulsant and to treat posttraumatic headache following TBI (Minen et al., 2016). However, topiramate is known to produce adverse effects that can include cognitive impairment (Knapp et al., 2015; Wandschneider et al., 2017; Aldenkamp et al., 2000; Batki et al., 2014), and concern has been raised about its potential for negative effects on cognition in patients with TBI (Tang et al., 2007). Because of its potential to treat both AUD and some aspects of TBI, we 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 Veterans with co-occurring AUD and mild TBI, with the primary aim of measuring efficacy in reducing alcohol use and secondary aims of assessing effects on symptoms of TBI and effects on cognition. The objectives were to advance knowledge regarding the feasibility of conducting a treatment study among understudied Veterans with co-occurring TBI and AUD and to establish preliminary indication that topiramate treatment is tolerable and associated with alcohol use and TBI symptom reduction in this complex population.

2. Materials and methods

2.1. 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 Health Care System (SFVAHCS) and the Department of Defense. Participants were recruited between March, 2013 and June, 2015 and all procedures took place at the SFVAHCS in San Francisco, CA. All study visits were completed in September of 2015. Study participants were 32 Veterans who had a history of mTBI and met DSM-IV-TR (American Psychiatric Association, 2000) diagnostic criteria for current AUD. All

participants also reported “heavy” drinking in accordance with NIH/NIAAA criteria (at least 15 standard drinks per week on average over the 4 weeks prior to consent 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 actively drinking as well as some who stopped shortly prior to random assignment. Participants were free to access any other standard psychosocial treatments for AUD, but they could not receive other AUD pharmacotherapy.

History of mTBI was established using a structured clinical interview adapted from the Veterans Health Administration Comprehensive TBI Evaluation (initially referenced as the TBI Second Level Evaluation) (Belanger et al., 2009). This comprehensive assessment gathers lifetime clinical history of head injury, occurrence and duration of loss of consciousness, alteration of consciousness, and posttraumatic amnesia. A history of mTBI was considered present if a participant endorsed VA/Department of Defense and the American College of Rehabilitation Medicine (ACRM) criteria of having a traumatically-induced physiological disruption of brain function as a result of an external force resulting in a loss of consciousness not exceeding 30 min, memory loss for events immediately before or after the event not exceeding 24 h, alteration in mental state at the time of the event (e.g., disorientation, confusion, slowed thinking), or neurological deficit(s) (e.g., loss of balance/coordination, change in vision, weakness). Any endorsement of clinical signs exceeding these limits at the time of the injury was considered to indicate a history of TBI more than mild, thus barring study inclusion.

Participants were excluded if they had any unstable psychiatric or medical conditions judged by study clinicians to pose unacceptable risks, or if they had made a suicide attempt or experienced suicidal ideation with intent in the six months prior to enrollment. Other exclusion criteria included acute alcohol withdrawal, history of nephrolithiasis or narrow angle glaucoma, topiramate use within the past four weeks or concurrent use of AUD treatment medication or participation in other AUD or TBI treatment studies.

2.2. Procedure

This was a randomized, double-blind, placebo-controlled, flexible-dose (25−300 mg/day) pilot trial of topiramate treatment. Screening consisted of 2–3 visits during which participants completed the measures and interviews described below. Those who met entry criteria were randomly assigned in a 1:1 ratio to receive 12 weeks of either topiramate or placebo treatment. Randomization was stratified by presence or absense of alcohol use in the 4 days prior to randomization and balanced using computer-generated block randomization with permuted block sizes of six, created by a study statistician. The allocation list was given to an independent SFVAHCS research pharmacist who assigned participants to study group and dispensed study medication according to the randomization list. Participants and all research staff 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 Batki et al. (Batki et al., 2014). The initial dose was 25 mg nightly for one week, and then increased weekly, as tolerated. The dose was

increased to 50 mg per day in two divided doses in week 2; to 100 mg per day in week 3; to 150 mg per day in week 4; to 200 mg per day in week 5, and in week 6–300 mg per day 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 adverse effects, then study medication dose would not be advanced, or, if needed, it would be decreased. All participants were also provided weekly Medical Management counseling (Pettinati et al., 2005), a manual-driven, low-intensity supportive counseling method designed by NIAAA to promote adherence to the medication regimen and reduction in alcohol use. Participants could be withdrawn from the study if in the judgment of the investigators, continued study participation was associated with clinically significant worsening of AUD, in which case they were referred to standard clinical treatment with known AUD medications.

2.3. Measures

Alcohol and other Substance Use Disorder Diagnosis and Depression/Anxiety Symptom Severity.—All participants were administered the Substance Use Disorders sections of the Structured Clinical Interview for DSM-IV-TR (First et al., 2001). Participants also completed the Beck Depression Inventory [BDI-II] (Beck et al., 1961) and the Beck Anxiety Inventory [BAI] (Beck et al., 1988) for patient characterization.

2.3.1. Alcohol use and craving measures—

Alcohol use was assessed using the Time Line Follow Back (TLFB; Sobell et al., 1985; Sobell and Sobell, 1992) interview which yields number of standard alcohol drinks per week, number of drinking days per week, number of heavy drinking days per week, and number of drinks per drinking day. The TLFB was administered at baseline to assess the 90-day period prior to the beginning of screening, weekly alcohol use between the first screening visit and randomization, and alcohol use between each subsequent treatment visit. Alcohol use data was aggregated to represent weekly averages for 7-day intervals between the 7 days preceding randomization and each subsequent week through end of follow-up at week-16. Alcohol craving-related obsessive thoughts and compulsions were measured with the Obsessive Compulsive Drinking Scale (OCDS; Anton et al., 1995) at screening, week 4, 8, and 12. The Clinical Institute Withdrawal Assessment for Alcohol, DSM-IV Version (CIWA-AD) (Sellers et al., 1991) was also administered at every research contact with participants. No participants were found to exhibit signs of clinically significant alcohol withdrawal during the conduct of the study.

2.3.2. Postconcussive syndrome symptoms—

The Neurobehavioral Symptom Inventory (NSI), a 22-item measure designed to evaluate self-reported vestibular, somatic, cognitive, and affective postconcussive syndrome (PCS) symptoms (e.g. headache, balance, nausea, etc.) was administered at baseline and at week 4, 6, 8, 12, and 16.

2.3.3. Neurocognitive assessment—

The battery was developed to assess performance in cognitive domains commonly affected by heavy alcohol use and TBI and to assess areas of cognition known to be adversely affected by topiramate. The battery

contains standardized instruments administered at baseline, Weeks 6, 12 and 16. When feasible, alternate forms were used for repeated administrations. Raw scores for available neurocognitive measures were converted to standardized scores via appropriate normative data adjusted for age, ethnicity and/or education. Domains and constituent measures included: *Premorbid verbal intelligence*: Wechsler Test of Adult Reading (Venegas and Clark, 2011); *Processing Speed*: Trail Making A (Reitan and Wolfson, 1985)*; Auditory-Verbal Learning and Memory:* Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt and Benedict, 2001)*; Working Memory:* WAIS-IV Arithmetic and Digit Span (Wechsler, 2008); *Mental Switching:* Trail Making Test B (Reitan and Wolfson, 1985); *Cognitive Inhibition:* Stroop Color Word (Golden et al., 1978); and *Verbal Fluency*: Controlled Oral Word Association (COWA; Benton et al., 1994).

2.3.4. Adverse effects—Adverse effects (AEs) were collected weekly using both an open-ended questionnaire and a checklist of the 18 most common AEs associated with topiramate as indicated in the FDA-approved labeling for topiramate (Janssen Pharmaceuticals, 2012).

2.4. Statistical analyses

Due to limited resources, this pilot study was designed with adequate power to allow the primary outcome analysis of *within-group* change in drinking days from baseline through week 12 in the topiramate treatment arm. Power estimates for the current study were limited as no studies to date have examined within group effects of topiramate on reducing average number of drinking days per week among Veterans with AUD and TBI. Consequently, there is no available data to estimate effect sizes specific to the hypothesized effects. However, power calculations based on a .05 alpha level reveal that 80 % power (1-β) will detect a significant within group effect over 12 weeks of treatment observations via F-testing of a medium to large effect size ($0.15 \leq$ Effect size $f2 \leq 0.35$), and would require a total sample size of 7–33 (G-Power 3.1.9.2). Given these power approximations, we estimate that our study sample of 15 within the topiramate condition is appropriately powered to detect hypothesized primary effect. In secondary analyses, we examine if topiramate is more efficacious than placebo *(between-groups)* in reducing drinking days per week, heavy-drinking days per week, drinks per week, drinks per drinking day, alcohol craving and PCS symptoms from baseline to week 12 of the trial among all participants enrolled (intent-to-treat). Safety was evaluated by comparing rates of reported emergent adverse events and by examining if topiramate acutely worsened cognitive performance relative to placebo from baseline to week 12 of the trial. In exploratory analyses, alcohol outcomes were re-examined among participants who completed week 12 of the study (per protocol).

All statistical analyses were performed with IBM SPSS Statistics Version 24 (IBM, 2012). Baseline characteristics and rates of emergent adverse events were compared using a one-way analysis of variance for continuous variables and the chi-square test (or Fisher's exact test when cell sizes were small) for categorical variables. Standard alcohol drinks per week, drinks per drinking day, PCS symptoms, and cognitive scores were continuously scaled, repeated measures analyzed with random-intercept linear mixed models using restricted maximum likelihood by SPSS's MIXED procedure. Number of drinking days per week

and heavy drinking days per week are count outcomes analyzed by Poisson log-linear mixed models using SPSS's GENLINMIXED procedure. Goodness-of-fit was evaluated by comparing the Akaike and Bayesian Schwartz Information Criteria (AIC and BIC) for the Poisson model compared with a negative binomial model. In each case, the AIC and BIC for the Poisson model was lower indicating a better fit. An auto-regressive correlation structure was used in general linear models and robust variance adjustments in Poisson models to adjust for repeated observations within participants. SPSS's MIXED and GENLINMIXED procedure allows for the inclusion of all available data. Therefore, for intent-to-treat analyses no imputation methods were used to attempt to account for missing data in these modeling procedures.

The within-topiramate group analysis of drinking days included a fixed predictor of time (weekly aggregates including the 7 days prior to randomization through week-12). Secondary models examining drinking days per week, heavy drinking days per week, drinks per drinking day, drinks per week, PCS symptoms, and neurocognitive function included fixed predictors of treatment (topiramate, placebo), time (treatment week) and the interaction term of treatment-by-time. In secondary models, amount of study medication taken and verified by pill count (milligrams of topiramate and placebo) was examined as a potential covariate. Alcohol use and frequency in the 90 days prior to consent were also used as covariates in their respective models. In cognitive function analyses, premorbid verbal intelligence was entered as a covariate in addition to milligrams taken. Potential covariates were trimmed from the final model when not predictive of the outcome variable. Analyses were intent-to-treat and used all possible observations. No imputation methods were used to attempt to account for missing data beyond endpoints in which subjects were no longer participating in the study (i.e., non-completion of the study due to non-adherence, exacerbation of alcohol use, disruptive behavior, and lost to follow-up). An alpha level of $p \leq 0.05$ was considered significant. In exploratory analyses, models were run using data available only from those who attended week 12 of the study (per protocol analyses). We also examined the stability of treatment effects at the 1-month follow-up assessment (week 16) using models similar to those outlined in our secondary analyses, except with the time factor including only week 12 and 1-month (week 16) follow-up data.

3. Results

3.1. Patient characteristics

Baseline characteristics for the topiramate and placebo groups are shown in Table 1. Of the 32 participants, 15 were randomly assigned to topiramate, 17 to placebo. There were no differences between treatment group characteristics at baseline except in total number of acquired blast related head injuries. Therefore, we included number of acquired blast related head injuries as an additional covariate in our statistical analyses. Of the 32 participants enrolled, eight topiramate and six placebo attended a 30-day community based residential rehabilitation treatment program that included a structured living environment with group therapy and individual case management. Participants in residential treatment programs were allowed to travel to and from the SFVAHCS to attend screening and study procedures. Medication was initiated when the participant passed the screening process and entered the

active treatment phase. Topiramate and placebo treatment groups did not differ in alcohol use in the 90 days prior to consent or in the 7 days prior to randomization. Of note, study participants had significant reductions in heavy drinking days ($p = 0.04$) per week, drinking days per week ($p = 0.001$), and drinks per week ($p = 0.02$) when we compared the averages in the 90 days prior to consent to the averages during the 7 days immediately prior to randomization to medication arm.

3.2. Study retention

Of the 32 randomized patients, 25 [78.1 %] (topiramate: 13/15 [86.6 %]; placebo: 12/17 [70.6 %]) completed the trial, attending week 12 study visit. Participants assigned to topiramate attended a significantly lower percent of study visits (84.8 %) than those assigned to placebo (93.6) during weeks 1–12 ($p < 0.01$). However, although not statistically different ($p = 0.40$), attrition in the placebo group was more than double that of the topiramate group over the course of the 12-week treatment phase (29.4 % and 13.3 % respectively). Subject flow is illustrated in Fig. 1. Study completion was defined as being present for the week 12 study visit. Mean number of weeks retained in treatment did not significantly differ between groups ($p = 0.25$). Participants were retained for 11.4 ± 1.6 weeks in the topiramate arm and 10.2 ± 3.7 weeks in the placebo arm of the study. Of the seven participants who did not complete the study: two topiramate participants were non-adherent (stopped taking study medication), two placebo participants were withdrawn due to exacerbation of alcohol use to levels judged by study clinicians to require clinical treatment with known AUD medications, one placebo participant was administratively withdrawn for disruptive behavior, and two placebo participants were lost to follow-up. No participants dropped out due to reported adverse effects related to study medication.

3.3. Maximum medication dose

This was a flexible-dose study. The maximum study dose (300 mg/day) was adjusted to participant tolerance, based on participant reports of adverse events, participant preferences and safety concerns as judged by the study clinicians. In participants with renal impairment (estimated creatinine clearance < 70 mL/min/1.173 m2), the maximum dose was reduced by 50 % as per the FDA prescribing information for topiramate. The average maximum study medication dose reached was 284 ± 82 mg/day for topiramate and 274 ± 136 mg/day for placebo. The difference in maximum dose reached by topiramate and placebo was not statistically significant ($p = 0.81$).

3.4. Primary analyses

3.4.1. Drinking days—Our primary analysis demonstrated a significant decrease from 3.6 ± 2.8 drinking days per week at baseline (7 days prior to first medication dose) to 2.2 ± 1.8 drinking days per week at week 12 within the topiramate arm ($p = 0.03$, incidence rate ratio [IRR] = −0.05; 95 % confidence interval [CI] = −0.09 to −0.01).

3.5. Secondary analyses

3.5.1. Drinking days, heavy drinking days, drinks per drinking day, drinks per week, and craving (Table 2)—There were no significant treatment-by-week interactions

on alcohol consumption or alcohol craving outcomes. There were significant main effects for time, indicating that both topiramate and placebo groups decreased in drinking days per week, heavy drinking days per week, OCDS Total and OCSD Obsessive and Compulsive subscale scores from baseline to week 12 (both $p < 0.01$).

Results remained unchanged in per protocol analyses, except for a significant treatment-by-week interaction in drinks per week ($F(1,53) = 4.13$, $p = 0.05$, beta [β] = −1.76; 95 % CI = −3.49 to −0.23; Fig. 2), indicating a significantly greater reduction in the topiramate group of 31.5 drinks per week (44.0 ± 53.8 at baseline to 12.5 ± 14.9 at week 12, $F(1,39) = 11.2$, $p < 0.01$, $\beta = -2.64$; 95 % CI = −4.23 to −1.05) compared with the 15.2 drinks per week reduction in placebo (28.2 ± 49.1 at baseline to 13.0 ± 28.1 at week 12, $F(1,66) = 8.4$, $p < 0.01$, $\beta = -0.68$; 95 % CI = −1.15 to −0.21). There were no significant findings between week 12 and the 1-month (week 16) follow-up assessment point.

3.5.2. Post concussive symptoms (Table 2)—

There were no significant treatment-by-week interactions on PCS outcomes. There was a significant effect for time, indicating that both topiramate and placebo groups decreased in self-reported cognitive symptoms from 6.78 ± 4.20 at baseline to 4.13 ± 3.88 at week 12 ($F(1,51) = 6.46$, $p = 0.02$, $\beta = -0.16$; 95 % CI = −0.30 to −0.25). Results remained unchanged in completer analyses and no significant findings were observed between week 12 and the 1-month follow-up assessment point.

3.6. Safety outcome (Table 3)

3.6.1. Cognitive function

3.6.1.1. Processing speed and mental switching.: There were no significant treatment-by-week interactions. However, there were significant effects for time showing an improvement in processing speed ($F(1,26) = 20.50$, $p < 0.01$, $\beta = 0.56$; 95 % CI = 0.22 to 0.89) and mental switching ($F(1,20) = 10.3$, $p = 0.04$, $\beta = 0.42$; 95 % CI = 0.03 to 0.82) from baseline through week 12 for all study participants, regardless of treatment arm. In completer analysis, results remained unchanged for processing speed, and the significant effect for time on mental switching dropped to trend levels ($F(1,20) = 6.7$, $p = 0.11$, $\beta = 0.32$; 95 % CI = −0.08 to 0.72).

3.6.1.2. Cognitive inhibition.: Although no significant effects were observed in the intent-to-treat analysis for cognitive inhibition, there was a significant effect for time ($F(1,25) = 8.6$, $p = 0.028$, $\beta = 0.43$; 95 % CI = 0.05 to 0.81) indicating an improvement in cognitive inhibition from baseline through week 12 for all study participants, regardless of treatment arm in completer analyses. No significant treatment-by-time or main effects for treatment or time were observed between week 12 and the 1-month follow-up assessment point.

3.6.1.3. Working memory.: There was not a significant treatment-by-week interaction. However, there was a significant effect for treatment ($F(1,35) = 4.56$, $p = 0.04$, $\beta = -1.32$; 95 % CI = −2.58 to −0.07) indicating that topiramate had significantly lower working memory scores than placebo during the study (topiramate = 8.6 ± 1.3, placebo = 10.1 ± 2.3). Follow-up univariate analyses indicated that at baseline, topiramate and placebo were similar in working memory performance ($p = 0.12$, topiramate = 8.9 ± 1.3 and placebo = 9.7 ± 2.7).

However, working memory in the topiramate group was significantly worse than placebo at week 6 ($p < 0.01$, topiramate = 8.1 ± 1.5, placebo = 10.3 ± 2.4) and 12 ($p < 0.01$, topiramate = 8.9 ± 1.0, placebo = 10.6 ± 1.4). Results remained unchanged in completer analyses, except that topiramate showed worse performance at baseline compared with placebo ($p = 0.02$, topiramate = 9.0 ± 1.4, placebo = 10.5 ± 2.8). No significant treatment-by-time or main effects for treatment or time were observed between week 12 and the 1-month follow-up assessment point.

3.6.1.4. Verbal fluency.: There was a significant treatment-by-time interaction for verbal fluency ($F(1,22) = 5.50$, $p = 0.03$, $\beta = -0.55$; 95 % CI = −1.05 to −0.06; Fig. 3.). Within the topiramate group, no effect of change in verbal fluency across time was evident from baseline to week 12 of the study ($F(1,10) = 1.42$, $p = 0.26$, $\beta = -0.22$; 95 % CI = −0.64 to 0.19), whereas placebo significantly improved across this interval ($F(1,12) = 5.46$, $p = 0.04$, $\beta = 0.36$; 95 % CI = 0.03 to 0.69). In follow-up analyses, we examined within group change in verbal fluency during each assessment interval (baseline to week 6, week 6 to week 12) and compared verbal fluency between topirmate and placebo at each assessment point (baseline, week 6, week 12). Topiramate significantly decreased by 9.3 t-score units in verbal fluency from baseline to week 6 ($F(1,13) = 11.4$, $p < 0.01$, $\beta = -1.49$; 95 % CI = −2.45 to −0.54) and then significantly increased 6.3 t-score units between week 6 and 12 ($F(1,10) = 8.9$, $p = 0.01$, $\beta = 1.20$; 95 % CI = 0.30–2.11). Placebo showed significant improvement in verbal fluency by 4 t-score units from baseline to week 6 ($F(1,13) = 10.2$, $p < 0.01$, $\beta = 0.79$; 95 % CI = 0.26–1.33), but showed no additional signifigant change from week 6 to week 12 ($F(1,11) = 0.0$, $p = 0.99$, $\beta = -0.01$; 95 % CI = −0.84 to 0.83). Topiramate and placebo only differed in mean verbal fluency scores at week 6 ($p = .03$), but not baseline or week 12. Results were similar in completer analyses, except the significant change in verbal fluency across time in Placebo from baseline to week 12 of the study dropped to a trend ($p = .06$). No significant treatment-by-time or main effects for treatment or time were observed between week 12 and the 1-month follow-up assessment point.

3.6.1.5. Auditory-verbal learning and memory.: There were no significant treatment-by-time interactions, effects of treatment or time in intent to treat, completer analyses, or between week 12 and the 1-month follow-up assessment point.

3.6.2. Adverse events—There were no significant differences between groups on any reported emergent adverse events. There was a trend for topiramate to report more vision problems compared with placebo (topiramate = 5, placebo = 1, $p = .076$). The most common reported emergent complaints were: taste, in 53 % of topiramate and 29 % of placebo; sleepiness in 47 % of topiramate and 18 % of placebo; itching in 40 % of topiramate and 29 % of placebo; numbness in 33 % of topiramate and 29 % of placebo. Four participants (1 placebo, 3 topiramate) experienced a total of five serious adverse events (SAEs). The single SAE in a participant randomized to placebo was for a pancreatomy and splenectomy judged to be unrelated to the study. The other four SAEs among participants randomized to topiramate were conservatively categorized as “possibly” related to the study. One participant had two hospitalizations due to chest pain related to cocaine use, one participant

was voluntarily hospitalized for homicidal ideation in the context of acute heavy cocaine use, and the final participant had a hospital admission due to alcohol withdrawal.

4. Discussion

This is the first study of the effects of topiramate as compared with placebo on alcohol use, TBI symptoms, and cognitive functioning in Veterans with mild traumatic brain injury and alcohol use disorder. As hypothesized, we observed significant reductions in heavy drinking in those receiving topiramate treatment, but comparable reductions in alcohol use were also observed among patients receiving placebo in intent-to-treat analyses. In per-protocol analyses, we observed nearly double the rate of reduction in alcohol drinks per week in topiramate compared with placebo. Although these reductions may have been partially driven by nonspecific effects, such as participant expectancy, placebo effects, the role of support provided by study staff, Medical Management counseling, and close monitoring, these findings also lend support for further investigation into the beneficial effects of topiramate on alcohol use reduction in this understudied population of AUD and mTBI. Surprisingly, the frequency of adverse events commonly associated with topiramate treatment was not significantly different between treatment arms. Neurocognitive testing revealed that topiramate, compared with placebo, was associated with poor performance on tasks of verbal fluency and working memory. Significant improvements were observed in processing speed, cognitive inhibition, and mental flexibility between weeks 1 and 12 of the study regardless of treatment arm. There were also significant reductions in self-reported post-concussive cognitive complaints in both arms of the study. All changes observed between baseline and week 12 of the trial remained stable at the 1-month follow-up assessment. Taken together, the results of this small pilot study establish that topiramate may be beneficial for alcohol use reduction and that it is associated with only expected adverse events in cognitive function for heavy drinking Veterans with mTBI. Further study is warranted to confirm topiramate's potential positive findings.

Although in intent-to-treat analyses, drinking days were significantly reduced in the topiramate treatment arm of the study, these reductions were not specific to topiramate. In fact, we observed reductions in alcohol use (drinking days per week and heavy drinking days per week), alcohol craving, and post-concussive cognitive complaints among all participants regardless of treatment arm. We also observed large reductions in weekly drinking days, heavy drinking days, and number of drinks during the variable length screening period that took place between consent and randomization – a period of time during which participants had not yet been exposed to study medication. Reductions in alcohol use during screening likely contributed to diminished ability to observe between-group treatment related effects in alcohol use in intent-to-treat analyses in this small sample. At the time of medication initiation, participants in both groups had already reduced their alcohol use, having only 3.5 ± 2.7 drinking days per week, with large variability, leaving only modest room for improvement on our primary outcome during the active treatment phase (weeks 1–12) of the study. However, in the 87 % who completed the study (per-protocol analyses), topiramate significantly reduced drinks per week compared with placebo, at approximately twice the rate than in the placebo arm. This is a promising signal for the beneficial effects of topiramate treatment and lends support for a larger confirmatory study. Taken together,

the results of this small pilot study establish that topiramate may be beneficial for alcohol use reduction and is associated with expected adverse events in cognitive function for heavy drinking Veterans with mTBI. Further study is warranted to confirm topiramate's potential positive findings.

Traumatic brain injury (Eshel et al., 2019; Wood and Worthington, 2017), heavy alcohol use (Rehm et al., 2019; Perry, 2016; Sachdeva et al., 2016; Verdejo-Garcia et al., 2018; Le Berre et al., 2017), and topiramate treatment (Knapp et al., 2015; Wandschneider et al., 2017; Aldenkamp et al., 2000; Batki et al., 2014) are all associated with cognitive deficits, raising concerns regarding topiramate pharmacotherapy for treating AUD among those with mTBI. However, the potential negative cognitive adverse effects of topiramate treatment were minimal in this pilot study, and resolved with tapering off medication. Neurocognitive testing revealed that topiramate was associated with significant worsening of verbal fluency compared with placebo between baseline and week 6 of the study, but also improved to a range of performance not significantly different than placebo by week-12 of treatment. This improvement is likely due study medication being tapered off over the course of week 12, the final week of study treatment. At week 6, average verbal fluency performance was within one standard deviation (10 t-score units) from baseline scores and were in a range of average to low-average functional performance compared with the general population (43.9 ± 10.3). Working memory scores were also lower in the topiramate arm compared with placebo, but were also within a typical average to low average range of functioning compared with a healthy population. The observed differences in working memory may be at least partially attributed to pre-treatment effects in our small sample, as baseline differences in working memory were observed in per-protocol analysis.

Taken together, topiramate's effects on cognitive functioning were comparable, and not substantially more severe than its effects in a sample of heavy drinking Veterans with AUD who were selected for study participation on the basis of co-occurring PTSD rather than TBI (Batki et al., 2014). That being said, there may be individuals who enter treatment with below average functioning in verbal fluency and working memory, and topiramate could cause additional deficits in these cognitive domains. A larger study would be needed to fully evaluate whether there are additive cognitive impairments associated with topiramate in Veterans with both mTBI and AUD, in contrast to those with just AUD, particularly among individuals with pre-existing cognitive deficits. Conversely, we observed significant improvements between baseline and week 12 regardless of treatment arm in processing speed, cognitive inhibition, mental flexibility, and no change in auditory-verbal learning and recall. These findings were inconsistent with negative topiramate effects on auditory-verbal learning and recall observed in a population of Veterans with AUD and PTSD (Batki et al., 2014). Topiramate's negative effect on cognitive function may be influenced by common co-occurring conditions (e.g., TBI, PTSD, etc.). Unfortunately, the small sample size and study design limited our ability to evaluate if cognitive improvements observed in the current study were related to reductions in alcohol use, post-concussive symptoms, or to practice effects.

Drop-out among our topiramate arm was due entirely to medication non-adherence. Unfortunately, the reasons for medication non-adherence among the two participants who

were withdrawn are unknown and it is not known if non-adherence was related to common topiramate adverse events. Nonetheless, this pilot study demonstrates that pharmacotherapy trials for AUD among Veterans with mTBI are feasible to conduct over a 12 week course of outpatient treatment, and that topiramate treatment may aid in reducing alcohol use while transiently impairing cognition during topiramate treatment, with impairment resolving immediately after tapering off the medication. While these results support enhanced efficacy of topiramate over placebo only among those participants who were adherent to medication, this is at least a first step toward finding pharmacotherapies for AUD treatment in patients with comorbid traumatic brain injury.

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 in intent-to-treat analyses. We may have had inadequate power to detect significant differences in adverse effects as well. However, the study was successful in establishing the feasibility of conducting a topiramate treatment study among Veterans with co-occurring TBI and AUD. Specifically, adverse events were minimal and adherence and retention were generally good among both treatment arms, which lends support for the successful completion of a larger trial. In addition, we established preliminary indication that topiramate treatment is associated with alcohol use reduction in those who maintain treatment across 12 weeks. These effects can be used to inform sample size estimation of a larger definitive study, one that also includes a short screening period, and targets primarily recent heavy drinkers.

Another limitation includes that our small sample size prevented the evaluation of alcohol and post-concussive symptom reduction in relation to improved cognitive function. Our final measure of cognitive functioning was at the end of Week 12, after completion of the one-week taper off study medication. This prevented us from assessing cognition at Week 12 with participants still taking full doses of topiramate or placebo, and therefore limited our ability to determine whether the continuation of topiramate or placebo from Week 6 to Week 12 led to tolerance to topiramate effects or to further worsening of impairment at week 12. 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; Fertig et al., 2012; Litten et al., 2012). Finally, we did not include a measure of quality of life related to traumatic brain injury, a valuable and common assessment among TBI studies. Despite these limitations, our *a priori* hypothesis of detecting change within the topiramate group was confirmed, and signals for between group differences in alcohol use were found to favor topiramate.

Topiramate's effect on reducing alcohol consumption among Veterans wanting to reduce or stop alcohol use are in line with larger topiramate trials in AUD patients without mTBI. Topiramate may thus be one possible treatment option for reducing alcohol use among Veterans with AUD and mTBI, with appropriate care being taken to monitor for negative cognitive effects. While topiramate appeared to be safe and well-tolerated, the benefits in alcohol use reduction and post-concussive symptom improvement must be interpreted in the light of the apparent potential for transient cognitive verbal fluency and working memory decrements seen in the topiramate-treated participants. We would recommend that future

studies of topiramate delay the taper off medication until the completion of the final set of neurocognitive measures, so as to more definitively assess topiramate related cognitive detriment at 12 weeks of treatment. Future studies should also preemptively plan to assess the relationship between pre-treatment cognitive impairment and the potential associated cognitive effects of topiramate treatment. In sum, the results of this study indicate the need for a larger placebo-controlled investigation to more definitively assess the efficacy of topiramate treatment in reducing alcohol use and post-concussive symptoms in individuals with co-occurring AUD and mTBI and for investigations of other medications that could reduce alcohol use and post-concussive symptoms in individuals with co-occurring AUD and mTBI while protecting – or possibly actually improving – cognitive functioning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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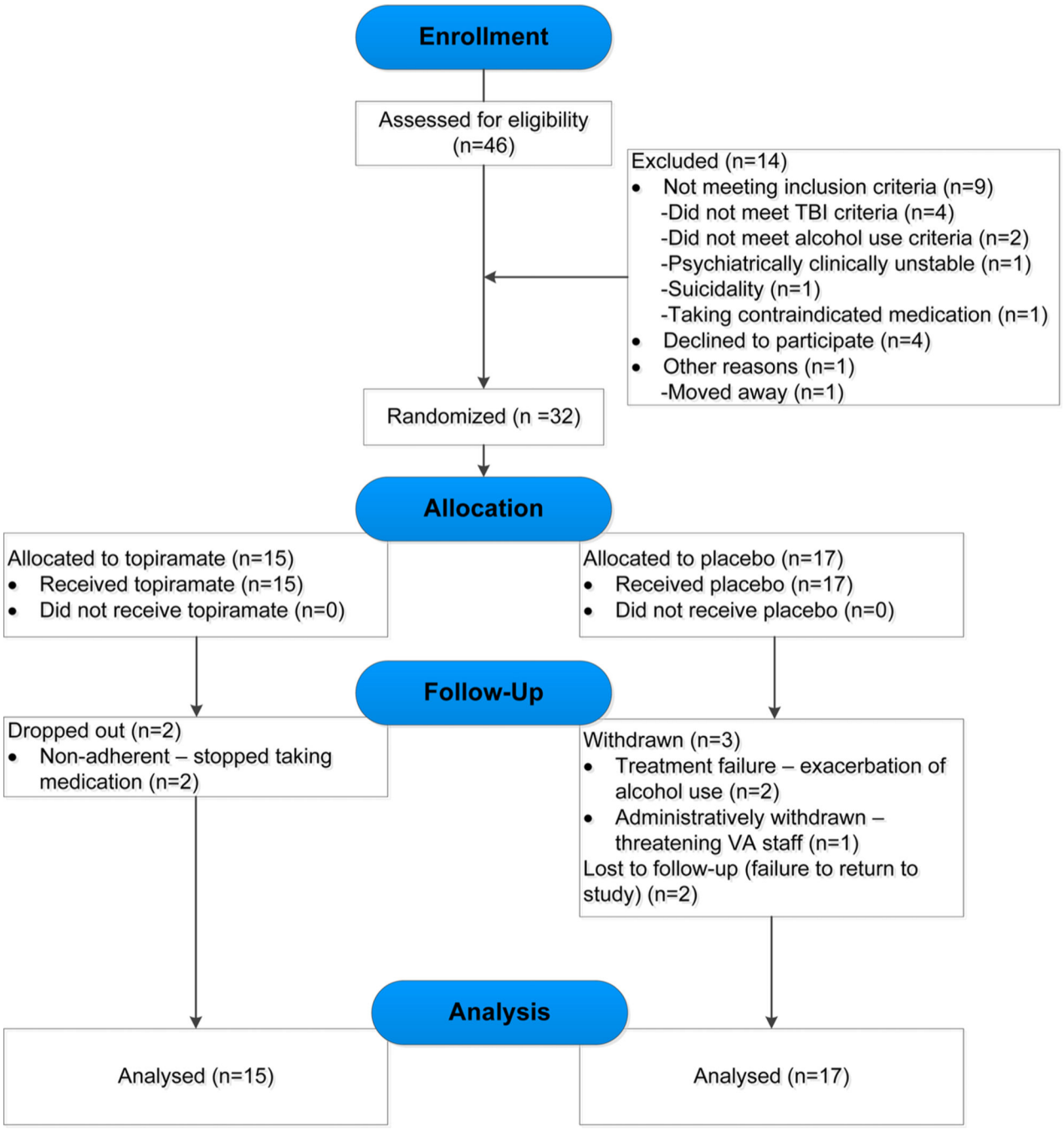

Fig. 1.
CONSORT flow diagram.

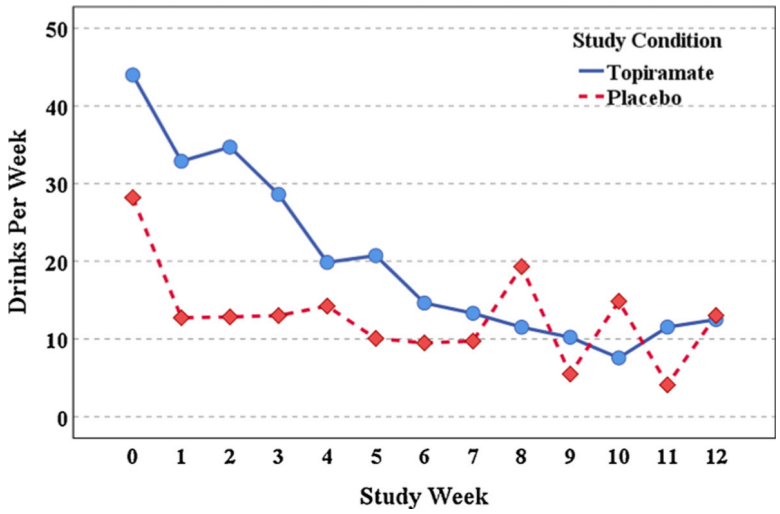

Fig. 2.
Mean drinks per week.

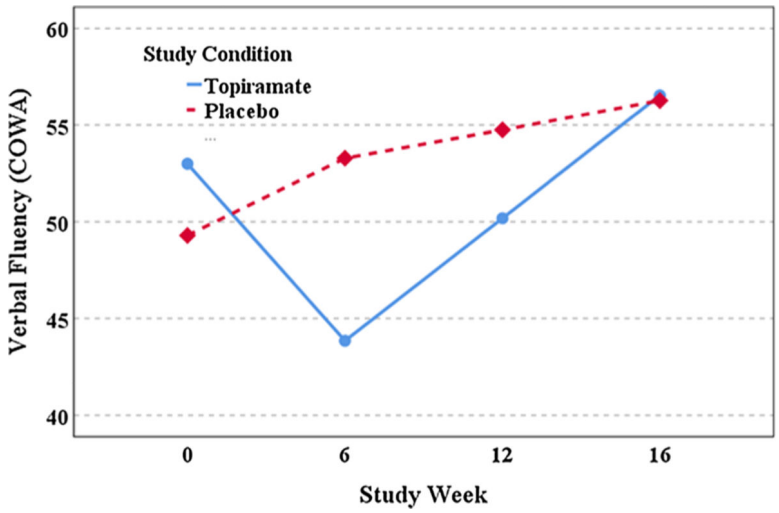

Fig. 3.
Mean Verbal Fluency (Controlled Oral Word Association; COWA) T-Scores.

Table 1

Participant Characteristics at Baseline (Means ± Standard Deviation).

	Topiramate	Placebo
n (female)	15 (1)	17 (1)
Age [years]	44.6 ± 13.5	48.5 ± 14.0
Education [years]	13.8 ± 1.5	13.9 ± 1.9
Hispanic or Latino	5	2
Caucasian	7	9
African American	5	4
Pacific Island Native	0	1
Mixed Race	2	3
Unknown/Not-Reported	1	0
Combat Exposed, n (%)	6 (40 %)	9 (53 %)
Comorbid Substance Use Disorder, n (%)	5 (33 %)	8 (47 %)
AUD Residential TX, n (%)	8 (53 %)	6 (35 %)
AUD Outpatient TX, n (%)	4 (27 %)	5 (29 %)
BDI	23.1 ± 11.5	20.1 ± 9.3
BAI	17.9 ± 10.1	19.8 ± 13.6
Drinking Days per Week	4.1 ± 2.0	5.0 ± 2.0
Heavy Drinking Days per Week	3.3 ± 2.3	3.6 ± 2.1
Avg. Drink per Week	49.6 ± 42.2	53.0 ± 34.2
Avg. Drinks per DD	14.6 ± 16.5	12.0 ± 8.0
Obsessive Compulsive Drinking Scale	16.3 ± 9.6	18.2 ± 8.9
mTBI	49	79
Blunt Trauma	24	31
Blast *	3	25
Fall	12	11
Motor Vehicle	10	12
Years Since Last Injury	11.1 ± 8.6	13.0 ± 13.1
Neurobehavioral Symptom Inventory	23.8 ± 15.4	28.5 ± 10.7
Vestibular	2.1 ± 2.1	3.0 ± 2.0
Somatic	6.5 ± 5.0	6.2 ± 3.5
Affective	9.5 ± 6.4	11.6 ± 4.1
Cognitive	5.7 ± 4.2	7.7 ± 4.1

Abbreviations: AUD, Alcohol Use Disorder; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; heavy drinking day (> 4 standard alcoholic drinks for men, > 3 standard alcoholic drinks for women). Drink consumption was averaged over 90 days preceding study consent.

$ standard alcoholic drink is defined as containing 13.6 g of pure alcohol.

* $p < .01$.

Table 2

Intention-to-Treat Analyses: Treatment-by-Time and Time Effects for Alcohol Consumption, Alcohol Craving, and NSI Symptoms.

		Baseline Mean ± SD	Week-12 Mean ± SD	Treatment-by-Time p-Value	Treatment-by-Time β (IRR)	Treatment-by-Time 95% CI	Time p-Value	Time β (IRR)	Time 95% CI
HDD per Week $	Topiramate	2.3 ± 2.6	0.9 ± 1.3	0.366	(0.06)	−0.06 to 0.17	0.001	(−0.15)	−0.23 to
	Placebo	2.1 ± 2.5	0.5 ± 1.0						
DD per Week $	Topiramate	3.6 ± 2.8	2.2 ± 1.8	0.501	(0.02)	−0.04 to 0.08	0.001	(−0.07)	−0.06 −0.11 to
	Placebo	3.4 ± 2.7	1.6 ± 2.1						
Drinks per Week $	Topiramate	39.7 ± 51.3	12.5 ± 14.9	0.823	−0.30	−2.94 to 2.34	0.101	−1.54	−0.03 −3.38 to 0.31
	Placebo	32.6 ± 45.8	12.0 ± 27.2						
Drinks per DD $	Topiramate	9.1 ± 7.6	3.9 ± 4.2	0.695	−0.11	−0.65 to 0.43	0.196	−0.24	−0.63 to 0.13
	Placebo	7.5 ± 8.4	4.0 ± 9.0						
OCDS Total	Topiramate	16.3 ± 9.6	9.1 ± 7.3	0.458	0.19	−0.33 to 0.71	< 0.001	−0.73	−1.09 to −0.37
	Placebo	18.2 ± 8.9	9.6 ± 11.0						
OCDS Compulsive	Topiramate	9.8 ± 4.7	5.7 ± 4.1	0.967	0.01	−0.31 to 0.32	0.008	−0.30	−0.51 to −0.08
	Placebo	10.6 ± 4.0	5.4 ± 5.8						
OCDS Obsessive	Topiramate	6.5 ± 5.5	3.4 ± 3.6	0.273	0.14	−0.12 to 0.40	< 0.001	−0.41	−0.59 to −0.24
	Placebo	7.6 ± 5.2	4.2 ± 5.6						
NSI Total #	Topiramate	23.8 ± 15.4	16.3 ± 13.1	0.832	0.07	−0.60 to 0.74	0.081	−0.43	−0.91 to 0.06
	Placebo	28.5 ± 10.7	19.3 ± 15.1						
NSI Vestibular #	Topiramate	2.1 ± 2.1	1.6 ± 1.6	0.581	0.03	−0.09 to 0.16	0.351	−0.04	−0.13 to 0.05
	Placebo	3.0 ± 2.0	2.2 ± 2.8						
NSI Somatic-Sensory #,&	Topiramate	6.5 ± 5.0	4.5 ± 3.8	0.515	−0.08	−0.33 to 0.16	0.607	−0.04	−0.23 to 0.13
	Placebo	6.2 ± 3.5	4.9 ± 4.0						
NSI Cognitive #	Topiramate	5.7 ± 4.2	3.6 ± 3.7	0.527	0.06	−0.13 to 0.25	0.022	−0.16	−0.30 to
	Placebo	7.7 ± 4.1	4.6 ± 3.9						
NSI Affective #	Topiramate	9.5 ± 6.4	6.6 ± 5.6	0.664	0.06	−0.21 to 0.33	0.110	−0.16	−0.03 −0.37 to 0.04
	Placebo	11.6 ± 4.1	7.6 ± 6.1						

Abbreviations: HDD, heavy drinking days (> 4 standard alcoholic drinks per day for men, > 3 standard alcoholic drinks per day for women; standard alcoholic drink is defined as containing 13.6 g of pure alcohol); DD, drinking days; OCDS, obsessive compulsive drinking scale; NSI, neurobehavioral symptom inventory; β, beta; IRR, incidence rate ratio (average relative change in outcome per week from baseline through week 12); CI, confidence interval; significant covariate predictor of

$ past 90 alcohol consumption

milligrams taken

& number of acquired blast related head injuries.

Table 3

Treatment-by-Time and Time Effects for Cognitive Function.

		Baseline Mean ± SD	Week-6 Mean ± SD	Week-12 Mean ± SD	Treatment-by-Time p-Value	Treatment-by-Time β	Treatment-by-Time 95% CI	Time p-Value	Time β	Time 95% CI
Processing Speed	Topiramate	48.4 ± 6.1	47.3 ± 6.1	53.5 ± 3.6	0.844	−0.05	−0.52 to 0.44	0.002	0.56	0.22 to 0.89
	Placebo	45.9 ± 13.5	51.6 ± 10.6	54.8 ± 12.7						
WorkingMemory $	Topiramate	8.9 ± 1.3	8.1 ± 1.5	8.9 ± 1.0	0.301	−0.05	−0.14 to 0.05	0.191	0.04	−0.02 to 0.11
	Placebo	9.7 ± 2.7	10.3 ± 2.4	10.5 ± 1.4						
Mental Switching	Topiramate	48.7 ± 9.3	49.5 ± 7.7	53.9 ± 7.7	0.902	0.03	−0.54 to 0.61	0.037	0.42	0.03 to 0.82
	Placebo	48.7 ± 11.6	52.6 ± 11.6	55.3 ± 9.0						
Cognitive Inhibition	Topiramate	44.4 ± 8.4	50.8 ± 8.1	47.6 ± 9.3	0.915	0.03	−0.58 to 0.64	0.127	0.32	−0.10 to 0.74
	Placebo	47.8 ± 11.0	47.7 ± 12.1	52.3 ± 12.2						
Verbal Fluency	Topiramate	53.0 ± 8.9	43.9 ± 10.3	50.2 ± 6.9	0.028	−0.55	−1.05 to −0.65	0.044	0.35	0.01 to 0.69
	Placebo	49.3 ± 12.9	53.3 ± 10.9	54.8 ± 11.9						
Auditory-Verbal Learning	Topiramate	37.9 ± 12.7	37.2 ± 10.6	38.3 ± 13.6	0.826	0.08	−0.62 to 0.78	0.953	0.01	−0.47 to 0.50
	Placebo	41.0 ± 10.9	42.4 ± 11.3	42.8 ± 12.7						
Auditory-Verbal Recall	Topiramate	39.7 ± 12.6	38.8 ± 13.6	39.4 ± 11.2	0.965	0.02	−0.80 to 0.84	0.911	0.03	−0.53 to 0.60
	Placebo	37.2 ± 12.3	43.0 ± 12.1	38.8 ± 17.3						

Abbreviations: SD, Standard Deviation; β, beta; CI, confidence interval; significant covariate predictor of

$ Wechsler Test of Adult Reading

milligrams taken; Mean scores for Processing Speed, Mental Switching, Cognitive Inhibition, Verbal Fluency, Auditory-Verbal Learning and Recall, and Decision Making are expressed in t-scores; Working Memory is expressed as a scaled score; Risk-Taking is the average number of adjusted pumps; Choice Impulsivity is the mean hyperbolic *k* parameter estimate; Motor Impulsivity is stop signal reaction time in milliseconds.