

Award Number: W81XWH-12-2-0137

TITLE: *[Illegible text]*

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REPORT DATE: OCTOBER 2014

[Illegible text]

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Telemedicine and Advanced Technology Research Center
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE			<i>Form Approved</i> <i>OMB No. 0704-0188</i>		
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1. REPORT DATE 30 OCTOBER 2014		2. REPORT TYPE Annual		3. DATES COVERED 30 SEPT 2013 – 29 SEPT 2014	
4. TITLE AND SUBTITLE A Controlled Trial of Topiramate Treatment for Alcohol Dependence in Veterans with PTSD			5a. CONTRACT NUMBER		
			5b. GRANT NUMBER W81XWH-12-2-0137		
			5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S) Principal Investigator: Steven L. Batki, MD Co-investigators: David L. Pennington, PhD; Thomas Neylan, MD; Angela Waldrop, PhD go ckrugxgp@cmk xcl qx			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Northern California Institute for Research and Education (NCIRE) San Francisco, CA 94121-1545			8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSOR/MONITOR'S ACRONYM(S)		
			11. SPONSOR/MONITOR'S REPORT NUMBER(S)		
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Alcohol use disorders (AUDs) and PTSD commonly co-occur, complicate assessment and treatment, and worsen clinical outcomes in veterans with both conditions. AUDs are potential consequences of PTSD, as many veterans may use alcohol in an attempt to "self-medicate" or ameliorate PTSD symptoms such as hyperarousal or emotional numbing. AUDs may also be a risk factor for the development of PTSD and may exacerbate PTSD symptom severity and impairment. Treatment for co-occurring PTSD and alcohol dependence among veterans is challenging. To date there has been little research to develop pharmacotherapies that would, ideally, reduce both alcohol use and PTSD symptom severity in patients with both of these conditions. Topiramate is one of the few medications for alcohol dependence that has also been separately tested as a potential medication to treat PTSD. Topiramate's efficacy in alcohol dependence in patients without PTSD has been shown in two recent large controlled trials. Open trials have suggested that topiramate may be effective in reducing PTSD symptoms in patients without AUDs, and a number of small controlled trials have also produced promising results. The PI recently completed the first pilot clinical trial of topiramate treatment in veterans with <u>both</u> alcohol dependence and PTSD, and preliminary analyses demonstrate feasibility, safety, tolerability, and efficacy in reducing alcohol use. Results also provide support for testing topiramate's potential efficacy in reducing PTSD symptoms.					
15. SUBJECT TERMS- Pharmacotherapy, Co-occurring Disorders, PTSD, alcohol dependence, topiramate					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			USAMRMC
			UU	41	19b. TELEPHONE NUMBER (include area code)

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INTRODUCTION:

The overall objective of the project is to improve the care of veterans with alcohol dependence and co-occurring PTSD. The investigators are conducting a controlled clinical trial to test the efficacy of topiramate treatment in reducing alcohol use in patients with PTSD.

Alcohol use disorders (AUDs) and PTSD commonly co-occur, complicate assessment and treatment, and worsen clinical outcomes in veterans with both conditions. AUDs are potential consequences of PTSD, as many veterans may use alcohol in an attempt to “self-medicate” or ameliorate PTSD symptoms such as hyperarousal or emotional numbing. AUDs may also be a risk factor for the development of PTSD and may exacerbate PTSD symptom severity and impairment. Treatment for co-occurring PTSD and alcohol dependence among veterans is challenging. To date there has been little research to develop pharmacotherapies that would, ideally, reduce both alcohol use and PTSD symptom severity in patients with both of these conditions. Topiramate is one of the few medications for alcohol dependence that has also been separately tested as a potential medication to treat PTSD. Topiramate’s efficacy in alcohol dependence in patients without PTSD has been shown in two recent large controlled trials. Open label trials have suggested that topiramate may be effective in reducing PTSD symptoms in patients without AUDs, and a number of small controlled trials have also produced promising results. The PI recently completed the first pilot clinical trial of topiramate treatment in veterans with both alcohol dependence and PTSD, and preliminary analyses demonstrate feasibility, safety, tolerability, and possible efficacy in reducing alcohol use as well as PTSD symptoms.

This project consists of a controlled clinical trial of topiramate treatment to reduce alcohol use and PTSD symptoms in veterans with these co-occurring disorders. The specific aims are to: 1) definitively test the efficacy of topiramate in reducing alcohol use in veterans with PTSD and alcohol dependence; 2) test the efficacy of topiramate to reduce PTSD symptoms; and 3) explore if measures of impulsivity and decision-making predict treatment response and improve with topiramate therapy. To achieve these aims, we are conducting a prospective randomized double-blind controlled parallel-groups clinical trial of topiramate or placebo up to 300 mg per day, combined with weekly alcohol counseling, over a 12-week treatment period with a week 16 follow-up. The study population will consist of 150 male and female veterans between the ages of 18-69 who have concurrent diagnoses of alcohol dependence and PTSD. Subjects will meet with research staff weekly to receive study medication, manualized alcohol counseling, and research assessments. The primary treatment outcome will be the percent of days of heavy drinking; the secondary outcome will be PTSD symptom severity. Exploratory measures will include assessments of impulsivity and decision-making.

A.1. PRIMARY AIM: To determine if topiramate treatment reduces alcohol use in veterans with PTSD

1.a. The primary aim is to definitively test the efficacy of topiramate in reducing alcohol use in veterans with PTSD and alcohol dependence.

1.b. The primary outcome will be the percent of heavy drinking days over the course of the study as measured by the Timeline Followback.

1.c. The primary hypothesis is that topiramate treatment will be more efficacious than placebo in reducing the proportion of heavy drinking days.

This hypothesis will be tested through a mixed-model statistical analysis of the between-groups differences in the proportion of heavy drinking days over the course of the clinical trial.

A.2. SECONDARY AIMS: To determine if topiramate reduces PTSD symptoms and alcohol use (using other alcohol use measures) in these patients.

The *secondary aims* are:

2.1.a To determine whether topiramate will be associated with a significant reduction in PTSD symptoms from baseline to the end of the trial, as measured by the PTSD Checklist (PCL); and to determine whether topiramate will be more efficacious than placebo.

2.2.a To determine whether topiramate treatment will be associated with significant reductions in other alcohol use measures (drinking days/week, drinks per drinking day, alcohol craving, and urine Ethyl Glucuronide [EtG]) from baseline to end of treatment; and to determine whether topiramate will be more efficacious than placebo

The *secondary hypotheses* are:

2.1.b Topiramate treatment -- combined with Medical Management alcohol counseling and added to ongoing TBI treatment as usual --will be associated with a significant reduction in PTSD symptoms from baseline to the end of the trial, as measured by the PTSD Checklist (PCL) from baseline to end of treatment; and there will be a significant effect of the treatment group, with the topiramate treatment group showing a greater reduction in PCL scores compared to placebo controls.

2.2.b Topiramate treatment -- combined with Medical Management alcohol counseling and added to ongoing PTSD treatment as usual --will be associated with a significant reduction in scores of other alcohol use measures from baseline to end of treatment; and there will be a significant effect of the treatment group, with the topiramate treatment group showing a greater reduction in scores on various alcohol use measures compared to placebo controls.

These hypotheses will be tested:

2.1.c Through a mixed-model statistical analysis of the within-topiramate group and between-groups differences in PCL scores over the course of the clinical trial.

2.2.c Through a mixed-model statistical analysis of the within-topiramate group and between-groups analysis differences in scores on alcohol use measures (drinking days/week, drinks per drinking day, alcohol craving and urine Ethyl Glucuronide [EtG]) over the course of the clinical trial.

A.3. EXPLORATORY AIMS:

The exploratory aims are:

3.1 Measure impulsivity, decision-making, and risk-taking at baseline to assess the relationship between these domains and:

- alcohol use at baseline
- alcohol use over the course of the study

3.2 Assess the relationship between *changes* in alcohol use over the course of the study and *changes* in:

- impulsivity
- risk-taking
- decision-making

3.3 Assess the effects of topiramate versus placebo treatment on:

- impulsivity
- risk-taking
- verbal fluency, verbal memory

The exploratory hypotheses are:

3.1 High impulsivity, high risk-taking, and poor decision-making at baseline will be associated with higher levels of alcohol use at baseline and over the course of the study;

3.2 Reductions in alcohol use will be associated with reductions in impulsivity and risk taking, and improvement in decision-making;

3.3 Topiramate will be associated with greater reductions in impulsivity and risk-taking, but also with greater impairment of verbal fluency and memory than placebo.

These hypotheses will be tested with mixed models similarly to the primary and secondary hypotheses.

3.1 is assessed by the effect of baseline impulsivity and risk-taking (tested separately) on alcohol use over time.

3.2 is tested by estimating subject-specific slopes from random coefficients mixed models predicting changes in alcohol use, impulsivity, and risk-taking, and calculating the Pearson correlation coefficients between slopes of change in alcohol use and changes in impulsivity and risk-taking.

3.3 is tested by the Group by Time interaction term in the mixed models predicting impulsivity, risk-taking, verbal fluency and verbal memory, from treatment group and time, with baseline values as covariates.

BODY:

This study was initiated 29 September 2012. Year 2 of this project covers the time period September 30, 2013 through September 29, 2014. As of September 29, 2014 we have met our overall Year 2 goals in terms of maintaining all regulatory approvals, hiring staff, and setting up the lab. Additionally, we have continued recruiting subjects and administering study intervention since the 2nd quarter of Year 1. Because recruitment was our main focus in Year 2, we developed many novel recruitment strategies that we'll continue to hone and expand upon as we move into Year 3. Two outstanding tasks leftover from Year 1 were completed: we rolled-out the remaining 20 forms in the Access database/interface and employed a 3rd Study Coordinator to bolster recruitment efforts. All tasks for Year 2 were predetermined in the approved Statement of Work; the steps taken to accomplish these tasks are outlined in further detail below.

STATEMENT OF WORK - TIMELINE

TIMELINE AND COST		YR1				YR2				YR3				YR4			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Obtain scientific regulatory approvals (4 months; Mos. 1 to 4)																	
Hire staff, set up lab (4 months; Mos. 1 to 4)																	
Recruit subjects (34 months; Mos. 5 to 38)																	
Conduct 12-week intervention & Wk 16 follow-ups (37 months; Mos. 5 to 41)																	
Collect data on 150 human subjects (37 months; Mos. 5 to 41)																	
Score and analyze data (2 months; Mos. 42 to 43)																	
Write/publish final report (5 months; Mos. 44 to 48)																	
Estimated Budget Year (\$K)	Direct	\$489,792				\$545,546				\$576,425				\$507,619			
	Indirect	\$254,692				\$283,684				\$299,741				\$263,962			

Proposed Timeline
 Actual Timeline

Task 1

Test the hypothesis that veterans with alcohol dependence and PTSD assigned to topiramate (TOP) treatment will have fewer heavy alcohol drinking days over the 12 weeks of the treatment trial than subjects receiving placebo (PBO)

Timeline: *Months 1-4:* production and all approvals of human use protocols, hiring staff, start-up/set up lab; *months 5-38:* recruitment of subjects; *months 5-41:* conduct treatment intervention, follow-ups; *months 5-41:* complete data collection on 150 subjects; *months 42-43:* analyze data; *months 44-48:* final report/manuscripts written and submitted.

TASK 1.a. *Months 1-4: production and all approvals of human use protocols, hiring staff, start-up/set up lab*

All DOD-funded studies that take place at the San Francisco VA Medical Center are required to receive approval from the local IRB [University of California, San Francisco Committee on Human Research (UCSF CHR)], the VA Clinical Research Workgroup (VA CRW), the Information Security Officer (ISO), the Privacy Officer (PO), the UCSF Clinical and Translational Science Institute (CTSI), the Subcommittee on Research Safety (SRS), and the VA Research and Development Committee (VA R&DC). In addition to gaining approval from the various regulatory bodies, we also applied for a NIH/NIAAA Certificate of Confidentiality (NIH/NIDA CoC), an IND exemption from the Federal Drug Association (FDA) and a Biological Use Authorization (BUA) for Clinical Research from the VA Biosafety Subcommittee as extra protection for our research subjects and study staff. All required approvals were received by 2/26/13 (Month 5).

All regulatory approvals were maintained during Year 2. An informed consent audit from the San Francisco VA Medical Center's Research Compliance Office in March 2014 found our study to be in compliance.

The hiring of lab personnel is complete. As of 9/29/14, we have hired the following essential employees: 1 Lab Manager, 3 Study Coordinators, 1 Research Psychologist, 1 Research Statistician, 1 Research Physician, 1 Research Nurse Practitioner, and 1 Database Developer/Manager. Additional staff that either work at a less percent effort or volunteer include: 2 Study Physicians, 1 Research Psychologist, 2 Nurse Practitioners, and 2 Data Programmer. We are also supporting a percent effort of our co-investigators. This past year we also brought on 2 research volunteers and 2 PhD student volunteers that have helped with recruitment, pre-screening, brief weekly alcohol counseling, neurocognitive testing, and structured psychological interviews.

The lab set-up is now complete as well. All study staff have been trained on the study protocol and standard operating procedures are in place for clarification and standardization purposes. Both the Access interface/database and the Qualtrics methods of online data collection are complete. All 57 measures and procedures are in active use, and we are now able to monitor drinking and medical data in real time for safety purposes.

TASK 1.b. *Months 5-38: recruitment of subjects*

Subject recruitment began on 2/27/13 and the first informed consent was signed on 3/20/13. Five hundred and thirteen potential subjects were referred to the study, either by self-referral or by medical/mental health practitioners. Four hundred and twelve prospective subjects were pre-screened for the study; 49 were enrolled (signed informed consent form) and 26 randomly assigned to treatment with topiramate (top) or placebo (PLA). The cohort is all male (n=26, 100%) and predominantly Caucasian (n=15, 58%). The planned rate of recruitment was 1 subject per week or 4 subjects per month; however, in order to complete recruitment according to schedule, we will need to randomize 9 subjects per month over the next 14 months. We are continuously developing new recruitment strategies to meet our enrollment goals.

TASK 1.c. *Months 5-41: conduct treatment intervention, follow-ups*

Inclusion for this study is based on the outcome of a screening phase which includes medical assessment, structured psychological interviews to determine diagnostic eligibility [Structured Clinical Interview for DSM-IV (SCID) and the Clinician Administered PTSD Scale (CAPS)] and additional measures to assess psychiatric severity and medical utilization. Of the 26 subjects randomized, 3 (11.54%) subjects dropped out, 6 (23.07%) subjects were withdrawn, and 12 (57.14%) subjects completed the study (as defined by attending the Week 12 visit). Of all subjects enrolled, the average number of study visits attended is 9 (81%).

TASK 1.d. *Months 5-41: complete data collection on 150 subjects*

In progress - not complete at this time.

TASK 1.e. *Months 42-43: analyze data*

Not complete at this time.

TASK 1.f. *Months 44-48: final report/manuscripts written and submitted.*

Not complete at this time.

Task 2.

Test the hypothesis that veterans with alcohol dependence and PTSD assigned to topiramate (TOP) treatment will have lower PTSD symptom severity over the 12 weeks of the treatment trial than subjects receiving placebo (PBO)

Timeline: same as Task 1

In progress - not complete at this time.

Task 3.

Explore the role of impulsivity and decision-making in the treatment of alcohol dependence and PTSD.

Subtask 3.a. To assess the predictive value of baseline measures of decision-making and impulsivity as related to study retention and alcohol use outcomes.

Subtask 3.b. To test whether reduction in alcohol use is accompanied by reductions in impulsivity/risk-taking and improvement in decision-making in veterans with alcohol dependence and PTSD.

Subtask 3.c. To test whether topiramate is more efficacious than placebo in reducing impulsivity/risk-taking and improving decision-making.

Design: same as Task 1

Human subjects: same as Task 1

Methods: Subjects will meet with research staff weekly to receive study medication, manualized alcohol counseling, and research assessments.

Assessments: The exploratory outcomes will be impulsivity/risk-taking as measured by the Balloon Analogue Risk Task (BART) and decision-making as measured by the Delay Discounting Test (DD).

Outcomes, products and deliverables: The *exploratory hypotheses* are:

Subtask 3a: high baseline impulsivity/risk-taking and poor decision-making will be associated with poor retention and worse alcohol use outcome over the course of the trial

Subtask 3b: reductions in alcohol use over the course of the trial will be associated with reduced impulsivity/risk-taking and improved decision-making over the course of the trial

Subtask 3c: topiramate treatment will be more efficacious than placebo in reducing impulsivity and risk-taking and improving decision-making.

These hypothesis will be tested through mixed-model statistical analyses of the between-groups differences in the appropriate measures.

Timeline: *same as Task 1*

In progress - not complete at this time.

KEY RESEARCH ACCOMPLISHMENTS: Bulleted list of key research accomplishments emanating from this research.

1. Developed a modified version of the VA TBI Level 2 Evaluation to be administered to all participants at screening. By collecting data on traumatic brain injury, we will be able to better characterize the study population and compare them to other studies.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include: manuscripts, abstracts, presentations; licenses applied for and/or issued; degrees obtained that are supported by this award; development of cell lines, tissue or serum repositories; informatics such as databases and animal models, etc.; funding applied for based on work supported by this award; employment or research opportunities applied for and/or received based on experience/training supported by this award

1. Two abstracts accepted for presentation at the 37th Annual Research Society on Alcoholism (RSA) Scientific Meeting in Bellevue, Washington. Full abstracts attached at the end of the report. 6/21/14-6/25/14

Batki, S.L., Pennington, D.L., Lasher, B.A., Herbst, E., Schrodek, E., Hong, E., Waldrop, A., Williams C., Abrams, G., Neylan, T.C., Seal, K., Carney, C., Besterman, A. (2014, June) "Alcohol use disorder and PTSD severity in veterans with and without comorbid TBI: Baseline subject characteristics in topiramate treatment trials". Poster presented at the Annual Research Society on Alcoholism, Bellevue, WA.

Pennington, D.L., Lasher B.A., Herbst, E., Schrodek, E., Hong, E., Waldrop, A., Williams, C., Abrams, G., Neylan, T.C., Seal, K., Carney, C., Besterman, A., Batki, S.L. (2014, June). "Cognition and self-regulation in veterans with alcohol use disorder, PTSD and TBI: Baseline subject characteristics in topiramate treatment trials". Poster presented at the Annual Research Society on Alcoholism, Bellevue, WA.

2. Abstract accepted for presentation at the 47th Annual meeting of the Association for Behavioral and Cognitive Therapies (ABCT). 11/21/13-11/24/13

Heinz, A.J., Waldrop, A., Kalapatapu, R., Pennington, D., Lasher, B., Roth, J., Batki, S.L. (2013, November). "The influence of executive functioning on the relation between alcohol use and PTSD symptom severity across treatment among military veterans". Poster presented at the 47th annual meeting of the Association for Behavioral and Cognitive Therapies, Nashville, TN.

3. Published the main outcomes paper from the pilot study [W81XWH-05-2-0094] in Alcoholism: Clinical and Experimental Research.

Batki, S.L., Pennington, D.L., Lasher B.A., Neylan, T.C., Metzler, M.A., Waldrop, A., & Herbst, E. (2014). "Topiramate treatment of alcohol use disorder in veterans with PTSD: A randomized controlled trial". Alcoholism: Clinical and Experimental Research, 38(8):2169-77. doi: 10.1111/acer.12496

4. Published a paper from from the pilot study [W81XWH-05-2-0094] in Psychiatry Research: Neuroimaging.

Pennington, D.L., Abé, C., Batki, S.L., & Meyerhoff, D.J. (2014). "A preliminary examination of cortical neurotransmitter levels associated with heavy drinking in posttraumatic stress disorder. Psychiatry Research: Neuroimaging.

5. Presented overview & progress of study and pilot [W81XWH-05-2-0094] study data at MOMRP Substance Abuse IPR in Ft. Detrick, MD. 9/22/14-9/24/14

CONCLUSION: Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

There are no conclusions to draw at this time.

REFERENCES: List all references pertinent to the report using a standard journal format (i.e. format used in *Science*, *Military Medicine*, etc.).

None at this time.

APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, study questionnaires, and surveys, etc.

ALCOHOL USE DISORDER AND PTSD SEVERITY IN VETERANS WITH AND WITHOUT COMORBID TBI: BASELINE SUBJECT CHARACTERISTICS IN TOPIRAMATE TREATMENT TRIALS

S.L. Batki; D.L. Pennington; B.A. Lasher; E. Herbst; E. Schrodek; E. Hong; A. Waldrop; C. Williams; G. Abrams; T.C. Neylan; K. Seal; C. Carney; A. Besterman

UCSF Department of Psychiatry, Addiction Research Program, San Francisco VA Medical Center, San Francisco, CA 94121

Background: PTSD, alcohol use disorder (AUD), and traumatic brain injury (TBI) frequently co-occur among veterans. Little is known about the interrelationships of these clinical conditions in treatment-seeking veterans.

Methods: Baseline measures were collected for 47 veterans who entered trials of topiramate treatment of co-occurring AUD, PTSD and mTBI. Two AUD groups were compared: those with comorbid PTSD and TBI (TBI; n=26) to those with PTSD but without TBI (no-TBI; n=21). Pretreatment measures were collected for: 1) demographics; 2) alcohol use amount and frequency (Timeline Follow Back), craving (Obsessive Compulsive Drinking Scale) and severity (Alcohol Use Disorder Identification Task); 3) PTSD symptoms (Clinician-Administered PTSD Scale [CAPS]); 4) TBI symptoms (Neurobehavioral Symptom Inventory); 5) depressive (Beck Depression Inventory) and anxiety symptoms (Beck Anxiety Inventory); 6) sleep problems (Insomnia Severity Index); 7) consequences of alcohol use (Short Index of Problems); 7) and self-report measures of risk (Evaluation of Risk Scale [EVAR]) and impulsivity (Barratt Impulsivity Scale-11). Baseline characteristics in AUD/PTSD veterans with and without TBI were compared using ANOVA. Alcohol use, PTSD symptom severity, and TBI symptoms were also correlated with pretreatment measures.

Results: AUD/PTSD veterans with TBI had significantly less PTSD avoidance symptoms, were younger, and had less education compared to those without TBI. Both groups exhibited severe PTSD, AUD and other clinical symptomology. Within the TBI group, more drinking days/week and heavy drinking days/week was associated with more danger-seeking (EVAR). CAPS total score was also associated with increased alcohol craving in the TBI group. The same pattern of correlations was not apparent in the no-TBI group.

Conclusions: Among veterans with AUD/PTSD entering trials of topiramate treatment, baseline measures showed severe alcohol and PTSD symptomology within both the TBI and no-TBI groups. Veterans with AUD/PTSD and TBI showed a differential relationship between clinical symptoms than those without TBI. These findings support the need for further exploration of the relationships between these comorbid disorders which may potentially contribute to differential responses to topiramate treatment.

Acknowledgment: Acknowledgment: Department of Defense (DOD) # W81XWH-12-2-0137, CDMRP PH TBI; DOD # W81XWH-05-2-0094; DOD # W81XWH-11-2-0245.

COGNITION AND SELF-REGULATION IN VETERANS WITH ALCOHOL USE DISORDER, PTSD AND TBI: BASELINE SUBJECT CHARACTERISTICS IN TOPIRAMATE TREATMENT TRIALS

D.L. Pennington; B.A. Lasher; E. Herbst; E. Schrodek; E. Hong; A. Waldrop; C. Williams; G. Abrams; T.C. Neylan; K. Seal; C. Carney; A. Besterman; S.L. Batki

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Background: PTSD, traumatic brain injury (TBI), and alcohol use disorder (AUD) are common and frequently co-occur among veterans. AUDs are associated with, or causal to, a wide variety of neurobehavioral harm that may also be related to TBI. These include impulsivity, risk-taking behavior, as well as impairment in attention, auditory-verbal learning and memory, and executive functioning. However, little is known about the neurocognitive functioning of veterans with all three co-occurring disorders.

Methods: We compared baseline measures of risk-taking (Balloon Analogue Risk Task), processing speed (Trails A; Stroop), divided attention (Trails B), and auditory verbal learning and memory (HVLRT-R) between 2 groups of veterans with AUD entering topiramate treatment trials: those with comorbid PTSD and TBI (TBI, n=26) to those negative for TBI (no-TBI, n=21). We also examined differences between inhibition (Stop-Signal Task), decision-making (Iowa Gambling Task), working memory (WAIS-III Digit Span/Arithmetic), and verbal fluency (COWA) in a smaller subset of this sample (TBI, n=9; no-TBI, n=7). Pretreatment measures of alcohol consumption (frequency and amount) and PTSD symptomology (Clinician-Administered PTSD Scale) were correlated with cognitive functioning.

Results: Within TBI, higher frequency of drinking days was related to greater risk-taking, and higher frequency of heavy drinking days was related to worse decision-making. Additionally, in the TBI group, higher total PTSD symptom severity and avoidance severity was related to greater risk-taking and worse processing speed respectively. Within the no-TBI group, higher frequency of drinking days was related to worse processing speed, while higher number of drinks per week and higher PTSD intrusion severity were associated with worse performance in auditory verbal learning. Surprisingly, the TBI group tended to exhibit better decision-making and performed significantly better in working memory (Arithmetic) than the no-TBI group.

Conclusions: These preliminary results show that tasks of decision-making and risk-taking along with measures of working memory and processing speed differentiate veterans with comorbid AUD and PTSD who also have TBI from those without TBI. Continued study of these differences is warranted and may contribute to differential response to topiramate treatment.

Acknowledgment: Department of Defense (DOD) # W81XWH-12-2-0137, CDMRP PH TBI; DOD # W81XWH-05-2-0094; DOD # W81XWH-11-2-0245.

THE INFLUENCE OF EXECUTIVE FUNCTIONING ON THE RELATION BETWEEN ALCOHOL USE AND PTSD SYMPTOM SEVERITY ACROSS TREATMENT AMONG MILITARY VETERANS

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Abstract Body: Compared to individuals with alcohol use disorder (AUD) or post-traumatic stress disorder (PTSD) alone, those with both disorders evidence worse psychosocial and medical outcomes and are less likely to benefit from treatment. Of note, AUD and PTSD are characterized by separate and overlapping deficits in higher-order cognitive skills known as executive functions (e.g., attention, planning, problem-solving, self-regulation), which are in turn, associated with poor treatment outcomes and retention. Given the wealth of literature showing that AUD and PTSD are functionally related (e.g., self-medication), it is critical to identify trans-disease (i.e., common) processes that underlie and perpetuate the maintenance of this devastating and often chronically impairing comorbidity. The present investigation examined the relation between PTSD symptom severity and quantity and frequency of alcohol consumption, and whether executive functioning moderated this relation. Participants were 30 veterans enrolled in a 16-week treatment study for AUD and PTSD. At baseline they completed Trail Making Test Part B, a measure of attention, speeded set-shifting and mental flexibility (i.e., executive functioning). In addition, participants reported the quantity and frequency of their alcohol use (Time Line Follow Back Interview) and PTSD symptom severity (PCL – PTSD symptom checklist) at baseline and 4 times across the study. Two hierarchical Poisson regression models were estimated using the expectation maximization procedure to determine the influence of PTSD symptom severity on quantity and frequency of alcohol use across treatment. Baseline Trails B t-score was entered as a moderator of the drinking/PTSD relation across treatment. Results demonstrated that higher PTSD symptom severity was associated with higher quantity and frequency of drinking throughout treatment and that these relations were stronger among veterans with lower performance on Trails B. Findings suggest that lower executive functioning may fortify the relation between PTSD and AUD and potentially impede the treatment process. Indeed, poor mental flexibility may limit ability to retrieve and utilize psychosocial and cognitive behavioral skills that promote healthy coping when PTSD symptoms and cravings for alcohol are heightened. Cognitive training interventions to improve executive functioning may help bolster existing empirically supported treatments for this vulnerable and high-risk population.

Acknowledgement: DoD grant W81XWH-05-2-0094

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.

AMONG 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

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Received for publication April 3, 2014; accepted May 27, 2014.

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Number: NCT01087736. URL: <http://clinicaltrials.gov/ct2/show/NCT01087736>.

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DOI: 10.1111/acer.12496



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 \pm Standard Deviation)

	TOP	PLA
<i>n</i> (female)	14 (1)	16 (1)
Age (years)	49.5 \pm 13.9	50.4 \pm 12.8
Education (years)	12.9 \pm 3.1	14.4 \pm 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, <i>n</i> (%)	10 (71)	12 (75)
Comorbid substance use disorder, <i>n</i> (%)	5 (36)	5 (32)
AUD residential TX, <i>n</i> (%)	4 (29)	2 (13)
AUD outpatient TX, <i>n</i> (%)	7 (50)	8 (50)
PTSD outpatient TX, <i>n</i> (%)	9 (65)	9 (56)
PTSD pharmacotherapy TX, <i>n</i> (%)	5 (37)	9 (56)
Alpha blocker (Prazosin) (%)	1 (7)	1 (6)
Antidepressants (%)	4 (29)	7 (44)
Bupropion (%)	0 (0)	1 (6)
Citalopram (%)	2 (14)	3 (19)
Fluoxetine (%)	0 (0)	1 (6)
Mirtazapine (%)	1 (7)	0 (0)
Sertraline (%)	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 \pm 11.6	26.3 \pm 12.3
BAI	20.4 \pm 12.7	27.4 \pm 13.3
AUDIT score	27.1 \pm 7.9	23.0 \pm 7.5
Days abstinent between last drink and initiation of study medication	12.8 \pm 13.6	4.8 \pm 9.2
Percent DD per week	73.3 \pm 30.3	80.4 \pm 21.5
Percent HDD per week	58.5 \pm 33.7	72.6 \pm 28.5
Avg. drinks ^a per week	52.4 \pm 34.2	58.2 \pm 25.4
Avg. drinks ^a per DD	11.1 \pm 6.1	10.9 \pm 4.7
Baseline CAPS total	72.8 \pm 14.3	83.1 \pm 17.3
Re-experiencing	18.2 \pm 4.3	21.9 \pm 6.9
Avoidance	31.1 \pm 6.1	34.8 \pm 8.9
Arousal	23.5 \pm 6.7	26.4 \pm 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.

^aStandard 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 ($94.2 \pm 23.5\%$) than PLA ($83.1 \pm 37.5\%$) 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

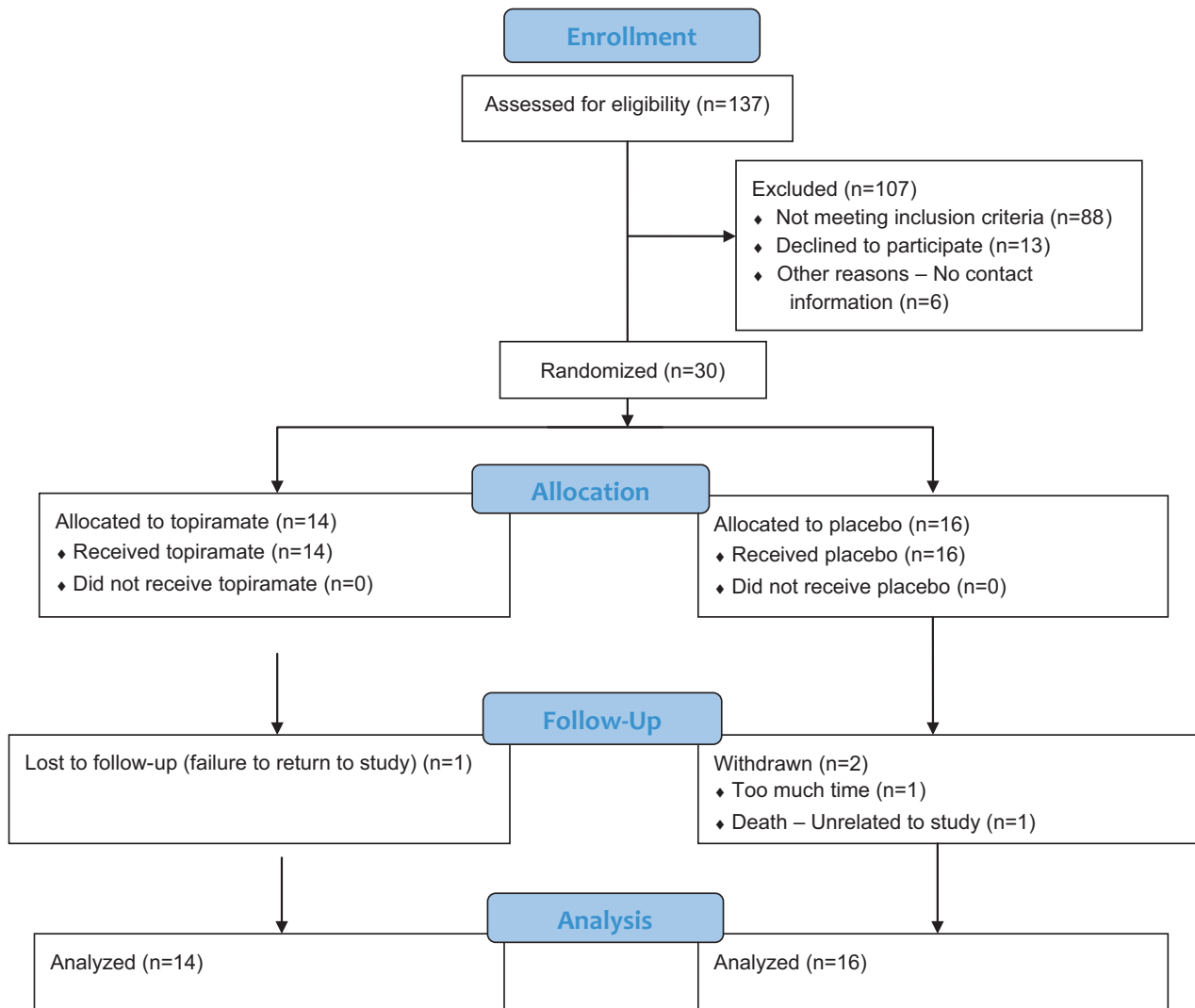


Fig. 1. CONSORT flow diagram.

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

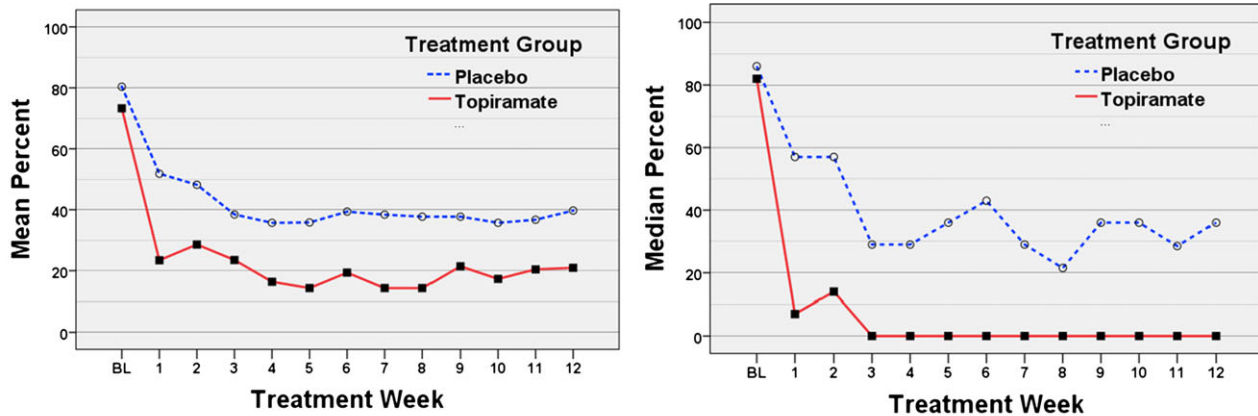
Percent Heavy Drinking Days, Drinks per Drinking Day, and Standard Drinks per Week. Each univariate analysis examining reductions of percent heavy drinking days, standard alcohol drinks consumed per week, and standard alcohol drinks consumed per drinking day within TOP found significant reductions and 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

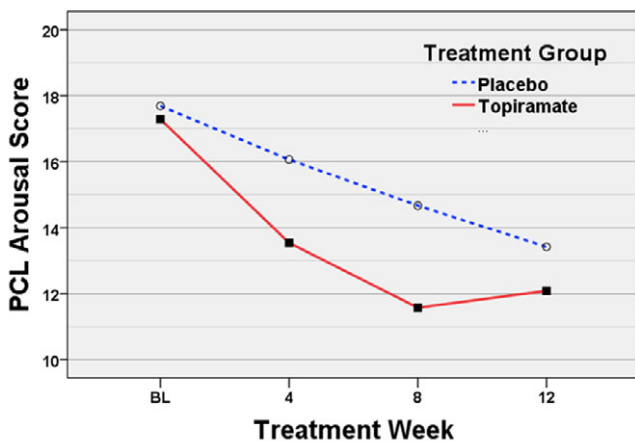
	TOP within-group analysis				Between-groups analysis					
	Baseline Mean \pm SD	Weeks 1 to 12		Weeks 1 to 12 Avg. Mean \pm SD	TOP Weeks 1 to 12 Avg. Mean \pm SD	PLA Weeks 1 to 12 Avg. Mean \pm SD	p-Value	IRR (β)	95% CI	%Diff.
		Mean \pm SD	SD							
Alcohol consumption										
% DD	73.3 \pm 30.3	19.5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

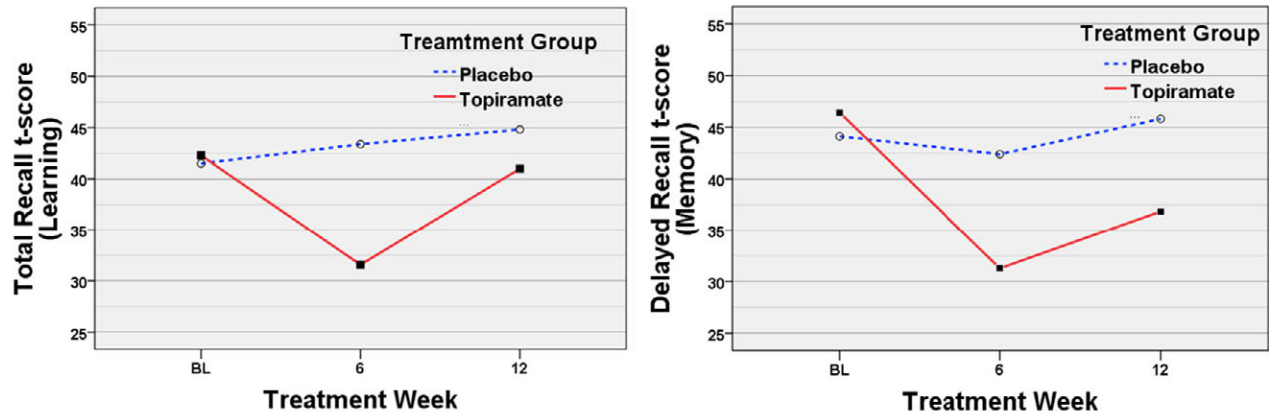
HVLT-R Total (Learning). There was a significant treatment by week interaction for HVLT-R total recall, $F(1, 21) = 6.63, p = 0.018$ (Fig. 4). Follow-up univariate analyses indicated that TOP decreased in performance between baseline and week 6, $F(1, 13) = 15.04, p = 0.002$, and then significantly regained 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.

ACKNOWLEDGMENTS

This work was supported by grants from the Department of Defense W81XWH-05-2-0094, W81XWH-12-2-0137, and W81XWH-11-2-0245 (SLB), National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health UCSF-CTSI UL1 RR024131, which were administered by the Northern California Institute for Research and Education, and with resources of the Veterans Affairs Medical Center, San Francisco, California.

DISCLOSURE

DLP, BL, AW, KD, and EH have no disclosures to make. SLB has served as a consultant to Gilead Sciences and TCN has consulted to Genentech. TCN has received study medication from Actelion for a study funded by the Department of Defense and received study medication from Glaxo Smith Kline for a study funded by the Department of Veterans Affairs.

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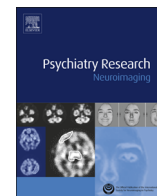
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journal homepage: www.elsevier.com/locate/psychresns

A preliminary examination of cortical neurotransmitter levels associated with heavy drinking in posttraumatic stress disorder

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ARTICLE INFO

Article history:

Received 8 February 2014

Received in revised form

2 August 2014

Accepted 7 September 2014

Keywords:

Alcohol dependence

Brain metabolite concentrations

GABA

Magnetic resonance spectroscopy

Neuronal injury

PTSD

ABSTRACT

Posttraumatic stress disorder (PTSD) patients have low cortical concentrations of γ -aminobutyric acid (GABA) and elevated glutamate (Glu) as measured by proton magnetic resonance spectroscopy (^1H MRS). Alcohol use disorder (AUD) is highly comorbid with PTSD, but the neurobiological underpinnings are largely unknown. We wanted to determine if PTSD patients with AUD have normalized cortical GABA and Glu levels in addition to metabolite alterations common to AUD. We compared brain metabolite concentrations in 10 PTSD patients with comorbid AUD (PAUD) with concentrations in 28 PTSD patients without AUD and in 20 trauma-exposed controls (CON) without PTSD symptoms. We measured concentrations of GABA, Glu, *N*-acetylaspartate (NAA), creatine- (Cr) and choline-containing metabolites (Cho), and myo-Inositol (ml) in three cortical brain regions using ^1H MRS and correlated them with measures of neurocognition, insomnia, PTSD symptoms, and drinking severity. In contrast to PTSD, PAUD exhibited normal GABA and Glu concentrations in the parieto-occipital and temporal cortices, respectively, but lower Glu and trends toward higher GABA levels in the anterior cingulate cortex (ACC). Temporal NAA and Cho as well as ml in the ACC were lower in PAUD than in both PTSD and CON. Within PAUD, more cortical GABA and Glu correlated with better neurocognition. Heavy drinking in PTSD is associated with partially neutralized neurotransmitter imbalance, but also with neuronal injury commonly observed in AUD.

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1. Introduction

Among individuals with posttraumatic stress disorder (PTSD), up to 85% suffer from alcohol use disorders (AUD) (Kessler et al., 1995; Baker et al., 2009; Javidi and Yadollahie, 2012). The co-occurrence of these disorders is associated with worse psychosocial and medical outcomes, higher rates of hospitalization and typical substance use-related problems (McCarthy and Petrakis, 2010). Although the recent biological literature on PTSD and AUD has each grown substantially (Volkow and Li, 2005; Spanagel, 2009; Pitman et al., 2012), little is known about the neurobiological underpinnings associated with comorbid PTSD and AUD

(PAUD). The purpose of this study is to contrast neuroimaging-based brain metabolite concentrations in PTSD patients with and without AUD.

In vivo proton magnetic resonance spectroscopy (^1H MRS) is an invaluable tool for non-invasive quantitation of regional brain metabolite levels related to the neuropathology of a disease. ^1H MRS has been used to investigate the deregulation of the glutamate and γ -aminobutyric acid (GABA) pathways posited to be involved in the pathophysiology of PTSD (Hageman et al., 2001). In a recent ^1H MRS study comparing PTSD patients with trauma-exposed individuals without PTSD symptoms, we found lower GABA levels in the lateral temporal (TEMP) and parieto-occipital cortices (POC), higher glutamate in TEMP cortex, and lower *N*-acetylaspartate levels (NAA, a marker of neuronal viability) in prefrontal cortex (Meyerhoff et al., 2014).

Other brain metabolites such as myo-inositol (ml), creatine- (Cr), and choline-containing compounds (Cho) serve as intracellular

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markers of membrane abnormalities and high-energy metabolism in psychiatric disorders (Vion-Dury et al., 1994). PTSD brain studies have mainly targeted regions with functional (Shin et al., 2001; Shin et al., 2004) and structural abnormalities (Pitman et al., 2012), namely the hippocampus and anterior cingulate cortex (ACC). A meta-analysis of 16 ¹H MRS studies that compared PTSD patients with healthy controls (Karl and Werner, 2010) revealed lower left and right hippocampal NAA measures (both NAA relative to Cr and absolute NAA concentration), reduced NAA concentration in the ACC, and higher left hippocampal Cho/Cr. These abnormalities indicate neuronal injury and membrane alterations in regions of the brain associated with memory encoding, fear extinction, and emotional control (Hamner et al., 1999).

Brain metabolite concentrations are also altered in individuals with AUD, primarily in the frontal lobes (Sullivan, 2000; Meyerhoff et al., 2004; Durazzo and Meyerhoff, 2007; Buhler and Mann, 2011; Mon et al., 2012). Using ¹H MRS methods identical to those employed in this study, we showed (Mon et al., 2012) lower concentrations of Glu, NAA, and Cr in the ACC of recently detoxified alcohol-dependent individuals compared with non-drinking or light-drinking controls, and normal ACC GABA and ml concentrations; however, metabolite levels in the dorsolateral prefrontal cortex and POC were not abnormal in these alcohol-dependent individuals (Mon et al., 2012).

One ¹H MRS study of PTSD investigated the effects of alcohol consumption on brain metabolite concentrations (Schuff et al., 2008). Both PTSD patients with little or no alcohol consumption and PTSD patients with a history of alcohol abuse within the 5 preceding years had low NAA/Cr in the ACC and mesial temporal lobe including the hippocampus. Given that we detected NAA deficits only in heavy drinkers who consumed at least 90 standard alcoholic drinks per month for extended periods (Meyerhoff et al., 2004), this was not necessarily surprising: The alcohol-drinking PTSD patients of the study of Schuff et al. consumed < 20 standard alcoholic drinks/month averaged over 5 years and only 34 drinks the month before the study. Such an amount of alcohol consumption is far below what is considered “at risk” or “heavy” drinking according to NIH/NIAAA guidelines (Willenbring et al., 2009).

Therefore, to our knowledge, no research has investigated the effects of heavy drinking on brain metabolite concentrations in PTSD patients with a current AUD diagnosis. This high comorbidity exists, at least in part, because alcohol use may be an attempt to “self-medicate” and/or respond to symptoms such as insomnia, anxiety, and hyperarousal (Leeies et al., 2010; Ouimette et al., 2010). Therefore, we hypothesized that the cortical neurotransmitter imbalances we described in PTSD patients without AUD (Meyerhoff et al., 2014) are attenuated in PTSD patients with AUD. Specifically, we hypothesized that GABA and Glu concentrations would be less abnormal in our comorbid sample than in patients with PTSD only. Additionally, we expected that cortical NAA, typically reduced in individuals with AUD, would also be reduced in patients with comorbid PTSD and AUD (PAUD) compared to both PTSD patients and trauma-exposed controls without AUD (CON). We also explored the degree to which the regional cortical metabolite levels reflected neurocognitive function, PTSD symptoms, and sleep quality.

2. Methods

2.1. Participants

All participants voluntarily provided written informed consent before the study, which had been approved by the human research committees of the University of California San Francisco, the VA Medical Center in San Francisco, and the Department of Defense. All PTSD, PAUD, and non-PTSD (CON) individuals were either trauma-exposed American veterans of war or trauma-exposed civilians

recruited at the San Francisco VA Medical Center, from among Northern California United States Army reservists, Army National Guard, or the Mental Health Service of the San Francisco and Fresno VA, regional Veteran Centers and mental health clinics. Exclusion criteria were a history of schizophrenia or schizoaffective disorder, past and current AUD (CON only), AUD and substance use disorder within the past 6 months (PTSD only), suicidal intention, or bipolar disorder as assessed by the Structured Clinical Interview for DSM-IV (First et al., 1998). Medical exclusion criteria included pregnancy, seizure disorders, head injury associated with post-injury memory loss for > 24 h or loss of consciousness > 10 min, history of stroke or neurodegenerative diseases, HIV infection, or medical instability. Participants were excluded if they were prescribed psychiatric medications or hypnotics within 2 weeks before magnetic resonance imaging (MRI), had any kind of metallic implants, lodged foreign objects, other contraindications for MRI, or likely traumatic reactions to MR scanner noise.

2.2. Clinical assessment

All participants completed a structured clinical interview to yield basic demographic information. PTSD diagnosis and symptom severity were measured 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 typical symptom clusters: Exposure to a traumatic event; Re-experiencing; Numbing and avoidance; Hyper-arousal; Chronology; and Functional impairment. A criterion was considered present if a participant endorsed a symptom with a score ≥ 1 in frequency and ≥ 2 in severity rating. Insomnia was assessed with the Insomnia Severity Index (ISI; Bastien et al., 2001), a valid and reliable self-report measure of perceived insomnia severity. Harmful and hazardous drinking was assessed using the Alcohol Use Disorder Identification Test (Saunders et al., 1993). Alcohol consumption was assessed using the Time Line Follow Back (Sobell and Sobell, 1992) interview, which yielded average drinks consumed over 90 days before the MRI study. To assess the influence of self-reported depressive and anxiety symptoms on regional metabolite levels, we administered the Beck Depression Inventory-II (Beck, 1978) and Beck Anxiety Inventory (Beck et al., 1988) on the day of the MRI examination.

2.3. Neurocognitive assessment

Within 3 days before the MRI study, PAUD participants completed a neurocognitive battery consisting of the following: Trail Making Test A and B (Reitan and Wolfson, 1985), a measure of processing speed and divided attention, Hopkins Verbal Learning Test-Revised (Brandt, 1991), including total recall and delayed recall which measure auditory-verbal learning and memory, and the Balloon Analogue Risk Task (Lejuez et al., 2002), a task-based measure of risk taking. Neither CON nor PTSD participants underwent neuropsychological testing.

2.4. MRI acquisition and processing

MR data were acquired on a 4-Tesla Bruker MedSpec system with a Siemens Trio console (Siemens, Erlangen, Germany) using an eight-channel transmit-receive head coil. Three-dimensional sagittal T1-weighted and 2D axial T2-weighted images were acquired using Magnetization Prepared Rapid Gradient imaging ($1 \times 1 \times 1 \text{ mm}^3$ resolution) and turbo spin-echo ($0.9 \times 0.9 \times 3 \text{ mm}^3$ resolution) sequences, respectively. ¹H MRS evaluated 3 volumes of interest (VOIs) known to be associated with PTSD and AUD, the ACC, TEMP and POC. These VOIs were evaluated because the ACC is metabolically abnormal in PTSD (Karl and Werner, 2010) and critically involved in the development and maintenance of all forms of addictive disorders (e.g., Goldstein et al., 2009; Volkow et al., 2012). The TEMP is functionally connected to the hippocampus, and together they contribute to the mesial temporal lobe memory system in humans (Kahn et al., 2008) associated with PTSD (Hamner et al., 1999). The POC has been targeted traditionally in ¹H MRS studies to measure levels of the inhibitory neurotransmitter GABA in various populations, and this general brain region has been recently implicated in altered neural activity in PTSD (Sripada et al., 2012; Chen and Etkin, 2013). MRS VOIs were placed over the ACC ($35 \times 25 \times 20 \text{ mm}^3$), POC ($20 \times 40 \times 20 \text{ mm}^3$) and right TEMP ($20 \times 40 \times 20 \text{ mm}^3$), maximizing gray matter content as displayed on the structural MR images. Fig. 1 (top) shows typical VOI locations on T2-weighted MR images, midline for ACC and POC, and always patient right for TEMP. NAA, Cr, Cho, ml and Glu signals were acquired at 12-ms echo time with a Stimulated Echo Acquisition Mode sequence (Frahm et al., 1987). Immediately afterwards, a reference water signal was collected from the same VOI with the same Stimulated Echo Acquisition Mode sequence but without water suppression and used for normalizing all metabolite peak areas across participants. Signals from GABA were acquired from the same VOIs with a J-editing sequence modified for optimal GABA signal-to-noise and improved suppression of water and macromolecular signal (Kaiser et al., 2008). MR images were segmented into gray matter, white matter, and cerebrospinal fluid (Van Leemput et al., 1999) to estimate tissue fraction and cerebrospinal fluid contributions to each VOI. Metabolite and J-edited spectra were processed by operators blind to participant diagnosis to yield metabolite levels in institutional units as peak area ratios relative to the unsuppressed voxel tissue water

(i.e., not corrected for relaxation times). A full description of the spectral processing and metabolite quantitation methods can be found elsewhere (Mon et al., 2012). The metabolite spectra yielded concentrations for NAA, Cr, Cho, ml and Glu, whereas GABA concentrations were derived from the J-edited spectra as described. Example spectra are given in Fig. 1 (bottom). Mostly due to time constraints, not all participants had spectral data acquired from all three VOIs, so that after data processing and rigorous quality control (Meyerhoff et al., 2014), the number of participants contributing to quantitative MRS data varied by group and VOI as indicated in Table 2.

2.5. Statistical analyses

Separate univariate analyses of covariance were performed for three VOIs and six metabolites (NAA, Cr, Cho, ml, Glu, GABA). Follow-up planned pairwise comparisons tested for group differences in metabolite concentrations among PAUD, PTSD, and CON. Each three-group-comparison was covaried for age and gray matter-tissue contribution to the VOI, as differences in these variables can affect metabolite levels (e.g., Schuff et al., 2001; Jansen et al., 2006). We left age and/or tissue contribution in the final model only when they predicted significant group differences. Analyses of covariance were also used to test for differences in participant characteristics. In pairwise group comparisons of metabolite levels, we accounted for the multiplicity of metabolite measures in each VOI by correcting alpha levels via a modified Bonferroni procedure (Sankoh et al., 1997). This approach yields adjusted alpha levels for each VOI separately using the number of metabolites under investigation (six) and their average inter-correlation coefficients (ACC: $r=0.35$, POC: $r=0.32$, TEMP: $r=0.26$); the corresponding adjusted alpha levels for pairwise group comparisons were 0.014 for ACC, 0.013 for POC and 0.012 for TEMP. Effect sizes were calculated via Cohen's d (Cohen, 1988). In PAUD, we correlated VOI-specific metabolite concentrations with the raw scores of our neurocognitive measures using Spearman's rho, and in both PTSD groups we also related metabolite concentrations to ISI and CAPS scores (p -values uncorrected). All analyses were completed with SPSS v20.

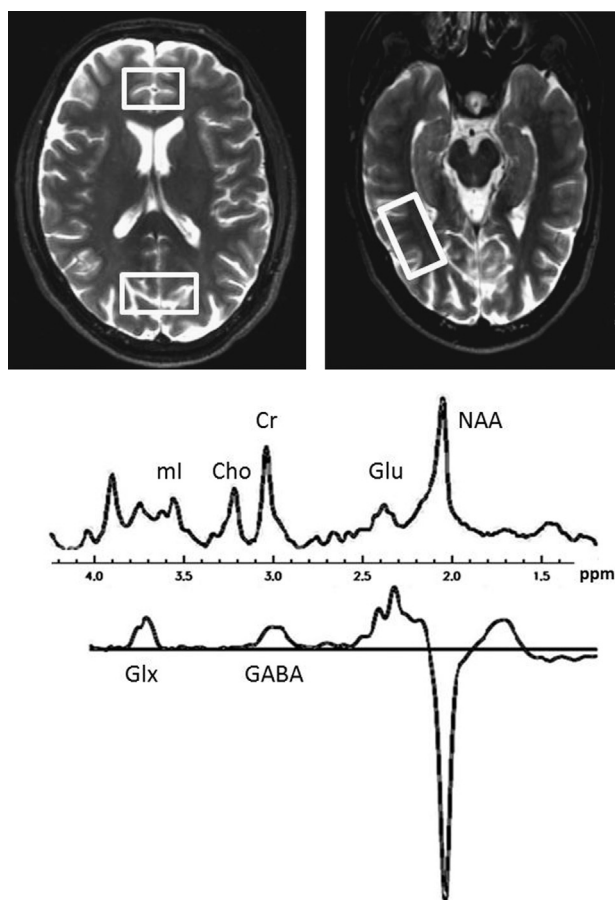


Fig. 1. Locations of volumes of interest on T2-weighted magnetic resonance Images (left: ACC and POC; right: TEMP). Examples of analyzed stimulated echo acquisition mode spectrum (top) and J-edited spectrum (bottom) from the POC. Spectra shown on different vertical scales for clarity. Major metabolite signals are labeled. The N-acetylaspartate (NAA) signal is fit separately from the neighboring N-acetylaspartylglutamate signal.

3. Results

3.1. Participant characteristics

Characteristics of the PAUD, PTSD, and CON groups are shown in Table 1. PAUD participants were older than both CON and PTSD participants, who were of similar age. Nine of the 10 PAUD participants were Caucasian, including one Latino, and one African American. The group of 28 PTSD patients comprised 14 Caucasians (50%), including three Latinos, eight African Americans (29%), three Asians (11%), two Native Americans (7%), and one Indian (3%). Of the 19 CON participants, 10 were Caucasians (53%), including one Latino, six Asian Americans (32%), two African Americans (11%), and one Pacific Islander (5%). All PAUD and PTSD were veterans of foreign wars in Vietnam, the Gulf Wars, and wars in Iraq and Afghanistan with war-zone and/or civilian related trauma exposure. CON participants (including 10 veterans) were all exposed to non-military trauma, but had no meaningful PTSD symptoms (i.e., total CAPS score < 14). PAUD participants had higher CAPS scores reflecting greater non-specific PTSD symptom severity than the PTSD group, but similar arousal scores. Both PTSD groups had significantly higher depressive symptoms on the Beck Depression Inventory and anxiety symptoms on the Beck Anxiety Inventory than CON, with PAUD having higher Beck Depression Inventory and Beck Anxiety Inventory scores than PTSD. CON did not differ from PTSD on any drinking variables, but – by design – the PAUD group consumed more standard alcoholic drinks over the last 90, 30 and 7 days before study than either the CON or PTSD group.

3.2. Three-group comparison of regional metabolite concentrations

Univariate tests were significant for group differences in the ACC: NAA ($p=0.048$), Cho ($p=0.008$), ml ($p<0.001$), Glu ($p=0.001$), and GABA ($p=0.046$); in the TEMP: NAA ($p<0.001$), Cho ($p=0.040$), and Glu ($p=0.006$); and in the POC: GABA ($p=0.050$). Table 2 shows mean metabolite concentrations by VOI and group, pairwise group statistics, and effect sizes.

In planned pairwise comparisons, PAUD showed normal GABA and Glu levels in both POC and TEMP. This was in contrast to PTSD, who had higher Glu in TEMP ($p=0.009$) and a trend toward lower GABA ($p=0.026$) in the POC compared with CON. Thus, TEMP Glu was also significantly lower in PAUD than PTSD ($p=0.009$). In the ACC, PAUD had lower Glu ($p\leq 0.001$) and tended to have higher GABA levels than both PTSD and CON ($p\leq 0.027$), whereas PTSD had normal Glu and GABA levels in the ACC.

In PAUD, TEMP NAA concentration was lower than in PTSD and CON ($p\leq 0.001$) and ACC NAA levels tended to be lower compared with CON levels ($p=0.024$). In addition, concentrations of ml and Cho in the ACC were much lower in PAUD than in both CON and PTSD (all $p\leq 0.005$), whereas PTSD tended to have only lower than normal NAA in the ACC ($p=0.059$). Similarly, Cho and ml tended to be lower in the TEMP of PAUD compared with both PTSD and CON ($p<0.092$). Effect sizes for all significant group differences were strong (effect sizes=0.91–2.13), in particular in the ACC. The total CAPS, Beck Depression Inventory, and Beck Anxiety Inventory scores, which were significantly higher in PAUD than PTSD, did not contribute significantly to the described regional metabolite group differences.

3.3. Correlations among main outcome measures within PAUD

3.3.1. Metabolite concentrations and neurocognition (See Table 3)

Within the 10 PAUD participants, ACC Glu was strongly related to divided attention (Trail Making Test-B: $r=0.73$, $p=0.025$) and GABA to auditory-verbal learning/memory (Hopkins Verbal

Table 1
Patient characteristics (mean ± standard deviation).

Variable	PAUD	PTSD	CON	PAUD vs. PTSD <i>p</i> -value	PAUD vs. CON <i>p</i> -value	PTSD vs. CON <i>p</i> -value
<i>n</i> (all male)	10	28	20	–	–	–
Age [years]	51.9 ± 13.9	35.4 ± 10.5	36.3 ± 12.4	< 0.001	0.001	NS
Education [years]	14.6 ± 2.1	15.1 ± 2.4	15.8 ± 2.2	NS	NS	NS
Smoker <i>n</i> (%)	5 (50)	8 (29)	5 (25)	–	–	–
Insomnia Severity Index	16.7 ± 7.3	14.8 ± 6.4	2.5 ± 2.6	NS	< 0.001	< 0.001
Beck depression Inventory	23.7 ± 10.5	14.4 ± 10.1	1.1 ± 2.0	0.009	< 0.001	< 0.001
Beck Anxiety Inventory	21.3 ± 12.9	12.8 ± 13.3	1.1 ± 2.9	0.057	< 0.001	0.003
AUDIT Score	25.1 ± 9.3	4.6 ± 6.2	0.9 ± 1.3	< 0.001	< 0.001	NS
Total# of alcoholic drinks ^a						
last week	39 ± 34	4 ± 8	2 ± 4	< 0.001	< 0.001	NS
last 30 days	169 ± 81	17 ± 34	10 ± 16	< 0.001	< 0.001	NS
last 90 days	588 ± 291	50 ± 101	29 ± 47	< 0.001	< 0.001	NS
CAPS Total	78.6 ± 17.9	55.2 ± 18.3	2.7 ± 4.5	0.000	< 0.001	< 0.001
Intrusion	19.5 ± 7.4	14.8 ± 6.6	0.5 ± 1.6	0.036	< 0.001	< 0.001
Avoidance	34.0 ± 6.2	19.3 ± 9.2	1.1 ± 2.8	< 0.001	< 0.001	< 0.001
Arousal	25.1 ± 6.6	21.0 ± 7.8	1.1 ± 2.1	NS	< 0.001	< 0.001
ACC GM-tissue (% of VOI) ^b	49 ± 3	45 ± 4	48 ± 3	0.009	NS	0.013
POC GM-tissue (% of VOI) ^b	64 ± 3	62 ± 3	63 ± 4	NS	NS	NS
TEMP GM-tissue (% of VOI) ^b	52 ± 7	44 ± 6	45 ± 5	0.001	0.003	NS

^a Standard alcoholic drink defined as containing 13.6 g of pure alcohol.

^b Volume of interest.

Table 2
Mean and standard deviation of metabolite concentrations (institutional units) by group and volume of interest.

Region	Metabolite	PAUD (<i>n</i>)	PTSD (<i>n</i>)	CON (<i>n</i>)	PAUD vs. PTSD <i>p</i> -value (ES)	PAUD vs. CON <i>p</i> -value (ES)	PTSD vs. CON <i>p</i> -value (ES)
ACC	NAA	5.08 ± 0.89 (10)	5.39 ± 0.83 (23)	5.92 ± 0.81 (14)	NS (0.36)	0.024 ^a (0.99)	0.059 ^a (0.64)
	Cr	3.72 ± 0.80 (8)	4.08 ± 0.80 (24)	4.44 ± 0.80 (14)	NS (0.45)	0.049 ^a (0.90)	NS (0.45)
	Cho	1.03 ± 0.25 (9)	1.32 ± 0.25 (24)	1.34 ± 0.25 (14)	0.004 (1.16)	0.005 (1.25)	NS (0.08)
	mI	2.68 ± 0.66 (9)	4.08 ± 0.66 (24)	3.93 ± 0.66 (14)	< 0.001 (2.13)	< 0.001 (1.90)	NS (0.23)
	Glu	3.06 ± 0.78 (9)	4.13 ± 0.78 (24)	4.38 ± 0.78 (14)	0.001 (1.38)	< 0.001 (1.70)	NS (0.32)
	GABA	1.43 ± 0.32 (9)	1.14 ± 0.31 (22)	1.10 ± 0.32 (12)	0.027 ^a (0.92)	0.023 ^a (1.05)	NS (0.13)
POC	NAA	5.50 ± 0.59 (10)	5.67 ± 0.59 (24)	5.64 ± 0.59 (16)	NS (0.29)	NS (0.24)	NS (0.05)
	Cr	4.46 ± 0.60 (10)	4.38 ± 0.56 (24)	4.28 ± 0.54 (16)	NS (0.14)	NS (0.32)	NS (0.18)
	Cho	0.82 ± 0.11 (10)	0.78 ± 0.11 (24)	0.75 ± 0.11 (16)	NS (0.38)	NS (0.65)	NS (0.27)
	mI	3.00 ± 0.58 (10)	3.34 ± 0.57 (24)	3.18 ± 0.58 (16)	NS (0.59)	NS (0.31)	NS (0.28)
	Glu	3.92 ± 0.50 (10)	4.17 ± 0.50 (24)	4.17 ± 0.50 (16)	NS (0.50)	NS (0.50)	NS (0.00)
	GABA	1.88 ± 0.31 (10)	1.67 ± 0.31 (23)	1.90 ± 0.31 (16)	NS (0.68)	NS (0.06)	0.026 ^a (0.75)
TEMP	NAA	4.58 ± 0.66 (10)	5.65 ± 0.66 (23)	5.52 ± 0.66 (14)	< 0.001 (1.62)	0.001 (1.42)	NS (0.20)
	Cr	3.53 ± 0.71 (10)	3.86 ± 0.70 (23)	3.71 ± 0.71 (14)	NS (0.47)	NS (0.25)	NS (0.21)
	Cho	0.81 ± 0.15 (10)	0.96 ± 0.15 (23)	0.94 ± 0.15 (14)	0.014 ^a (0.97)	0.058 ^a (0.84)	NS (0.13)
	mI	2.69 ± 0.59 (10)	3.09 ± 0.59 (23)	3.12 ± 0.59 (14)	0.082 ^a (0.68)	0.092 ^a (0.73)	NS (0.05)
	Glu	2.56 ± 0.83 (10)	3.43 ± 0.77 (23)	2.73 ± 0.76 (14)	0.009 (1.08)	NS (0.21)	0.009 (0.91)
	GABA	1.23 ± 0.23 (6)	1.10 ± 0.22 (22)	1.22 ± 0.22 (12)	NS (0.58)	NS (0.04)	NS (0.55)

^a Trend (*p* < 0.10) after adjusting alpha levels to 0.014 for ACC, 0.013 for POC, and 0.012 for TEMP.

Learning Test-Revised-Total Recall: $r=0.69$, $p=0.040$; Hopkins Verbal Learning Test-Revised-Delay Recall: $r=0.89$, $p=0.002$). ACC Cho was negatively associated with auditory-verbal memory (Hopkins Verbal Learning Test-Revised-Delay Recall: $r=-0.89$, $p=0.002$). In the TEMP of PAUD, GABA was positively associated with processing speed (Trail Making Test-A: $r=0.87$, $p=0.019$). Brain metabolite concentrations did not significantly correlate with measures of risk-taking (Balloon Analog Risk Task) in this small group.

3.3.2. Metabolite concentrations and PTSD symptomatology, sleep and drinking measures

Within PAUD participants, there were no significant associations of ACC, POC, and TEMP metabolite levels with CAPS measures or the ISI score. However, in the larger PTSD group, lower TEMP Cho levels had a moderately strong relationship to high CAPS total scores ($r=-0.64$, $p=0.001$) and to high arousal scores ($r=-0.49$,

Table 3
Significant ($p < 0.04$) correlations (r) between metabolite concentrations and neurocognition in PAUD.

Region	Metabolite	Neurocognitive domain			
		Auditory-verbal learning	Auditory-verbal memory	Divided-attention	Processing speed
ACC	Cho	-0.89			
	Glu			0.73	
	GABA	0.69	0.89		
TEMP	GABA				0.87

$p=0.017$). Similarly, low Glu in the ACC related to high CAPS total ($r=-0.41$, $p=0.048$) and arousal scores ($r=-0.59$, $p=0.002$). High arousal scores also correlated moderately strong with lower NAA ($r=-0.43$, $p=0.040$) and Cr ($r=-0.48$, $p=0.018$) in the ACC. High

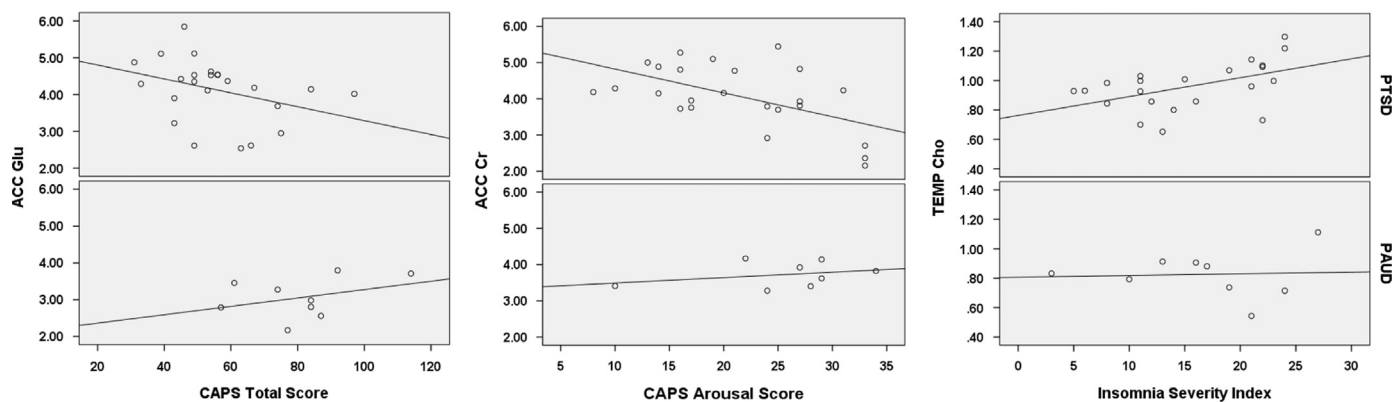


Fig. 2. Examples of different relationships between metabolite concentrations, PTSD symptomology and sleep problems by PTSD group.

intrusion scores related to low ml in the ACC ($r = -0.60$, $p = 0.002$) and POC ($r = -0.49$, $p = 0.015$) as well as low POC Cr ($r = -0.43$, $p = 0.034$) in PTSD. Whereas in the smaller PAUD group none of the regional metabolite concentrations correlated significantly with ISI, PTSD exhibited moderately strong positive correlations between ISI and POC Glu ($r = 0.49$, $p = 0.018$) and Cho ($r = 0.54$, $p = 0.007$), as well as a negative association of ISI with POC GABA ($r = -0.55$, $p = 0.008$). TEMP Cho in the PTSD group was also positively associated with ISI ($r = 0.50$, $p = 0.018$). Examples of these relationships are illustrated in Fig. 2. Self-reported alcohol consumption in the PAUD group over 90 days before the study did not correlate significantly with any of the regional metabolite concentrations, PTSD symptom measures, or ISI.

4. Discussion

We used high-field ^1H MRS to compare brain metabolite concentrations in frontal, parietal, and temporal cortices of PTSD patients with and without alcohol use disorder. PTSD patients showed considerable metabolic variability in the ACC and TEMP as a function of AUD diagnosis. As hypothesized, we found normal GABA and Glu concentrations in the TEMP and POC of PTSD patients with AUD (PAUD), metabolite levels that were previously shown to be lower (GABA) and higher (Glu in TEMP) in PTSD patients without AUD (Meyerhoff et al., 2014). Furthermore, PAUD had lower Glu and tended to have higher GABA levels in the ACC than both PTSD and CON, whereas PTSD did not differ from CON on these prefrontal measures. In PAUD, higher TEMP GABA and higher ACC GABA and Glu levels were related to better neurocognitive performance. In total, these findings demonstrate significant effects of comorbid AUD on cortical GABA and Glu levels in PTSD. Importantly, these findings suggest that this PAUD population may be consuming alcohol in an attempt to regulate PTSD-associated glutamatergic and GABAergic deficits throughout the lateral cortices (POC and TEMP), thereby inadvertently damaging these systems in medial prefrontal cortex (ACC) and promoting neuronal injury.

In addition to these neurotransmitter alterations, the PAUD group demonstrated dramatically lower NAA concentrations in the TEMP as well as lower Cho and ml concentrations in the ACC and TEMP compared with both the PTSD and CON groups. The PTSD group, on the other hand, was indistinguishable from CON on these same measures. These results indicate that PAUD have metabolite alterations that are associated with their AUD diagnosis (i.e., they are above and beyond those abnormalities related to PTSD alone), but that are not related to quantitative estimates of alcohol consumption. Since we did not include a matched AUD group without PTSD in this analysis, we do not know if these

differences of moderate to strong effect size are greater in comorbid PAUD than in AUD alone. However, an AUD population without PTSD, which we earlier studied with ^1H MRS (Meyerhoff et al., 2004) and which had consumed similar amounts of alcohol to our PAUD group, did not exhibit measurable frontal or temporal gray matter NAA reductions. Taken together, this suggests greater metabolic injury in PTSD participants with comorbid AUD than in individuals with AUD alone.

Within PAUD, higher GABA in the ACC correlated with better performance in auditory-verbal learning and memory, while high GABA in the TEMP was equally beneficial to processing speed. Although higher Glu in the ACC was related to better performance on a task of divided attention in PAUD, this group exhibited lower ACC Glu levels than both CON and PTSD. This pattern, along with our findings above, suggests that chronic drinking in PTSD is associated with better cortical GABAergic function but worse glutamatergic abnormalities related to cognitive performance typically associated with PTSD (Golier and Yehuda, 2002). As we did not test neurocognition in PTSD or CON, a direct comparison between participant groups could not be made.

Interestingly, PTSD symptoms and sleep quality in PAUD were not strongly related to metabolite concentrations, whereas both were significantly associated with metabolite concentrations in the PTSD group (see Fig. 2). Inasmuch as different group sizes (10 PAUD and 28 PTSD participants) were not the main reason for these different associations, the observation suggests that a comorbid AUD diagnosis modulates these relationships, consistent with our *a priori* hypothesis. Specifically, this different correlation pattern across both PTSD groups suggests that drinking in PTSD may positively influence sleep quality via normalizing GABA and Glu levels in the POC. On the other hand, as lower concentrations of NAA, Glu, and Cr in the ACC of PTSD were robustly associated with higher PTSD symptom scores, the corresponding metabolite reductions seen in PAUD likely did not serve to alleviate PTSD symptoms overall. To the contrary, PAUD had generally greater PTSD, depression, and anxiety severities than PTSD in addition to similar ISI scores. Although AUD may partially modulate PTSD symptoms, the associated level of drinking is not related to any overall symptom relief. This suggests a complex relationship between an AUD diagnosis and PTSD symptoms that is modulated by other factors not examined in this study.

As chronic drinking in PTSD appears to be associated with neutralized parieto-occipital and temporal cortical neurotransmitter levels but also with more severe PTSD symptoms, our findings only partly support the theory that individuals use psychoactive substances to successfully cope with psychiatric distress (Hall and Queener, 2007). Glutamatergic and GABAergic pathways are involved in the mechanism for encoding memory, and they are likely affected by extreme stress related to trauma (Hageman et al.,

2001). Although still unclear, the downregulation of the inhibitory GABA system is likely mediated by the experience of trauma, which also implies excessive activation of the excitatory glutamate system, a pattern reflected in metabolite levels measured in the TEMP of PTSD patients (Meyerhoff et al., 2014). Here, we showed that inasmuch as the measured static metabolite concentrations reflect corresponding metabolic processes, glutamatergic and GABAergic processes in PAUD were attenuated in two of the three cortical brain regions examined. Although this study links the presence of AUD to altered inhibitory and excitatory processes in PTSD, we cannot assume this link to be causal. The PAUD participants investigated here could simply share a greater common liability to developing both disorders (Berenz and Coffey, 2012) or AUD may have been present before the defining traumatic event.

4.1. Study limitations

The presented comparisons of PTSD and PAUD groups were retrospective and the data were obtained for two different projects without an original intent to compare the groups. Therefore, we did not have data on the onset of AUD in PAUD. However, our analyses were directed by *a priori* hypotheses based on previous reports, and our group comparisons were valid, as data acquisition and processing methodologies were identical and most of the data for the two projects were acquired contemporaneously. Since the PAUD group was small, probing for significant associations between outcome measures was probably underpowered. However, we did observe rather large effect sizes in group comparisons; this should be considered even when the comparisons did not meet statistical significance after controlling for multiple comparisons. Additionally, we did not obtain cognitive data in our CON or PTSD groups to illuminate further the functional relevance of metabolite concentrations. Nevertheless, our analyses underscore clear metabolic and symptomatic differences between PTSD patients with and without AUD.

Given the high prevalence of PTSD and AUD in recently returning veterans (Hoge et al., 2004; Seal et al., 2011), there is an urgent need to improve the treatment approaches to these co-occurring disorders. However, there is a lack of consensus on the optimal use of medications for treating these comorbid conditions (McCarthy and Petrakis, 2010). Given our novel findings of cortical GABA and Glu differences between PTSD patients with and without AUD and differential associations with cognition and various diseases symptoms, our findings need to be confirmed in larger samples. Although any conclusions must be speculative at this time, further supporting evidence for group differences of neurotransmitter levels would obviate the need for advancing targeted treatment approaches for PAUD that are different from those traditionally used to treat PTSD or AUD. A better understanding of the GABAergic and glutamatergic processes in PAUD could inform future pharmacotherapy and behavioral intervention studies, thus enhancing specialized treatment of PAUD.

4.2. Conclusions

Heavy drinking in PTSD is associated with normal GABA and Glu levels in the POC and TEMP, levels which are abnormal in non-drinking PTSD patients. Several regional metabolite levels associated with drinking in PTSD were altered in such a way as to favor better sleep; however, other metabolite levels in PAUD, in particular in the ACC, served to worsen PTSD symptoms or sleep quality. Thus, our data overall can only be interpreted to partly support the self-medication hypothesis in anxiety disorders. Equally as important, PTSD patients with AUD have metabolic abnormalities that are consistent with neuronal, specifically

glutamatergic, injury in prefrontal and temporal cortical gray matter not seen in PTSD patients without AUD. The significant abnormalities in the ACC may have implications for self-monitoring as well as regulation of emotional and affective tone and behavior, which is highly relevant to both PTSD and alcohol misuse (Bush et al., 2000; Bush et al., 2002). These prefrontal alterations may affect fear conditioning, extinction, and memory encoding in PTSD, which are subserved by temporal brain structures that also show metabolite abnormalities. Altogether, these differences may relate to the more severe PTSD, depression, and anxiety symptoms of the PTSD patients with AUD in this study. If further substantiated, the observed metabolic group differences suggest, that along with their relationships to neurocognition, PTSD and insomnia symptoms, different treatment strategies – both pharmacological and behavioral – should be considered for PTSD patients with and without a comorbid AUD diagnosis.

Acknowledgments

This project was supported by grants from the National Institutes of Health (NIH) AA10788 (DJM), AA10788-15S1 (DJM), the Department of Defense (DOD) DAMD17-03-1-0532 (DJM), DOD W81XWH-05-2-0094 (SLB), and the Mental Illness Research and Education Clinical Center (MIRECC) of the US Veterans Health Administration. This material is the result of work supported with resources and the use of facilities at the Veterans Administration Medical Center, San Francisco, California.

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Subject # _____-_____-_____

Level 2 TBI EvaluationDate / /

[1.] Have you ever had any of the following head injuries (check all that apply)

[1a] Bullet Yes No

Number of episodes: 1 / 2 / 3 / 4 / 5 or more

Description:WHEN? Month Year
 Unknown

If Month and Year are both unknown, approximately how many years ago was your Bullet injury?

Years
 Unknown

[1b] Vehicular Yes No

Number of episodes: 1 / 2 / 3 / 4 / 5 or more

Description:WHEN? Month Year
 Unknown

If Month and Year are both unknown, approximately how many years ago was your Vehicular injury?

Years
 Unknown

[1c] Fall Yes No

Number of episodes: 1 / 2 / 3 / 4 / 5 or more

Description:WHEN? Month Year
 Unknown

If Month and Year are both unknown, approximately how many years ago was your Fall injury?

Years
 Unknown[1d] Blunt trauma other than from blast/vehicular injury,
e.g., assault, blunt force, sports related or object hitting
head

Yes No

Number of episodes: 1 / 2 / 3 / 4 / 5 or more

Description:WHEN? Month Year
 Unknown

If Month and Year are both unknown, approximately how many years ago was your Blunt trauma injury?

Years
 Unknown

[1e] Blast [COMPLETE SECTION 1e1-1e5 if this is endorsed]

Yes No

Number of episodes: 1 / 2 / 3 / 4 / 5 or more

Description:WHEN? Month Year
 Unknown

If Month and Year are both unknown, approximately how many years ago was your Blast injury?

Years
 Unknown

[1e1.] Blast Primary (When a high explosive bomb or IED goes off there is a "blast wave" which is a wave of highly compressed gas that hits solid objects like a person's body and may feel almost like smashing into a wall.) Did you remember experiencing this type of "blast wave" or were told that you experienced it? Yes No

Number of blasts in which this occurred: 1 / 2 / 3 / 4 / 5 or more

Estimated distance from closest blast:

- < 10 feet
- 10 to < 30 feet
- 30 to < 50 feet
- 50 feet or more

[1e2.] Blast Secondary (This "blast wave" is followed by a wind in which particles of sand, debris, shrapnel, and fragments are moving rapidly.)

Were you close enough to the blast to be "peppered" or hit by such debris, shrapnel, or other items?

Yes No

Number of blasts in which this occurred: 1 / 2 / 3 / 4 / 5 or more

[1e3.] Blast Tertiary

Were you thrown to the ground or against some stationary object like a wall, vehicle or inside a vehicle by the explosion? (This is not asking if you "ducked to the ground" to protect yourself).

Yes No

Number of blasts in which this occurred: 1 / 2 / 3 / 4 / 5 or more

[1e4.] Blast Quaternary

Did you experience any of the following injuries as a result of an explosive blast: burns, wounds, broken bones, amputations, breathing toxic fumes, or crush injuries from structures falling onto you? Yes No

Number of blasts in which this occurred: 1 / 2 / 3 / 4 / 5 or more

[1e5.] Type of blast exposures (all that apply)

- Improvised Explosive Device (IED)
- Rocket Propelled Grenade (RPG)
- Mortar
- Grenade
- Bomb
- Other
- Unknown

[2] Did you lose consciousness immediately after any of these experiences?

Yes No Uncertain

If yes, number of occurrences 1 / 2 / 3 / 4 / 5 or more

If yes, estimate the duration of longest period of loss of consciousness

- Less than 1 minute
- 1 minute to 30 minutes
- Greater than 30 minutes to 6 hours
- Greater than 6 hours to 24 hours
- Greater than 24 hours to 7 days
- Greater than 7 days

[3] Did you experience a period of disorientation or confusion immediately following the incident?

Yes No Uncertain

If yes, number of occurrences 1 / 2 / 3 / 4 / 5 or more

If yes, estimate the duration of longest period of disorientation or confusion

- Less than 30 minutes
- 30 minutes to 24 hours
- Greater than 24 hours to 7 days
- Greater than 7 days to 1 month
- Greater than 1 month to 3 months
- Greater than 3 months

[4] Did you experience a period of memory loss immediately before or after the incident?

Yes No Uncertain

If yes, number of occurrences 1 / 2 / 3 / 4 / 5 or more

If yes, estimate the duration of longest period of memory loss (Post Traumatic Amnesia (PTA))

- Less than 30 minutes
- 30 minutes to 24 hours
- Greater than 24 hours to 7 days
- Greater than 7 days to 1 month
- Greater than 1 month to 3 months
- Greater than 3 months

[5] At the time of the injury, were you evaluated by medical personal and given a Glasgow Coma Scale (GCS) rating?

Yes No Uncertain

If yes, number of occurrences 1 / 2 / 3 / 4 / 5 or more

If yes, estimate the lowest GCS rating

- Less 9
- 9 to 12
- 13 to 15

[6] At the time of the injury, did you experience any focal neurological deficit(s) (that may or may not be transient)?

Yes No Uncertain

If yes, number of occurrences: 1 / 2 / 3 / 4 / 5 or more

If yes, type of focal neurological deficit (all that apply)

- Aphasia (problem understanding/speaking words)
- Dysarthria (problem making sounds)
- Vision problems
- Hearing problems
- Facial drooping
- Paralysis
- Loss of muscle control (weakness/coordination/fine motor control)
- Paresthesia (abnormal skin sensation, i.e., burning, prickling, itching, tingling with no apparent cause)
- Numbness
- Tremor
- Neglect
- Poor gag reflex
- Other _____
- Other _____
- Other _____
- Unknown

[7] During this/these experience(s), did an object penetrate your skull/cranium?

Yes, penetrating No, non-penetrating

[8] Were you wearing a helmet at the time of most serious injury?

Yes No

[9] Were you taken to a hospital or evacuated from theatre (if occurred during a deployment)?

No Yes, for TBI Yes, for other medical reasons

[10a] Prior to this evaluation, had you received any professional treatment (including medications) for your TBI related symptoms?

No Yes, in the past Yes, currently

[10b] (only if 10a is yes) Have you ever been prescribed medications for symptoms related to your TBI?

No Yes, in the past Yes, currently

[11] Since the time of your injury/injuries, has anyone told you that you were acting differently?

Yes No

[12] Overall, in the last 30 days how much did these difficulties (symptoms) interfere with your life?

- ___ Not at all
- ___ Mildly
- ___ Moderately
- ___ Severely
- ___ Extremely

[13] In what areas of your life are you having difficulties because of these symptoms?

Comment:

[14a] In the last 30 days, have you had any problems with pain?

Yes No

If yes, location(s) (check all that apply) Head/headaches

- ___ Leg(s)
- ___ Arm(s)
- ___ Neck
- ___ Shoulder(s)
- ___ Low back
- ___ Upper back
- ___ Other

If other: _____

[14b] If yes, in the last 30 days, how much did pain interfere with your life?

- ___ Not at all
- ___ Mildly
- ___ Moderately
- ___ Severely
- ___ Extremely

[14c] In what areas of your life are you having difficulties because of pain?

Comment:

[15] Since the time of your injury/injuries, are your overall symptoms:

Better Worse About the same

Other Information

Additional history of present illness, social history, functional history, patient goals, and other relevant information

COMMENT:

PROFESSIONAL CONCLUSION/ASSESSMENT

[16a] Psychiatric Symptoms

Yes Suspected/Probable No Not assessed

[16b] (Only if 16a is yes or suspected/probable) Symptoms of which disorders?

- Depression
- PTSD
- Anxiety disorder (other than PTSD)
- Alcohol abuse/dependence
- Drug abuse / dependence
- Psychotic disorder
- Other AXIS I disorder
- Somatoform disorder

[17] Have you ever had a spinal cord injury Yes No

Description:

[18] Have you ever had an amputation Yes No

Description:

Amputation Classification

- None
- Single hand
- Double hand
- Single upper extremity, above elbow
- Single upper extremity, below elbow
- Single lower extremity, above knee
- Single lower extremity, below knee
- Double lower extremity, above knee
- Double lower extremity, above/below knee
- Double lower extremity, below knee
- Upper extremity and lower extremity amputation

[19] Other significant medical conditions/problems

Yes No Not assessed

Comments:

[20a] Are the history of the injury and course of clinical symptoms consistent with a diagnosis of a TBI?

Yes No

[20b] In your clinical judgment the current clinical symptom presentation is most consistent with:

- Symptom resolution (patient is currently not reporting symptoms)
- A related Traumatic Brain Injury (TBI) residual problems
- Behavioral Health conditions (e.g., PTSD, depression, etc.)
- A combination of TBI and Behavioral Health condition(s)
- Other condition not related to TBI or Behavioral Health condition(s)

21. Are the history of injury and course of symptoms consistent with a diagnosis of Mild TBI, as defined by the American Congress of Rehabilitation Medicine (ACRM) (J Head Trauma Rehabil 1993;8(3):86-87)			
(1) any period of loss of consciousness (Q2)	LOC ≤ 30 mins LOC > 30 mins No LOC Unknown		
(2) any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or confused) (Q3)	YES	NO	Unknown
(3) any loss of memory for events immediately before or after the accident (post-traumatic amnesia (PTA) (Q4)	PTA ≤ 24 hrs PTA > 24 hrs No PTA Unknown		
(4) focal neurological deficit(s) that may or may not be transient (i.e., aphasia, dysarthria, vision/hearing problems, facial drooping, paralysis, loss of muscle control, paresthesia, numbness, tremor, neglect, poor gag reflex, etc.) (Q6)	YES	NO	Unknown
(5) after 30 minutes post injury, what was the initial Glasgow Coma Scale (GCS) rating (Q5)?	13-15 9-12 < 9 Unknown		
Meets Mild-TBI criteria (Defined by ACRM): a patient who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the above criteria but where severity does not exceed 30 minutes LOC, Glasgow Coma Scale <13 after 30 minutes post injury, or PTA not greater than 24 hours.	YES	NO	Unknown
Meets Moderate/Severe TBI criteria (Defined by ACRM): a patient who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the above criteria where severity exceeds 30 minutes LOC or PTA greater than 24 hours.	YES	NO	Unknown

SUPPORTING DATA: All figures and/or tables shall include legends and be clearly marked with figure/table numbers.

Data analyzed for DSMB Meeting (9/17/13)

Demographics of Randomized Participants, as of 9/17/14

Mean Age, years	56.7
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Gender	n	Percent
Male	22	100
Female	0	0
Total	22	100

Ethnicity	N	Percent
Latino/Hispanic	7	31.8
Non-Latino	15	68.2
Total	22	100.0

Race	n	Percent
Asian and Pacific Islander	0	0.0
Black/African American	5	22.7
Mixed	0	0.0
Native American	0	0.0
Other	4	18.2
White	13	59.1
Total	22	100.0

Time Line Follow Back: Baseline drinking (past 90 days) as of 9.17.14

Drinking Aggregate	Mean ± Standard Deviation (n=13)
Average Drinking Days per Week	5.5 ± 1.8
Average Heavy Drinking Days per Week	4.7 ± 2.3
Average Drinks [§] per Drinking Day	14.6 ± 11.1
Average Drinks [§] per Week	73.3 ± 62.0

-Data has not finished quality check

-Heavy Drinking Day (>4 standard alcoholic drinks for men, >3 alcoholic drinks for women)

[§] standard alcoholic drink defined as containing 13.6 g of pure alcohol

Total Adverse Events (Percent), as of 9.17.14***

Adverse Event Organ System and Dictionary Term (MedDRA) n=22	Baseline Adverse Events n (%)	Treatment Emergent Adverse Events n (%)
Neurologic		
Numbness/Tingling	14 (63.6)	7 (31.8)
Taste Alteration	12 (54.5)	11 (50.0)
Difficulty with	16 (72.7)	3 (13.6)
Concentration/Attention		
Difficulty with Memory	18 (81.8)	2 (9.1)
Slow Thinking	14 (63.6)	8 (36.4)
Confusion	10 (45.5)	5 (22.7)
Language Problems	11 (50.0)	5 (22.7)
Systemic***Data has been entered but not cleaned		
Fatigue	19 (86.4)	4 (18.2)
Loss of Appetite	13 (59.1)	8 (36.4)
Dizziness	15 (68.2)	8 (36.4)
Itching	12 (54.5)	5 (22.7)
Sleepiness	16 (72.7)	4 (18.2)
Psychiatric		
Nervousness	16 (72.7)	2 (9.1)
Depression	17 (77.3)	2 (9.1)
Suicidal Thoughts	2 (9.1)	1 (4.5)
Gastrointestinal		
Diarrhea	14 (63.6)	10 (45.5)
Ophthalmologic		
Abnormal Vision	11 (50.0)	9 (40.9)
Eye Pain	3 (13.6)	2 (9.1)

NOTE: Not all participants completed 12 weeks of study at time of analysis.

*****Data has been entered but not cleaned**

NOTE: Not all participants completed all 12 weeks of study at time of analysis.