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TITLE: A Controlled Trial of Topiramate Treatment for Alcohol Dependence in Veterans with PTSD

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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 both 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

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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 4 of this project covers the time period September 30, 2015 through September 29, 2016. As of September 29, 2016 we have met our overall Year 3 goals in terms of maintaining all regulatory approvals, hiring staff, and setting up the lab. Additionally, we have continued recruiting participants and administering study intervention since the 2nd quarter of Year 1. Because recruitment was our main focus in Year 4, we developed many novel recruitment strategies that we'll continue to hone and expand upon as we move into our one-year no-cost extension in Year 5. All tasks for Year 4 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				NCE - YR5			
		Q1	Q2	Q3	Q4	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 10/30/15, 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 as volunteers include: 2 Study Physicians, 1 Research Psychologist, 1 Nurse Practitioners, and 1 Data Programmer. We are also supporting a percent effort of our co-investigators. This past year we also brought on a new research volunteer and 6 PhD students/Research Practicum Trainees 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. Two thousand one hundred and seventy potential participants were referred to the study, either by self-referral or by medical/mental health practitioners. All prospective participants were pre-screened for the study; 157 were enrolled (signed informed consent form) and 85 randomly assigned to treatment with topiramate (top) or placebo (PLA). The cohort is mostly male (n=77, 91%) and predominantly Caucasian (n=35, 41%). The planned rate of recruitment was 1 participant per week or 4 participants per month; however, in order to complete recruitment by the end of the no-cost extension, we will need to randomize 5-6 participants per month over the next 12 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 85 participants randomized, 16 (18%) participants dropped out, 12 (13%) participants were withdrawn, and 6 (7%) participants were lost to follow-up. At the time of the report, 3 (3%) participants are active. Forty-eight (53%) participants completed the study (as defined by attending the Week 12 visit). Of all participants 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 trail
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.

None at this time.

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

PRESENTED ABSTRACTS RELATED TO THIS PROJECT:

Hoyman, L. C., Pennington, D. L., Wong, T., Dack, J., Bielenberg, J., Tomlinson, E., Lasher, B., Schrodek, E., Yohannes, S., McDonald, J., & Batki, S. L. (2016, February). Preliminary effects of heavy drinking and age on cognitive functioning in veterans with posttraumatic stress disorder. Poster presented at the International Neuropsychological Society, Boston, MA.

S.L. Batki, D. L. Pennington, B. Lasher, S. Yohannes, J. McDonald, A. Kinzler, J. Bielenberg, J. Dack, E. Tomlinson, L. Hoyman, E. Herbst, T. Wong. (2016, June) Topiramate treatment for alcohol use disorder in veterans with mild traumatic brain injury: Preliminary results of a pilot controlled clinical trial. Poster to be presented at the Research Society on Alcoholism, New Orleans, LA.

D.L. Pennington, E.S. Tomlinson, B. Lasher, S. Yohannes, T. Wong, J. McDonald, J. Dack, J. Bielenberg, L.C. Hoyman, A. Kinzler, E. Herbst, S.L. Batki. (2016, June) Associations of PTSD, AUD, and TBI severity in cognitive function in veterans entering controlled trials of topiramate treatment. Poster to be presented at the Research Society on Alcoholism, New Orleans, LA.

McDonald, J., Yohannes, S., Pennington, D.L., Lasher, B., Yohannes, S., Wong, T., Dack, J., Bielenberg, J., Hoyman, L. C., Tomlinson, E.S., Kinzler, A., Gibbons, J., Batki, S.L. (2016, June) An examination of medical comorbidities and cigarette use among veterans with alcohol use disorder and comorbid PTSD. Poster to be presented at the Research Society on Alcoholism, New Orleans, LA.

Yohannes, S., Pennington, D.L., Lasher, B., Wong, T., McDonald, J., Dack, J., Bielenberg, J., Hoyman, L. C., Tomlinson, E.S., Kinzler, A., Gibbons, J., Batki, S.L. (2016, June) Education predicts attendance and retention in a randomized trial of topiramate treatment for veterans with AUD and PTSD. Poster to be presented at the Research Society on Alcoholism, New Orleans, LA.

A. Kinzler, D. L. Pennington, B. Lasher, S. Yohannes, J. McDonald, T. Wong, J. Bielenberg, J. Dack, E. Tomlinson, L. Hoyman, E. Herbst, S.L. Batki (2016, June) Absorption subtype of distress tolerance predicts drinking behavior in veterans with AUD and PTSD. Poster to be presented at the Research Society on Alcoholism, New Orleans, LA.

J. Dack, D. L. Pennington, T. Wong, J. Bielenberg, L. Hoyman, E. Tomlinson, B.A. Lasher, S. Yohannes, J. McDonald, A. Kinzler and S. L. Batki. (2016, August).Relationships between Risk-Taking Behavior, Emotion Regulation, and Distress Tolerance in Veterans with Comorbid Posttraumatic Stress Disorder and Alcohol Use Disorder. Poster to be presented at the American Psychological Association, Denver, CO.

A. Kinzler, D. L. Pennington, B. Lasher, S. Yohannes, J. McDonald, T. Wong, J. Bielenberg, J. Dack, E. Tomlinson, L. Hoyman, E. Herbst, S.L. Batki. (2106, October) Emotion Dysregulation Subtypes and Alcohol Use in Veterans with PTSD. Poster to be presented at the Association for Behavioral and Cognitive Therapies, New York, NY.

E. Tomlinson, D. Pennington, T. Wong, J. Dack, J. Bielenberg, L. Hoyman, B. Lasher, A. Kinzler, S. Batki. (2016, October) Insomnia and heavy alcohol use synergistically impact cognitive function in veterans with PTSD. Poster submitted for presentation at the National Academy of Neuropsychology, Seattle, WA.

PEER-REVIEWED PUBLICATION:

Heinz, A., Pennington, D.L., Cohen, N., Schmeling. B., Lasher, B., Schrodek, E., Hong, E., Batki, S. (2016) Relations Between Cognitive Functioning and Alcohol Use, Craving, and Post-Traumatic Stress: An Examination Among Trauma-Exposed Military Veterans With Alcohol Use Disorder. Military Medicine, 181(7):663-71, PMID: 27391620

PRESENTATION AT MOMRP SUSBSTANCE ABUSE IPR IN FT. DETRICK, MD:

Presented overview & progress of study and pilot [W81XWH-05-2-0094] study data.

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.

PRELIMINARY EFFECTS OF HEAVY DRINKING AND AGE ON COGNITIVE FUNCTIONING IN VETERANS WITH POSTTRAUMATIC STRESS DISORDER

Hoyman, L. C., Pennington, D. L., Wong, T., Dack, J., Bielenberg, J., Tomlinson, E., Lasher, B., Schrodek, E., Yohannes, S., McDonald, J., & Batki, S. L.

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

OBJECTIVES: Heavy alcohol use and age are known to have a synergistic impact on cognitive functioning beyond normal aging effects. We sought to examine age and heavy drinking effects on cognitive functioning in 52 veterans with PTSD entering a RCT of topiramate treatment.

METHODS: Veterans completed measures of cognitive reserve, processing speed, mental flexibility, working memory, cognitive inhibition, verbal fluency, auditory-verbal learning and recall, decision-making, risk-taking, and choice inhibition. Average standard drinks per week (DPW) were calculated during the 90 days prior to cognitive testing. A four-step hierarchical regression model (HRM) was conducted for each cognitive domain. The following independent variables were entered at each step: 1) cognitive reserve; 2) DPW; 3) age; and 4) an interaction term of age-by-DPW. Cognitive reserve was trimmed from the HRMs when it was not significantly associated with cognition.

RESULTS: The HRMs containing the age-by-DPW interaction term significant predicted performance on working memory [$F(4,44) = 5.53$, $p<.01$, $R^2=.27$], auditory-verbal learning and recall [$F(4,46) = 3.93$, $p<.01$, $R^2=.19$; $F(4,46) = 2.96$, $p<.04$, $R^2=.12$, respectively], and tended to predict choice impulsivity [$F(4,41) = 2.28$, $p=.08$, $R^2 =.10$]. Whereas, only step 2 of the HRM containing DPW significantly predicted verbal fluency [$F(2,48) = 4.04$, $p<.02$, $R^2=.11$]. Multiple correlations were observed between cognitive reserve, age, DPW, and the various cognitive domains.

CONCLUSIONS: Evidence suggests age and heavy alcohol use has a negative synergistic impact on working memory, auditory verbal learning and recall, and choice impulsivity. These domains may be potential targets in developing cognitive training paradigms for aging veterans with PTSD entering alcohol treatment. Clinicians are encouraged to consider a standard assessment of cognitive functioning in treatment planning and delivery for heavy drinking veterans with PTSD.

TOPIRAMATE TREATMENT FOR ALCOHOL USE DISORDER IN VETERANS WITH MILD TRAUMATIC BRAIN INJURY: PRELIMINARY RESULTS OF A PILOT CONTROLLED CLINICAL TRIAL

S.L. Batki, D. L. Pennington, B. Lasher, S. Yohannes, J. McDonald, A. Kinzler, J. Bielenberg, J. Dack, E. Tomlinson, L. Hoyman, E. Herbst, T. Wong.

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

BACKGROUND AND PURPOSE: Mild traumatic brain injury (mTBI) is highly prevalent among veterans of the Iraq and Afghanistan conflicts. mTBI is also strongly associated with alcohol use disorder (AUD). Post mTBI diagnoses of AUD are common, and military personnel with mTBI are at increased risk for AUD compared with similarly injured non-mTBI personnel. The authors conducted a pilot controlled trial of topiramate (TOP) or placebo (PLA) to 1. obtain a preliminary assessment of TOP efficacy in reducing alcohol use in veterans with mTBI and co-occurring AUD; 2. obtain preliminary assessment of TOP efficacy in reducing mTBI symptoms; 3. assess the feasibility/safety/tolerability of TOP in patients with AUD and mTBI; and 4. explore the effects of topiramate on impulsivity and cognitive functioning.

METHODS: The study enrolled 32 veterans with mTBI and AUD. 2 (6.3%) were female. Mean age was 47 years; 12 (38%) were African-American, 12 (38%) were Caucasian, 8 (25%) ,were mixed race or other. 15 (47%) had combat exposure. 75% had more than 1 TBI. 56% had co-occurring PTSD. Mean Neurobehavioral Symptom Inventory (NSI) total severity score was 1.88. Participants underwent a 12-week trial of flexible-dose TOP or PLA, up to 300 mg/day plus weekly medical management counseling and a Week 16 follow-up.

RESULTS: 27 (84%) completed the study. Medication was generally well-tolerated; there was a trend for more TOP than PLA participants to experience sedation and vision abnormalities. Amount and frequency of alcohol use was reduced in both TOP and PLA groups over the 12-week trial; but there were no between-group differences. NSI symptom severity also reduced in both TOP and PLA groups over the 12-week trial, without differences between groups. Processing Speed improved in both groups over the 12-week trial. There was a trend toward reduced Auditory Verbal Recall and Verbal Fluency in the TOP group. Following the completion of the 12-week trial and discontinuation of TOP and PLA, participants were brought back for a Week 16 follow-up. At Week 16, several measures of alcohol use increased in the group formerly receiving PLA, while no such increase was seen in the group that had received TOP. Similarly, NSI Affective Symptoms increased from Week 12 to Week 16 in the PLA group but not in the TOP group.

CONCLUSIONS: Veterans with mTBI and AUD can be successfully recruited into a treatment trial employing pharmacotherapy and counseling. Significant improvement occurred in both the TOP and PLA groups over 12 weeks of treatment in alcohol use and NSI symptoms, raising the possibility that any medication effects were washed out by counseling, placebo effect, and other nonspecific effects. At Week 16 followup, improvement persisted in the TOP group, but was significantly reduced in the placebo group in some measures of alcohol use and NSI symptoms, suggesting some possible benefit for TOP. However, the TOP group experienced cognitive impairment in the form of verbal recall and fluency while on study medication, raising concerns regarding the use of TOP in veterans with AUD and mTBI. These results are preliminary and should be interpreted with caution.

ASSOCIATIONS OF PTSD, AUD AND TBI SEVERITY IN COGNITIVE FUNCTION IN VETERANS ENTERING CONTROLLED TRIALS OF TOPIRAMATE TREATMENT

D.L. Pennington, E.S. Tomlinson, B. Lasher, S. Yohannes, T. Wong, J. McDonald, J. Dack, J. Bielenberg, L.C. Hoyman, A. Kinzler, E. Herbst, S.L. Batki.

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

PURPOSE: Posttraumatic stress disorder (PTSD), alcohol use disorder (AUD), and mild traumatic brain injury (mTBI) are common and frequently co-occur among military veterans. However, there are few studies investigating how the severity of each co-occurring disorder affects cognitive function. We sought to examine these relationships and to determine if time since traumatic brain injury mitigates cognitive function in a group of veterans entering two randomized controlled trials of topiramate treatment.

METHODS: Upon screening into two RCT's of topiramate treatment, 43 (2 female) veterans with AUD (SCID DSM-IV), PTSD (Clinical Administered PTSD Scale: CAPS) and mTBI (American Congress of Rehabilitation Medicine) were assessed for baseline PTSD severity, average standard drinks per week consumed in the 90 days prior to screening (Timeline Followback), and total number of traumatic brain injuries. Veterans were also assessed on domains of cognition including processing speed, working memory, auditory-verbal learning and recall, verbal fluency, mental flexibility, cognitive inhibition, response inhibition, choice inhibition, risk-taking, and decision making. Multiple 3-step, hierarchical regression models were conducted to determine the extent to which number of brain injuries, PTSD and AUD symptom severity, and time since last brain injury accounted for variance in cognition. In each model, we accounted for estimated pre-morbid verbal IQ (Wechsler Test of Adult Reading) by entering it at Step 1. CAPS total score, average drinks per week, and brain injury count were entered at Step 2, and time since last brain injury at Step 3. Variables were trimmed from the model when not significantly related to the dependent variable.

RESULTS: Average drinks per week was a reliable predictor ($B=.34$, $t(39)=2.06$, $p=.05$), while CAPS total score tended to predict ($B=-.32$, $t(39)=-1.91$, $p=.06$) processing speed. Together they tended to account for 9% of the variance in processing speed ($R2=.09$, $F(2, 37)=2.89$, $p=.07$). Average drinks per week and brain injury count were reliable predictors ($B=-.31$, $t(39)=-2.20$, $p=.04$; $B=.28$, $t(57)=2.10$, $p=.04$), accounting for 25% of the variance in auditory verbal learning ($R2=.25$, $F(2, 36)=5.27$, $p<.01$). Years since last brain injury was a reliable predictor ($B=.42$, $t(39)=2.89$, $p<.01$) and accounted for 16% of the variance in verbal fluency ($R2=.16$, $F(1, 38)=8.34$, $p<.01$). Years since last brain injury also tended to predict ($B=-.27$, $t(35)=-1.65$, $p=.11$) and account for 6% of the variance in decision-making ($R2=.06$, $F(1, 34)=2.73$, $p=.11$). Average drinks per week was correlated with auditory verbal learning ($p=.01$, $r=-.35$). Years since last brain injury was correlated with verbal fluency ($p<.01$, $r=.42$).

CONCLUSION: Results provide evidence showing alcohol use, number of brain injuries and amount of recovery time since brain injury affect different and overlapping domains of cognition. Alcohol use in the 90 days prior to screening affected processing speed and auditory-verbal learning. Number of traumatic brain injuries were also related to auditory-verbal learning. Additionally, longer recovery from traumatic brain injury was related to better performance in verbal fluency. These relationships are particularly important regarding topiramate treatment trials in veterans with AUD, PTSD and TBI because topiramate has been shown to negatively affect auditory-verbal recall and verbal fluency. Longitudinal studies of topiramate treatment in this comorbid veteran population will need to investigate alcohol use, TBI severity and cognitive function as moderators of treatment outcome.

AN EXAMINATION OF MEDICAL COMORBIDITIES AND CIGARETTE USE AMONG VETERANS WITH ALCOHOL USE DISORDER AND COMORBID PTSD

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PURPOSE: Cigarette smoking may exacerbate the prevalence and severity of medical comorbidities frequently observed in veterans with alcohol use disorder (AUD) and posttraumatic stress disorder (PTSD). We sought to examine the prevalence of medical comorbidities among smoking and non-smoking veterans entering a RCT of topiramate treatment for AUD and PTSD.

METHODS: Twenty-five (1 female) non-smoking and 42 smoking (2 female) veterans completed measures assessing PTSD symptoms (CAPS), cigarette and alcohol use (Timeline Follow Back) in the 90 days prior to screening. Veterans also completed a baseline medical evaluation of body systems and specific diagnoses commonly associated with cigarette and alcohol use. We compared rates of reported medical diagnoses using Fisher's exact test. We also compared groups on PTSD symptoms, average standard alcohol drinks consumed per week and average heavy drinking days per week using univariate analysis of covariance. Correlations were examined among these baseline characteristics.

RESULTS: Smokers compared to non-smokers reported a significantly higher rate of gastrointestinal diagnoses ($p=.05$; 33% vs. 12%) and tended to report a higher rate of cardiovascular diagnoses ($p=.07$; 50% vs. 28%). In assessing specific diagnosis commonly associated with cigarette and alcohol use, smokers compared to non-smokers had significantly higher rates of hypertension ($p=0.05$; 43% and 20%) and hyperlipedmia ($p=0.03$; 17% and 0%) and tended to report higher rates of diabetes ($p=0.09$; 12% vs. 0%). Smokers also reported significantly more drinks per week ($p<.01$; 45 vs. 27) and more heavy drinking days per week ($p<.01$; 4.6 vs 3.2) than non-smokers. Among smokers, average cigarettes smoked per day was positively associated with diastolic blood pressure ($p<.01$, $r=.41$) and CAPS total score was positively associated with average drinks per week ($p<.01$, $r=.59$) and average heavy drinking days per week ($p<.01$, $r=.40$). Similar associations were not observed in the non-smoking group.

DISCUSSION: Our findings suggest that veterans with PTSD and AUD who also smoke cigarettes are at higher risk for hypertension, hyperlipidemia, and gastrointestinal related medical diagnoses than non-smokers. Change in rates of medical comorbidities in relation to change in cigarette and alcohol use should be examined in longitudinal studies. At the least, our preliminary evidence lends support for the consideration of simultaneous treatment for both alcohol and cigarette cessation.

EDUCATION PREDICTS ATTENDANCE AND RETENTION IN RANDOMIZED TRIAL OF TOPIRAMATE TREATMENT FOR VETERANS WITH AUD AND PTSD

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PURPOSE: Retention of participants is critical to the success of research studies, but specific causes for attrition are rarely discussed in the literature. Socioeconomic advantage, posttraumatic stress disorder (PTSD), alcohol use severity, and involvement in concurrent treatment can affect a patient's ability to stay engaged in a new treatment program. We sought to test how these variables affect attendance and retention in a double-blind, placebo controlled study of topiramate treatment for veterans with alcohol use disorder (AUD) and PTSD.

METHODS: Upon entry into a randomized clinical trial of topiramate treatment, 57 (3 female) veterans with AUD (SCID DSM-IV) and PTSD were assessed for baseline PTSD severity (Clinical Administered PTSD Scale) and average standard drinks per week consumed in the 90 days prior to screening (Timeline Followback). Participants also reported total years of education as a proxy of socioeconomic advantage and their acuity of involvement in other AUD treatment programs (none, outpatient, or residential). Two, 3-step, hierarchical regression models were conducted to determine the extent to which education, PTSD and AUD symptom severity, and treatment acuity explain variance in total visits attended and total duration of weeks spent in our 12-week study. In each model, years of education was entered at Step 1, CAPS total score and average drinks per week at Step 2, and treatment acuity at Step 3.

RESULTS: Education was a reliable predictor (B=.28, t(57)=2.10, p=.04) and average drinks per week tended to predict (B=.27, t(57)=1.96, p=.06) total visit attendance. Step 2 of our model tended to account for 7% of the variance in total visit attendance (R2=.07, F(2, 54)=2.50, p=.07). In model 2 assessing the duration of study attendance, education was a reliable predictor (B=.31, t(57)=2.38, p=.02) and average drinks per week and CAPS total score tended to predict the total duration of weeks spent in the study (B=.27, t(57)=1.90, p=.06; B=-.25, t(57)=-1.75, p=.09). Step 2 of our model tended to account for 9% of the variance in total duration of weeks spent in the study (R2=.09, F(2, 53)=2.89, p=.04). Adding treatment acuity at Step 3 did not account for any additional variance in either model. Zero-order correlations revealed that total visit attendance was correlated with education (p=.04, r=.23) and tended to be correlated with average drinks per week (p=.06, r=.20). Additionally, duration of weeks spent in study was correlated with education (p=.02, r=.25) and tended to correlated with average drinks per week (p=.06, r=.16) and CAPS total score (p=.09, r=-.07).

DISCUSSION: In a RCT of topiramate treatment for veterans with AUD and PTSD, less education was associated with poorer visit attendance and shorter duration of engagement in the study. Increased alcohol use may also be related to greater study attendance and retention, whereas greater PTSD severity may be related to poorer study retention. Surprisingly, engagement in concomitant treatment regimens was not related to study attendance or retention. In sum, education as a proxy of socioeconomic advantage may be an important factor when evaluating retention and attrition in clinical trials of topiramate treatment for AUD and PTSD.

ABSORPTION SUBTYPE OF DISTRESS TOLERANCE PREDICTS DRINKING BEHAVIOR IN VETERANS WITH AUD AND PTSD

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PURPOSE: Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) frequently co-occur, resulting in poorer medical outcomes, higher rates of hospitalization, and more impaired psychosocial functioning than either PTSD or AUD alone. Distress tolerance is associated with both PTSD and AUD, yet there is a dearth of research investigating distress tolerance in a comorbid PTSD and AUD population. The current research utilizes the DTS and its subscales in an effort shed light on possible underlying mechanisms related to both AUD and PTSD symptom severity in this dually-diagnosed veteran population.

METHODS: We assessed 67 veterans (5 female) with AUD and PTSD entering an RCT of topiramate treatment at the San Francisco Veterans Affairs Medical Center. Upon enrollment in the RCT, participants completed an assessment of PTSD symptom severity (Posttraumatic Stress Disorder Checklist: PCL), perceived distress tolerance (Distress Tolerance Scale: DTS), and reported their amount and frequency of alcohol use over the 90 days prior to consenting to participate (Timeline Followback: TLFB). Multiple, 2-step, hierarchical regression models were conducted to determine the extent to which DTS total scores and subdomains (absorption, tolerance, appraisal, regulation) explained the variance in PTSD symptoms (PCL Total Score and subdomains) and alcohol use (drinks per week and heavy drinking days per week). Participants age, race, and education were entered at step 1 and DTS total and subdomains at step 2 of each model. Demographics were trimmed from the model if they were not associated with the dependent variables.

RESULTS: DTS Absorption was demonstrated to be a reliable predictor (B=-.46, t(67)=-2.54, p=.01), and explained 16.5% of the variance in drinks per week (R2=.165, F(2, 63)=5.36, p<.01). DTS Total and DTS Absorption tended to be reliable predictors (B=-.20, t(67)=-1.66, p=.10; B=-.23, t(67)=-1.96, p=.07), accounting for 3% and 4% of the variance in PCL Avoidance (R2=.03, F(1, 65)=2.74, p=.10; (R2=.04, F(1, 65)=3.45, p=.07, respectively). DTS Absorption was significantly correlated with PCL Avoidance (r^2 =-0.22, p<0.05) and tended to be correlated with average drinks per week (r^2 = -.19, p=.06). DTS Total tended to be correlated with PCL Avoidance (r^2 = -.20, p=0.051).

CONCLUSION: Absorption is defined as the extent to which one's attentional resources are focused on- absorbed by- distress. In our sample, absorption was the only reliable predictor (of the subscales and including the total DTS score) of drinking behavior. Poorer scores on the domain of absorption were related to higher PTSD avoidance symptoms and more drinks per week. One theory explaining the common co-occurrence of PTSD and AUD highlights the negatively-reinforcing nature of alcohol use in dampening the intensity of PTSD symptoms. The results of the current study add support that DTS absorption may be one potential mechanism by which veterans with PTSD are more prone to turn to alcohol use as an emotion regulation behavior. Helping patients with PTSD and AUD cultivate an ability to pay attention to more than one emotion or idea (increase DTS absorption) when experiencing distress may result in improved PTSD and AUD symptomology. Longitudinal study on DTS absorption as a mechanism of change in this co-morbid population of veterans with PTSD and AUD is warranted.

RELATIONSHIPS BETWEEN RISK-TAKING BEHAVIOR, EMOTION REGULATION, AND DISTRESS TOLERANCE IN VETERANS WITH COMORBID POSTTRAUMATIC STRESS DISORDER AND ALCOHOL USE DISORDER

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A Statement of the Problem: It is common for individuals with posttraumatic stress disorder (PTSD) to experience emotion dysregulation and difficulty tolerating distress. PTSD symptoms, emotional dysregulation and poor distress tolerance are all linked to increased risk-taking behavior (i.e. reckless driving, sexual behavior, and substance use). This study examines the associations between PTSD symptom severity, emotion regulation, distress tolerance and self-reported risk-taking propensity within a veteran population.

Subjects Used: We assessed 67 veterans (5 female) with alcohol use disorder (AUD) and PTSD entering a RCT of topiramate treatment at the San Francisco Veterans Affairs Medical Center.

Procedure: Upon entering the RCT, participants were assessed on PTSD symptom severity (PTSD Checklist for DSM-IV: PCL), emotion dysregulation (Difficulties in Emotion Regulation Scale: DERS), distress tolerance (Distress Tolerance Scale: DTS), and risky behavior (Evaluation of Risk Scale: EVAR). Veterans also reported the number of standard alcoholic drinks consumed per week in the 90 days prior to assessment (Timeline Follow Back method). Three-step hierarchical multiple regression (HMR) models were conducted with the EVAR subdomains and average drinks per week in the past 90 days as the dependent variables. PCL total score was entered at the first step of the model, DERS total score at step 2, and average DTS score at step 3.

Results: The HMR for the EVAR subdomain of Self-Confidence at study entry revealed that PCL total score significantly accounted for 7% of the variance at step 1, $F(1, 65) = 4.87$, $p=.03$. Introducing DERS total score significantly explained an additional 5% of the variance at step 2, $F(1, 64) = 4.49$, $p=.05$. Adding DTS score at step 3 did not significantly explain any additional variance of EVAR Self-Confidence. EVAR Self-Confidence was significantly correlated with PCL total score, $r(65)=-.26$, $p=.02$, and DTS total score, $r(65)=-.32$, $p<.01$. DERS total score was significantly correlated with PCL total score $r(65)=.43$, $p<.01$, and DTS total score $r(65)=-.40$, $p<.01$. The HMR for average drinks per week in the past 90 days showed that PCL total score significantly accounted for 6% of the variance at step 1, $F(1, 65) = 3.91$, $p=.05$. Adding DERS and DTS scores at steps 2 and 3 did not significantly explain any additional variance. PCL total score was significantly correlated with average drinks per week, $r(65)=.24$, $p=.03$.

Conclusions: PTSD symptom severity and difficulty in emotion regulation, but not distress tolerance was related to risk taking propensity. Less distress tolerance and greater PTSD severity was associated with greater difficulty in emotion regulation. Only PTSD symptom severity was related to drinking amount in the 90 days prior to assessment. Interventions that aim towards treating emotion regulation may be useful in decreasing risk-taking propensity in veterans with PTSD and AUD. Longitudinal study of the interplay of emotion regulation, PTSD and AUD symptoms is warranted in veterans.

EMOTION DYSREGULATION SUBTYPES AND ALCOHOL USE IN VETERANS WITH PTSD

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PURPOSE: Posttraumatic stress disorder and alcohol use disorder frequently co-occur, and this comorbidity can be particularly clinically harmful, as each disorder can magnify the detrimental effects of the other. Research has shown that emotion dysregulation may explain some of the variance of posttraumatic symptom severity, yet no study has attempted to investigate difficulties in emotion regulation as a potential moderator of alcohol use behavior in a comorbid AUD and PTSD sample. This study attempts to do just that, while considering individual subtypes of emotion dysregulation as predictors of alcohol use behavior.

METHODS: We assessed 67 veterans with AUD and PTSD entering an RCT of topiramate treatment at the San Francisco Veterans Affairs Medical Center. Upon enrollment in the RCT, participants completed the Difficulties in Emotion Regulation Scale (DERS), a well-validated self-report measure for assessing emotion regulation problems, and reported amount and frequency of alcohol use over the 90 days prior to study entry using the Timeline Followback. Multiple, 2-step, hierarchical regression models were conducted to determine the extent to which DERS total scores and each subscale (Nonacceptance, Goals, Impulse, Aware, Strategies, and Clarity) explained the variance in alcohol use. Participants' age, race, and education were entered at step 1 and DERS total and subscales at step 2 of each model. Demographics were trimmed from the model if they were not associated with the dependent variables.

RESULTS: DERS Strategies was demonstrated to be a reliable predictor ($B=.24$, $t(67)=2.10$, $p<.05$) and explained 15% of the variance ($R2=.15$, $F(1, 64)=6.93$, $p<.05$) in average drinks per week. DERS Impulse tended to be a predictor ($B=.20$, $t(67)=1.78$, $p=.08$) and accounted for 14% of the variance ($R2=.14$, $F(1, 64)=6.24$, $p=.08$) in average drinks per week. Total DERS tended to be a predictor ($B=.20$, $t(67)=1.72$, $p=.09$) and accounted for 13% of the variance ($R2=.13$, $F(1, 62)=6.11$, $p=.09$) in average drinks per week.

DERS Strategies was found to be a reliable predictor ($B=.24$, $t(67)=2.07$, $p<.05$) and accounted for 9% of the variance ($R2=.09$, $F(1, 64)=4.20$, $p<.05$) in average heavy drinking days per week. Neither total DERS nor DERS Impulse were found to be predictors of average heavy drinking days per week.

CONCLUSION: These results, showing the Strategies subscale as the most reliable predictor of drinking behavior in our sample, give support to the theory that patients with PTSD who engage in harmful and hazardous use of alcohol may do so in part because they lack alternate coping strategies. A review of the items that make up the DERS Strategies subscale reveals a theme of perceived longevity of one's unwanted emotions (e.g. "When I'm upset, I believe I will remain that way for a long time"). These findings may support the utility of research to design a clinical intervention for co-occurring AUD and PTSD that emphasizes the impermanent nature of strong emotions. More inquiry into the influence of emotion dysregulation on harmful and hazardous drinking within a PTSD population is warranted.

INSOMNIA AND HEAVY ALCOHOL USE SYNERGISTICALLY IMPACT COGNITIVE FUNCTION IN VETERANS WITH PTSD

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OBJECTIVE: Insomnia and heavy alcohol use are common in Veterans with PTSD, and associated with cognitive impairment. However, the interactive effects of insomnia and heavy alcohol use on cognitive function in Veterans with PTSD have not been previously reported.

METHOD: We assessed baseline insomnia (Insomnia Severity Index), amount of alcohol use (standard drinks per week [DPW]), and frequency of heavy drinking days (HDD) in 63 heavy drinking Veterans with PTSD enrolling in a RCT of topiramate treatment. We used random-intercept linear mixed models to investigate the interaction of insomnia and alcohol use on the following cognitive domains: processing speed, working memory, auditory-verbal learning and recall, cognitive flexibility, response inhibition, motor inhibition, choice inhibition, risk-taking, and decision-making.

RESULTS: Significant HDD-by-insomnia ($F(1,22)=4.32$, $p=0.05$) and DPW-by-insomnia ($F(1,57)=5.88$, $p=0.02$) interactions were observed for processing speed and a DPW-by-insomnia interaction for auditory-verbal recall ($F(1,58)=7.35$, $p<0.01$). Additionally, results showed significant main effects of insomnia on response inhibition (p=0.05) and insomnia, DPW and HHD on motor inhibition (all p<0.01). DPW was significantly correlated with processing speed ($r^2=-.24$, p=.05) and motor inhibition ($r^2=-.312$, p=.05).

CONCLUSIONS: Findings suggest that insomnia interacts with amount and frequency of heavy alcohol use to synergistically negatively impact processing speed and recall. Interventions that address both sleep disturbance and alcohol use may be beneficial for improving cognitive function in heavy drinking Veterans with PTSD. Improved cognitive function may, in turn, moderate alcohol treatment efficacy. Future studies investigating the potential moderating effects of sleep, alcohol use, and cognition on alcohol use disorder and PTSD treatment are warranted.

Relations Between Cognitive Functioning and Alcohol Use, Craving, and Post-Traumatic Stress: An Examination Among Trauma-Exposed Military Veterans With Alcohol Use Disorder

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ABSTRACT Cognitive dysfunction is commonly observed among individuals with alcohol use disorder (AUD) and trauma exposure and is, in turn, associated with worse clinical outcomes. Accordingly, disruptions in cognitive functioning may be conceptualized as a trans-disease phenomenon representing a potential high-yield target for intervention. Less is known though about how different cognitive functions covary with alcohol use, craving, and post-traumatic stress symptom severity among trauma-exposed individuals with AUD. Sixty-eight male and female trauma-exposed military veterans with AUD, entering treatment trials to reduce alcohol use, completed measures assessing alcohol use and craving, post-traumatic stress symptom severity, and cognitive functioning. In multivariate models, after controlling for post-traumatic stress symptom severity, poorer learning and memory was associated with higher alcohol consumption and higher risk taking/impulsivity was associated with stronger preoccupations with alcohol and compulsions to drink. Alcohol consumption and craving, but not performance on cognitive tests, were positively associated with post-traumatic stress symptom severity. Findings suggest that interventions to strengthen cognitive functioning might be used as a preparatory step to augment treatments for AUD. Clinicians are encouraged to consider a standard assessment of cognitive functioning, in addition to post-traumatic stress symptom severity, in treatment planning and delivery for this vulnerable and high-risk population.

INTRODUCTION

Problematic alcohol use is common among patients exposed to traumatic events,[1] and alcohol use disorder (AUD) is the most prevalent and costly substance use disorder among military veterans.[2,3] In civilians, 8 to 20% of those exposed to trauma will go on to develop post-traumatic stress disorder (PTSD)[4–6] and among military veterans, trauma exposure is dramatically elevated with rates as high as 87% in a recent large national study.[7] Importantly, compared to AUD alone, those with co-occurring post-traumatic stress symptoms experience worse occupational, psychosocial, and health outcomes; lower reported quality of life; increased interpersonal problems; higher rates of hospitalization and service utilization; and increased risk of suicide and mortality.[8–11] Unfortunately, despite availability of empirically supported treatments for co-occurring AUD and post-traumatic stress,[12,13] rates of relapse and nonresponse indicate an urgent need to identify risk factors that will better inform interventions for this growing and highly vulnerable population.[14,15]

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In order to advance AUD treatment research and clinical practice for trauma-exposed individuals, it is critical to obtain greater knowledge of the common factors that may be associated with symptom presentation on treatment entry. There is compelling evidence to suggest that neurocognitive dysfunction is one such factor that may represent a high-yield, trans-disease target for intervention. However, at present, there is a dearth of research available to help profile how cognitive functions are associated with symptoms resulting from AUD and trauma exposure. This knowledge gap is unfortunate because higher levels of clinical severity on treatment entry (i.e., alcohol use, craving, post-traumatic stress symptom severity), significantly increase risk for reduced AUD treatment success.[16–19]

Neurocognitive Functioning, AUD, and Post-Traumatic Stress

Trauma exposure has been prospectively associated with changes in neuropsychological functioning[20] and the neuropsychological sequelae of AUD and PTSD psychopathology include deficits in basic attention, processing speed, learning, memory, and executive functioning.[21–27] Executive functions are higher order cognitive skills that are involved in the planning, initiation, and regulation of goal-directed behavior.[28,29] A wealth of research demonstrates that individuals with either AUD or post-traumatic stress have cognitive impairments compared to healthy controls. For instance, an estimated 50 to 70% of persons diagnosed with an AUD demonstrate some degree of neurocognitive deficit.[22] In a comprehensive meta-analysis of studies examining cognitive dysfunction among

individuals with AUD, the domains of speed of processing, problem solving/executive functions, inhibition/impulsivity, verbal learning, and verbal memory were found to be moderately impaired after 2 to 12 months of abstinence.[27] Reviews and meta-analyses indicate that compared to controls, those with post-traumatic stress tend to demonstrate reduced auditory attention and working memory, selective and sustained attention, inhibitory functions, and cognitive flexibility/rapid attention switching.[21,24,26,30–32] Of particular importance, such cognitive deficits are linked with poorer treatment outcomes and lower retention.[33–41]

Impulsive and risky behavior, a clinical profile of suboptimal decision making commonly observed in both AUD and trauma-exposed populations,[42,43] is considered a manifestation of poor executive control.[44,45] This is because deficits in "supervisory" executive control make it difficult to combat the automatic habit responses unleashed by the reward-seeking system (e.g., by employing positive coping strategies).[46] Indeed, individuals with AUD are more inclined to respond automatically and struggle to problem solve, learn from reward prediction errors, and consider the long-term consequences of an action[47–51] and similar patterns are observed among individuals with post-traumatic stress.[52–54]

Although cognitive dysfunction has been well-documented in uni-morbid AUD and trauma-exposed populations,[21,22,26] little research has described and examined how these functions are associated with indices of clinical severity among individuals with both AUD and trauma exposure. Given the established associations between cognitive dysfunction and poor treatment outcomes coupled with the cognitive demands made of patients during the treatment process, it is critical to better characterize relations between cognitive functioning and clinical severity outcomes on treatment entry. The objective of this study is to examine associations among key measures of cognitive functioning (processing speed, executive functioning, risk taking/impulsivity, verbal learning, and memory) and indices of clinical severity (post-traumatic stress symptom, quantity and frequency of alcohol use, and craving) among a sample of trauma-exposed military veterans with AUD entering pharmacotherapy treatment trials for AUD.[55–58] Several hypotheses were advanced to address study objectives. First, after accounting for post-traumatic stress symptom severity, we expect that lower processing speed, executive functioning, and verbal learning and memory, and higher risk taking/impulsivity will be positively associated with quantity and frequency of drinking and craving for alcohol. Second, after accounting for alcohol consumption and craving, we expect a similar pattern of relations to emerge between cognitive domains and post-traumatic stress symptom severity.

METHODS

Participants

Participants were 68 U.S. military veterans (mean age = 49.74, standard deviation [SD] = 12.93; 90% male; 57% Caucasian, 24% African American, 12% mixed race, 3% Asian, 4% other; 21% identified ethnicity as Hispanic/Latino) who were drawn from three different randomized controlled trials of topiramate treatment for AUD. Participants were included in these studies if they met Diagnostic and Statistical Manual of Mental Disorders IV-TR (DSM-IV) criteria[59] for current AUD as assessed by the Structured Clinical Interview for DSM-IV.[60] All participants also reported "at-risk" or "heavy" drinking in accordance with National Institutes of Health/National Institute on Alcohol Abuse and Alcoholism criteria (at least 15 standard drinks per week on average over the 4 weeks before study entry for men and at least 8 standard drinks per week on average for women)[61] and all expressed a desire to reduce alcohol consumption with the possible long-term goal of abstinence. For inclusion in this study, participants must have also endorsed exposure to trauma as assessed by the Life Events Checklist,[62] which is strongly associated with PTSD symptoms in combat veterans.[63] Participants were excluded if they were known to have any clinically significant unstable psychiatric or medical conditions that would interfere with study participation, or had a suicide attempt or suicidal ideation in the 6 months before enrollment.

Procedure

Participants were recruited, and all procedures took place at the San Francisco Veterans Affairs Medical Center. All participants provided written informed consent and underwent procedures approved by the University of California, San Francisco, the San Francisco Veterans Affairs Medical Center, and the Department of Defense. Each participant was assessed in 2 to 3 visits extending over approximately 1 week during which they completed the measures and tasks described below. Assessments for this report were completed before randomization to each trials study group. No participants were assigned to receive topiramate at the time of the assessments.

Psychiatric Assessment

Alcohol Use

The Time-Line Follow-Back (TLFB) interview[64,65] was conducted with participants to assess quantity and frequency of alcohol consumption before entering treatment. Data from the TLFB interview were used to calculate average number of drinks consumed per week and average number of drinking days per week in the 90 days before treatment. TLFB is considered the standard for alcohol use outcome measurement in clinical trials.[66]

Alcohol Craving

Craving for alcohol was assessed with the Obsessive Compulsive Drinking Scale (OCDS), which is widely used in clinical AUD populations and possesses strong psychometric properties.[67,68] The OCDS is designed to measure obsessive thoughts and behavioral compulsions and urges associated with alcohol craving among heavy drinkers and comprises

two subscales; drinking obsessions (obsessive thoughts related to drinking) and compulsions (compulsive drinking urges and behaviors). Participants respond to items using a 5 to 6 point Likert-type scale and items are summed to yield a total score that ranges from 0 to 56.

PTSD Symptom Severity

PTSD symptom severity was assessed with the 17-item PTSD Checklist (PCL) for Civilians[69,70] and directly corresponds to the DSM-IV[59] symptoms of PTSD and subscales (B: re-experiencing, C: avoidance/numbing, and D: hyperarousal). Respondents indicate the extent to which they have been bothered by each symptom, in response to a stressful life situation, within the past month, using a 5-point Likert-type scale (1 = not at all bothered; 5 = extremely bothered). Responses are summed to yield a total score, ranging from 17 to 85, which is reflective of global PTSD symptom severity. The currently recommended cutoff score of 50[70,71] indicates that present symptoms are suggestive of PTSD.

Neurocognitive Assessment

Processing Speed

Trail-Making Test Part A requires the respondent to connect a series of 25 numbered circles on a worksheet, as quickly as possible, and is often used an index of processing speed.[72]

Executive Functioning

In Trail-Making Test Part B, the respondent connects a series of circles on a worksheet, alternating between numbers and letters, with instructions to work as quickly as possible.[72] Trail-Making Test Part B is commonly used to assess executive functioning because it requires mental flexibility and speeded set-shifting.[73] Performance on Part B is correlated with other well-established measures of mental flexibility (Wisconsin Card Sorting Test perseverative errors)[74] and domains of executive function including working memory (WAIS-III digits backwards).[75] Time to complete Trail-Making Test Part A and Part B was recorded and the revised comprehensive norms (corrected for age, education, gender, and ethnicity) for the expanded Halstead-Reitan Battery[76] were used for scoring.

Risk Taking/Impulsivity

The balloon analogue risk task (BART) is a behavioral measure of impulsivity and risk taking.[77,78] The BART displays a computer-generated balloon, programmed to explode randomly, and the participant uses the click of a mouse to gradually inflate the balloon, earning 5 cents per click. After each click, the participant has two options, (1) to continue to inflate the balloon at the risk of bursting it and losing all of the money from that balloon trial, or (2) stop clicking and save the accumulated money to a permanent bank. The primary outcome, adjusted average pumps (i.e., the average number of pumps on trials in which the balloon does not explode), has been shown to relate to self-reports of substance use and other health-risk behaviors.[77,78]

Verbal Learning and Memory

The Revised Hopkins Verbal Learning Test (HVLT-R)[79,80] was used to assess verbal learning and memory. The HVLT-R measures recall for a 12-word list across three learning trials, and after a delay (free recall after 20 minutes). Scoring is normed for participant age. A composite score, used as an index of verbal learning and memory was calculated by taking the average of the T scores for total recall across the three trials and delayed recall.

Data Analyses

Descriptive statistics and alpha reliability coefficients were calculated for study measures. The average drinks consumed per week variable was positively skewed and thus, was log transformed before statistical analysis. Zero-order correlations were conducted to assess relations between alcohol use, craving, post-traumatic stress symptom severity, and cognitive variables (processing speed [Trail-Making Test Part A], executive functioning [Trail-Making Test Part B], risk taking/impulsivity [BART], verbal learning and memory [HVLT-R]). Correlation analyses were also conducted between clinical severity outcomes and demographic variables (gender, age, race, and education) to determine whether demographic variables should be included as covariates in regression models. Four hierarchical multiple regression (HMR) models were tested to determine the extent to which cognitive variables explained variance in alcohol use (average drinks per week, average drinking days per week), craving, and post-traumatic stress symptom severity. In the first three HMRs, post-traumatic stress symptom severity was entered on Step 1 as it was robustly correlated with alcohol outcomes. Cognitive variables were entered on Step 2. In the fourth HMR, post-traumatic stress symptom severity was entered as the dependent variable. Quantity of alcohol consumption and craving was entered on Step 1 and cognitive variables were entered on Step 2. Gender, race, age, and education were trimmed from the HRMs because they were not associated with outcomes. All continuous variables were standardized before entry.[81]

RESULTS

Descriptive statistics for all study variables and estimates of internal consistency for measures are presented in Table I. The sample was composed of heavy drinkers, consuming an average of 12.62 drinks (SD = 8.44; range: 2.24–49.29) per drinking day in the 90 days before treatment trial enrollment. Participants demonstrated average T scores on Trail-Making Test Part A (processing speed) and B (executive functioning) though T scores for verbal learning and memory were approximately 1 SD below the mean of 50 indicating somewhat worse performance in this domain relative to the general population. The sample had a mean total score of 56.72 (SD = 13.73) on

TABLE I. Descriptive Statistics for Alcohol Use, Craving, Post-Traumatic Stress Symptoms, and Measures of Cognitive Functioning

	M (SD)	Alpha (α)
Average Drinks per Week Past 90 Days	63.53 (47.77)	
Average Drinking Days per Week Past 90 Days	5.30 (1.71)	
OCDS	24.10 (10.11)	0.91
Obsessions	8.28 (4.90)	0.89
Compulsions	15.82 (6.14)	0.84
PCL	56.72 (13.73)	0.92
B—Re-experiencing	16.06 (5.01)	0.88
C—Avoidance/Numbing	22.96 (6.20)	0.84
D—Hyperarousal	17.71 (4.33)	0.81
Trail Making Test Part A[a]—Processing Speed	46 (11.22)	
Trail Making Test Part B[a]—Executive Functioning	50 (13.12)	
BART[b]—Risk Taking/Impulsivity	37.72 (15.65)	
HVLT—Verbal Learning[a]	39.62 (11.32)	
HVLT—Delayed Recall[a]	41.66 (11.01)	
HVLT—Learning Memory Composite[a]	40.64 (10.50)	

[a]Standardized T scores; [b]$n = 64$, average adjusted pumps. BART, Balloon Analogue Risk Task; HVLT, Hopkins Verbal Learning Test; OCDS, Obsessive Compulsive Drinking Scale; PCL, PTSD Checklist.

the PCL indicating moderate to high post-traumatic stress symptom severity and a range generally in line with diagnosis cutoff levels standard in PTSD research.[70,71]

Zero-Order Associations Between Alcohol Use, Craving, Post-Traumatic Stress Symptoms and Cognitive Variables

Total post-traumatic stress symptom severity and symptom clusters were positively associated with craving and quantity of alcohol consumption but not frequency. Higher craving was associated with higher quantity and frequency of alcohol consumption. Riskier performance on the BART was associated with higher total post-traumatic stress symptom severity and avoidance and numbing symptoms (Cluster C) as well stronger alcohol obsessions and cravings. Verbal learning and memory, processing speed, and executive functioning were not associated with post-traumatic stress symptom severity. Poorer learning and memory performance on the HVLT was associated with higher quantity and frequency of drinking in the 90 days before treatment. Table II provides a complete correlation matrix.

HMR

Four independent HMR analyses were conducted to address the primary study objectives. In the first and third HMR, post-traumatic stress symptom severity was positively associated with both average drinks per week and alcohol craving. After controlling for post-traumatic stress symptom severity, lower verbal learning, and memory performance was associated with higher average number of drinks per week and average drinking days per week in the first and second HMR and higher risk taking/impulsivity (BART) was associated with greater alcohol craving in the third HMR. In the fourth HMR, average drinks per week and craving were positively associated with post-traumatic stress symptom severity; cognitive variables demonstrated no relation with post-traumatic

TABLE II. Correlations of Alcohol Use, Craving, Post-Traumatic Stress Symptom Severity, and Measures of Cognitive Functioning

	1	2	3	4	5	6	7	8	9	10	11	12
Drinks per Week	—											
Dnking Days per Wk	0.37**	—										
OCDS	0.31*	0.26*	—									
Obsessions	0.33**	0.17	0.89**	—								
Compulsions	0.25*	0.30*	0.93**	0.68**	—							
PCL	0.34**	0.24	0.41**	0.42**	0.34**	—						
Re-experiencing	0.31*	0.16	0.40**	0.42**	0.33**	0.88**	—					
Avoidance/numbing	0.25*	0.24	0.35**	0.35**	0.30*	0.90**	0.67**	—				
Hyperarousal	0.37**	0.23	0.33**	0.34**	0.28*	0.86**	0.68**	0.66**	—			
Trail Making Test A	−0.16	−0.11	−0.16	−0.12	−0.17	−0.22	−0.17	−0.24	−0.18	—		
Trail Making Test B	−0.02	−0.16	−0.17	−0.14	−0.18	−0.22	−0.20	−0.19	−0.18	0.66**	—	
BART	0.22	0.09	0.39**	0.38**	0.34**	0.28*	0.20	0.30*	0.24	−0.03	0.07	—
HVLT Composite	−0.35**	−0.25*	−0.17	−0.22	−0.10	−0.04	−0.06	−0.01	−0.08	0.13	0.04	0.04

$N = 64$ to 68. *$p < 0.05$; **$p < 0.01$. BART, Balloon Analogue Risk Task; HVLT, Hopkins Verbal Learning Test; OCDS, Obsessive Compulsive Drinking Scale; PCL, PTSD Checklist.

TABLE III. Results From Hierarchical Multiple Regression Analyses

		β	R^2	ΔR^2
Regression 1 DV: Average Drinks per Week Past 90 Days				
Step1			0.12	
	PCL—PTSD Symptom Severity	0.35**		
Step 2			0.25	0.11
	PCL—PTSD Symptom Severity	0.30*		
	Trail-Making Test Part A	–0.13		
	Trail-Making Test Part B	0.13		
	BART—Risk Taking	0.14		
	HVLT—Verbal Learning and Memory	–0.31*		
Regression 2 DV: Average Drinking Days per Week Past 90 Days				
Step 1			0.06	
	PCL—PTSD Symptom Severity	0.25*		
Step 2			0.14	0.08
	PCL—PTSD Symptom Severity	0.21		
	Trail-Making Test Part A	0.07		
	Trail-Making Test Part B	–0.15		
	BART—Risk Taking	0.06		
	HVLT—Verbal Learning and Memory	–0.26*		
Regression 3 DV: Alcohol Craving—Obsessive Compulsive Drinking Scale				
Step1			0.17	
	PCL—PTSD Symptom Severity	0.41**		
Step 2			0.29	0.13*
	PCL—PTSD Symptom Severity	0.29*		
	Trail-Making Test Part A	0		
	Trail-Making Test Part B	–0.12		
	BART—Risk Taking	0.33**		
	HVLT—Verbal Learning and Memory	–0.17		
Regression 4 DV: Posttraumatic Stress Symptom Severity				
Step1			0.22	
	Average Drinks per Week	0.24*		
	Alcohol Craving—OCDS	0.34**		
Step 2			0.27	0.05
	Average Drinks per Week	0.26*		
	Alcohol Craving—OCDS	0.28*		
	Trail-Making Test Part A	–0.08		
	Trail-Making Test Part B	–0.12		
	BART—Risk Taking	0.1		
	HVLT—Verbal Learning and Memory	0.11		

**$p < 0.01$; *$p < 0.05$. n = 63 to 64. BART, Balloon Analogue Risk Task; DV, dependent variable; HVLT, Hopkins Verbal Learning Test; OCDS, Obsessive Compulsive Drinking Scale; PCL, PTSD Checklist.

stress symptom severity after controlling for alcohol consumption and craving. See Table III for details.

DISCUSSION

The aim of this study was to examine the extent to which key domains of cognitive functioning were associated with measures of clinical severity among trauma-exposed military veterans seeking treatment for AUD. Consistent with patterns commonly reported in the literature,[82] post-traumatic stress symptom severity was positively associated with the quantity of alcohol (but not frequency) consumed in the 90 days before treatment and craving for alcohol. After controlling for post-traumatic stress symptom severity, lower verbal learning and memory was associated with higher quantity and frequency of drinking; no relations emerged between processing speed, risk taking/impulsivity or executive functioning, and alcohol use. Higher risk taking/impulsivity, but no processing speed, verbal learning, and memory or executive functioning, was associated with stronger obsessions and cravings for alcohol. After controlling for alcohol consumption and craving, no relations emerged between cognitive functions and post-traumatic stress symptom severity, which suggests cognitive functioning may hold more relevance for alcohol use and craving than for severity of post-traumatic stress symptoms. Overall, this profile of relations highlights that examination of different aspects of cognitive functioning in relation to markers of clinical severity can yield unique information to inform case conceptualization and treatment planning and delivery.

Counter to hypotheses, executive functioning as indexed by Trail-Making Test B was not related to any outcomes. This task represents just one component of executive functioning,

mental (cognitive) flexibility, and thus may not be sensitive to all executive functions relevant to drinking behavior and craving. Additional tests of mental flexibility and other measures of executive functioning are necessary to definitively assess these complex relationships. In addition, risk taking/impulsivity as indexed by the BART was unrelated to alcohol use but was positively associated with obsessions and craving for alcohol. Craving represents a form of negative urgency, a facet of impulsivity characterized by a tendency toward rash and impulsive action in the face of negative affect,[83] and is highlighted in predominant models of addiction whereby users shift from engaging in reward-seeking behavior (e.g., drinking) to avoiding negative, aversive states.[84,85] Accordingly, risk taking/impulsivity appeared to hold more relevance for craving and obsessions with alcohol rather than drinking behavior.

Of note, risk taking/impulsivity was positively associated with post-traumatic stress symptom severity and cluster C symptoms in particular, which include persistent avoidance of trauma-related thoughts, feelings and situational reminders, social disconnection, numbing and restricted range of affect, anhedonia, and poor memory. Future research should examine the extent to which emotion dysregulation, post-traumatic stress symptom severity, and aspects of impulsivity interact to increase the risk for substance abuse and related problems.[86–90] Finally, post-traumatic stress symptom severity was positively associated with risk taking/impulsivity but not processing speed, executive functioning, or verbal learning and memory. This is consistent with mixed results in the literature concerning the relation between PTSD and cognitive dysfunction among different samples.[21,24,26]

In this heavy-drinking sample, participants tended to perform (on average) within normal limits on normed neuropsychological measures. Yet, even with normal performance, associations with clinical symptom severity emerged. Therefore, although not necessarily disrupted, strengthening of neurocognitive functions critical for achieving emotional and behavioral control may be fruitful in promoting treatment success.[21,22,37,91] Difficulties with learning, memory, cognitive flexibility, inhibition, and planning can represent a significant obstacle for patients across many aspects of the recovery process (e.g., navigation of a health care system, medication management, absorption of clinical materials, and implementation of new skills, anticipation of and planning for triggering situations). Further, given that clinicians are often poor at identifying cognitive struggles among substance abusing patients,[92] and empirically supported treatments have been slow to recognize and address it,[91,93] lack of treatment engagement and progress (e.g., inattention, failure to do homework; denial and minimization of problem severity) may be inappropriately interpreted as treatment resistance or lack of motivation.[94] Clinicians are thus encouraged to consider a standard assessment of cognitive functioning, in addition to assessing for trauma exposure and post-traumatic stress symptom severity, when treating individuals with AUD.

Limitations and Future Directions

Despite several strengths of this study, including a clinically and theoretically informed multivariate model and examination of research questions within a treatment-seeking sample, limitations should be noted. First, this study was cross-sectional thus longitudinal examination is required to confirm directionality of relations. For instance, heavy drinking may cause deficits in verbal learning and memory, which subside as abstinence continues.[27] Second, this study did not investigate cognitive functioning in relation to treatment outcomes (e.g., relapse, adherence, drop-out) and research is sorely needed to examine such questions within this population. For instance, addressing deficits in learning and memory and elevations in risk taking and impulsivity may potentially help optimize recovery outcomes among patients with greater clinical severity at treatment entry. Third, in addition to examining clinical severity outcomes, future studies should also consider functional outcomes that capture domains such as occupational and interpersonal functioning and self-care. Fourth, the current sample size was relatively small, and these findings should be replicated in a larger sample to improve generalizability. Fifth, when examining these relations, future studies should control for the potential effects of traumatic brain injury and use of other psychotropic medications (e.g., benzodiazepines) and substances that are known to negatively impact cognition.[95,96] Finally, tests of moderation and mediation may help to elucidate the extent to which neurocognitive dysfunction serves to functionally connect post-traumatic stress symptoms with alcohol use and craving. Specifically, poor cognitive functioning may limit the ability to retrieve and employ adaptive coping skills to avoid or reduce alcohol use when post-traumatic stress symptoms are elevated.

In summary, this study offers a novel contribution to the literature via a multivariate examination of four key cognitive domains in relation to alcohol use, craving, and post-traumatic stress symptom severity among a sample of trauma-exposed veterans with AUD. Examination of these research questions within a treatment-seeking sample with a range of post-traumatic stress symptom severity has direct implications for clinicians and researchers to better address the role of cognitive dysfunction in the recovery process. Specifically, risk taking/impulsivity and verbal learning and memory may offer a malleable target to help reduce risk factors that contribute to poor AUD treatment outcomes, especially among those exposed to traumatic events. One possible clinical practice interpretation is that memory compensatory strategies (e.g., external cuing and reminders, repetition, increased monitoring) may be beneficial in helping patients who initially present with higher levels of alcohol consumption. Interventions that address aspects of impulsivity (e.g., contingency management) may be well suited to individuals experiencing high levels of craving on treatment entry. In addition, neuroscience-informed approaches to remediating disrupted cognitive processes may improve clinical and functional outcomes and reduce public health burdens associated

with these recalcitrant and highly comorbid conditions. For instance, interventions to reduce impulsivity and improve cognitive functions (e.g., inhibition, planning, memory) such as computerized cognitive training[97–99] may be used as a preparatory step to precede as well as augment existing empirically supported treatments for this vulnerable and high-risk population.

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SUPPORTING DATA: All figures and/or tables shall include legends and be clearly marked with figure/table numbers.
Data analyzed for DSMB Meeting (9/1/16)

Demographics of Randomized Participants, as of 8/31/16

Mean Age, years	53.7
Gender	N (percent)
Male	76 (92%)
Female	7 (8%)
Ethnicity	N (percent)
Latino/Hispanic	20 (24%)
Non-Latino	63 (76%)
Race	N (percent)
Asian and Pacific Islander	3 (4%)
Black/African American	25 (30%)
Mixed	15(18%)
White	32 (39%)
Other	8 (9%)

TAP2 – TIME LINE FOLLOW BACK: BASELINE DRINKING (PAST 90 DAYS), AS OF 8/31/2016

Drinking Aggregate	Mean ± Standard Deviation
Average Drinking Days per Week	5.2 ± 1.9
Average Heavy Drinking Days per Week	4.2 ± 2.4
Average Drinks[$] per Drinking Day	12.0 ± 7.9
Average Drinks[$] per Week	61.3 ± 48.3

-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

TAP2 - TOTAL ADVERSE EVENTS (PERCENT), AS OF 08/31/2016* (n=83)**

Adverse Event Organ System and Dictionary Term (MedDRA)	Baseline Adverse Events n (%)	Treatment Emergent Adverse Events n (%)
Neurologic		
Numbness/Tingling	35 (42)	17 (20)
Taste	7 (8)	30 (36)
Difficulty w/Concentration/Attn	54 (65)	9 (11)
Difficulty with Memory	53 (64)	10 (12)
Slow Thinking	40 (48)	14 (17)
Confusion	26 (31)	17 (20)
Language Problems	37 (45)	10 (12)
Systemic		
Fatigue	52 (63)	12 (14)
Loss of Appetite	21 (25)	28 (34)
Dizziness	26 (31)	16 (19)
Itching	29 (35)	17 (20)
Sleepiness	44 (53)	20 (24)
Psychiatric		
Nervousness	59 (71)	6 (7)
Depression	59 (71)	6 (7)
Suicidal Thoughts	12 (14)	4 (5)
Gastrointestinal		
Diarrhea	23 (28)	31 (37)
Ophthalmologic		
Abnormal Vision	17 (20)	20 (24)
Eye Pain	7 (8)	12 (14)

NOTE: Not all participants completed 12 weeks of study at time of analysis.
***Data has been entered but not cleaned